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Science and Technology Options Assessment



MAKING PERFECT LIFE

BIO-ENGINEERING (IN) THE 21st CENTURY

INTERIM STUDY

Monitoring Report

(IP/A/STOA/FWC-2008-96/LOT6/SC1)

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SCIENCE AND TECHNOLOGY OPTIONS ASSESSMENT

MAKING PERFECT LIFE BIO-ENGINEERING (IN) THE 21st CENTURY

INTERIM STUDY Monitoring Report - Phase II

Abstract

The report describes four fields of bio-engineering: engineering of living artefacts (chapter 2), engineering of the body (chapter 3), engineering of the brain (chapter 4), and engineering of intelligent artefacts (chapter 5). Each chapter describes the state of the art of these bio-engineering fields, and whether the concepts "biology becoming technology" and "technology becoming biology" are helpful in describing and understanding, from an engineering perspective, what is going on in each R&D terrain. Next, every chapter analyses to what extent the various research strands within each field of bio-engineering are stimulated by the European Commission, i.e., are part and parcel of the European Framework program. Finally, each chapter provides an overview of the social, ethical and legal questions that are raised by the various scientific and technological activities involved. The report's final chapter discusses to what extent the trends "biology becoming technology" and vice versa capture many of the developments that are going on in the four bio-engineering fields we have mapped. The report also reflects on the social, ethical and legal issues that are raised by the two bio-engineering megatrends that constitute a new technology wave.

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General information

This monitoring report *Making Perfect Life: Bio-engineering (in) the 21st Century* is the result of the second phase of the STOA-project "Making Perfect Life". This phase ran from December 2009 to November 2010. This document provided input for a conference which involved both Members of the European Parliament (MEPs) as well as other experts, which was held on 10 November 2010 in Brussels, in the European Parliament.

This phase elaborates on the horizon scan and preliminary research that was done during the first phase, which ran from September to November 2009. That preparatory phase led to an interim study (Van Est et al., 2010), which was instrumental in defining the research focus of the current second phase of the STOA-project "Making Perfect Life" and setting up a team of researchers from the Dutch Rathenau Institute in the Hague, the Austrian Institute of Technology Assessment (ITA) in Vienna, the Fraunhofer Institute for Systems and Innovation Research (Fraunhofer ISI), and the Institute for Technology Assessment and Systems Analysis (ITAS) at the Karlsruhe Institute of Technology (KIT). The latter two German institutes are both located in Karlsruhe.

This study presents the state of the art of four domains of bio-engineering: engineering of living artefacts, engineering of the body, engineering of the brain, and engineering of intelligent artefacts. Moreover, this study depicts the relevance of each of these four engineering fields within the European Framework program, and it provides an overview of the various social and ethical issues that relate to the further development of these fields. The third and final phase of the project will take place in 2011 and focus on the policy implications related to bio-engineering in the 21st century.

Acknowledgements

The project *Making Perfect Life* continues our intellectual search for the social meaning of NBIC convergence, the powerful combination of nanotechnology, biotechnology, information technology, and cognitive sciences (Van Est et al., 2006, 2008; Coenen et al., 2009). Many people have inspired us. In particular, this report builds both on earlier STOA projects on converging technologies (Berloznik et al., 2006) and human enhancement (Coenen et al., 2009) as well as earlier discussions with Bart Walhout, Tsjalling Swierstra and Marianne Boenink in preparing for the book *Life as a Construction Kit* (in Dutch: *Leven als bouwpakket* – Swierstra et al., 2009a, 2009b). Our project has been developed in parallel to the Danish ISSP's (Initiative for Science, Society and Policy) project on *Living technologies*, led by Mark A. Bedau and Pelle Guldborg Hansen. The results of the ISSP project (Bedau et al., 2009, 2010) as well as participating in that project have strongly stimulated our work. Finally, we would like to thank the many experts who were interviewed or responded in writing to our questions. The names of the various experts that helped us are listed in each chapter separately.

1. INTRODUCTION

Rinie van Est & Ira van Keulen

"In the mid-twentieth century, the conception and development of computing laid the basis for the next transformation of our world. Since the latter half of the twentieth century, I think the equivalent transformative intellectual groundswell has been the move towards understanding, at a systems level, how living things work, and exploiting this to develop interesting and useful artefacts." (Inman Harvey 2010: 86)

Europe has just recovered from the shocks that were caused by public controversies on cloning and genetically modified food. New ambitions of modern science, however, seem to have the potential to drastically broaden the bio-debate. For example, molecular medicine promises the early diagnosis and treatment of cancer, and affective computing artefacts that can 'understand' human emotions and respond in adequate way. Researchers at IBM are building a virtual brain to deepen their understanding of the brain, and the Venter Institute is constructing a microbe with a minimal genome in order to investigate what the smallest set of genes is that life needs. This study tries to come to grips with numerous developments at the forefront of science and technology and the social and political issues it raises. To do this we will investigate four fields of bio-engineering: engineering of living artefacts (chapter 2), engineering of the body (chapter 3), engineering of the brain (chapter 4), and engineering of intelligent artefacts (chapter 5).

1.1. NBIC convergence: The new technology wave

To apprehend how bio-engineering is currently developing, it is crucial to pay attention to "NBIC convergence". NBIC refers to four key technologies: nanotechnology, biology, information technology and cognitive sciences. Convergence points to the belief that progress depends on the mutual interplay between those four key technologies. NBIC convergence is thought to be essential for the successful development of a broad set of new and promising bio-engineering areas such as molecular medicine, service robotics, ambient intelligence, personal genomics and synthetic biology. This joint set of engineering fields promises a "new technology wave" (Nordmann 2004). Will such a new technology wave come true and stand its ground? And what kind of technical, economic and social expectations will it involve?

The upcoming intellectual debate around NBIC convergence can be characterised by two perspectives: science dynamics and a social view. From a science dynamics perspective, convergence is positioned as a key factor in the development and organisation of the natural sciences, because it challenges the historical divide between the physical and biological sciences. The science and engineering involved takes place at the interface between living and nonliving material; between mind and machine; between nature and technological artefacts. Van Est et al. observe that *"NBIC convergence, as an actual and anticipated development, stimulates and substantiates both practically and ideologically the arrival of a new engineering approach to life"* (Van Est et al., 2010: 33).

Traditionally, engineering was mainly about manipulating external nature. We are used to using nonliving building blocks of nature to build sky-scrapers, computers and put a man on the moon. At the start of this century, our engineering ambitions have expanded *"into the domain of living nature, ourselves included"* (Swierstra et al., 2009b). For example, biochemists show an ambition to build artificial cells from scratch, and stem cell science promises to provide the fundamental living building blocks for regenerating certain parts of the body.

The arrival of the bio-engineering ambition to (re)design and (re)build the organic world directly brings up a second, social perspective. Precisely because NBIC convergence challenges basic categories that people use to understand the world – like living and nonliving, mind and machine – it is an explicitly value-loaded development. As Staman explains that *"the concept implies that nanosciences and convergence (should) break through the boundaries of man, nature and technological artefacts"* (Staman, 2004). Accordingly, it is self-evident that the fundamental broadening of our engineering ambitions towards biological and cognitive processes is in need of social reflection and political and public debate. This study wants to contribute to that debate by providing Members of the European Parliament (MEPs) with information about this fundamental development; bio-engineering (in) the 21st century.

In two ways our study presents a rather ambitious and unconventional technology assessment exercise. First of all, it does not focus on one specific technology, like radio frequency identification (RFID), pre-implementation genetic screening and selection or deep brain stimulation (DBS). We hope to provide the reader with a broad trans-technological overview of the above mentioned 'new technology wave', and the social and ethical issues it raises. For this we focus on four bio-engineering fields: engineering the body, engineering the brain and engineering living and intelligent artefacts. Second, since this study reflects on a broad range of bio-engineering ambitions, it does not seem sufficient to list the various developments and their related social and ethical issues. At the end of such an exercise the reader would probably not be able to see the wood for the trees. Therefore, we aim to provide the reader with a certain vocabulary that will help make sense of the trends in bio-engineering and capture and discuss its social meaning. In particular, the metaphors "biology is becoming technology" and "technology is becoming biology" play a central role in our description and analysis. We hope to use the above two 'slogans' as a kind of sensitising concepts in order to depict the state of the art of bio-engineering and reflect on its social meaning.

1.2. Two bio-engineering megatrends

"Conceptually at least, biology is becoming technology. And physically, technology is becoming biology. The two are starting to close on each other, and indeed as we move deeper into genomics and nanotechnology, more than this, they are starting to intermingle." (W. Brian Arthur 2009: 208)

Traditionally, the natural sciences have been divided into the physical sciences and biological sciences. While the physical sciences, like chemistry and physics, were involved in studying nonliving systems, the biological sciences were involved in studying living organisms. As indicated above, NBIC convergence points at the gradual dissolving of the tight borders between the physical and biological sciences. The convergence of the physical and biological sciences goes both ways, and each way represents a bio-engineering megatrend. W. Brian Arthur denotes these two megatrends with the catchphrases "biology is becoming technology" and "technology is becoming biology" (Arthur, 2009), respectively. From an engineering view on life, "biology is becoming technology" implies that we are increasingly looking at living organisms in mechanical terms. Seeing biology as a machine, however, is an old idea. "What is new is that we now understand the working details of much of the machinery" (Arthur, 2009: 208). The second megatrend "technology is becoming biology" implies that technologies are acquiring properties we associate with living organisms, like self-assembly, self-healing, reproduction, and cognition. "Technology is becoming biology" is about bringing elements of life-like systems into technology. Bedau et al. (2009) therefore speak about "living technology".

1.2.1. Biology is becoming technology

The first megatrend concerns the way the physical sciences (nanotechnology and information technology) enable progress in the life sciences, like biotechnology and cognitive sciences. This type of technological convergence has created a new set of engineering ambitions with regards to biological and cognitive processes, including human enhancement. One might say that developments in nanotechnology and information technology boast the dream that complex living systems, like genes, cells, organs, and brains, might in the future be bio-engineered in much the same way as nonliving systems, like bridges and electronic circuits, are currently being engineered. In this respect, the ongoing influx of the physical sciences in the biological sciences seems to go hand in hand with a growing influence of an engineering approach to life.

1.2.2. Technology is becoming biology

The second bio-engineering megatrend is driven by convergence in the opposite direction. Here the life sciences – insights in biological and cognitive processes – inspire and enable progress within the physical sciences, like material sciences and information technology. This development relies heavily on so-called biomimicry or biomimetics. The basic idea behind biomimetics is that engineers can learn a lot from nature. Engineers want to emulate nature to enhance their engineering capabilities. In this line of thinking, algae may provide a bio-solar system that is more efficient than the silicon-based solar cells our engineers have created. But although nature's achievement is impressive, engineers are convinced that there is still plenty of room for improving the engineering skills of nature. For example, algae absorb blue and red light, but not a lot of green light. Engineers would like to design more efficient bio-solar systems that can do it all. The bottom line is that our technological capability and level of understanding enables engineers to go beyond the 'simple' mimicking of nature, and make a bold step in the direction of biologically, neurologically, socially and emotionally inspired approaches towards science and engineering.

1.3. A societal debate perspective

As indicated above, we also use the metaphors "biology becoming technology" and vice versa to reflect on the social, ethical and legal issues that are associated with the new technology wave. Here we just aim to give the reader a first feel for the state of the debate surrounding the two engineering trends, and how these trends may raise different types of societal questions.

1.3.1. Biology is becoming technology

Society is quite familiar with discussing the megatrend "biology is becoming technology", considering the steady growth in the number of engineering tools for studying, modifying and copying (parts of) living organisms. In particular since the 1990s, society became acquainted with these through a range of heated public debates around GM food, cloning, xeno-transplantation, embryonic stem cells, embryo selection, and so on. Themes like "messing with nature", "playing God" and "the instrumentalisation and commercialisation of life" play at centre stage within the public debate. In this study we aim to understand how NBIC convergence with its promise of the total constructability of humanity and nature will add to that ongoing debate. NBIC convergence has already led to a growing international expert debate on human enhancement; that is, the promises and perils of engineering the human body and mind (cf. Van Est et al., 2006, 2008).

1.3.2. Technology is becoming biology

When compared with "biology is becoming technology", the social debate on "technology is becoming biology" is far less developed. Various authors, however, argue that this unfamiliar 'bottom-up' conception of engineering requires close scrutiny and ethical inquiry (cf. Ferrari and Nordmann, 2009: 52; Bedau et al., 2009). This study would like to put this bio-engineering megatrend on the radar and provide a first overview of some social and ethical issues involved. One major topic related to "technology is becoming technology" is the fear of loss of engineering control. At the start of this century, computer scientist Bill Joy made this argument in his pamphlet Why the future doesn't need us (Joy, 2000). He warned that the 'living' character of gene technology, nanotechnology and robotics are "threatening to make humans an endangered species," because they bring the processes of self-reproduction and evolution within the realm of human intervention. Joy's main argument is that since "technology was becoming biological", such manmade technology could get beyond the control of engineers. In the early stages of the debate on nanotechnology, the so-called Grey Goo scenario, in which self-replicating nano-robots destroy the world, played a role, but it was rapidly removed from the agenda for being unrealistic. Current developments in the field of synthetic biology and robotics, however, are breathing the new life into the debate that Joy tried to put on the public agenda.

1.4. Content

The report describes four fields of bio-engineering: engineering of living artefacts (chapter 2), engineering of the body (chapter 3), engineering of the brain (chapter 4), and engineering of intelligent artefacts (chapter 5). Each chapter describes the state of the art of these bio-engineering fields, and whether the concepts "biology becoming technology" and "technology becoming biology" are helpful in describing and understanding, from an engineering perspective, what is going on in each R&D terrain. Next, every chapter analyses to what extent the various research strands within each field of bio-engineering are stimulated by the European Commission, i.e., are part and parcel of the European Framework program. Finally, each chapter provides an overview of the social, ethical and legal questions that are raised by the various scientific and technological activities involved. The report's final chapter discusses to what extent the trends "biology becoming technology" and vice versa capture many of the developments that are going on in the four bio-engineering fields we have mapped. The report also reflects on the social, ethical and legal issues that are raised by the two bio-engineering megatrends that constitute a new technology wave.

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2. ENGINEERING OF LIVING ARTEFACTS: SYNTHETIC BIOLOGY

Helge Torgersen, Markus Schmidt & Karen Kastenhofer

2.1. Introduction

The core vision of the emerging field of Synthetic Biology (henceforth SB) is to 'engineer living artefacts'. In the wake of recent developments in molecular and systems biology and artificial life research, SB no longer holds the traditional life sciences' goal to describe and understand biological systems but increasingly focuses on designing and constructing forms of life by its own means¹ (cf. De Vriend, 2006). Within a bio*technological* paradigm, new biotechnical devices, engineering approaches and data processing further promote the convergence of science and technology. Biology closes in on technology not only on a metaphorical or programmatic level, but also in practical terms, putting practices of intervention, control, construction and design centre stage. Technology approaches biology as biological processes and parts turn into ever more important instruments, targets and products of engineering projects.

This very general trend is impressive, but what exactly does it mean in concrete research contexts as well as on broader scientific and societal levels? Is it really about making organisms into living machines, or constructing mechanical organisms with traits like self-replication and self-assembly? Is biology really becoming technology or technology turning into biology (Carlson 2010, Bedau et al., 2009)? And if so, should we as a society care? Should politicians start to react to such a development? To find answers, a closer look at actual developments within SB is necessary.

When mentioning the term SB, media reports featuring the American scientist-inventor Craig Venter come to mind. In the search for a minimal genome, he and his research team aim to reprogram organisms, using synthesised genomes. Starting with a natural organism and transforming it step by step into a technical artefact, he follows a 'top-down' engineering approach. In doing so, he claims not only to revolutionise our perception of life and natural organisms, but also to provide technological solutions to important societal problems like climate change, hunger and severe illnesses. This approach can be understood as an attempt to transform organisms into machines, turning biology into technology. Actually, the metaphor applies even better to another field, encapsulated in the popular image of Lego bricks². A group of US scientists used this analogy to explain their bottom-up approach using standardised genetic building blocks.

Some scientists were sceptical regarding the novelty of SB and its aims. Apart from the sheer reductionism of approaches such as genetic building blocks, they argued that biology and technology had been related in many ways for a long time already. In particular, the recombinant-DNA technology ('genetic engineering') developed in the early seventies already allowed cutting and pasting DNA segments and inserting foreign DNA-pieces in recipient organisms, providing a molecular editing system. It made all life forms potentially reprogrammable and rendered them technological artefacts to some degree.

¹ It thereby builds upon long-standing attempts at introducing an engineering perspective in biology which date back to Descartes' mechanistic models of living systems as well as to the formation of a genetic engineering approach which goes back as far as the 1930's.

² For example, in September 2009 the "New Yorker" showed a cartoon of a couple putting together the image of a human child from a pile of Lego bricks under a picture of the double helix.

However, progress has been fast since. From the 1990's on, the international Human Genome Project and other projects on the genomes of various bacteria, fungi, animals and plants not only established DNA sequence information but also gave rise to increasingly powerful DNA sequencing and synthesis technologies. In combination with bio-informatics, this profoundly altered the possibility to change genomes in two ways, at least in theory. In a top-down approach, scientists aim at deliberately redesigning genomes of existing organisms, for example by introducing genes for whole metabolic pathways rather than manipulating merely one or a few genes as in genetic engineering. In a bottom-up fashion, scientists seek to combine, from prefabricated elements, whole genomes on a simple (bacterial) genetic 'chassis'. The so-called 'digitisation' of biology brought about an important change as organisms and information are interchangeable: organisms considered to be entirely defined by their genome could be 'printed out' with the help of appropriate devices based on electronically available information. These are basic approaches of today's SB that profoundly (re)construct the genetic material of organisms for useful purposes.

What societal implications arise from these ideas? Early on, the perspective of Man creating Life evoked the interest of social sciences, ethics and technology assessment (de Vriend, 2006). It also interested NGOs; for the cover of their report on 'Extreme Genetic Engineering', the Canadian technology-critical ETC group changed Leonardo da Vinci's ceiling painting of the Creation of Man to God raising a warning finger while Man keeps playing with Lego bricks in order to build a double helix (ETC Group, 2007)³. Such interest did not go unnoticed by scientists. Today, SB is not only an emerging field pursuing a novel scientific-technological perspective; it also provides an example of scientists approaching the public more directly and professionally. This does not only pertain to simple public relations but also to serious dealing with possibilities and problems from engineering living artefacts such as intentional misuse, accidents, benefit distribution to the feasibility of fulfilling the aims proclaimed.

In the following section we will first describe the framing of the field and the scientifictechnological context, describe how particular visions guide the field and flag streams of development. We will investigate the engineering perspective and the problem of fulfilling promises and define novelty in the sense of 'disruptiveness'. We will then provide an overview over major projects in Europe. We will discuss ontological and ethical aspects and implications such as risk mitigation, benefit distribution and governance and finally come back to living machines and artificial life.

2.2. Scientific-tecnological state-of-the-art

The first department dedicated to the new field was set up in 2003 at the Lawrence Berkeley Laboratories, and officially aimed at applying engineering principles to molecular biology. Ever since, the field has taken off. Special institutions have been set up around the world and the number of groups, publications and grants has steeply increased. The European Commission issued an official report in 2005, and numerous articles have addressed various aspects from playful innovation to risk, from engineering principles to moral issues, from industrial application to threats of potential misuse. In a very short time, SB became one of the 'next wave' technologies, converging with info, nano and cognitive sciences and it entered the well-known cycle of hype, hope, partial successes and possibly, disillusionment⁴.

³ See http://www.etcgroup.org/en/node/602. The ETC Group has issued several critical reports on SB since, available on their website.

⁴ see Gartner's Hype Cycle: http://www.gartner.com/pages/story.php.id.8795.s.8.jsp

2.2.1. Framing the Field

As with every field of science and technology, SB is associated with certain basic tenets that emerge from particular properties and characteristics, assigned to the field by practitioners and commentators. These tenets subsequently frame an understanding among not only scientists and stakeholders but also among politicians and the public. In particular, three partially overlapping groups succeeded in influencing the understanding of what SB is: the Biobrick/iGEM community at MIT with Drew Endy, the SB group at Berkeley with Jay Keasling and the group surrounding Craig Venter and his institute. Each of these approaches not only constitutes a distinct scientific way of giving content to the term SB; their understanding is also associated with a particular social attitude.

Regarding the definition of SB, the bottom-up framing as communicated by Drew Endy and the Biobrick community rhetorically prevail. They aim at introducing a 'true'⁵ engineering mindset to biology via the standardisation and modularisation of genetic building-blocks – so-called 'bioparts' as captured in the Lego brick metaphor. This attitude resulted in efforts at attracting pre-grad students to a competition in constructing novel organisms (the 'international genetically engineered machine' competition, iGEM⁶). The playful engineering spirit of this competition, obviously adopted from similar events in the IT and robotics communities, clearly distinguishes the bioparts approach from the more sober commercially driven product development thinking in applied, industrial and agricultural biotechnology. The absence (so far) of large companies' commercial interest in standard biological parts and the open source way of dealing with IPR helped to create an image of the field: SB as 'ours', not 'theirs', and as an engineering field like IT, not as traditional biotechnology.

A second famous attempt at engineering living organisms in a more thorough way was the transfer of an entire metabolic pathway as an example of top-down engineering. With regard to social issues, Jay Keasling put forward a particular philanthropic quest with an 'orphan' microbial Malaria drug as a first example of a practical application. Within the frame of ethically guided engineering, the quest involved philanthropic societies (e.g. the Gates Foundation) and was announced as being pursued for the better of mankind rather than for commercial purposes that are eventually turned into a viable business. Compared to similar plans in agricultural biotechnology (e.g. the 'Golden Rice'⁷), prospects are decidedly brighter.

Finally, Craig Venter's team succeeded in making an artificial functional bacterial genome as a necessary step towards 'constructing' organisms. As such, this work combines a topdown approach (introducing changes in existing organisms) and a bottom-up approach (building an entire minimal genome from chemical substances). The idea is to consider an organism fully determined by its DNA sequence, highlighting the dual nature of a genome as information determining a living organism and as a non-living chemical substance. In the same vein, Venter claimed to have created the first artificial organism (which others disputed, as the cell harbouring the genome pre-existed). From a societal point of view, his entrepreneurial attitude can be considered paradigmatic for scientists taking a strong stance in the public, who address controversial issues and seek support for their agendas by unconventional means.

⁵ accordingly, genetic engineering was not engineering proper as it still needed a lot of handicraft. Thanks to the bioparts approach, the supporters and engineers no longer need to know what is going on within the standardised parts; they may freely use them to solve problems according to their label.

⁶ see http://2010.igem.org/

⁷ see http://www.goldenrice.org/

2.2.2. Ambitions and activities in the field of SB

Although the bioparts approach and the artificial minimal genome are often taken as synonyms for 'engineering life', there are many other fields of interest in SB. Its characteristic element is a rational engineering perspective on life (Koide et al., 2009); that is, the intelligent and rational design of genetic constructs for programming organisms not existing in nature, for rendering them capable of fulfilling useful purposes, or for gaining insight into fundamental processes of life. As an enabling instrument, SB thus bridges the living and non-living, biology and technology. Broadly, the Synthetic Biology community website⁸ defines SB as

- the design and construction of biological parts, devices and systems, and
- the redesign of existing, natural biological systems for useful purposes.

Hence, emphasis is laid, on the one hand, on a bottom-up construction from simpler to more complex genetic entities and, on the other hand, on a top-down re-engineering of pre-existing genetic systems. We use this bottom-up and top down distinction as preliminary guidance, although we have already seen that some approaches can be understood in both directions.

The technical basis is provided by **DNA synthesis**: developments in the rapid sequencing of genes and whole genomes go along with increased capabilities to chemically synthesise DNA into ever longer, and cheaper, DNA strings.⁹ Over recent years, scientists have been able to synthesise the genomes of different viruses without the need of a natural template. The J. Craig Venter Institute came up with the first-ever complete de novo synthesis of a whole bacterial genome (*Mycoplasma genitalium* with 580.000 base pairs) and recently repeated the effort with *Mycoplasma mycoides* (over one million base pairs) that was also successfully booted up in a natural bacterium (Gibson et al., 2010). As a future vision, artificial small eukaryotic chromosomes, so-called mini-chromosomes, open up perspectives towards engineering or fundamentally altering eukaryotic cells. DNA synthesis is the basis for bottom-up constructing genomes – and, in this understanding of SB, organisms – as well as for redesigning existing organisms by introducing artificial 'genes'.

Advanced genetic constructs are also used in **metabolic engineering**; however, the increase in DNA synthesis capacities is much larger than current engineering abilities. Today's attempts at altering metabolic pathways in a meaningful top-down way or at designing properly working genetic systems and circuits are limited to the complexity presented by no more than about 10-15 genes. Nevertheless, there is substantial practical progress, for example, there are realistic attempts at finding novel ways of producing biofuels from cellulose or other raw materials. The most celebrated achievement is the design of a metabolic pathway to produce a precursor of the anti-malaria compound Artimisinin, a substance naturally found in wormwood plants that could so far not be synthesised in production micro-organisms. However, its design and construction, representing the state of the art of enhanced metabolic engineering, was a tedious process that took about 150 person years. No wonder rationalisation and reduction in design complexity appear necessary.

⁸ see http://syntheticbiology.org

⁹ Frequently, analogies have been drawn between the progress in DNA synthesis cost and speed and the increase in memory capacity of computer chips according to "Moore's law" (Carlson 2010, see http://www.synthesis.cc/).

A possible solution could come from so-called **standard biological parts** (also known as bioparts or biobricks¹⁰), a toolbox of well-characterised, prefabricated, standardised and modularised genetic compounds (i.e. sequences of DNA) for engineering biological systems¹¹. The vision is that in a bottom-up way, such standard biological parts could be freely combined and built into larger 'devices' that fulfil certain defined functions, and these are again made into 'systems' or larger genetic circuits that ought to work as designed, or so it is hoped (Canton et al., 2008; Arkin, 2008). However, few properly working devices have been arrived at so far and few parts have been thoroughly characterised. Typical applications were rather simple, e.g. a chemical oscillator, banana-scent producing E.coli, light-sensitive bacteria etc. Conceptually, the parallel to the world of electronic circuits made of simple interchangeable building blocks is no coincidence, and some ideas in electronics are emulated into the worlds of molecular genetics. Tellingly, the pertaining website is called 'openwetware'. The emphasis on the application of engineering for making organisms, i.e. to technology becoming biology, is obvious.

In pursuing the total understanding of a living object, another vision is to reduce complexity. To do so, a cellular platform or 'chassis' is created, which is a simple cell with a **minimal genome** or the least possible number of genes for survival under laboratory conditions. The minimal genome can also serve as a cellular platform for engineered biological circuits, reducing possible interactions between the chassis and the genetic constructs introduced. The construction of minimal genomes already starts from small natural genomes (e.g. Mycoplasma) by eliminating 'unnecessary' genes even further in a top-down approach. However, the resulting truncated organism is dependent on stable laboratory conditions (supply of essential substances, no viruses, etc.) for survival. In a bottom-up process then, they may be completed again to give rise to organisms pursuing useful tasks.

In a parallel bottom-up attempt at constructing organisms (and not only genomes), synthetic cells or **protocells** are created, i.e. minimal versions of life such as synthetic celllike aggregates from non-living chemical components. Constituents are membrane-like structures that separate the inner from the outer as well as they aid simple metabolism and procreation by fission, i.e. the emergence of 'daughter cells'. Attempts at constructing metabolically active protocells have been made for some time, independent of the more genomic stream of SB, and focus on different life functions such as metabolism. Visions include combining both streams with the aim to create artificial cell-like devices able to propagate genetic information, i.e. to contain genome-like sequences that are copied before fission. If successful, these attempts may come nearest to the ideal of 'creating life' as they do not rely on pre-existing cells.

These streams of development make use of the same or a similar biochemistry as natural life forms do. However, for practical reasons metabolic engineering aims at separating the newly introduced constructed pathways from the naturally occurring ones. In other words, it seeks to introduce a certain degree of **orthogonality** (or differentness) while using the same or very similar chemical building blocks. Alternatively, the biochemistry of life could be conceived entirely differently. From a radical 'bottom-up' understanding, visions of fully orthogonal systems include artificial biochemistries that cannot interfere with naturally occurring ones at all. In **xenobiology** (or chemical SB), the very basics of the biochemistry of life are changed in order to create biological systems truly different both in metabolism and on the genetic information level.

¹⁰ Bioparts is the technical expression, while BioBricks is a trademark created to promote the underlying approach.

¹¹ See http://bbf.openwetware.org/

There is a long road ahead for this approach, so less radical top-down approaches dominate today. Examples start from altered or non-naturally occurring bases within the DNA and comprise an idea of different information storage molecules that cannot interact with naturally occurring DNA. Another example is the use of unnatural building blocks such as artificial phospholipids or non-canonical amino acids. Visions, however, also encompass possible life forms using not only foreign elements but also architectures entirely different from 'life as we know it'.

2.2.3. The engineering approach in SB: its role and limits

Usually, the goal of science is to gain insights into natural phenomena, i.e. knowledge, and that of technology to develop applications for useful purposes, i.e. benefit. Practitioners in SB often emphasise the engineering perspective and thus its character as a technology. However, synthetic biologists not only aim at designing organisms for useful purposes such as drugs or biofuels. Rather, following the engineering motto 'what I cannot construct I do not understand', SB has also become a means to acquire knowledge about the fundamental principles of life in a bottom-up way. For example, the design of functional circuits allows for testing hypotheses derived from systems biology, and basic concepts of life can be tested through orthogonal systems. Thus, engineering becomes science, and scientific insights drive engineering while, at the same time, scientists need engineering to gain insights. Nevertheless, the application character 'to solve problems out there' is put forward. In other words, the boundaries are blurred. We can no longer apply familiar distinctions such as 'pure science' versus 'technology development' in order to address what is going on in SB. Philosophers and sociologists of science have argued that newly emerging fields in general, and in the life sciences in particular, are characterised by a mix of scientific as well as technological attributes. The term technoscience has been coined to address this twofold identity, although it remains unclear what exactly it implies for research and for science governance.

Since engineering as a catchword appears frequently, the engineering approach is apparently important in SB; therefore we need to address it in more detail, drawing on opinions from scientists, philosophers of science and STS researchers in expert debates and interviews. For example, an interviewee captured his understanding of the big issue within SB in one sentence:

"... Can you actually engineer biology as engineers would engineer anything? (...) The step change (...) that molecular biology needs to take forward is the ability to actually construct itself in a conceptual framework around engineering." (Paul Freemont, LSE debate Nov. 2009)

However, the engineering approach to influencing science and its actual manifestation within science seem difficult to explain. On a practical basis, it is represented by a multidisciplinary collaboration of biologists, physicists, mathematicians, computer scientists and engineers on equal level.

"Taking engineering into the actual biological discipline (...), bringing the engineering discipline and how engineers approach problems, in design, in modelling and in how they build things into biological systems, that, to me, is synthetic biology. (...) It has to be a completely equal partnership" (I SB 1)

Accordingly, the integration of engineers and the engineering approach within biology goes hand in hand with a focus on delivering technological applications aimed at solving societal problems. This orientation may compete with the traditional curiosity driven orientation in biology.

"[The engineering approach] won't select out those people who are curiosity driven because those people wouldn't be suited necessarily to synthetic biology, because they just want to go where there mind takes them, where there curiosity takes them and if it is something which is far removed from anything that is applicable it doesn't matter; you know, those sort of people are probably not necessarily people who would be attracted to synthetic biology which has this very strong application downside but, on the other hand, there is a lot of really interesting problems to solve before you get towards the application and just how you do synthetic biology, how do we build all these [pathways?]." (I SB 1)

The orientation towards technology or the adoption of an engineering paradigm is said to result in a different research approach and outcome. The research process builds upon individual modules that are developed, characterised, standardised and archived as ready to use parts.

"Once you've developed your standard parts, once you developed your light bulb, something like that, you can plug the light bulb into a circuit without really knowing how the light bulb works." (Nik Rose, LSE debate Nov. 2009)

"its getting all the libraries, the parts, the characterization, the facilities for characterizing them all, and then the tools and the design tools and how we do things" (I SB 1)

The knowledge, understanding and expertise necessary to work with these standard parts are kept at a minimum by means of a clever design. The 'Lego' metaphor can also be found in Craig Venters account of the engineering of Synthia, the first organism with an artificially synthesised genome:

"We start with the pieces of DNA coming out DNA synthesisers, they are only about 50 to 80 letters long... So everything we make from that has to be put in these little pieces together, much like having a box of Legos and having to assemble them back in the right order to get what you started with." (Craig Venter, interview)

Within this engineering approach, biological diversity, idiographic characteristics and emergent properties such as individual shape or behaviour are interpreted as obstacles for perfecting control that have to be overcome rather than as interesting objects of research: "*We thought we would have this almost three years ago, but we kept running into very significant biological roadblocks*" (Craig Venter, interview). Against this background, biology is no more an epistemic realm than a tool and a product of engineering:

"This is now the first time where we've started with information in the computer, built that software molecule, ..., put that into a recipient cell and had this process start with that information, converted that cell into a new species. So this becomes a very powerful tool for trying to design what we want biology to do." (Craig Venter, interview)

"Its not really about nature, is it? It is about using nature's building blocks to build different things." (I SB 1)

The new adoption of an engineering approach is described as a logical consequence of the new developments within genomics (focussing on information: "*we have all this genome information, why would we not want to fragment it all up into usable bits that we could put together in different ways?*" SB 1) and as different from the engineering approach within earlier genetic engineering and biotechnology (*"it is like putting the engineering back into genetic engineering, where there was never [a real engineering approach realised]"*, (I SB 1).

Still, some scientists are more cautious in their depiction of what counts as a proven possibility and what will be possible in the future. Paul Freemont, a renowned synthetic biologist at Imperial College, points at uncertainties concerning the extent to which molecular biology will be able to actually *"construct itself in a conceptual framework around engineering"*, because *"biology is not used to be an engineer[ing science]"* and we cannot predict yet whether you can *"actually engineer biology as engineers would engineer anything"*. (Paul Freemont, LSE debate Nov. 2009). Furthermore, biologists are not

"used to thinking in a kind of engineering way, the idea of building things from parts or genes and putting them together in different combinations and maybe testing each one on how they would work. ... So biologists would have to come into that kind of feeling and biological engineering kind of thing". [And engineers] "...will find it quite demanding because biological systems don't behave in a predictable and robust way." (I SB 1)

2.2.4. The Promise to deliver

The example of the Human Genome Initiative shows that these days, big scientific endeavours almost invariably seem to be accompanied by exaggerated promises for practically relevant outcomes that eventually turn out to exceed the ones actually delivered by far.¹² This is not confined to biology. Active promotion of new ideas and approaches to funding organisations, industries, politicians, the press and the public at large are common in many fields of modern technoscience, for example in nanotechnology. Promises to contribute to economic welfare, fight serious illnesses, alleviate hunger and – most recently – help to prevent climate change are ubiquitous elements of campaigning for novel research fields. Synthetic biology is no exception; on the contrary, the emphasis on engineering useful applications may boost expectations. Over less than a decade, protagonists succeeded in establishing SB as one of the 'next big issues', i.e. in a row with information technology, biotechnology, nanotechnology and technologies derived from cognitive sciences. As a 'converging technology', SB is either seen as the result of a convergence or expected to converge with other similar fields, being subject to the far-flung expectations that accompany the term.

Promises build upon the idea that modern sciences are able to deliver specified outcomes in a more or less predictable and controllable way, similar to projects of innovation and application development, for example in the information technology sector. However, practical experiences illustrate that the anticipation and planning of technological innovation is not trivial. Synthetic biology practitioners themselves see this selling endeavour and their role in advocating SB in an ambivalent light. Some enthusiastically project a grand future for SB in rather strong formulations:

"For me SB is a really exciting new area (...) and I firmly believe (...) that this could well produce a new industrial revolution and that there will be many applications in many different fields." (Richard Kitney at the LSE panel on Synthetic Biology in November 2009)

With growing pressure to promise positive societal effects and economic returns as a means to legitimate public and private investments, others perceive the rhetoric of hypes and hopes as precarious and give more cautious comments.

¹² The phenomenon of hope as a driving force in demand-based technology development is particularly prominent in the medical sector, see e.g. Novas (2007).

"The field in ten years time may go nowhere; might be like gene therapy; the bubble could burst and everyone may be saying, well what is the great deal about it?" (I SB 1)

The pressure to promise and to then actually deliver is sketched as an irrational development in the interaction of science and science policies.

"There [is] probably over-hyping in that field and I think that's a natural problem and it's a big problem we have got. There has been so much hype to the extent that it has gone absolutely mental. (...) if we are to deliver it is going to take quite a long time to get to this level in delivering and the trouble is we need to start delivering things now. So one has to buy into the concept that this is the right way to do it (...) because at the moment its just being rather piecemeal; (...) this is the problem with any research and it is very frustrating; it would be much better if you could have rational discussions with politicians but unfortunately, no; and so you have a hype and suddenly you get the funding in and the research is much harder, it doesn't deliver, then the government says, we put all this money and nothing has happened [and so on]." (I SB 1)

Overall, the ability to deliver has become an important new point of reference when talking about Synthetic Biology (or other emerging technosciences), often combined with ambivalence and ambiguities. The orientation towards problem solving and its impact on research practices are depicted with an ambiguous sentiment: "*Its still 'we've got a technology let's find the problem.' But they talk about the problems more."* (Richard Kitney at the LSE panel on SB in November 2009). Taken together, it appears as if there is a double rhetoric; on the one hand, SB is perceived to be, and advocated as, an exciting field full of promises, on the other hand, the pressure to actually live up to those promises is felt as an increasingly heavy burden.

2.2.5. The novelty of SB

SB practitioners claim to introduce an entirely novel approach to biology; yet, as in every new field in science and technology, they build on established insights and previous practices. This tension gives rise to different interpretations whether SB is novel or not, or in which respect it might be so. To what degree these activities are considered revolutionary or rooted within established practices makes a difference; not only in terms of how novel SB is considered to be scientifically. They also entail different views whether or not fundamental tenets on the nature of life are at stake, with all imaginable ethical consequences, and ultimately impinge on perceptions on how society should deal with challenges posed by SB. In other words, they render particular aspects of SB more or less disruptive.¹³

Since SB comprises of a variety of activities, the character of SB is not the result of a consistent epistemology. Apart from the engineering spirit, the aims and projects involved shed some light on this character. One of the main aims, of course, is the construction of living artefacts. Today, this is only possible to some degree with genetic material derived from bacteria, i.e. on a limited complexity level. However, not only the activity of construction elicits fascination or repulsion; even more important is the 'unnaturalness' of the constructs. Different activities in the field reflect various ambitions to move away from 'given' forms of life.

¹³ A closer look reveals that novelty and disruptiveness are by no means identical; however, there are close relations (see below). For the purpose of this chapter we may apply novelty in the sense described as a proxy for disruptiveness.

To gain an overview we propose to sort activities and aims according to the complexity, on the one hand, and the familiarity, on the other, of objects, substances, procedures and aims involved. The dimensions are explained as follows:

- Activities in SB are aimed at different complexity levels found in the living world. Altering the basic biochemical building blocks of life takes place on another level than the development of a toolbox of standard biological parts, from which larger devices and systems can be put together. Synthesising whole genomes is even more complex, as is the complete construction of totally synthetic chromosomes or partly functional proto-cells. Building entire cells or organisms by far exceed the complexity levels within reach today.
- Another difference lies in the profoundness of the alteration between the artificial product and its naturally occurring counterpart, in other words, in the former's 'unfamiliarity'. Whether or not the constructions are based on naturally occurring functional molecules or functions within an existing living system determines the degree of unfamiliarity.

Table 1 shows five areas of SB activities (as explained above) according to their complexity and unfamiliarity levels14. From left to right: increasing unfamiliarity, from top to bottom: increasing complexity.¹⁵ For references to every cell see References for Table 1 at the end of this chapter.

	A: DNA synthesis	B: Genetic circuits	C: Minimal genomes	D: Protocells	E: Chemical SB
1: Biochemistry	standard	standard	standard	Standard or alternative biochemistry	Alternative biochemistry (XNA, unnatural bases, amino acids)
2: Genes/parts	Synthetic genes	Genes and bioparts, bioparts	-	Engineered phospholipids	Changing the codon assignment of genes
3: Biological systems	Artificial chromosomes synthetic viruses	Enhanced metabol. engineering (e.g. artimisinin) bioparts devices	-	Cellular vesicles lacking key features of life	Development of novel polymerase and ribosomes
4: Cells organelles single-cell organisms	Whole genome synthesis	-	Top-down SB reducing existing organisms' genomes	Synthetic cells, Bottom-up SB manufacturing whole cells	Xeno- organisms chemically modified organisms (CMOs)

Table 1: Complexity levels and 'unfamiliarity' in SB¹⁶

¹⁴ The list is far from exhaustive – for example with regard to complexity, in a more distant future we could also think of engineered tissues and organs, of altered multi-cellular and higher organisms or even of entirely synthetic ecosystems composed of fully synthetic organisms.

¹⁵ The area of metabolic engineering could be considered to constitute a separate column; however, if it largely follows the established practices of genetic engineering (though more ambitious) it would clearly have to be considered "familiar"; more advanced forms would perhaps fall under column B (genetic circuits).

^{16 &}quot;Normal" GMOs would technically fall into category B1 in this list but they are, of course, whole organisms. However, they are only slightly modified on the basis of organisms occurring in nature.

Our table might help sorting out what we mean exactly when we refer to SB as 'novel'. In this understanding, the term is applied not to indicate disciplinary scientific uniqueness or innovative potential; rather, it indicates a deviation from what we know and are accustomed to with respect to living organisms. For example, Craig Venter's famous experiment of introducing an artificial genome into a bacterium would to be assigned to A4, DNA synthesis on a cellular level, and hence rather 'familiar' though 'complex'. This shows that some activities that command huge attention in popular press do not necessarily need to be considered as those that are the most ambitious in terms of turning technology into biology. It also shows that the field is more varied than it appears to be from the perspective of a lay observer.

Accordingly, we have a novelty scale that ranges from standard biochemical DNA synthesis to the (hypothetical) construction of 'xeno-organisms', with many different research and development projects in between that can be considered 'novel' to different degrees. For example, the bioparts approach draws its novelty from an engineering rationale but keeps using molecules and structures familiar to biology. Other activities within SB not only follow the engineering paradigm but also apply different substances for engineering life.

With respect to the top-down/bottom-up distinction, it can be noted that top-down types are centred at the left of the table, although DNA synthesis is surely a prerequisite for many bottom-up endeavours. As minimal genomes appear on a medium level regarding unfamiliarity and on a high complexity level, the bottom-up/top-down distinction falls somewhat short in convincingly explaining novelty, at least by this understanding. The 'technology becoming biology' paradigm seems to be represented better towards the lower right, while the 'biology becoming technology' notion is associated with more 'familiar' projects. Starting from newly designed (bio)chemical building blocks, both the protocell research community and the chemical SB community attempt to design and construct life forms that are very different from those we know.

It also becomes clear that the different aims of gaining knowledge and solving problems through application do not seem to render much of a distinction between more or less 'novel' (i.e. complex and unfamiliar) fields. After all, it is not only scientific curiosity that fuels a drive for more unnatural systems but also a need to address issues of safety, robustness, performance and reliability in engineering biological systems.

2.3. Relevance to European research

2.3.1. Research programmes

SB may be considered a North American brainchild and many groups officially dedicated to the field are in the US; however, Europe and, more recently but rather dedicatedly, also Asia are catching up. This is true particularly in the UK, where interest and funding opportunities are considerable, but SB is also gaining momentum in other countries. In this section we will give a summary of relevant SB research funding programmes in Europe.

EC/FP6 and FP7

For the European Commission, SB has been of comparatively high importance over recent years. Under FP6, 18 projects covering different aspects of SB received funding through the NEST (Newly Emerging Science and Technology) Pathfinder Initiative dedicated to 'blue sky' research. Under FP7, different funding programs (7 ERC, 2 PEOPLE, 1 KBBE, 2 SiS) supported research on SB. The somewhat lower number does not indicate a lessened interest; rather, it can be interpreted as a division of labour between FP7 and the European Science Foundation (ESF). For more information on individual projects see Annex 1.

European Science Foundation

In the call launched by the ESF, which was undertaken within the EUROCORES programme EUROSYNBIO ('Synthetic Biology: Engineering Complex Biological Systems'), 14 national funding organisations issued a joint call for proposals.¹⁷ In total 24 outline proposals were submitted. 16 were invited to submit a full proposal, of which up to 9 proposals will finally be funded. Each project has to include at least 3 partners from different eligible countries. An estimated budget of 12-15 million \in will be spent between all EUROSYNBIO calls that will be carried out between 2010 and 2013. The call text emphasised four main topics:

- 1) System assembly and molecular and cellular complexity in a context of Darwinian evolution: autonomous parts, subsystems, synthetic systems, re-factoring genomic chassis, understanding ... the performance of synthetic circuits;
- Computational design tools: computational interchange standards, ontology and collaborative environment, data mining & integration, parts design, model-based systems design, analysis and optimisation;
- The biosystems design laboratory: megabase-scale DNA synthesis, the role of analysis, automated system assembly;
- 4) The social context: philosophical and ethical implications, safety and security, governance and regulation, intellectual property rights, effective public dialogue.

European national funding examples

BBSRC Networks: The UK Biotechnology and Biological Sciences Research Councils (BBSRC) is funding 7 networks to facilitate multidisciplinary work and development of a 'common language' between bioscience, engineering and ELSI research groups. Some Networks address generic approaches, focusing on multi-disciplinarity and the development of basic 'tool kits'. Others are exploring specific technical challenges and specific potential applications. In total about 200 participants from all across the UK and some other European countries take part in the networks; the budget for all 7 networks is almost 1 million GBP.¹⁸ For more information see annex 1.

- Synbiostandards: standards and characterisation in SB, led by the University of Edinburgh¹⁹.
- Synbiont: SB network for modelling and programming cell-cell interactions; led by the University of Nottingham²⁰.
- MATE: Microbial Applications to Tissue Engineering; led by the University of Sheffield²¹.
- RoSBNet: From robust synthetic biological parts to whole systems: Theoretical, practical and ethical challenges; led by the University of Oxford²².
- SPPI-NET: network for synthetic plant products for industry, led by the University of Durham²³.
- Synbion Network: led by the University College London²⁴.

¹⁷ see http://www.esf.org/activities/eurocores/running-programmes/eurosynbio.html

¹⁸ see http://www.bbsrc.ac.uk/funding/opportunities/2007/synthetic-biology.aspx

¹⁹ see www.synbiostandards.ac.uk

²⁰ see www.synbiont.org

²¹ see www.sheffield.ac.uk/synbio/home.html

²² see www.eng.ox.ac.uk/control/RoSBNet

²³ see www.sppi-net.org/index.php

• Synthetic Components Network: Towards Synthetic Biology from the Bottom Up, led by the University of Bristol²⁵.

New research institutes in Europe dealing specifically with SB

Over recent years, institutions have been set up in several European countries with a focus on more specifically supporting research in SB. The following institutions stand out as centres of excellence:

- Imperial College London and London School of Economics: Centre for Synthetic Biology and Innovation (UK, established 2009)²⁶.
- Department of Biosystems Science and Engineering, ETH Basel (Switzerland, established 2006)²⁷.
- University of Groningen, Centre for Synthetic Biology (Netherlands, established 2008)²⁸.
- Center for Synthetic Microbiology (SYNMIKRO) at the Philipps-Universität Marburg and the Max Planck Institute (MPI) for Terrestrial Microbiology (Germany, established 2010)²⁹.
- Institute for Systems and Synthetic Biology (ISSB), upon a joint request by the CNRS and the UEVE, Genopole® (France, established 2009).³⁰ It includes both 'dry' and 'wet' labs to link modelling and experimental work and is set to host about 125 people by 2012.

2.3.2. Criteria for assessing projects

A detailed comparison of project subjects, aims and structure is beyond the scope of this report. Nevertheless, it is obvious that there are differences between situations in various European member countries. Using table 1 above for providing practical examples, we assign different levels of 'novelty' (in the above understanding rather than according to disciplinary scientific criteria) to the efforts currently made in Europe in the field of SB. If we consider the aims of these projects according to their levels of complexity and unfamiliarity, we arrive at table 2.

	A: DNA synthesis	B: Genetic circuits	C: Minimal genomes	D: Protocells	E: Chemical SB
1: Biochemistry				SYNTHCELLS	ORTHOSOME
2: Genes/parts		HYBLIB, TARPOL		SYNTHCELLS	ECSUB ORTHOSOME
3: Biological systems		BIOMODULAR H2 BIONANOSWITCH*CELLCOMPUT COBIOS EUROBIOSYN FUSYMEM PROBACTYS		SYNTHCELLS	
4: Cells Organelles single-cell organisms		CELLDOCTOR	PROBACTYS	SYNTHCELLS	

Table 2: Com	plexity levels	and 'unfamiliari	tv' in European	projects or	ו SB
				p. 0j 00.0 0.	

24 see www.biochem.ucl.ac.uk/synbion

²⁵ see www.bris.ac.uk/scn

²⁶ see http://www3.imperial.ac.uk/syntheticbiology

²⁷ see http://www.bsse.ethz.ch/

²⁸ see http://www.rug.nl/fwn/onderzoek/instituten/csb

²⁹ see http://www.uni-marburg.de/synmikro/synmikro?set_language=en

³⁰ see http://www.issb.genopole.fr/?lang=en

For five projects (CHEMBIOMECH, NMSSBLS, NMU-LIPIDS, REPEATSASMUTATORS, ZINC-HUBS, mostly new ERC grants), assigning levels of complexity and unfamiliarity remains difficult for various reasons. For eight projects (EMERGENCE, INEST, SYBHEL, SYNBIOCOMM, SYNBIOLOGY, SYNBIOSAFE, SYNTH-ETHICS, TESSY), such an assignment is inappropriate as they focus on ELSA or community building. The majority of projects (nine) involve genetic circuits on the systems or parts level. Only three projects deal with more 'unfamiliar' issues or conduct investigations on a higher complexity level. One project (SYNTHCELL) appears particularly novel as it deals with objects that are quite unfamiliar (protocells) on a variety of complexity levels. This shows that European research in SB, for the time being, centres at more mainstream activities on a medium complexity level dealing with objects still relatively familiar.

Tentatively, we can so identify particular properties of individual approaches and projects and assign novelty according to two dimensions. We are aware that there may be many more dimensions, but it becomes clear that unless we do not identify criteria, it does not make sense to call a particular project in SB novel or not. It also becomes obvious that applying such reasoning cannot determine once and for all whether SB at large is to be considered novel.

2.4. Ethical, legal and social issues

2.4.1. Disruptive technoscience – or business as usual?

The question of novelty is clearly related to notions of disruptiveness. If it is considered novel, SB could be expected to deliver disruptive insights and consequences, which would demand novel assessment criteria and procedures. If it appears as just an extension of previous activities and concepts, in other words, business as usual, any consequences would sensibly be assessed according to established criteria and following known procedures, perhaps with some amendments.

To find out whether or not SB has disruptive consequences, the following aspects can be considered:

- Changes in techno-scientific character, for example, in the dimensions of complexity and unfamiliarity (see above, table 1 and 2), assuming that a certain threshold of their combination must be set that indicates novelty;
- Changes in the projected impacts on entrenched notions such as 'nature'/'artefacts' or 'life'/'technology';
- Changes in the societal ramifications through benefits and harm, as well as in their adequate governance.

These epistemological, ontological and societal frames of meaning are interdependent; they jointly structure scientific, public and political debates about SB. More concretely, the various activities and ambitions of SB display either a reconfiguration of established disciplines and approaches and an ambition to further move away from forms of life as we know it, or an extension of current practices, rooted in established scientific disciplines and approaches with basically similar aims.

This has profound practical consequences. For those who see SB as 'business as usual', there might be no reason for concern as activities labelled SB are considered familiar; hence, for example, no new regulation would be necessary. Likewise, implications can be understood in familiar terms, therefore no disruption of established general concepts (e.g. of life) would need to be envisaged.

In contrast, for those who perceive SB as a potentially revolutionary endeavour, it may appear disruptive both for current regimes of regulation and for culturally entrenched notions and beliefs. However, as with almost every new technological field, both notions may be applied differently according to ideological background or constellation of interests: proponents stress, with regard to concerns, the familiarity of possible risks and, with regard to benefits, the disruptiveness of novel technological developments. Critics work the other way round.

2.4.2. Playing God, altering nature - An ontological argument?

In the context of SB, ethical reasoning has frequently been invoked with a variety of arguments that are not necessarily new (Deplazes et al., 2009). For example, the argument of commodifying common resources (ETC Group, 2008) has often been applied in the past when discussing biotechnology. In addition, ontological arguments have been raised that focus on constructing life. From the first depiction of the Michelangelo painting of the Creation, SB has been subject to discussions on whether it implies 'playing God' by 'creating Life'. Accordingly, the possible construction of entities with certain properties of living organisms from non-living matter by ways of SB amounts to a process of creation. The highly ambiguous yet ubiquitous rhetorical figure of 'playing God' was frequently evoked in popular descriptions of SB, its aims and the scientists involved. Not in the least Craig Venter heats the debate by applying a similar wording ('created a new species').

The learned discussion on whether or not the 'creating Life' rhetoric is adequate has focussed on the genetic side so far, emphasising DNA synthesis and the bottom-up rational construction of gene assemblies. What life is, essentially, remains as contested as ever (Regis 2008), although many would agree that life is not DNA synthesis only; for example, viruses are not considered living organisms as they lack metabolism. In the same vein, prominent scientists such as Nobel laureate David Baltimore argued that the synthesis of genomic DNA is an important step but not akin to creating life proper (whatever that is).³¹ Artificial life forms need to feature something like a cell with a metabolism – hence there need to be bottom-up attempts at creating a protocell endowed with a genome of some sort. Even then it is questionable when exactly to call the result artificial life or, in the terms used here, when exactly technology becomes biology.

One prominent argument in favour of pertaining disruptiveness is based on SB being part of a number of technologies subsumed under the term 'digital biology', i.e. the confluence of molecular biology/genetics and computer science (Rai/Boyle, 2007). According to this 'information paradigm of life', biological objects turn into information proper and, assuming that an organism is essentially defined by its DNA sequence, can be re-created as a biological object from this information. On this basis, Boldt/Müller argued that it will no longer be necessary to breed the respective organism; all that is needed is sequence information, which can electronically be retrieved anywhere (Boldt/ Müller, 2009). As a consequence, it is no longer clear whether we speak of material objects or immaterial information. In practical terms, it also implies that the written and unwritten rules from computer science and engineering become salient to biology. Thus, the meaning of life as we know it changes; the technique responsible therefore must be considered disruptive, with appropriate consequences to be drawn.

³¹ Covering Craig Venter's announcement of having "created life", the New York Times wrote on May 20th, 2010: "Some other scientists said that aside from assembling a large piece of DNA, Dr. Venter has not broken new ground. 'To my mind Craig has somewhat overplayed the importance of this,' said David Baltimore, a geneticist at Caltech. He described the result as 'a technical tour de force,' a matter of scale rather than a scientific breakthrough. 'He has not created life, only mimicked it,' Dr. Baltimore said." (The New York Times, http://www.nytimes.com/2010/05/21/science/21cell.html?_r=1)

Another stream of ethically controversial activities is the profound top-down alteration of existing living organisms in ways that do not take place in nature, i.e. 'deep' genetic engineering involving novel mechanisms and/or building blocks or, in our words, involving biology becoming technology. Non-religious opponents, too, consider this an illegitimate intervention into the order of Nature. However, the argumentation pattern of hubris or illegitimate intervention has been invoked consistently over all periods of technological progress in the life sciences, especially when it involved the human body. From organ transplantation, test tube babies, research on embryos to cloning and the deciphering of the human genome; each technology has given rise to arguments that allegedly crossed a threshold, which often formed a barrier for rapid technology implementation. After some discussion, though, other developments raised attention among the public and experts and elicited moral concerns, and again the argument of the crossed boundary was applied to these next achievements. In the meantime, the previously debated technology became less interesting and was eventually established (with moral arguments possibly still being debated, but at lower salience). With hindsight it seems that there have always been moral boundaries where it concerns technological possibilities, and a majority considered them not to be crossed, while these boundaries themselves are shifting all the time with technological possibilities always staying ahead.

Similarly, a blurring of the boundaries between Nature and man-made artefacts has frequently been invoked (Deplazes and Huppenbauer, 2009). This metaphor dates back centuries (e.g. to baroque clockwork driven android automata). Since such boundaries are to be considered culturally contingent, the invocation of this argument indicates a perceived radical novelty irrespective of whether the boundary crossed will persist. In all these questions, the difference with genetic engineering mainly lies in the enhanced capabilities of SB to alter living organisms. Whether or not this entails a new quality and requires novel approaches remains contested (Rabinow/Bennett, 2009). The important factor is time: what appears science fiction today may turn out to become reality in a not too distant future, giving rise to ethical questions that are not fundamentally new but gain in salience.

Thus, some authors question whether a particular 'SynBioEthics' is needed, or whether it will be more adequate to put effort into a technology ethics that takes into account generic issues of technological change, with some specifications in certain fields (Parens et al., 2008; Ganguli-Mitra et al., 2009). With regard to SB, the main question, therefore, is whether the prospect of being able to create artificial life (in whatever definition) indeed marks a watershed or not (Bedau/Parke, 2008). If so, the ensuing problem is how to deal with present watersheds that may become future normalities.

2.4.3. Playing God as a metaphor of disruptiveness

Not only ethicists but also scientists, and researchers in SB in particular, have noticed that doing science may comprise more than contributing to a merely epistemic process. Rather than focussing on whether or not the popular rhetoric adequately describes the implications of research, they take it as an indication of unease or even spearhead the issuing of concerns. Craig Venter explicitly speaks of the *"scientific as well as philosophical step changes"* that are affected by his research.

"We think this is an important step both scientifically and philosophically. It certainly changed my views of definitions of life and how life works. Its pretty stunning when you just replace the DNA software in the cell and the cell instantly starts reading that new software, starts making a whole different set of proteins; and within a short while all the characteristics of the first species disappear and a new species emerges from this software that controls that cell going forward." (Craig Venter interview³²)

He also describes Synthetic Biology as a practice through which "*new species emerge*", solely by the use of *"four bottles of chemicals"* and a computer model. Besides the metaphors stemming from computer technology, it is the creationist character of the activities described that forms the basis of the public ascription of playing God. It is easy to understand the triggers:

"... the scale of what the possibilities are will make some strong challenges, I mean, if we can sit at our computers and design new genomes for micro-organisms and send and hit the return button and then get the genome back in the post, that is going to create some uncomfortable feeling for people, because essentially you will be making synthetic organisms." (Paul Freemont, LSE panel, Nov. 2009)

However, the meaning it conveys is less self-evident. To this day, scientists, politicians and STS scholars mostly interpret it as a moral or religious argument.

Q: "Do you see the accusation of 'playing God' as relevant?"

A: "No, I don't. Playing god is sort of, phew, sort of religious basing, isn't it? I think I would argue people, mankind, humans, have been using, manipulating, changing, whatever, nature for as long as time has existed, for as long as humans have been on the planet; ... therefore the better question would be: can we use synthetic biology in a responsible way?" (I SB 1)

The accusation of playing God is interpreted as infringing the set norm or command that 'you should not play God'. Along this reading, a reference to this argument comes with a pre-modern bearing and a simple choice between acting for or against it. In the current discourse on technoscience regulation in Western societies, it counts as an argument that may be voiced but will also be dismissed easily, as religion is mostly considered a matter of private life beyond the constitution.

In recent discussions among STS scholars however, the metaphor of playing God is revisited. What if, so the argument goes, it is not a purely pre-modern, religious argument? What if it includes an epistemic and political horizon that goes beyond such an interpretation? Hugh Whittall, director of the Nuffield Council on Bioethics, allowed for such a more open interpretation as seen by his statements at the LSE panel on Synthetic Biology in Nov. 2009:

"This inarticulate, or unarticulated – if that is the word – anxiety which is sometimes expressed in these terms which are about 'playing God' and 'messing with nature' and, you know, things that we hear a lot and its very easy to dismiss them, because they are not based on the kind of lines of thought in science that we are talking about. But there is something in there and I am not here to say what they mean or, what part they should play in the discussion. But I am simply acknowledging that they are there; they must have some meaning and we need to explore that." (Hugh Whittall, LSE panel, Nov. 2009)

³² http://www.guardian.co.uk/science/video/2010/may/20/craig-venter-new-life-form

The philosopher Mark Bedau goes a step further and attempts to delineate different components prevalent in the metaphor of playing God. In a discussion panel at the Woodrow Wilson Centre in May 2010 ("Synbio in Society: Toward New Forms of Collaboration?", 12.5.2010), he comments:

"[the accusation of playing God] is going in one ear and out the other; that was the initial reaction of a lot of people, it was my initial reaction, but after thinking about this more, I've come to now adopt a different perspective (...) I think in fact that one of the reasons why people raise these worry is, it doesn't actually come from religion and ethics, it comes with a concern about making things, changing our world in ways that have unpredictable and powerful consequences. I am not saying we shouldn't do this, I am saying that we will feel comfortable about doing this only if you do it without hubris, only if you do it with a proper kind of humility and proper kinds of constraints and these constraints are roughly triangulated by a certain kind of picture of what a deity is." (Mark Bedau, 12.5.2010)

He then compares specific godly properties with abilities invoked by synthetic biologists. These are the assumed omniscience implied by a total understanding of the engineered organisms and the consequences of their engineering; the assumed omni-benevolence implied by a proper evaluation of alternative options, and the assumed omnipotence implied by the ability to fix all problems that arise. SB, so it seems, to some extent is based upon the desire to build an omniscient, omni-benevolent and omnipotent science. Anxiety may then be based upon scepticisms concerning the success, sincerity or desirability of this project.

Less scepticism is aimed for concerning the perception of SB. Though its position and activity are not divine, they go beyond a mere quest for understanding. Scientists are getting closer to the process of biological evolution, to shaping our understanding of life and to the policy process. They have also developed certain ways of governing and professionalising these relationships.

"I think we are seeing a time for the recent years where scientists, not just scientists, medics as well are starting to realise how much closer they've got to get to the policy process (...) and I think that science as an organised discipline has become probably much more efficient at having that engagement at different stages of the process. ... I don't think we have worked out what is the best way to configure that set of relationships from the initial kind of raising of an issue – whether it comes from the scientists or others – right through to governance and all the different strands that it can have, whether it is legislation, regulation, cultural influences or other things, how all these things play in together." (Hugh Whitall, LSE panel, Nov. 2009)

Thus, the argument of playing God is extended beyond a narrow quasi-religious meaning to indicate a more general discomfort with a scientific endeavour perceived to be disruptive in various respects (Dabrock, 2009). This disruptiveness could impact on policy even if the value basis is not determined religiously (Kaebnick, 2009). The focus on policy leads us to the more mundane world of risks, benefits and governance as major elements of society's dealing with new technologies.

2.4.4. The mundane world of risks and benefits

Disruptiveness is a concept that captures concerns that often manifest in (ethical) discourse. Regulation only rarely results from such discourse. Risk, in contrast, is often considered an issue for regulation, provided it is acknowledged to exist. Risk controversies usually are about different claims of truth drawing on cognitive arguments about the properties of the issue at stake. These properties are compared to those of a comparator considered to be equivalent or ontologically of same kind. For example, the current biosafety regulations and risk assessment schedules are built around the idea that there is such a thing as a parent organism. Within the notion of biology is becoming technology it is quite a logical assumption.

From the perspective of technology becoming biology, however, existing organisms are no longer the natural starting point of engineering, so the nature of the issue at stake becomes unclear. Artefacts are usually dealt with differently than living organisms are, but what if we can no longer distinguish between biological objects and mere information, between organisms and artefacts? The blurring distinction between technology and biology entails a blurring of concepts and how to deal with controversial topics – must we deal with them along the lines of biology, or according to the rules of (information) technology, or both, or do we need an entirely novel set of guidelines? Depending on which face of the coin is up, we may experience the same thing being framed as technology in one instance or biology in another. This issue manifests in different areas – examples are risk, intellectual property rights and public perception; they are considered subject to governance through regulation, standard setting or public outreach, respectively.

2.4.5. Safety and security: accidents and intentional misuse

In his letter to the newly formed Presidential Commission for the Study of Bioethical Issues, the President of the United States framed a political problem with SB. He requested the Commission to

"undertake, as its first order of business, a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research. In its study, the Commission should consider the potential medical, environmental, security, and other benefits of this field of research, as well as any potential health, security or other risks." (Barack Obama May 20, 2010)

Hence, from a prominent political point of view, all that might oppose reaping benefits is risk, and risk is considered most salient for regulation. The existence of risk from SB is less debated today than with biotechnology three decades ago. Especially in the US, concerns exist over biosecurity, i.e. preventing the intentional release of pathogens and toxins for sinister purposes (WHO, 2004). Less unanimous is the possibility of unintentional exposure or accidental release. Its prevention, biosafety, is often considered a matter of the past sufficiently dealt with today. In contrast, the general public, media, civil society organisations and many scientists in Europe are also concerned about safety issues (Schmidt, 2006; de Vriend, 2006; Kelle, 2007; Kronberger, 2008).

Both concerns draw on different properties of SB. Biosecurity worries can be understood to have resulted from the wide distribution of a powerful technology. Biosafety concerns emerge from potential intrinsic differences with products of more conventional biotechnology. In other words, biosecurity is a question of proliferation, while biosafety is a problem of appraisal. With biosecurity, the nature of the technological product is less problematic than the distribution of the knowledge that is needed to produce it through its conversion into electronically retrievable information.³³ On the contrary, with biosafety it is unclear what to compare the product to in order to establish its potential risk.

Security

The consolidation of the research field of SB came right after the US events of 9/11, 2001, and the subsequent Anthrax letters. With the presentation of former US secretary of defence Colin Powell before the UN security council on Iraq's (fictional) mobile bio-weapon of mass destruction units, the scene was set for a rigid scrutiny of biotech R&D.

Increasing concerns in the US that research in the life sciences might be misused for bioterrorist or bio-warfare purposes were fuelled by a number of experiments that triggered substantial debate.³⁴ These experiments drew the attention of the security community to synthetic genomics and SB. Ever since, US security institutions and think tanks like the National Security Advisory Board on Biotechnology³⁵, the Strategic Assessment Group of the National Academy of Sciences³⁶, the FBI³⁷, the Commission on the Prevention of Weapons of Mass Destruction, Proliferation and Terrorism (Graham et al., 2008³⁸), the National Academies and others have published reports. In 2004, George Church, one of the lead scientists in SB, put forward "A Synthetic Biohazard Non-proliferation Proposal"³⁹ to address some of the biosecurity concerns.

³³ Not only the potential misuse by criminals and/or terrorists but also the distribution of information itself might be considered a problem, at least for IPR departments and industrial espionage counter intelligence agencies.

³⁴ In particular three experiments gave rise to such debates (Kelle 2007). 1) Unintentionally enhancement of the virulence of the mouse pox virus through inserting an IL-4 gene into the mouse pox genome. While this experiment had the unexpected result of the creation of a killer mouse pox virus, subsequent work by another scientist, Mark Buller at Saint Louis University, has knowingly carried these experiments one step further by increasing the lethality of the mouse pox virus and by carrying out similar manipulations in the cowpox virus. 2) Synthesis of the poliovirus genome from 'chemically synthesised oligo-nucleotides that were linked together and then transfected into cells', thereby creating an infectious virus from scratch, combining knowledge of the viral DNA with assembly of the correct chemical compounds. 3) Transfer of the virulence factor of variola major (which causes smallpox) into the vaccinia virus, which is of much lower virulence and usually used for vaccinations against smallpox.

³⁵ http://oba.od.nih.gov/biosecurity/about_nsabb.html

³⁶ A darker Bioweapons Future 2003

³⁷ e.g. arresting the innocent biotech-artist Steve Kurtz for having biotech equipment in his house, pre-emptive investigation of, and attempts to cooperate with, the synthetic biology Do-It-Yourself DIYBio community

³⁸ Graham et al. 2008. World at Risk. Random House, New York

³⁹ George Church, A Synthetic Biohazard Nonproliferation Proposal, 18 June 2004, available at http://arep.med.harvard.edu/SBP/Church_Biohazard04c.htm

Recently, the debate on the biosecurity implications of SB has made some progress, again most notably in the US (Kelle, 2007⁴⁰), leading to several official reports⁴¹. Over recent years most of the debate gravitated around the risks that stem from DNA synthesis. Several papers and draft guidelines have been produced, both from industries (US and Europe) and governments (in the US), stressing the customer and the ordered DNA sequence as the main points of assessment (Bügl et al., 2007; Bernauer et al., 2008; USDHHS, 2009; IGSC, 2009; IASB, 2009). In an effort to arrive at a more comprehensive approach, Kelle suggested the inclusion of a variety of parameters, though this would render control more ambitious (Kelle, 2009).

We can see two interpretations of SB behind the attempts at coming to terms with biosecurity. On the one hand, the proposed measures were inspired by those in force to prevent the spread of nuclear material or chemicals that could give rise to explosives, and whose material distribution had to be controlled. On the other hand, the control of proliferation was directed at knowledge and skills, since the material ingredients for SB are easily obtained while the necessary information can now widely be retrieved in electronic form by anybody including criminals and terrorists – the field thus was considered similar to computer science and information technology. Both interpretations thought of SB as disruptive, not because it constituted a fundamentally new threat, but because it is a novel way to arrive at long-standing, sinister aims. The proposed measures to prevent these aims from becoming reality, however, were rather classical: a mix of surveillance and professional self-control.

More abstract in terms of top-down or bottom-up, we may consider biosecurity a problem of biology becoming technology. In this understanding, sinister aims would suggest particular ways of realising them with the help of the technology. Risk is generated in a top-down, purpose-oriented way, starting from a criminal aim through technological means.

Safety

There is no doubt that negative public reactions towards GMOs in Europe reinforced the motivation of many scientists to look into biosafety issues in SB (Serrano, 2007). Apart from public opinion, there are also scientific arguments in favour of a more thorough discussion on possible shortcomings of the conventional approach in biosafety assessment. The most salient argument is that it largely builds on a comparison between a new construction and parent organisms. In SB, there might be no parent organisms to compare with, so how should risk assessment then proceed? So far, there have been few answers to this 'ontological gap', mostly because the imminent technological risks were considered low or contained by established methods of mitigation. Nevertheless, for the more distant future many scientists agree that something has to be done mostly in three areas:

⁴⁰ Kelle A. 2007. Synthetic Biology & BiosecurityAwareness In Europe. Available at www.synbiosafe.eu

⁴¹ Fink Committee: the work of the Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, of the US National Academies of Sciences, chaired by Gerald R. Fink on seven categories of problematic experiments.

Lemon-Relman Committee: The National Academies Press, 2006. Globalization, Biosecurity and the Future of the Life Sciences, Report by the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, Washington D.C.,

Declaration of the Second International Meeting on Synthetic Biology (synthetic biology 2.0) 41

CSIS-MIT-Venter report: Garfinkel M, Endy D, Epstein GL, Friedman R. 2007. Synthetic Genomics: Options for Governance.

NSABB synthetic biology working group: NSABB, Addressing Biosecurity Concerns Related to the Synthesis of Select Agents, Washington DC, December 2006, available at http://www.biosecurityboard.gov/pdf/Addressing Biosecurity Concerns Related to the Synthesis of Select Agents.pdf

Controlling Dangerous Pathogens project: John Steinbruner, Elisa D. Harris, Nancy Gallagher, Stacy M. Okutani, 2007. Controlling Dangerous Pathogens. A Prototype Protective Oversight System, College Park: University of Maryland, available at http://www.cissm.umd.edu/papers/files/pathogens_project_monograph.pdf

- For risk assessment, SB requires new methods to decide whether a new technique or application is safe for human or animal health as well as the environment in contained and/or non-contained use. According to prominent scientists, several cases already warranted a review and adaptation of current risk assessment practices (Church 2005, Tucker and Zilinskas 2006, Fleming 2007, NSABB 2007, NSABB 2008, NIH 2009; Schmidt et al., 2009, Schmidt 2009, Bedau et al., 2009, Marliere 2009, Schmidt 2010).⁴²
- Regarding synthetic safety systems, SB itself may contribute to overcoming future biosafety problems by contributing to the design of safer biosystems (Schmidt et al., 2009; Bedau et al., 2009, Herdewijn and Marliere 2009, Carr and Church 2009, Marliere 2009, Schmidt 2010).⁴³
- Finally, amateur biologists raise a question on how diffusing SB skills (e.g. do-ityourself biology, amateurs, biohackers) also impinge on biosafety issues, mostly due to a lack of problem awareness among lay users. The consequences of deskilling are not clear today and need to be investigated (Anonymous 2003, Schmidt 2008, Schmidt et al., 2009, Bennett et al., 2009).⁴⁴

The latter points at the nature of the problem: in contrast to biosecurity, biosafety can be considered a bottom-up problem. The risk develops from technology to biology, from technological tinkering with life forms to living organisms that potentially grow, multiply and eventually spread into an environment where they do not belong. Disruptiveness is therefore a property of technology as such – a qualitative jump from the still comparable to the incomparable. Although SB by and large is considered similar to existing biotechnology and its problems, the safety concepts and measures which are successful so far may one day fail. Hence, SB itself is called to contribute to the solution in a top-down way, by applying technological means for arriving at the containment of biological objects, even if they have come into being by SB itself.

^{42 1)} DNA-based biocircuits consisting of a larger number of DNA 'parts', where failure mutation of a single part affect the characteristics of the whole genetic circuit, e.g the reversal of a biological circuit that produces insulin depending on the sugar level in the blood, as proposed by the NEST COBIOS project; 2) The survivability, infectiousness and evolvability of novel minimal organisms in different environments; 3) Foreseeable breakthroughs in the development of self-replicating, potentially infectious protocells that may establish themselves in the environment; 4) Exotic biological systems based on an alternative biochemical structure, e.g. a genetic code based on novel types of nucleotides, or an enlarged number of base pairs.

^{43 1)} The design of less competitive organisms by changing metabolic pathways – although this could lead to a "Verschlimmbesserung" (Philippe Marliere 2007, personal communication); 2) The replacement of metabolic pathways with others that have an in-built dependency on external biochemicals; 3) The design of evolutionary robust biological circuits; 4) The use of biological systems based on an alternative biochemical structures to avoid gene flow to and from wild species, by establishing a parallel biological world (a genetic firewall or genetic enclave); The design of protocells that lack key features of living entities, such as growth or replication.

⁴⁴ Accordingly, care should be taken to ensure that everyone using the resources of synthetic biology does so safely and has sufficient awareness of and training in relevant biosafety techniques and approaches. Moreover, proper mechanisms such as laws, codes of conduct, voluntary measures, access restrictions to key materials, institutional embedding and mandatory reporting to Institutional BiosafetyCommittees [IBCs] need to be in place to avoid unintentional harm.
2.4.6. How to govern benefits: intellectual property protection

If SB lives up to the promises made, substantial benefits will entail.⁴⁵ This renders questions on access to the technology important in several respects. On the one hand, the efforts of the developers need to be remunerated, which brings intellectual property protection into the picture. On the other hand, new technologies should be available to those who need them (e.g. for drug development or further research). In the same vein, questions on commodifying common resources for individual economic benefit arise (ETC Group, 2008). As with other forms of biotechnology, it is not clear what exactly can be considered 'natural' and what is to be seen as 'artificial'.

Such questions are common for recent and rapidly evolving biotechnological fields, but here they appear in a new light. Firstly, SB promises to provide extremely powerful methods, in other words, a quantitative difference. Secondly, as already stated, SB is part of 'digital biology', where the written and unwritten rules from computer science and engineering become salient. Consequently, the question is whether the way of intellectual property protection should be derived from biology and the pharmaceutical industry (practice of heavy patenting which sometimes reaches its limits of practicality (Hope, 2008)) or from software development and computer engineering (different forms of protection, but also featuring a long-standing discussion over open and/or shared access; sincere problems for IPR in the world wide web). Again, this can be seen as an aspect of disruptiveness. It is a question of whether SB is something radically new and distinct from biotechnology as we know it, or part of biotechnological practices with their own rules and codes. In other words, the trend of biology becoming technology is thwarted, in part, by the concurrent trend of technology becoming biology.

This partial reversal is not only a result from SB's ontology, so to say; it is also driven by interests. Especially in the bioparts community, many scientists argue for a form of open source and/or compulsory licensing schemes. They build on experiences with extensive gene patenting resulting in patent gridlocks. In addition, much effort must be spent in the preparatory phase of a research project in order to sort out possible patent infringements and to negotiate permits and IPR swaps.⁴⁶ In the light of the patent thicket, researchers have to bushwhack their way through before starting their work. A call for simplification appears understandable even if major incentives for research and development may be at stake. With SB as a new field, the opportunity may be seized. Thus, the establishment of an intellectual property regime reflects the emergence of new power relations (Wellhausen/Mukunda, 2009).

⁴⁵ As with other emerging technologies, hypes and hopes about potential benefits span a wide range. On 20th May, The Guardian reported that Craig Venter had signed an agreement with ExxonMobil to create algae that can absorb carbon dioxide from the atmosphere and convert it into fuel — an innovation he claimed could be worth more than a trillion dollars." (http://www.guardian.co.uk/science/2010/may/20/craig-venter-synthetic-life-genome)

⁴⁶ In contrast, lack of clearly defined property rights lead to the so-called "anti-commons problem", a situation where nobody wants to use the IP for fear of unknown IP infringements (Oye and Wellhausen 2009).

2.4.7. The relation to the public

Agricultural biotechnology and its failure to attract public esteem in Europe is a recurring rhetorical figure in interviews and statements on SB from scientists and policy-makers. They fear that European experiences with genetically modified crops and food could be emulated with the new technology (e.g. McIlwain, 2010). This analogy and fear of a hypothetical controversy is also prominent in the US, where the GM-debate was restricted to more confined parts of the public. Many scientists and commentators still suspect the broader public of being a priori hostile, mostly from ignorance ('scientific illiteracy'), and consistently emphasise the need to reach out to members of the public with educational ('public understanding of science') activities. Others interpret public unease as a sign of mistrust in the scientists' and regulators' contribution to the socially robust governance of science and technology. Accordingly, they aim at reassuring the public that this time, scientists and politicians have learned their lesson, engage in pertinent activities and are more open to concerns than with GM crops. A third interpretation holds that public protest is motivated by a wish of the public to be included in the governance process. Scientists and regulators react to this interpretation with opinion surveys (e.g. Hart Research Associates, 2009), public consultation exercises, dialogue events (e.g. the UK 'Synthetic Biology Dialogue' initiated by BBSRC and EPSRC) and participatory activities. Here, the public is considered an important actor that needs to be involved more actively and earlier on ('upstream') in technology development. However, without clearly explicating and agreeing on what exactly went wrong with biotechnology, it often remains unclear what the engagement should lead to, and how it should be brought about. Moreover, how exactly 'the public' is conceptualised remains unspecified or differs widely among various actors and contexts.

Empirical evidence for the hostility hypothesis is scarce (Torgersen, 2009) as surveys would render only mixed support. The Hart Research Associates report (2009) suggests that the plurality of Americans consider risks and benefits about equal, but when potential risks and benefits of synthetic biology are outlined the greatest shift in public opinion is toward risk (ibid: 1). The dialogue event initiated by BBSRC and EPSRC in 2009 showed conditional support for synthetic biology among the British public. Formulated reservations referred to fears about control, doubts about a just distribution of benefits, and concerns over health or environmental impacts, misuse and the governance of science under uncertainty (TNS-BMRB, 2010).

Media analyses in the US and Europe (Pauwels, 2008; Gschmeidler/Seiringer forthcoming) showed ambivalent or positive reporting.⁴⁷ Finally, focus group analyses indicated a tendency of lay people to think that the promises of SB had already been achieved by traditional genetic engineering (Kronberger et al., 2009). The public novelty value of achievements – if they materialise – might therefore be restricted. This highlights the 'business as usual' character of the issue in the public eye despite the moral contention of the engineering metaphor or even the 'creation' metaphor.

⁴⁷ Coverage so far featured personalisation and emphasis on useful applications; the rhetorical figure of "creating life" appeared in connection with particular scientists, but much less than metaphors linked to the engineering paradigm (Gschmeidler/Seiringer forthcoming).

How can we understand possible public reactions in the light of the top-down/bottom-up distinction? The public at large may be inclined to understand SB in terms of conventional biotechnology, i.e. as a top-down endeavour to make biology into technology. Some members of the public even have difficulties in seeing much novelty with the aims of SB, so the perceived disruptiveness may be limited – some lay people seem to already expect from conventional biotechnology what SB might deliver.

The opposite direction plays a role in two ways: one is the fear of a loss of control, when artificial organisms may escape and establish a life of their own. The question of artificial life has to be seen in this light, too, but despite pertaining claims in the headlines now and then, it is doubtful whether this rhetorical figure will cause rejection among the public. So far, it seems to be mostly an elite discourse. Nevertheless, past experiences show that potentially contested issues can develop into serious questions of public debate in the right context. Then perhaps it will not only be a question of biology becoming technology, such as with conventional biotechnology, but of technological objects being turned into artificial life, with potentially unforeseeable consequences both technologically and with respect to public opinion.

2.5. Governance issues

Rather than top-down regulation, governance is considered more adequate today for a sound development of, and avoiding problems with, novel technologies. Technology governance can be understood as the co-ordinated steering of a politically sensitive field of technology involving political actors, important stakeholders and relevant experts. It applies a variety of tools such as statutory regulations, norms, voluntary agreements, incentives and self-regulation. Governance is a multi-actor approach and highly dependent on discourse and negotiation; it can thus be considered combining top-down and bottom-up policy initiatives in order to prevent the potential disruptiveness of a field from becoming deleterious and, at the same time, expand its beneficial effects. However, this is far from being easily implemented. The concept of technoscience may help to illustrate the problem: science is traditionally viewed as a self-governing system, characterised by epistemic serendipity and organised peer-review. Technology is viewed as highly regulated and controlled by the state to advocate the public good. When science and technology merge as they do in SB, the governance regime has to be re-scrutinised.

If SB is considered to be an extension of conventional biotechnology, i.e. a top-down endeavour with the aim of making biology into technology, established ways of governing may be adequate. Amendments are necessary here or there, but overall, no major changes would have to be made. If, however, SB is considered a new and disruptive endeavour that aims at making technology into biology in a bottom-up way, established methods of governance may prove insufficient. Therefore, whether new ways of governance would be considered necessary both with risk mitigation and intellectual property protection is not only a matter of the 'ontology' of the field; it is also a matter of perspective.

Governing risks and intellectual property

The potential for unintended and intended harm elicited calls for preventive measures of various sorts.⁴⁸ Regarding the novelty of benefits and risks, there seems to be a split in the prominent discourse: while emphasising that techno-scientific advances in SB are unheard of, many scientists advised against overstating the novelty of potentially negative consequences. Accordingly, pending risks would not differ from those posed by conventional biotechnology. At high-level conferences such as the NAS/Royal Society/OECD Washington workshop in 2009⁴⁹, new regulations advocated by critical NGOs were considered unnecessary for the time being, a conclusion supported by independent reports (e.g. IRGC, 2010). Rather, the National Institutes of Health (NIH) guidelines were somewhat modified to cater for pertaining concerns. Thus, in biosafety issues, the dominant view on SB is that of biology becoming technology as in conventional biotechnology, and existing schemes are deemed sufficient for the moment.

The double emphasis on the novelty of technological achievements and the familiarity with risk aspects can be seen in other new technologies as well. It may be in the interest of developers to prevent burdensome regulations, introduced not in the least to reassure a critical public (Weir/Selgelid, 2008). However, from a governance point of view, self-regulation as advocated by many scientists was one of the factors that eroded public trust in the biotechnology sector in Europe in the past, so relying entirely on self-regulation may not dispel concerns. However, regulation has a huge impact on new technologies, especially if regimes differ country to country and provide arguments in international trade conflicts.⁵⁰ This highlights the need for international coordination in designing rules. It appears much easier to leave risk assessment schemes and mitigation provisions as they are, especially if there is no generally accepted imminent risk.

For the mid-term future, though, doubts exist whether the present regulatory apparatus for genetic engineering will suffice to mitigate risk from an increasingly disruptive SB. Among the aspects disputed are the possible implications of 'digital biology', where information rather than real organisms are propagated. Another problem may arise from do-it-yourself (DIY) biology or 'garage shops', where regulatory oversight is difficult to implement. These are more organisational aspects; substantially, SB might result in organisms unheard of with entirely new properties for which assessment criteria need yet to be developed.

Concerning questions on ownership and patenting, as with risk mitigation, experts agree that a framework needs to be developed and implemented (BBT, 2010). Many scientists think they can learn from the area of IT, not in the least since many have a track record in computer sciences. Open source is a main model referred to by scientists. On the other hand, the specific character of synthetic biology research, especially the costliness of some activities and the related dependency on private funding, are seen as a reason to promote patenting. The resulting question is where to draw the line between open source and private property.

"... these parts should be freely available, should be open source. [It] should be at the next level, that maybe protection can be made, when companies take parts and build new things where you've got novel applications; there is no reason why you couldn't protect that and still retain the open source nature of the parts." (I SB 1)

⁴⁸ The distribution of concerns – biosecurity mostly in the US, biosafety as well in Europe – suggests differences in proposed governance approaches; however, they are rather similar. The reason may be that in the US, too, technology developers increasingly fear a critical public, and that the synthetic biology scientific community is highly international.

⁴⁹ http://sites.nationalacademies.org/PGA/stl/PGA_050738

⁵⁰ For example, the conflict over "process versus product" regulation and the precautionary principle between European countries and the US hampered the development of biotechnology.

This ambivalence seems to have had an impact on industry interest as well (for the relation between SB and industry see Gaisser/Reiss, 2009). Despite the extremely high input spent on the Artemisinin example there is a strong involvement with certain top-down applications such as biofuels, where the biology-becomes-technology paradigm dominates. Regarding bottom-up approaches, the overall attitude still appears to be observant, which might be due to the current lack of practically applicable results. It may, however, also be due to the unclear situation regarding intellectual property protection, where a dominant practice for technology becoming biology has not yet evolved. Despite frequent reference to the IT sector, there are limits to a close comparison, as the industrial context is not that of the computer but of the pharma and/or biofuel industry. If SB is seen as part of the biotechnology movement (Bauer and Gaskell, 2002), it can be expected that avoiding IPR practices customary in these industries will be difficult.⁵¹

Towards new ways of governance?

For SB governance, a variety of measures are advocated: apart from combining state and self-regulation, instruments such as ethical reviews, stakeholders and other actors should be involved into the debate and the decision-making (Stemerding et al., 2009). All comments about SB and society in the interviews include observations of, ideas about or requests for specific new modes of science governance that not only rely on regulation but also bring leverage for bearing on the early development process of the technology. Craig Venter stressed that his Synthetic Biology project for engineering an artificial organism represents

"...the first incidence in science where the extensive bioethical review took place before the experiments were done and it is part of an ongoing process that we have been driving, trying to make sure that the science proceeds in an ethical fashion." (Craig Venter, interview⁵²)

Since many scientists in the field of SB seem to be particularly sensitive to the implications of their work, it was easier than in other areas to interest them in questions beyond scientific research and to involve them in governance issues (Schmidt et al., 2008).⁵³ This may also have to do with the particular SB culture and reluctance from their side to wholeheartedly identify with the interests of big industry.

Reflecting on past problems with agricultural biotechnology, particular emphasis is often placed on the role of the public, which is considered an important actor that needs to be involved 'upstream' in the development.⁵⁴ Input came from new research on ethical, legal and social issues. Ever since, the ELSA program of the Human Genome Initiative (the narrow working description for investigating the so-called consequences from new technological developments, and for coming up with advice to avoid implementation obstacles) has been criticised. Are the consequences a result of the properties of technology or rather of the dominant societal context? Apart from the emphasis on security in the US after 9/11, open source debates may be related to lock-in tendencies in genomics IPR, to the popularity of biofuels for energy problems and global warming, to calls for public outreach to controversy prevention after conflicts over agricultural biotechnology, to orientation at public benefit after high-tech investment bubbles, etc.

⁵¹ Initiatives such as the IGEM competition may have kept themselves in an area less afflicted by IPR struggles, although in the long run it might be difficult to uphold this as commercial interest rises.

⁵² http://www.guardian.co.uk/science/video/2010/may/20/craig-venter-new-life-form

⁵³ For example, Marc Bedau concludes from his discussion that "scientists have to have a stronger sense of their responsibility ... similar to corporate responsibility".

⁵⁴ Some experts even warn against involving too many "naysayers" and demand stronger rules for engagement (Tait 2009).

In other words, rather than assessing consequences from technology deployment as if technology develops separately from the societal context, recent attempts at a post-ELSA approach focus on the places, context factors, individuals and their motivation, and established points of decisions, involving those who take them as well as those who are affected.⁵⁵

2.6. Conclusion: living machines and artificial life

Synthetic biology is a novel field in engineering in two respects. Firstly, it is novel in its quest for a profound reconstruction of living organisms for useful purposes in ways not found in nature. Reconstruction is to be considered in a top-down way, with biology becoming technology, resulting in a kind of living machine. Secondly, it aims at constructing organisms from non-living matter, which points at the bottom-up approach of turning technology into biology, resulting in artificial life. This is undoubtedly a radical program, which can be expected to entail far-reaching consequences.

While the distinction between top-down and bottom-up approaches in SB offers interesting perspectives, it does not show the whole picture. Many properties of the field can be explained by looking at it as a modern technoscience. From its origin, SB is a hybrid technology, characterised, on the one hand, by its origin in genetic engineering and genomics. On the other hand, it is heavily influenced by computer sciences and informatics, and proponents emphasise the systematic and comprehensive adoption of practices in computer engineering for biology. In other words, it transgresses the boundaries between science and technology, and between biology and computer engineering. This does not only pertain to the research and development methods. Emulations from practices in the IT sector also influence intellectual property protection, public outreach, industry relation and, not in the least, the involvement of mostly young enthusiasts in playful technology developments that do not necessarily lead to useful products. Thus, a new engineering culture emerges from hybridisation, which heavily influences the SB community.⁵⁶ Although there are basic research endeavours within SB that are different, the combination of a strong engineering perspective and the hybridisation aspect gives rise to something new. A mere differentiation between 'bottom-up' and 'top-down' approaches would only acknowledge inherent engineering logics, ignoring that the scientific aspects of SB are just as important.

Looking at the state of the art, different endeavours embody aims and visions that are novel to a varying degree, if we consider novelty in our understanding as a proxy for disruptiveness. Many of the big projects today are only partially disruptive as they deal with not-too-unfamiliar approaches or not-so-complex structures. Today still, the top-down perspective of living machines or of modifying organisms to desired purposes prevails. Discussing benefits presupposes that SB successfully turns biology into technology. Discussing the prevention of risks from intended harm (biosecurity) does the same, albeit the intentions assumed are different.

⁵⁵ For example, the "human practices" approach (Rabinow/Bennet 2009).

⁵⁶ There are other fields of digital biology where biology and informatics meet in which this particular mindset cannot be found, as for example systems biology.

The bottom-up approach, in contrast, offers two different perspectives of concerns. On the one hand, it suggests technology going awry through accidents, i.e. the issue of biosafety. On the other hand, it includes the perspective of creating artificial life that gives rise to ethical concerns. The bottom-up approach also embodies a particular engineering perspective, and offers a possibility to radically reduce complexity in construction by devising little black boxes from which organisms (qua genomes) can be put together or built. All this is based on the (reductionist) premises that genetic parts can be designed to sufficient standardisation, performance and reproducibility, and that organisms are sufficiently defined by their genome sequence. This would fulfil the promises encapsulated in the analogy of Lego bricks which are good for a variation of tasks that are always similar. An important part of the SB community aims at such standardisation; however, elements have yet to be built and proven to function. Even if progress is rapid, current efforts have nevertheless to be seen as preparatory steps towards eventually establishing the machining of living artefacts through engineering.

Taken together, and regarding the aims and visions involved, SB is working towards the construction of hybrid entities, blurring traditional boundaries between biology and technology. On the one hand, the aim of producing novel types of organisms implies a use of existing organisms and turning them into 'living machines'; on the other hand, it implies a production of life from non-living matter, creating 'artificial life'. Thus, SB may indeed be seen as contributing to the transformation of the relation between biology and technology, building bridges and tearing down walls. This development may well lead to further public unease regarding both the cultural denotation and the adequacy of the governance of the resulting practices, products and application contexts.

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ANNEX 1: PROJECTS FUNDED BY EU FUNDED INSTITUTIONS

Title: BIOMODULAR H2: Engineered Modular Bacterial Photoproduction of Hydrogen Duration: 36 months Coordinator: Prof. Alfonso Jaramillo, Ecole Polytechnique (France) Website: http://biomodularh2.epigenomique.genopole.fr/ Funding: 2.4 Mio€ FP 6 NEST

Title: BIONANOSWITCH: developing a bionanotechnological device that can be used as a nanoactuator/biosensor Duration: 36 months (October 2006 to end 2009/beginning 2010) Coordinator: Keith Firman, School of Biological Sciences, University of Portsmouth (Uk) Website: http://www.bionano-switch.info/ Funding: 2.6 Mio€ FP 6 NEST

Title: CELLCOMPUT: Biological Computation Built on Cell Communication Systems Duration: 48 months (exact dates unknown) Coordinator: Prof. Stefan Hohmann, Göteborg University, Department of Cell and Molecular Biology (Sweden) Website: http://complex.upf.es/~ricard/CELLCOMPUT.html Funding: 1.7 Mio€ FP 6 NEST

Title: CELLDOCTOR: Quantitative understanding of a living system and its engineering as a cellular organelle Duration: 60 months (01.03.2009-28.02.2014) Coordinator: Prof. Luis Serrano, System Biology CRG - Centre de Regulatió Genòmica (Spain) Website: http://www.crg.es Funding: 2.4 Mio€ ERC-AG-LS2

Title: CHEMBIOMECH: Exploring mechanism in chemical biology by high-throughput Duration: 60 months (01.09.2008-31.08.2013) Coordinator: Florian Hollfelder, THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF CAMBRIDGE (Uk) Website: http://www.cam.ac.uk Funding: 0.6 Mio€ ERC-SG-PE4

Title: COBIOS: Engineering and Control of Biological Systems: a New Way to Tackle Complex Diseases and Biotechnological Innovation Duration: 36 months (01.06.2007 to 01.06.2010) Coordinator: Dr Diego di Bernardo, Telethon Institute of Genetics and Medicine (Italy) Website: http://lnx.cobios.net/ Funding: 2.5 Mio€ FP 6 NEST Title: ECSUB: Encoded Cellular Synthesis of Unnatural Biopolymers Duration: 60 months (01.01.2009- 31.12.2013) Coordinator: Jason William Karl Chin, Medical Research Council London (Uk) Website: http://www.mrc.ac.uk, www.le.ac.uk/ieh Funding: 1.8 Mio€ ERC-SG-LS7

Title: EMERGENCE: Coordination puts SB on firm footing Duration: 36 months Coordinator: Prof. Sven Panke, ETH Zürich, Institute of Process Engineering (Switzerland) Website: http://www.emergence.ethz.ch/ Funding: 1.5 Mio€ FP 6 NEST

Title: EUROBIOSYN: A modular platform for biosynthesis of complex molecules Duration: 36 months Coordinator: Prof. Sven Panke, ETH Zürich, Institute of Process Engineering (Switzerland) Website: http://www.eurobiosyn.org/ Funding: 2.7 Mio€

Title: FUSYMEM: Functional Synthetic Membranes for GPCR based Sensing Duration: 36 months Coordinator: Dr. Eva-Kathrin Sinner, MPI for Polymer Research (Germany) Website: http://fusymem.epfl.ch/ Funding: 1.4 Mio€ FP 6 NEST

Title: HYBLIB: Human monoclonal antibodies from a library of hybridomas Duration: 48 months (4/29/2005 to 4/28/2009) Coordinator: Dr. Frank Breitling, German Cancer Research Centre, Department of Molecular Genome Analysis (Germany) Website: not available Funding: 3.5 Mio€ FP 6 NEST

Title: INEST: Intuitive ethics and sensitive technologies Duration: 24 months (01.20.2008-30.09.2010) Coordinator: Bhimla Dheermojee, London School of Economics and Political Science (Uk) Website: www.lse.ac.uk Funding: 1.7 Mio € FP 6 PEOPLE

Title: MECHANOSENSATION: What is the molecular mechanism of mechano-sensation? Duration: 60 months (01.09.2008-31.08.2013) Coordinator: ARMAGAN KOCER, RIJKSUNIVERSITEIT GRONINGEN (NETHERLANDS) Website: http://www.rug.nl Funding: 1.5 Mio€ ERC-SG-LS7

Title: NANOMOT: Synthetic Biomimetic Nanoengines: a Modular Platform for Engineering of Nanomechanical Actuator Building Blocks Duration: 46 months (01.02.2006 – 30.11.2009)

Coordinator: Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V. (Germany) Website: http://www.mpibpc.mpg.de/home/grubmueller/teaching/Nanomot/index.html Funding: 2.4 Mio FP 6 NEST

Title: NEONUCLEI: Self-assembly of synthetic nuclei: key modules for semibiotic chemosynthetic systems Duration: 48 months Coordinator: Prof. George Attard, School of Chemistry, University of Southampton (Uk) Website: www.neonuclei.soton.ac.uk (not working anymore) Funding: 2.4 Mio€ FP 6 NEST

Title: NETSENSOR: Design and Engineering of gene networks to respond to and correct alterations in signal transduction pathways Duration: 36 months (exact dates unknown) Coordinator: Prof. Luis Serrano, System Biology CRG - Centre de Regulatió Genòmica (Spain) Website: http://netsensor.crg.es/ Funding: 1.9 Mio€ FP 6 NEST

Title: NMSSBLS: Nonlinear mechanisms of spatial symmetry breaking in living systems Duration: 48 months (01.10.2009-30.09.2013) Coordinator: Carlos Manuel Abad, Agencia Estatal Consejo Superior de Investigaciones científicas (Spain) Website: not available Funding: 0.1 Mio€ FP7-PEOPLE

Title: NMU-LIPIDS: Biomimetic lipid structures on nano- and microfluidic platforms Duration: 60 months (01.07.2008-30.06.2013) Coordinator: Petra Stephanie Dittrich, Eidgenössische Technische Hochschule Zürich (Switzerland) Website: www.isas.de www.ethz.ch Funding: 1.9 Mio€ ERC-SG-PE6

Title: ORTHOSOME: An Orthogonal Episome: an Artificial Genetic System Based on a Novel Type of Nucleic Acids Duration: 36 months Coordinator: Prof. Piet Herdewijn, Katholieke Universiteit Leuven (Belgium) Website: <u>www.kuleuven.be/research/researchdatabase/project/3M06/3M060323.htm</u> Funding: 1.5 Mio€ FP 6 NEST

Title: PROBACTYS: Programmable Bacterial Catalysts Duration: 36 months (2006-2009) Coordinator: Dr. Vitor dos Santos, Helmholtz Center for Infection Research (Germany) Website: http://www.probactys.eu/ Funding: 2.5 Mio€ FP 6 NEST Title: REPEATSASMUTATORS: The biological role of tandem repeats as hypervariable modules in genomes Duration: 60 months (1.12.2009-30.11.2014) Coordinator: Kevin Joan Verstrepen, VIB, Zwijnaarde - Gent (Belgium) Website: http://www.kuleuven.be/research/erc/verstrepen.html Funding: 1.8 Mio€ ERC-SG-LS2

Title: SYBHEL: Synthetic Biology for Human Health Ethical and Legal Issues Duration: 2009-2010 Coordinator: Dr Ainsley Newson, The University of Bristol (Uk) Website: http://sybhel.org/ Funding: 0.8 Mio€ FP 7 SiS

Title: SYNBIOCOMM: Towards a European Synthetic Biology Community Duration: 24 months (December 2005 to December 2007) Coordinator: Prof. Sven Panke, ETH Zürich, Institute of Process Engineering (Switzerland) Website: www.syntheticbiology.ethz.ch/synbiocomm/index Funding: 0.2 Mio€ FP 6 NEST

Title: SYNBIOLOGY: An Analysis of Synthetic Biology Research in Europe and North America Duration: 15 months (January 2006 to March 2007) Coordinator: Prof. Augusto Eduardo Guimarães de Medina, Sociedade Portuguesa de Inovação (Portugal) Website: www2.spi.pt/synbiology Funding: 0.2 Mio€ FP 6 NEST

Title: SYNBIOSAFE: Safety and Ethical Aspects of Synthetic Biology Duration: 24 months (01.01.2007 to 31.12.2008) Coordinator: Dr. Markus Schmidt, Organisation for International Dialogue and Conflict Management, IDC (Austria) Website: http://www.synbiosafe.eu/ Funding: 0.2 Mio€ FP 6 NEST

Title: SYNTH-ETHICS: Ethical and regulatory challenges raised by SB Duration: 30 months (March 2009 - August 2011) Coordinator: Professor Patricia Osseweijer, Department of Biotechnology, Delft University of Technology (The Netherlands) Website: http://synthethics.eu/ Funding: 0.5 Mio€ FP 7 SiS

Title: SYNTHCELLS: Approaches to the Bioengineering of Synthetic Minimal Cells Duration: 42 months (01.03.2007-01.09.2010) Coordinator: Prof Pier Luigi Luisi, University of RomaTre, Dipartimento di Biologia (Italy) Website: www.synthcells.org Funding: 1.8 Mio€ FP 6 NEST

Title: TARPOL Consortium: Targeting environmental pollution with engineered microbial systems à la carte Duration: 24 months (01.07.2008-30.06.2010) Coordinator: Angeles Sanchis, Universitat de Valencia (Spain) Website: http://www.sb-tarpol.eu/ Funding: 1.2 Mio€ FP 7 KBBE

Title: TESSY: Towards a European Strategy for Synthetic Biology Duration: 24 months (01. Jan. 2007 – 31. Dec. 2008) Coordinator: Dr. Thomas Reiss, Fraunhofer Institute for Systems and Innovation Research (Germany) Website: http://www.tessy-europe.eu/ Funding: 0.2 Mio€ FP 6 NEST

Title: ZINC-HUBS: Engineering zinc fingers to target cancer hub genes Duration: 60 months (01.10.2008-30.09.2013) Coordinator: Mark Isalan, Fundacio Privada Centre de Regulacio Genomica (Spain) Website: http://www.crg.es Funding: 1.3 Mio€

3. ENGINEERING OF THE BODY

Bärbel Hüsing & Ingrid Geesink

3.1. Introduction to the field

Biomedicine in the 21st century is very much about 'biology becoming technology' and 'technology becoming biology' in two respects. First, the human body is a source of information and inspiration for gaining knowledge on how biological systems work. Second, the human body, or parts of it, can increasingly be used as starting material for a range of applications in biomedicine and beyond. This chapter will further analyse these two trends by taking information and human biomaterial as two leading tracks in explaining recent innovations in engineering the body. Both tracks are closely interlinked and interact synergistically (see figure 1). We focus on the human body as a source of information and the body as locus for engineering material.

Both of these depart from our understanding of novel ways of intervening into the human body, in the sense that the human body, or parts of it, or bodily functions become increasingly "mouldable", can increasingly be controlled, designed, built and exploited. The main focus is on the biomedical field, on humans in their role as patients and on interventions intended to treat and cure diseases. However, we will also discuss (more or less visionary) applications beyond biomedicine, as well as functions of the human body not related to disease, such as human enhancement. Finally the human body is our main concern, while the brain and cognitive functions are described elsewhere in this study.



Figure 1: Engineering of the body

Information and Molecular Medicine

For centuries and triggered by newly gained knowledge in the natural sciences (e.g. mechanics and biochemistry) and engineering, the human body has often been understood as a delicate machine or technological artefact. Following this machine metaphor, bodies may not function properly and need repair, or may even be further optimised beyond normal performance. A large number of different technologies and tools for repair, i.e. for treating and curing diseases, have been developed - ranging from drugs to surgery or prostheses. These interventions are not only applied for repair and reinstating health, but also for shaping the human body according to one's wishes - be it by physical exercise, cosmetics, aesthetic surgery or pharmacological enhancement. From an engineer's perspective, machines are built according to a blueprint; and further development and improvement as well as repair can be done most effectively, rationally and efficiently, if the underlying design principles and mechanisms are well known and understood. Because machines are man-made, this information about machine design is readily available. In analogy, natural sciences and medicine have been inspired and driven, over the centuries, to elucidate the blueprint of man. The best-available tools at a given time were employed for this purpose. From a historical perspective, it can be observed that advances in the treatment of disease have often been preceded by a better understanding of how the body functions through the study of aspects which had not been accessible - either technically or culturally – before. For example, surgery has only become possible through understanding the morphology and anatomy of inner organs by post-mortem studies of human bodies; the application of biochemistry and physiology in studies of human metabolism provided a basis for pharmacology and the development of new drugs.

Since the discovery of DNA, the genetic code and the development of DNA sequencing methods, it has been a major target to elucidate humans and life processes on a genetic level. In the 1990s the international Human Genome Project was started in order to provide a complete sequence of a human reference genome. This endeavour was often compared with missions similar to the "Man on the Moon" project because it comes closest to elaborating the blueprint of human bodies and their functioning. The expectation to fully understand life processes once the information in the genome is known is reflected in the "decoding life" or "deciphering the code of life" narrative. In 2001, the first draft of the complete sequence of a human reference genome has been published (The International Human Genome Mapping Consortium, 2001; The Celera Genomics Sequencing Team, 2001). It has boosted scientific research which aims at revealing underlying information on how the human body functions at a molecular level (genomic and post-genomic research, see box 1). It also had a major impact on establishing molecular medicine, which aims at developing a profound understanding of biological processes at the molecular level and at elucidating and treating diseases at the cellular and molecular level (see box 1). The related technologies which significantly improve researchers' abilities to glean information on the human body by probing and interpreting bioprocesses at the molecular level are "omics technologies", i.e. miniaturised high-throughput analytical technologies which allow the highly parallel investigation of all genes (genomes), all gene transcripts (transcriptomes), all proteins (proteomes) and metabolites (metabolomes) of an organism (see box 1).

BOX 1: molecular medicine and -omics technologies

Molecular Medicine

Molecular medicine aims at elucidating and treating diseases at the cellular and molecular level. Methods and findings from molecular biology, molecular genetics, cell biology, physiology and developmental biology are applied to clinical problems in human medicine in order to create the knowledge base for the development of new diagnostic and therapeutic approaches.

Genome research

Genome research is closely related to molecular medicine. It investigates the entire set of genes of an organism (genome) and associates the genetic make-up with functions of the organism. Since the publication of the first draft of the sequence of the human reference genome in 2001, focus is no longer on single genes, but on the entire set of genes (genome). Research topics are the mapping of genes in the genome, the identification of disease-associated genomic biomarkers and the elucidation of the function of disease-associated loci. In this way, enormous data sets are created which are analysed with the help of bioinformatics tools.

Post-genome research: Functional genomics and other -omics

The Human Genome Project focussed on elucidating the sequence ("structure") of the human genome. Since its completion, research in the post-genomic era now focuses on putting meaning into the sequence information, especially on analysing the functions of genes and their role in biological processes. Within this effort, the products of genes, especially transcripts, proteins and metabolites are also studied. Here again, the focus is no longer on single genes, proteins, signalling molecules or metabolites, but on the entire set of genes (genome), transcripts (transcriptome), proteins (proteome) and metabolites (metabolome). This is made possible by miniaturised, highly parallel high-throughput technologies (e.g. DNA arrays).

Biomarkers

Correlates and causes of disease at the molecular level are identified as biomarkers which are objective measures of normal and pathological bioprocesses. Biomarkers can be biochemical or anatomical measures (e.g. cholesterol level in blood or the diameter of blood vessels) or mutations in the genome or specific proteomic profiles, information from medical imaging, etc.

Getting hold of this information helps to gain a deeper understanding of the mechanisms and can be used to build and refine *theoretical models* of bodily functions. Based on the knowledge from the theoretical models, (established) interventions into the human body can be refined and developed in a more rational, more targeted, knowledge-based way (figure 1). Examples are more specific diagnostics, new drugs aimed at previously unknown targets, targeted therapies, personalised therapies or intelligent control of medical implants. A major breakthrough and paradigm change in the sense of "biology becoming technology" was the development of biopharmaceuticals, i.e. proteins from the human body which can be used as drugs. Their industrial production did not become possible until the synergistic exploitation of analysing the sequence information of human genes which encode the respective proteins. This helped glean the relevant information which could be expressed in the form of cloned genes in production microorganisms through genetic engineering. Thus, genetic information from the human body was transformed into a medicinal product in a technical process, and biological information had become technology. However, besides biopharmaceuticals, the efforts to develop new tools to engineer the human body itself starting from molecular information has so far remained limited. The development is much more dynamic in the field of engineering living organisms other than humans, as deployed further elsewhere (see chapter Engineering of living Artefacts).

All in all, molecular medicine significantly contributes to elucidating the underlying information and mechanisms of key life and disease processes, and also to using this information in medicine. This is further described in section 3.2.1.

Materials and Regenerative Medicine

The intricate interplay between biology and technology in the body dates back decades. "Parts" of the human body have been used for treatments, like blood transfusions and organ transplantations. Transplantation medicine has traditionally been about implanting whole organs from one human (or animal) body to another in order to replace failing kidneys, hearts, livers and lungs. However, these treatments rely on bodily materials which are (rather) easily accessible, such as blood, and only require minor engineering for use. On the other hand, other, more intensively engineered materials and devices have been used successfully as some kind of "spare parts". For example, it is well-established in the clinic to transplant tissue such as cornea, bone or heart valves, taken from dead bodies, or skin, sometimes with the patient donating to himself from another site of the body (autografts).

Also, a long tradition exists of using synthetic materials to repair bodily functions. Wellknown examples include medical devices such as pacemakers, artificial hip implants and heart valves, or the next generation of smart implants. Half a century ago, biomedical science relied on all kinds of plastics and polymers, but also synthetic fabrics such as Dacron or Gore-Tex have been used as artificial replacement for, among others, blood vessels. Materials were further developed for clinical application, which gradually led to hybrid materials with bio-active or living ingredients, such as combinations of cells and scaffolds. Several labs now work according to biologically inspired engineering principles to replicate nature's design for potential application in humans, for example with nanofabrics to replicate the extracellular matrix.

Whether stemming from transplantation biology or material sciences and engineering, the underlying principle of these efforts is similar, however: mimicking nature in the best possible way to repair or replace failing human body parts. Material scientists and engineers have developed alternatives that are more biological, more biodegradable and more bioactive. As one scientist explained, the aim back then was to create more hybrid artificial organs: "As engineered implants evolve to approach the biological ideal, scientists engaged in research in the field of artificial organs seek to develop devices that can more effectively replace complex organ function. A bridge between artificial organs constructed with synthetic material and the longer-term goal of completely biologically derived organs is the 'hybrid artificial organ', in which synthetic materials and cells are brought together in engineered systems." (Martin et al., 1997: 77-78) And similarly: *"Biomaterials, instead of fighting biology, will smoothly integrate into living systems. The possibility for new devices and applications are limitless when materials and biology work together"* (Ratner, 1993: 847).

BOX 2: Regenerative Medicine

A paradigm change from "repair medicine" to regenerative medicine is a long term goal. Regenerative medicine aims at stimulating or imitating the body's natural ability to repair damaged tissues and organs so as to bring about functional recovery (KNAW, 2009). The use of cells and tissues as "smart material" components in therapeutic applications, could enhance the effectiveness with respect to, e.g., physiological behaviour, biocompatibility, functionality, adaptability, and self-repair and could thus overcome inherent limitations of existing therapeutic strategies, such as supplementation of metabolic products in the form of drugs, hormones and enzymes; prosthetic substitution; surgical excision or reconstruction, or organ transplantation (Lalan et al., 2001; Hüsing et al., 2003a). The use of cells and tissues as "smart materials" in therapeutic interventions is a complementary approach to intelligent prostheses (see chapter "Engineering of intelligent artefacts").

Advanced therapies

Advanced therapies are gene therapies, cell therapies and tissue engineering. They use engineered bodily materials such as human genes, cells and tissues as new tools to intervene into the human body for therapeutic purposes.

Cell therapies

Cell therapies are therapies in which living cells are transferred into the human body for therapeutic purposes. There is a broad scope of therapeutic interventions, differing in the origin of and type of cells used; the ability of the cells to grow and differentiate, the level of cell manipulation, route of administration, duration of exposure, use of combination products, etc. Each of these different concepts has its advantages and disadvantages, in view of clinical therapeutic use. Inherent limitations are the small sample sizes and the short shelf life of the cells, and specific risks stem from possible contaminations with microorganisms, the impossibility of standardising the cell products and the potential immunogenicity and tumourigenicity of the cells. This calls for a flexible, case-by-case regulatory approach for these products (Salmikangas et al., 2010).

Gene therapies

Present research focuses on somatic gene therapy. This means that the genetic modification is only incorporated into the somatic cells of the treated person, and will therefore not be passed on to the patient's offspring. Gene therapy could, however, also be applied to cells in the germ line, with the consequence that the deliberately introduced alterations of the genetic make-up would also be inherited by the patient's children and thus have long-term effects.

Tissue Engineering

Tissue engineering is the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules. The therapeutic intention of tissue engineered products is to replace the failing tissue with a functionally equivalent tissue structure that preferably persists at the desired location. The cell component serves as "smart material" which should endow the resulting product with properties such as physiological function, adaptability to changing conditions, and growth. Widely applied examples are tissue engineered skin for the treatment of severe burns and ulcers and tissue engineered cartilage for repair of knee cartilage defects.

Thus from a material perspective, over time technology has become more biological. The aim of these transplant technologies is to provide properties that are associated with living organisms, with dreamed of characteristics such as self-organising and self-healing properties (Bedau & Parke, 2009). We can witness the contours of this ambition by studying the latest exit in engineering the body, the search for biological substitutes via tissue engineering and stem cell therapies, also known under the heading of regenerative medicine. As such, regenerative medicine aims not just to repair or replace, but to regenerate human biological material by imitating the body's natural ability to repair. Here, too, we witness the continuous interplay between being inspired by biological systems and using this knowledge for reconstructing or redesigning human biological functions.

Investigations which aim at studying and engineering the material - molecules and suband supracellular structures of the human body - are on the one hand taken for regenerative medicine and for providing "human spare parts". On the other hand, they are being used to build, refine and engineer laboratory in vitro models of bodily functions. These cellular in vitro systems can then also be exploited as engineered material or tools in diverse technological applications, ranging from screening for new drugs or studying toxicological effects. In addition, these parts of the human body can themselves be engineered in a way that they may be used for intervening into the human body, thus engineering human bodies with bio-based tools originally derived from human bodies. Emerging tools for intervening into the human body comprise gene therapy, cell culture and somatic cell therapies (including stem cell therapies), human tissue engineered medicinal products, and even human cloning. Even more refined intervening tools and techniques are being developed in the context of synthetic biology (see chapter Engineering of living artefacts); however, they are not yet ripe for application to humans. Thus, biology (i.e. parts of the human body) becomes technology which may serve diverse technical and commercial purposes as well as modify and design the human body. Regenerative medicine and "Advanced therapies" contribute to this thread, as described in more detail in section 3.2.2.

However, the knowledge and technology base developed in these two tracks is not restricted to treating impaired bodily functions and diseases; it may well also be used to address bodily functions not associated with diseases, thus potentially contributing to enhancing bodily functions beyond "normal levels" as well as bringing human bodies to perfection far beyond the biomedical field. Transhumanists' visions of enhancing the performance of human bodies, of merging with other forms of life, of eternal life and of identical replication (cloning) of human beings form an extreme end of this emerging development.

Structure of the chapter

After providing an overview of the scientific and technological state of the art in both the information and the material fields, we present a synopsis of the research that is presently funded within the EU 7th framework research programme. In the following sections, ethical, legal, and social aspects are discussed and conclusions drawn.

3.2. Scientific and technological state of the art

In developed countries, complex diseases such as cancers, metabolic diseases like diabetes, cardiovascular and neurodegenerative diseases such as Alzheimer's and Parkinson's disease pose a major public health challenge. In most cases, no effective prevention or cure is available, so that most of these diseases are chronic conditions with reduced quality of life. Moreover, treatment of these lifelong diseases is costly, requiring a substantial share of the resources of health care systems. Incidence and prevalence of these diseases will increase due to the ageing population and life style factors.

Against this background, there is an urgent need for new improved interventions which reduce mortality and improve the quality of life; improve the allocation of health care resources to those patients who can benefit from the respective intervention, e.g. by reducing adverse effects or better stratification of patient populations; help prevent diseases instead of treating them, and finally to regenerate diseased tissue instead of functionally replacing it.

Investigations into the "information track" (molecular medicine) and "bodily materials track" (regenerative medicine and advanced therapies) of "biology becoming technology" and vice versa are embedded into life science and biomedical research which aim at achieving the following goals:

- The improved treatment and cure of diseases, in terms of reduced mortality and improved quality of life;
- the improved targeting of interventions to those patients who can benefit from the respective intervention, thus reducing adverse effects and preventing misallocation of health care resources;
- paradigm shifts from treatment of disease to prevention of disease, and from repair of impaired body functions to regeneration.

This section provides an overview of the main research trajectories and challenges of these two engineering fields.

3.2.1. Elucidating information on how the body functions: Molecular Medicine

Through genome and post-genomic research (see box 3), correlates and causes of disease at the molecular level in the form of biomarkers are being identified which form the basis for new theoretical models of disease pathways. Using these models, the information is used for the following purposes:

- R&D
- as a resource for life science research and for the generation of hypotheses for further research
- more efficient, rational pharma R&D, especially for the development of
 - conventional investigational new drugs
 - new therapeutic principles, e.g. RNA-based therapeutics
 - identification of new molecular targets
 - molecularly targeted therapies, drug and companion diagnostics
 - pharmacogenomics and pharmacogenetics
 - more efficient tests for toxicology, etc.
- in health care provision for
 - new diagnostic options which are characterised by being more specific, more sensitive, earlier, presymptomatic, predictive
 - the specification of individual health status and disease risk with the aim of prevention
 - monitoring of health status, disease progression and response to therapeutic intervention

- treatment
- guide rational choice of therapeutic options: stratification of patient groups, pharmacogenetics, avoid adverse effects
- monitoring of response to therapeutic options
- intelligent monitoring or therapeutic medical devices which use biomarkers as input signal

The present focus in molecular medicine is on R&D. Academic research focuses on the identification of biomarkers as causes and correlates of disease in genome-wide association studies and the development of methods and tools for their measurement and analysis. In industry, the focus is on biomarkers for making pharmaceutical development more efficient (e.g. toxicology biomarkers, biomarker programmes in drug development and clinical trials).

BOX 3: Recent trends in genome and post genome research

Research is most advanced for genomic biomarkers in the form of single nucleotide polymorphisms (SNPs), but other genetic variations such as epigenetics and copy number variations are also intensively investigated. Technology development is very dynamic with respect to DNA sequencing, aiming at sequencing whole human genomes at unprecedented speed and lowest cost ("\$1,000 genome"). At least several dozens individual genomes have been deep-sequenced up to now (Pushkarev et al., 2009; Drmanac et al., 2010; http://www.1000genomes.org/; http://www.personalgenomes.org), with the USA and China having established large sequencing facilities (Cyranoski, 2010; Fox, Kling, 2010). Worldwide, at least two dozens companies offer SNP-based genome analyses directly to consumers (Hennen et al., 2008).

Since 2007, the results of a large number of genome-wide association studies for a broad variety of complex diseases have been published (Witte, 2010) that identify genomic biomarkers associated with certain common diseases. Moreover, genomic biomarkers for rare diseases (Check Hayden, 2009a) and for non-disease traits are also being identified (e.g. Stuckelberger, 2008; Visscher, 2008; Neame, 2009; Lee, Silva, 2009; He et al., 2009). Most advanced is the investigation of genomic biomarkers in cancers. In addition to the formation of large international research consortia aiming at elucidating the molecular alterations that lead to cancers, translational research is ongoing which aims at translating these findings into improved diagnosis, prognosis and treatment of cancer patients; i.e. personalised cancer treatments (van der Brug, Wahlestedt, 2010; Stratton et al., 2009; Check Hayden, 2009b; Potti, Nevins, 2008; 't Veer, Bernards, 2008). Research into proteomic, transcriptomic, and metabolomic biomarkers is ongoing, but technologically more challenging than genomic biomarkers.

Prerequisites for this type of research are well-developed research infrastructures which can only be operated in international cooperation, especially

- high-quality and large biobanks, representing a variety of diseases and ethnic populations,
- interoperable databases and bioinformatics tools for their analysis
- genome-wide association studies in large, diverse populations

• technical, ethical and legal, internationally enforced standards.

These infrastructures have been set up in recent years and are presently being expanded and refined. All in all, we witness vastly expanded possibilities for acquiring disease-associated information from patients at the molecular level. However, the ability to interpret this data with respect to its clinical relevance is severely lagging behind, and the possibilities for evidenced-based interventions are not expanded at a similar speed or scope. The resulting R&D and R&D policy challenges arising from this situation will be discussed in section 3.3 which also gives an overview of ongoing research within the 7th framework programme in Europe.

3.2.2. Studying and engineering materials of the human body: Advanced therapies and regenerative medicine

"Parts" of the human body have been used for decades for certain forms of treatments. Examples are blood transfusions or organ transplantations. A severe drawback, however, is the limited supply of these bodily materials and the sources from which the materials are derived (e.g. brain dead persons, aborted human foetuses as cell source for cell therapies for Parkinson's disease, potentially infected donors). This evokes ethical controversies and legal questions (e.g. brain death concept in the context of organ donation, legal status of aborted foetuses and dead bodies and tissues derived from them, how to guarantee safety and quality).

Due to progress in cell biology, cell culture techniques and cell engineering (e.g. by genetic engineering, tissue engineering, induction of pluripotency), it seems possible that the problem of limited supply of bodily materials could be overcome. As a consequence, a new quality of using body parts for biomedical purposes is emerging. It is characterised by

- an extension of the scope of body parts that are being used. There is no longer a restriction to use only easily accessible cells and tissues or take material from dead bodies. Rather, living cells and tissues can be derived which cover a diverse set of differentiated cells and tissues, as well as gametes (i.e. sperm and eggs), human embryos, and human embryonic stem cells
- an extension of the diseases and conditions that are amenable to treatment with body parts, due to the broadened range of useable cells and tissues
- a substantial engineering of the bodily materials, making this both technologically challenging as well as economically attractive due to the knowledge-intensive valuegeneration
- the development of new forms of biomedical interventions into the body, e.g. gene therapy, cell therapies and combinations thereof (Sheyn et al., 2010)
- an extension of the uses of bodily materials outside direct medical treatment of patients in more technical applications, e.g. use for research purposes, alternatives to animal testing, toxicology testing
- an increase in banking, long-term storage and transfer of bodily materials between institutions
- a broadening of the scope of actors dealing with bodily materials
- a move from altruistic donation to commercial uses.



Figure 2: Strategies of regenerative medicine. Source: Sheyn et al., 2010

Figure 2 depicts the strategies of regenerative medicine with specific reference to the advanced therapies of gene therapies, cell therapies and tissue engineering. They can be used alone, or in combination, and the targeted tissue can be regenerated outside the body with subsequent transplantation, or the regeneration process can be stimulated within the body (Figure 2). At the research level, the borderlines between the approaches are increasingly blurring and synergies are being exploited, and the future will increasingly see the use of genetically modified cells in all three trajectories and thus a convergence of these approaches. This convergence has already been anticipated in the European regulation for market authorisation of these advanced therapies (European Parliament and Council, 2007; European Parliament and Council, 2004).

Cell therapies

Several cell therapies are well-established in the clinic, but even more are under development. The most comprehensive clinical experience with cell-based therapies has been gained with haematopoietic stem cells (HSC) over the last 50 years (Jenq, van den Brink, 2010), not in the least because these cells are readily accessible: because they can be obtained from the blood stream, but they can also be taken from bone marrow, or from cord blood immediately after birth. Because haematopoietic stem cells replenish red blood cells and generate the cells of the immune system, they are transplanted mainly for two purposes: inherited anaemia or immune deficiencies can be treated by replacing the abnormal haematopoietic system with one from a healthy individual.

Second, when cancers are treated by high dose radiation and/or chemotherapy (so called myeloablative therapies), haematopoietic stem cells are transplanted in order to quickly restore immune functions (Jeng, van den Brink, 2010).

According to the EBMT database,⁵⁷ approximately 25,000 patients are treated annually in Europe with haematopoietic stem cell transplants. Since 1980, a total of nearly 280,000 patients have received this type of treatment. Italy is the leading country with respect to the number of blood stem transplantations per million inhabitants (55.4), followed by France and Sweden (58), Germany (55.4), the Netherlands (52.9), Switzerland (49.9), Spain (44.6) and the United Kingdom (40.9) (DRST, 2009).

Because haematopoietic stem cells can be readily obtained and so much experience has been collected with their clinical application, it is an area of active preclinical and clinical research to exploit this cell type also for the treatment of other diseases. Research is underway to differentiate and engineer haematopoietic stem cells into various cell types, including bone cells (osteoblasts), muscle cells (myocytes) (Janssens, 2010), cartilage cells (chondrocytes), adipocytes as well as insulin-producing cells, and to use them as cell source in regenerative medicine, cell therapies and tissue engineered products. Taken these developments together, haematopoietic stem cell transplantation is at the interface of three promising areas of current clinical research: stem cell therapies, immunemodulating techniques, and the individualisation of cancer therapeutics (Jenq, van den Brink, 2010).

In addition to haematopoietic stem cell-based cell therapies, the most common product types of somatic cell therapies are cancer immunotherapy products (cancer vaccines). Some of them are already in advanced clinical development, but have not been licensed so far in the EU. The cancer vaccines under clinical development aim at mobilising the patient's immune system against cancer-associated self antigens, using antigen-loaded dendritic cells and tumour-specific T cells (Salmikangas et al., 2010; Westwood et al., 2010).

Human embryonic stem cells and pluripotent cells

An inherent drawback of cell therapies is the limited supply of human cells suitable for therapy. Therefore, intensive research is devoted to overcoming the bottleneck of limited cell and tissue supply. When an egg cell is fertilised and subsequently divides, each of the resulting embryonic cells has the ability for a short period of time to give rise to an entire organism. This ability is called pluripotency. Such human embryonic stem cells (hESC) would be most interesting as material, because all cell types and tissues of the human body could be derived from them on demand in vitro, without time and quantity restrictions (Wobus et al., 2006: 119f).

However, hESC were inaccessible because of the fact that natural fertilisation and the earliest stages of embryo development take place within the female body. It was not before the development and synergistic combination of in vitro fertilisation (IVF) for the treatment of infertility, cell culture techniques, extensive knowledge from embryology and cell biology, and the permission to experiment with human embryos in vitro, that human embryonic stem cells could be derived in vitro. This was a major breakthrough in 1998 (Thomson et al., 1998).

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http://www.ebmt.org/; accessed 16.5.2010

However, the procedure to derive human embryonic stem cell lines from the inner cell mass of human in vitro blastocysts inevitably leads to the destruction of the embryos. Therefore, different methods have been developed to derive hESC, driven by the intention to overcome the ethical concerns associated with the destruction of human embryos. Table 3 gives an overview of the most important approaches and indicates to which extent they are related to ethically controversial procedures, especially the intentional generation of human embryos only for research purposes, the requirement for large numbers of human oocytes, the use of surplus embryos, and the methodological proximity to pre-implantation diagnosis, and reproductive cloning (Nationaler Ethikrat, 2004a).

BOX 4: Human therapeutic and reproductive cloning

One way to derive embryonic stem cells is through the procedure of somatic cell nuclear transfer (SNCT). The cell nucleus from a somatic cell is transferred into an enucleated egg cell. If successful, an embryo develops which is genetically identical to the donor of the somatic cell. Embryonic stem cells can be derived from this in vitro embryo; the process is also called therapeutic cloning, because the embryonic stem cells are intended to be used in cell therapies for therapeutic purposes.

Another option would be to generate whole organisms from these embryonic stem cells, a process called reproductive cloning which promises to identically duplicate humans. This had been achieved in 1997 with the sheep Dolly (Wilmut et al., 1997) and raised a controversial debate whether human cloning should be permitted. Despite intensive research efforts, it has not yet been shown to derive hESC via the SCNT procedure of "therapeutic cloning" which is feasible for mouse ESC (Munsie et al., 2000) and is methodologically very close to reproductive cloning. Reports claiming success (Hwang et al., 2004; Hwang et al., 2005) turned out to be scientific fraud.

Since 1998, at least 677 human embryonic stem cell lines were derived in 68 institutions in 22 countries (Müller-Röber et al., 2009: 69). The stem cell registry lists 154 cell lines as characterised and 134 as available (Müller-Röber et al., 2009: 72).

Should it become possible to derive hESC from single blastomeres without damage to the embryo, in principle the following "package" could become an option within in vitro fertilisation: after in vitro fertilisation, a blastomere could be picked from the in vitro embryo, and after cell division, it could be used for pre-implantation diagnosis as well as for deriving a hESC line. The remaining embryo could – after negative result from pre-implantation diagnosis – be transferred to the maternal uterus. At birth, cord blood stem cells could also be extracted, rendering a second option for providing individual-specific stem cells for future regenerative treatments. Thus, not only the creation of a new individual by combination of egg and sperm would be subject to engineering during in vitro fertilisation, but the earliest stages of life, too, would be quality-checked and exploited for deriving raw materials for future therapies.

Whether human embryonic stem cell lines are actually suited for clinical cell therapies still remains to be shown. The first clinical trial phase I for a cell therapy with certain nerve cells derived from a hESC line for patients with acute spinal cord injury received clearance by the US regulatory authority FDA in 2009, but was then put on hold twice by the FDA because of safety concerns. Only in July 2010 the clinical hold was lifted and the company was allowed to proceed with the trial, injecting hESC-derived progenitor cells into the patient's injured spinal cord (www.geron.com).

The trail delay and on/off decision has been explained by commentators as uncertainty on behalf of both scientists and regulators on the behaviour of human embryonic stem cells in the body: *"While thousands of patients around the world have been treated with adult stem cells and have shown mixed results, no humans have been given cells derived from embryos in an approved trial"* (NY times, 2009).

Since 2007, even higher potentials are assigned to human induced pluripotent stem cells (hiPSC). Their derivation neither requires human oocytes nor human in vitro embryos, as they are obtained via reprogramming of somatic cells (Yu et al., 2007; Park et al., 2008). It has been shown that pluripotency can be induced in various cell types of mice, rats, non-human primates, pigs and humans by the expression of several transcription factors (de Souza, 2010). In 2009, the science journal "Nature" awarded the reprogramming of somatic cells to the state of pluripotency as the "method of the year". Many human induced pluripotent stem cell lines have been established, especially from patients with defined genetic defects, thus making patient- and disease-specific human cells widely available. The direct benefit of iPSC lies in disease modelling, providing complementary tools to animal models of disease. They will be of great use in basic research, toxicology, drug development and alternatives to animal testing (Lee, Studer, 2010). However, it will still take several years to assess the potential of human induced pluripotent stem cells for cell therapies.

However, the reprogramming of differentiated cells without going through an embryonic stage might turn out as an even superior approach for cell therapies (Nicholas, Kriegstein, 2010). Proof of concept that such a reprogramming is possible was recently shown for mouse fibroblasts (Vierbuchen et al., 2010).

Although it cannot be decided yet which of the above mentioned approaches will turn out the best for providing cells for cell therapies, it seems to be only a matter of years until this goal can be reached. However, with respect to the clinical and therapeutic use of stem cellderived or reprogrammed cells, the clinical efficacy and safety issues will have to be addressed thoroughly both by researchers as well as regulatory agencies in the coming years (Heinemann, Kersten, 2007: 85f.; Hüsing et al., 2003b: 49f).

		Ethical acceptability			
Approach	State of the art	Destruction of human embryos	Proximity to ethically controversial procedures*		
Derive hESC from a single blastomere, followed by embryo transfer into uterus	Mouse: proof of concept Experiments show feasibility also for humans	No, but risky	yes		
Derive hESC via somatic cell nuclear transfer (SCNT)	Mouse: proof of concept Humans: not achieved yet	yes	Yes; large numbers of human oocytes required		
Derive hESC from parthenogenetic embryos which cannot develop beyond the blastocyst stage	Humans: proof of concept	yes	No; but: large numbers of human oocytes required		
Derive pluripotent spermatogonial stem cell lines from stem cells in the testes	Humans: proof of concept	no	no		
Human induced pluripotent stem cells (hiPSC)	Mouse: proof of concept	no	no		
Induced transdifferentiation of somatic cells	Mouse: proof of concept	no	no		

Table 3:	Approaches	for derivina	human plur	ipotent cell	lines for cell	therapies
1 4 6 1 6 .	7.pp10401100	ioi aoiiiing				

*in vitro fertilisation to create embryos for research purposes, use of surplus embryos, pre-implantation diagnosis, reproductive cloning.

Source: Information compiled from Green 2007, Heinemann, Kersten, 2007, Müller-Röber et al., 2009, p. 30

Tissue engineering

Most closely related to the trajectory of developing smart prostheses (see chapter Engineering of intelligent artefacts) is tissue engineering. This is the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules. The therapeutic intention of tissue engineered products is to replace the failing tissue with a functionally equivalent tissue structure that preferably persists at the desired location (The Committee for Advanced Therapies (CAT), 2010). Tissue engineering is a dynamically growing, interdisciplinary research field which is well underway and which is grounded in the fields of developmental biology, cell biology, biomaterials science, and imaging technologies (Sheyn et al., 2010; van den Besselaar, Gurney, 2009).

Several products are in clinical use, especially bone products, skin products for the treatment of severe burns and hard-to-heal ulcers, cartilage products for the treatment of cartilage lesions the knee and other joints, and cell-coated medical devices, e.g. stents and heart valves. In 2005/2006, the sales figures for tissue engineered bone products amounted to approximately \in 160 million, for cartilage products to approximately \in 37 million in Europe, and for skin products to \in 108 million in Europe and the USA.

In 2009, the first human tissue engineered product obtained EU marketing authorisation via the newly established centralised procedure for advanced medicinal products in the EU; this was an autologous cartilage product for the treatment of large cartilage lesions.⁵⁸

However, the human tissue engineered products in clinical application are "the low hanging fruits", because they consist of only few cell types (less than the natural tissue they replace), have no or only limited vascularisation and only a simple three-dimensional structure (Sheyn et al., 2010). Clinical studies into other products and applications have only been carried out on a restricted scale (KNAW, 2009: 56). They comprise, in addition to bone, cartilage and skin, tendons and ligaments, skeletal muscle, adipose tissue engineering, cardiovascular tissue, pancreatic tissue, tissue of the central nervous system, and liver tissue (Sheyn et al., 2010).

Despite considerable progress in the last decade, the major challenges in the coming years remain more or less those that have already been identified by Langer and Vacanti in 1993 and are outlined in section 3.3: Progress in regenerative medicine will require additional basic research on stem cells, biomaterials and their interaction (KNAW, 2009: 56; Sheyn et al., 2010; Langer, Vacanti, 1993). Moreover, enabling technologies are crucial for progress (KNAW, 2009). They comprise: biomarkers, imaging technologies, high-throughput technologies, in vitro and in vivo modelling systems (see Molecular Medicine), bioreactors, and tools for minimally invasive administration of tissue engineered products. This highlights the synergistic co-evolution of the two tracks "molecular medicine" and "regenerative medicine".

Gene therapies

Triggered by breakthroughs in the genetic engineering of microorganisms and further stimulated by the Human Genome Project, the genetic modification also of human genomes was deemed an attractive research goal. It should open up a possibility for an unprecedented, completely new therapeutic option - gene therapy (see box 5). While its primary intention is to "repair" mutated or non-functional genes, the technology itself would be a stepping stone towards the engineering of the human genetic make-up, both of disease and non-disease traits. Thus, engineering approaches which have already been or are being established for non-human organisms and especially microorganisms (see chapter Engineering of living artefacts) could also become applicable to humans.

Present research focuses on somatic gene therapy. This means that genetic modification is only incorporated into the somatic cells of the treated person, and will therefore not be passed on to the patient's offspring. Gene therapy could, however, also be applied to cells in the germ line, with the consequence that the deliberately introduced alterations of the genetic make-up would also be inherited by the patient's children and thus have long-term effects.

The present state of gene therapy is far away from realising these visions: Up to now, only one gene therapy medicinal product has been approved for commercial use. This is Gendicine, a treatment for cancer developed by SiBiono GeneTech Co. of Shenzhen, China. It was approved for clinical use and commercial production by the Chinese State Food and Drug Administration in 2004; however, without data from a standard phase III trial. Up to now, more than 4,000 patients have been treated with this product, according to the company (Edelstein et al., 2007).

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http://www.emea.europa.eu/pdfs/human/opinion/ChondroCelect_38336609en.pdf

The vast majority of gene therapy clinical trials performed to date are still in the early phases I or I/II (79.2 % of all gene therapy trials), 16.3% are phase II trials, and phase II/III and III trials represent only 4.2%. The share of trials in phase II, II/III and III has slowly risen over the years (2004: 15 %; 2007: 19.1 %; 2009: 20.5 %) possibly indicating that gene therapy is slowly moving closer to clinical applications (Journal of Gene Medicine, 2010).

BOX 5: Clinical trials in human gene therapy

Since the first human gene therapy trial was approved in 1989, 1,575 clinical trials have been started in 28 countries from 1989 to 2009 (status of Dec. 2009; Journal of Gene Medicine 2010). After a steady rise from 1989 to 1999, annually approximately 100 clinical gene therapy trials have been approved worldwide since 1999. The leading world regions are America (64%, 1,010 trials), followed by Europe (29.6%, 467 trials), Asia (3.7%, 58 trials), Australasia (1.9%, 30 trials), Africa (0.1%, 1 trial) and multi-country trials (0.8%, 13 trials). Within Europe, the United Kingdom holds the leading position (12.2% of the worldwide trials, 193 trials), followed by Germany (5%, 79 trials), Switzerland (3%, 46 trials), France (2.6%, 41 trials), the Netherlands (1.6%, 26 trials) and Belgium (1.5%, 24 trials) (Journal of Gene Medicine, 2010; Edelstein et al., 2007).

In the early days of gene therapy, this concept was first applied for treatment of inherited monogenic disorders, because no other causal treatment exists for these types of diseases, and the concept of replacing a well-defined defective gene with its correctly functioning counterpart has an obvious appeal and rationale. However, the vast majority of gene therapy clinical trials have addressed cancer (64.5%), followed by cardiovascular diseases (8.7%), infectious diseases (8.0%) and inherited monogenic diseases (7.9%). A broad range of different strategies has been applied to cancer gene therapy, from inserting tumour-suppressor genes, to immunotherapy, to gene-directed enzyme prodrug therapy (Edelstein et al., 2007).

Several severe adverse events in the last years have slowed progress considerably and have dampened the expectations in the gene therapy field. Some patients died after gene therapy because they developed a severe immune reaction against the inserted vectors; and other patients developed leukaemia because the gene therapy vectors had integrated into their genome at sites where they disrupted normal gene function which led to leukaemia (Couzin, Kaiser, 2005; Baum et al., 2006). However, these adverse events have prompted more detailed investigation into the behaviour of viral vectors and more careful testing of all approaches (Tan et al., 2008). Nevertheless, there are still major hurdles to be overcome, especially the large scale vector manufacture, proof of clinical efficacy, and the improvement of safety (The Committee for Advanced Therapies (CAT), 2010; Schüle et al., 2010).

Visionary applications

In visionary applications, the tools for advanced therapies are employed within anti-ageing strategies (Stuckelberger, 2008), thus aiming at general rejuvenation of the body, healthy ageing and extending the (healthy) life span. Other visions comprise novel interventions into human reproduction (Pearson, 2008): according to leading experts in reproductive medicine, developments within the coming three decades could involve the production of in vitro embryos from sperm and eggs which were derived from human embryonic or induced pluripotent stem cells lines.

By using gametes which were derived in the laboratory, but not taken from living donors, embryos could be created for research, thus overcoming the scarcity of human embryos for research purposes. Sperm cells and oocytes from different cell lines could be deliberately combined. Genetic modifications could be introduced into the gametes or the embryos, using gene cassettes or artificial chromosomes. Bioreactor technology in tissue engineering could yield an artificial womb which could enable the cultivation of human embryos for longer times and to advanced developmental stages, perhaps even birth, with significant impacts such as making human reproduction independent of the natural reproductive phase. Human reproductive cloning is also a visionary application, but has been banned in the EU.

With respect to nutrition, tissue engineering could enable the production of meat in bioreactors for nutritional purposes. Irrespective of the costs which will be much higher than for meat production in animal husbandry, the niches and needs for this option still remain to be defined.

3.3. Research in the 7th framework programme

3.3.1. Gaining information about key life processes – Research needs and challenges for research policy

Main research challenges in gaining information about key life processes and their role in health and disease lie in three areas:

- establishing the technological capabilities (analytical tools) and organisational infrastructure as prerequisites for carrying out this type of research;
- in the identification and characterisation of new biomarkers, and
- in putting meaning into biomarkers, i.e. interpreting the data in a clinically useful way and translating the enormously expanded knowledge in basic biology into improved diagnostic and therapeutic options.

These three areas are prominently addressed in the 7th framework programme, especially within the thematic area "Health" in the Collaborative research programme ("Cooperation"). The objective of the FP7 thematic area Health is to improve the health of European citizens, increase competitiveness and boost the innovative capacity of the European health-related industries and businesses.

The Cooperation programme Health is divided into three major pillars:

- <u>Pillar I</u> comprises the development of generic tools and medical technologies for human health, namely with a focus on high-throughput research.
- <u>Pillar II</u> aims at translating research for human health, including the integration of biological data and processes by means of large-scale data gathering and systems biology, and translational research in major diseases.
- The goal of <u>pillar III</u> is to optimise the delivery of health care to citizens by translating clinical research into practice, improving health care systems and enhancing health promotion and disease prevention.

Thus, FP7 funding for research in gaining information about key life processes (molecular medicine) takes place mainly within pillars I and II. A short outline of the contents of the calls issued and projects funded is given below:

One focus of research activities within the FP7 is the development of new technologies and research tools for high-throughput data generation and analysis. It comprises new analytical technologies for high-throughput sequencing, gene expression, genotyping and structural and functional genomics, and other -omics. phenotyping, Moreover, computational tools for analysing and interpreting this information, such as genome annotation, genotype/phenotype data integration, systems biology and data mining are also being developed. As these are generic tools, there are synergies with corresponding activities within the thematic area "Food Agriculture and Fisheries and Biotechnology" where similar tools for obtaining information within the context of "Engineering of living artefacts" are being developed. In addition to using these new tools in basic research, activities also aim at making them available for biomedical and clinically relevant research, e.g. for the identification and the detection of biomarkers in clinical samples and patients, as well as for pharmaceutical research. Within pharmaceutical R&D, the tools are expected to contribute to enhancing the safety and efficacy of drugs, accelerating drug development processes and reducing attrition rates. These activities take place in close interaction with the innovative medicines initiative. Specific calls aim at developing norms and standards for these tools and data analyses in order to ensure high quality standards, reproducibility, comparability and interoperability.

In addition to tools, the implementation and maintenance of large scale human research biobanks are other important prerequisites for research within molecular medicine. Within the FP7, emphasis is being put on obtaining high quality and reproducible data sets. To improve both the acquisition of biological specimens (biosampling) as well as their characterisation (phenotyping), three paths are being followed: the development and application of high-throughput tools and technologies to phenotype large sets of human biological samples, the setting up of well-characterised population cohorts, and emphasis on the standardisation of technologies and processes. The goal to glean information on rare genetic variants as causes of common diseases requires very large population cohorts or high numbers of well-characterised biosamples in order to achieve sufficient statistical power. Often, individual biobanks are not large enough to fulfil these requirements. Therefore, FP7 aims at supporting networking for synergies between different biobanks in Europe. This comprises also a harmonisation of norms and standards, both on a scientifictechnical as well as on regulatory and ethical levels, in order to achieve interoperability of European biobanks.

Having established analytical tools and biobanks as prerequisites, another focus in FP7 is large scale data gathering and biomarker identification. By using high-throughput technologies on samples from biobanks, molecular information is to be obtained. The emphasis is on information on key biological processes and multifactorial diseases, information that may be useful for diagnosis and treatment of disease, as well as information on functions with potential industrial applications for health, such as detoxification pathways, metabolic networks and new bioactive products. Two activities aim at generating a reference knowledge base: Comparative studies of genetic variation in humans are carried out in order to compile an integrated genetic variation catalogue of the European population, so that a "reference population" as a research resource for other projects can be established. Another activity focuses on elucidating the molecular origin and determinants of cancer by analysing large numbers of cancer tumours.

Because the insights gained from individual biomarkers or biomarker classes (such as genes or proteins) are limited, emphasis is also given to data integration in order to obtain "the full picture" of the system and in order to be able to model the relevant biological processes.
The aim is to integrate a wide variety of biological quantitative data sets (e.g. transcriptomics, proteomics, metabolomics, structural biology, RNAi screening, physiology and/or patho-physiology) in different areas, such as general genetic variation, cancer, cardiovascular disease, published studies, specific populations and pharmacogenomics. This will lead to the design of robust theoretical or *in silico* models of important biological processes with relevance to human health. For this purpose, mathematical algorithms for systems biology also have to be improved or developed, respectively.

Within biomedical research activities that aim at the detection of biomarkers in clinical samples and patients, FP7 also offers research funding for stratification approaches and methodologies to select, from a wide range of biomarkers, relevant candidates for clinical validation as well as for validation efforts.

The transfer of knowledge from bench to bedside, i.e. the use of information from basic research for the improvement of health care, is also being funded. Translational research can be carried out on topics such as disease aetiology; new medicines and therapies; identifying and validating drug targets and biological markers that aid in the prevention, early diagnosis, treatment and monitoring, and assessing the effectiveness of preventive, prognostic, diagnostic and therapeutic interventions. Specific emphasis is given to three disease classes, namely cancers, cardiovascular diseases, and diabetes and obesity. Research on brain and brain diseases is another focus which will be discussed in more depth in the chapter Engineering of the Brain.

3.3.2. Material derived from humans for technology: Research needs and challenges for research policy

For the exploitation of materials derived from humans for technical applications or novel therapeutic interventions, the following challenges will have to be mastered:

- Identification and validation of the best cell source for specific applications
- Development of methods and tools for deriving, manipulating and using human materials, informed by a deepened understanding of the underlying processes, such as cell growth and differentiation, cell survival and function in artificial environments or in the human body, respectively
- Cell design and engineering for the specific applications, drawing among others on molecular information and theoretical models
- Understanding and control of risks, improvement of quality and safety also with respect to regulatory requirements, but also studies of the presently unknown long-term effects
- early clinical research for therapeutic intervention, in order to establish proof of clinical efficacy and safety
- Scale up and large scale (industrial, automated) production under Good Manufacturing Practice conditions in order to produce large amounts of human material of high, defined and standardised in vivo bioactivity
- infrastructures and logistics for clinical procedures, due to the limited shelf life of the materials.

Research on novel uses of human materials is predominantly funded in FP7 within the thematic area "Health" in the Collaborative research programme ("Cooperation"). In Pillar I, which aims at developing generic tools and medical technologies for human health, one focus is on innovative therapeutic approaches and interventions, namely the advanced therapies cell-based therapies, gene therapies and tissue engineering, which all contribute to regenerative medicine or unprecedented ways of intervening into the human body.

As tissue engineering requires the use of sophisticated materials, there are synergies with corresponding tissue engineering activities within the thematic area "Nanosciences, nanotechnologies, materials & new production technologies (NMP)".

The funding activities focus on gene and cell therapy, regenerative medicine, transplantation, immunotherapy and vaccines. The goal is to design the research projects in a way that they address the interplay between the understanding of underlying processes, tool development and clinical investigation. Research is being funded which develops tools and technologies that are common to regenerative medicine, gene therapy and cell-based immunotherapy, especially identifying and validating the best cell source for specific applications, controlling cell proliferation and differentiation, optimising cell survival and function after transplantation, preventing toxicity or other adverse effects, addressing regulatory requirements and carrying out clinical trials.

For gene therapy, funding is provided for developing tools and technologies, which correct genetic defects, e.g. by genome editing and repair (RNAi, site specific recombination), and mediate gene transfer to patients (new techniques such as novel virus vectors, targeted nanoparticles). Moreover, important topics to be addressed are biological activity, pharmacokinetics and toxicology of the gene therapy vector, as well as the transfer to early clinical research for therapeutic intervention.

The focus in Regenerative Medicine is on the identification of a potential therapy to move into the clinic and to surround this with necessary ancillary research. Specific emphasis is given to three approaches: Cell therapy for tissue and organs, regeneration of tissue using bio-compatible materials and cells, and activation of endogenous cells as an approach to regenerative medicine.

Another focus is on the development of common tools and standards for culturing and banking stem cells (e.g. serum-free media, supporting biomaterials, cell amplification and differentiation techniques, surface markers for recognition, protocols for screening, separation and banking).

All in all, calls in this field tend to address early-stage research within pillar I which aims at the development of novel approaches, techniques and proofs-of-concept. Nevertheless, it should be noted that individual tissue engineering projects involve phase I and even phase II clinical trials (LIFEVALVE, REBORNE).

3.3.3. Conclusion

The analysis showed that major research challenges, both with respect to obtaining information and using bodily materials, are being addressed within FP7, mainly within the thematic area "Health", which is the second largest research area within the FP7 and has a budget of 6 billion euro. Evaluation of the projects currently funded through FP7 revealed that projects related to information and material benefit from approximately 20% of the predicted total budget of the FP7 Cooperation Health Programme. Comparable budgets are designated to small- and medium-scale focused research projects and to large-scale integrating projects.

The majority of the projects deals with fundamental research and has not reached the stage of preclinical trials yet. This focus on basic research may simply reflect the present state of knowledge and technology which does not allow the transition into clinical studies in most cases yet. However, in the years to come, in order to apply the information field's activities relating to the validation of biomarkers and translational research in the clinic, they will have to be expanded considerably if they are to meet the challenges. In the materials field, production issues, infrastructures and logistics for clinical procedures as well as research into long-term function and risks will gain in importance as the field matures.

Overall, the major focus is on the development of generic tools rather than on the treatment of a given disease or condition. However, specific emphasis is given to cancers, cardiovascular diseases, brain-related diseases and diabetes and obesity.

Despite the fact that most projects are still in an early phase of development and revolve around the development of generic tools and technologies rather than the establishment of a specific therapy for a given condition, industrial partners are involved in all projects, suggesting an orientation towards future commercial applications.

The FP7 ethical framework excludes three areas of research from funding: human reproductive cloning, intentional germ line modification (unless related to gonad cancer), and the creation of human embryos for research or stem cell procurement. Moreover, applicants must address the potential ethical issues of their proposals, both in the methodology and the possible implications of their results. Even though it is not evident from the project's descriptions to what extent these requirements are being met, this clearly illustrates that ethical issues are considered an integral part of each project. It cannot be excluded that certain techniques or tools which are being developed within FP7 may serve other functions than to cure in the future. However, the thematic orientation of FP7 at present state clearly focuses on the establishment of a broad spectrum of tools and techniques committed to allowing the development of novel therapies for diseases. We could not identify efforts to stimulate the improvement of the human being per se to make "perfect life".

3.4. Ethical, legal, social, R&D policy impacts

3.4.1. General considerations

BOX 6: General considerations in biomedical research and medicine

One main concern in biomedical research and medicine more broadly, is balancing innovation and public health & safety. Research into these areas has the double purpose of enhancing the performance and competitiveness of the health sector (e.g. by filling the "leaky pharma pipeline") as well as on improving people's quality of life by making innovations in health care provision possible. As a consequence, the challenge for health innovation regulation – mainly on the EU level – is to strike an appropriate balance between rapid market access for innovations on the one hand, and sufficient proof of safety, quality and effectiveness of new options before approval on the other hand. An additional balance must be found, on a national level, between keeping overall health care costs at an acceptable level while making possible the access to adequate treatment for all patients in need of care. This may require national frame conditions which favour applications with proven clinical utility (which goes beyond the criteria assessed in market authorisation) and which might link reimbursement by the public health care system or the statutory health insurance, respectively, to evidence for clinical utility.

Safety, quality, and effectiveness of medicines are a major concern. In order to safeguard the safety of the patients, market access of innovations in molecular and regenerative medicine requires the proof of safety, quality, and effectiveness of the novel interventions. The respective regulatory frameworks for medicinal products and/or medical devices, respectively, are harmonised throughout the EU. Providing the evidence of safety, quality, and effectiveness has been and will continue to be a major issue in public and private research both in molecular as well as regenerative medicine. Recently, a lex specialis for advanced therapies medicinal products (ATMPs) has been put into force within the medicinal products regulatory framework⁵⁹. The implementation process is currently underway. Especially the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) makes intensive effort to define requirements that ensure the quality, efficacy and safety of advanced therapies. An increasing number of advanced therapies are expected to apply for market authorisation at EMA. Therefore, the implementation process for the ATMP regulation should be monitored and assessed in order to identify any needs for amendments in a timely manner.

The focus of this chapter is on developments in the biomedical field and health care. As with all innovations in health care, several social, ethical and legal issues which are characteristic for biomedicine are also relevant to both molecular as well as regenerative medicine. These general concerns are described in the box above, while the next section discusses, in more detail, the issues that are specific for the "biology becoming technology" or "technology becoming biology" theme.

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 $http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm$

3.4.2. Ethical, legal, social, R&D policy issues related to elucidating and using genetic and medical information

Within the "information" track of molecular medicine, major ethical, legal, social and R&D policy impacts arise from the question of how the relevant information is being obtained, what the information means and how it can be interpreted or used. This will be elaborated on in more detail in the following sections.

3.4.2.1. Obtaining information: biobanks

Biomedical research into the molecular basis of normal and pathological biological processes depends, to a large extent, on the willingness of the general population as well as patients to provide bodily materials and health related information. Biobanks are collections of both samples and data; they comprise samples of human bodily substances (e.g. cells, tissue, blood, or DNA) which are linked with personal data and medical information on their donors (OECD 2006). They are therefore an important infrastructure and resource for biomedical research in molecular medicine.

Setting up and running biobanks comprises challenging scientific-technical and research policy issues, such as defining the mission and goals of a given biobank, designing the biobank accordingly, providing it with sufficient statistical power to study also complex diseases, and implementing quality assurance and interoperability with other biobanks and databases.

The international debate in the last decade has shown that biobanks also present several ethical, legal and social challenges which need a framework of consistent rules, especially as present biomedical research increasingly requires cross-border cooperative use of biobanks, and a balance has to be struck between the diverse interests involved: Optimum utilisation of the collected samples and data in medical research is desirable, bearing in mind the main concern: protection of donors and other potentially affected parties. This protection must prevent the uncontrolled use of samples and data; it must prevent donors from assuming unreasonable risks or imprudently divulging personal information and it must protect against genetic discrimination and stigmatisation (Nationaler Ethikrat, 2004b; Deutscher Ethikrat, 2010).

In setting up the rules governing biobanks and their use, the guiding ethical and legal principle is the donor's right of self-determination. This means that the collection of bodily substances and the gathering of personal data for subsequent use in biobanks must be subject to the donor's voluntary, informed consent. However, in the past, information and consent have often been incomplete and not been suitable to strike a balance between the donor's right of self-determination and the freedom of research. Recommendations for which information should be given for obtaining consent have been published (e.g. Nationaler Ethikrat, 2004b). Discussions on, further development of and setting rules for governing biobanks are being done by, for example, the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), funded within the FP7 Capacities FP7 programme (http://www.bbmri.eu; BBMRI GA No. 212111).

Parallel to and largely independent of the establishment of larger population-based biobanks is the introduction of electronic health records in health care, e.g. in the UK. In principle, electronic health records could be another valuable source of information for biomedical research, with substantial synergies when combined with biobanks. However, evaluations of the implementation process of electronic health records show that adoption rates are low due to various reasons and concerns in the stakeholder groups involved (Greenhalgh et al., 2008; Greenhalgh et al., 2010), which would most likely be even more serious if electronic health records were systematically linked with biobanks.

3.4.2.2. Types of information

The information that is gleaned from patients or research subjects can have specific characteristics which have ethical, social and legal impacts, as elaborated below.

Reductionism

When the Human Genome Project was started, scientists were very enthusiastic that this project would deliver a complete understanding of normal and diseased processes within the human body – or even of human nature. Meanwhile it has become obvious that the contribution of genetic information to disease processes is not at all as dominant as had formerly been assumed. Against this background, one has to be aware that research into the molecular – and especially genetic – basis of life processes and disease is inherently reductionistic. This approach bears the risk of seeing disease primarily as a molecular event and of overestimating the influence of genetic factors in disease processes (Eichler et al., 2010; Thomas, 2010a; Witte, 2010). Therefore, the information-oriented genomic research should be complemented by R&D in environmental and lifestyle factors as causes for disease, and R&D in gene-environment interactions (Thomas, 2010b), together with an appropriate allocation of research funding.

Challenge to established genetic counselling, informed consent procedures and privacy concepts

With progress in genome-wide association studies, a vast amount of genetic factors linked to pathological and non-disease traits has become testable and known. In the past, genetic testing was mainly confined to rare monogenic hereditary diseases (i.e. controlled by a single pair of genes), only one or a few defined genes were analysed, and testing was carried out in specialised units with medical staff specifically educated in human genetics. This is changing significantly: technological advances now allow for parallel testing of a large number of genetic traits at unprecedented speed and low costs, with the aim of sequencing an entire human genome at \$1,000 within days (Metzker, 2010). Genetic testing is therefore likely to be extended to highly prevalent complex diseases and carried out by medical staff that is not specifically trained in human genetics, challenging the established genetically counselling practice. Direct-to-consumer testing and "fun genetics" are already being offered to consumers. The sheer volume of conditions being tested in parallel, together with the highly probabilistic data, the low penetrance of genetic traits and the delegation to not specifically trained staff all challenge the way how genetic testing is being dealt with today and which ethical and legal concepts may apply. Today, the principle of the right of self-determination is a usual standard, as well as the idea of genetic exceptionalism, informed consent, the right not to know one's genetic status, and genetic counselling before and after testing. It is unclear if and how these standards will be implemented in the future.

Whole genome sequencing of individual genomes

In the context of whole genome sequencing of individual genomes, it has been pointed out that privacy and confidentiality of personal genetic and medical information can no longer be guaranteed in research settings: precautions against misuse of sensitive information (e.g. anonymisation) as well as informed consent as established in genetic testing are not feasible anymore. Therefore, it has been suggested to abandon the traditional concept of medical confidentiality and to replace it by an open-consent approach (Lunshof et al., 2008) which has been chosen for the US Personal Genome Project (Church, 2005).

Surplus information, incidental findings

Research and diagnostic procedures employed in molecular medicine are likely to yield surplus information (e.g. information about non-disease related traits, about relatives, about behaviour, e.g. in the (automated) monitoring of a health/disease state). This has to be taken into account in informed consent and confidentiality. Moreover, incidental findings of unexpected, potentially pathological anomalies are likely to occur in research. As a consequence, there is a need to establish informed consent and management procedures to deal with this effectively (Hüsing et al., 2006: 76ff).

Knowledge base for selection and enhancement

Probing genetic factors contributing to non-disease related traits, e.g. cognitive abilities, talents, gifts, psychological aberrant behaviour, addiction, physical performance (e.g. sports), sexual orientation, pedigree analysis and ancestry, has become possible. It is conceivable that these options may be used to provide selective access to interventions (e.g. higher education or training), depending on the genetic profile. Should these options be used in prenatal testing or pre-implantation screening after in vitro fertilisation, selection for these traits might be possible. As non-disease-correlated biomarkers are identified with increasing frequency and therefore open up the possibility to also intervene into non-disease traits, guidance for their use should be developed.

Predictive information

Molecular medicine will reveal predictive information on health risks for individuals which is, however, highly probabilistic and may be of limited clinical value. Nevertheless, if the scientific and technological advances in molecular medicine are used for risk specification and presymptomatic diagnosis, this may lead to a new understanding of what is normal, healthy or ill, and where to draw the line between health and disease (see also Boenink, 2009): if presymptomatic conditions are seen as treatable, this could lead to medicalisation of larger patient groups, with yet unknown impacts on health care costs and health outcomes. Moreover, the concept of health is gradually changing from passive to active: disease is no longer governed by fate; it is rather the absence of health, and health is "not simply there", but it is understood as a permanently challenged condition that must be actively maintained and strived for. If, as a consequence, health is seen as the product of constant effort in self-management and a healthy lifestyle, then disease is no longer one's fate; it is rather a lack of will and self-management, thus putting the blame on ill persons (ABFTA, 2009). This could lead to (perceived or factual) social and/or financial pressure on individuals to take (more) responsibility for their own health in terms of behaviour or higher health insurance premiums.

Prevention concepts

Together with a reductionism gene-centred view which neglects the complex interactions of genes and environment, there is a tendency to put the task of prevention into the discretion of the individual (behaviour-oriented prevention). On the one hand, this raises the question how larger parts of the population can be empowered to engage in effective preventive behaviour. On the other hand, it bears a risk of neglecting structural preventive approaches which may be more effective.

Validity of information

In order to translate the enormously expanded knowledge in basic biology into improved diagnostic and therapeutic options, the major R&D challenge that will have to be mastered in the coming years is to put meaning into the information gleaned; to be able to interpret the huge amount of data in a clinically useful way; to use only "meaningful" information and to deliver innovative diagnostic and therapeutic products from this knowledge base.

As high-throughput technologies churn out a vast amount of new biomarkers, it will be most important to separate the wheat from the chaff, i.e. to identify and validate those biomarkers which have the potential to improve health care because their clinical usefulness can be established. The policy challenge is to shape frame conditions in a way that the very time- and resource intensive process of biomarker validation becomes possible; that promising biomarkers can be taken from bench to bedside through translational research. Moreover, the danger exists that insufficiently validated biomarkers are being brought into the clinic or to consumers by direct-to-consumer marketing, with negative impacts in terms of disease prevention and treatment, psychological stress for patients, and misallocation of resources on the patient and health care system level. Policy measures are required to prevent premature use and misuse of information.

3.4.3. Ethical, legal, social, R&D policy impacts of using material derived from humans for medical technology - Efficacy, safety and quality

The focus of research, legislative and administrative activities is on establishing the safety, quality and effectiveness of novel treatments which use bodily materials; the regulatory framework is in the process of being implemented.

Moral status

The use of bodily materials for technology requires reflections and deliberations on the ethical and legal status of bodily material and what this means in practice for the use of this material. Human dignity does not allow for treating material of human origin as objects and for using them deliberately. Rather, depending on the moral status assigned to this material in the respective context, graded approaches are required. Extensive discussions in the past have led to guiding ethical principles which govern the use of dead bodies, brain-dead bodies and non-heart-beating bodies for the explantation of organs and tissues for transplantation and tissue engineering. Also regulations are in place, albeit to varying degrees, on the use of gametes in reproductive medicine, on the moral status of human in vitro embryos created in the context of reproductive medicine, research, human reproductive cloning and for deriving human embryonic stem cells. The destruction of human embryos in the process of deriving human embryonic stem cells from the inner cell mass of blastocysts (Thomson et al., 1998) has led to a very controversial discussion on which ethical criteria should be applied in order to assess the derivation of human embryonic stem cell lines and their use for therapeutic purposes, and on which legal instruments should apply (see also Prainsack et al., 2008; Geesink et al., 2008). The EU's 27 Member States take different regulatory positions on human embryonic stem cell research, reflecting the diversity of ethical, philosophical and religious beliefs throughout Europe. Consequently, in Europe hESC research is regulated according to the principle of subsidiarity according to which national regulation takes precedence over EU regulation (see also Faulkner et al., 2008). However, there is consensus that the following issues shall apply to all aspects of hESC research: informed consent, transparency/traceability and no reproductive intent. The FP7 ethical framework excludes the creation of human embryos for research or stem cell procurement as well as human reproductive cloning from research funding (EGE, 2008).

It is likely that in future, deliberations on the moral status of human embryos, created from artificial gametes (Pearson, 2008), will be required. Relevant questions with respect to informed consent have already been listed in the context of biobanks (chapter 3.4.2.1); moreover, the question whether obligatory informed consent (narrow, by the donor himself, or broader, also by relatives) or presumed consent with explicit objection should be chosen, is to be discussed. In general, there is a need for frame conditions which do not exploit people as sources of cells, tissues, or organs.

Integrity and identity

From organ transplantation, it is well-known that in addition to the performance of the transplant, the mental state and psychological reaction of the recipient must also be taken into account: the introduction of foreign material into a body does not only affect the bodily integrity but may also have an impact on the identity of that person.

Bodily materials as goods

One major impact of biology becoming technology is that bodily materials and products and services derived from them are goods. This relates to the subject of intellectual property rights and the extent to which "patenting life" is possible. Moreover, the "goods character" may challenge the principle of respect for human dignity and integrity, which asserts the principle of non-commercialisation of the human body. With respect to organ and tissue donation, a conflict arises between altruistic donation and the commercialisation of the resulting products. This does not only lead to competition between different tissue organisations for donors (e.g. public sector tissue banks, private commercial tissue banks, tissue engineering companies), but may also have a negative impact on the willingness of the general population to donate bodily materials. This commercialisation, as well as the scarcity of donated organs and tissues in relation to demand, have led to deliberations whether to abandon the concept of altruistic donation and replace it by models of donor compensation. Organ, tissue and embryo trade as well as cross-border traffic of patients and bodily materials and the exploitation of the desperate situation of poor people, are also a result of commercialisation and scarcity.

In cord blood banking, there is a competition between cord blood banks which collect cord blood samples for allogeneic use and rely on altruistic donation, and private cord blood companies which offer the storage of cord blood samples to individuals for later autologous use. As a consequence, a conflict has arisen between altruistic donation and selfish use (EGE, 2004; Virt, 2010), which may also reflect a tendency in health care systems of eroding solidarity.

Beginning and end of life

Biology becoming technology in the context of regenerative medicine also has a major impact on the attitude towards the beginning and end of life. The beginning of life and the concept of parenthood and family is challenged by the deliberate creation and use of human embryos in vitro for research purposes and the derivation of embryonic stem cells and by using "artificial gametes", differentiated from embryonic stem cells.

The wide availability of tissue replacements could support a spare parts and repair mentality instead of a mindful treatment of one's body. Moreover, regenerative medicine, especially when looked at in the context of lifestyle medicine and anti-ageing interventions, is closely linked to visions of eternal life which are also propagated by transhumanists. The use of artificial gametes derived from embryonic stem cell lines could drastically expand reproductive ability beyond the natural reproductive life span, with major consequences for the concept of offspring, family and parenthood.

3.5. Conclusions

This chapter focused on engineering of the body in the biomedical field. Many developments in recent years could be observed which support the notion that biology is becoming technology and technology is becoming biology, also with respect to the human body. These developments were explored along the lines of "information" on how the body functions (its genetic "blueprint") and an increasing ability to use and engineer materials derived from the human body for technical and engineering purposes.

All in all, we witness vastly expanded and still expanding possibilities for obtaining detailed information on the molecular level of the present state of a human body, be it in health or disease. This detailed information is used to build theoretical models of human body functions, which can then serve as starting points for improving interventions, such as improved ways to diagnose, treat and manage disease.

In parallel, and also in synergistic interplay with the "information activities", new tools are being developed such as gene therapy, cell therapy and tissue engineering which could allow a completely new quality of intervention into the human body, thus allowing for "engineering" or "moulding" that goes far beyond the established treatment options. A specific characteristic of these interventions is that they rely on the use of bodily materials (e.g. genes, cells), which are engineered to tools or technologies for altering the human body. These modifications comprise the alteration of the genetic makeup, establishing new ways of human reproduction independent of biological parents or reproductive phases, and a paradigm shift from repair medicine to regenerative medicine. However, these options are far from being realised in the short or medium term.

Significant scientific-technical hurdles are still to be overcome, and present research activities in the EU 7th framework programme address most of these challenges by focussing on the identification of new information about the human body on the molecular level, and by exploring advanced therapies from basic tools to early stages of clinical trials. However, in the years to come, in order to apply the information field's activities relating to the validation of biomarkers and translational research in the clinic, they will have to be expanded considerably if they are to meet the challenges. In the materials field, production issues, infrastructures and logistics for clinical procedures as well as research into long-term function and risks will gain in importance as the field matures. The thematic orientation of FP7 at present clearly focuses on the establishment of a broad spectrum of tools and techniques committed to allow the development of novel therapies for diseases. We could not identify efforts focused primarily on the improvement of human beings.

Challenges with respect to ethical, legal, social and political issues arise in the information track mainly from the type of information that is or could be gleaned. Here, established concepts and procedures of informed consent in research and medicine, genetic counselling, as well as the privacy of patients and research subjects are being challenged, and need to be developed further for the specific contexts and applications within molecular medicine. From a social perspective, especially predictive information about health risks bears the potential to alter our understanding of (still) being healthy or (already) being ill, with major implications for health education and the competence of citizens, for the delivery of health care, and for prevention concepts.

While bodily materials of human origin have been used for decades, a severe drawback is the limited supply of these bodily materials and the sources from which they are derived. This evoked and still evokes ethical controversies and legal questions (e.g. the brain death concept in the context of organ donation, the legal status of dead bodies and tissues derived from them, the use of aborted human foetuses as the cell source for cell therapies for Parkinson's disease, and the moral status of human in vitros and the legitimacy of deriving human embryonic stem cells from them).

One major impact of biology becoming technology is that bodily materials and products and services derived from them become goods. This relates to the subject of intellectual property rights and the extent to which "patenting life" is possible. Moreover, the "goods character" evokes conflicts between, on the one hand, the principle of non-commercialisation of the human body, grounded in human dignity, and altruistic donation versus donor compensation; and cell, tissue and organ trade on the other hand. Another conflict arises between altruistic donation and selfish use of bodily materials which may also reflect a tendency in health care systems of eroding solidarity.

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4. ENGINEERING OF THE BRAIN

Ira van Keulen & Mirjam Schuijff

4.1. Introduction

The brain is one of the most complex systems known to mankind. Since the late nineteenth century, neuroscientists have been striving for a 'cognitive revolution': a scientific description of the brain and the mind. So far, neuroscience has been largely an *experimental* and a *technology-driven* science. Every new (research) technology has pushed forward the field with a large step. For example, in the nineteenth century, neuroscience made progress because of the invention of better microscopes and a staining procedure to reveal the intricate structures of single neurons. Later on, patch clamp technology made studying single, living brain cells possible. More recently, neuroscientists started using modern neuroimaging techniques like functional Magnetic Resonance Imaging (fMRI) and magnetoencephalography (MER) to study the mechanisms of the living brains of animals and humans. The inventions that allowed this non-invasive imaging of activity in the functioning brain finally opened up the possibility of coupling higher functions in the brain with activity in the underlying neural substrate.

All these different technologies explain the brain in a reductionist way, describing the brain in all of its physical details on different levels: molecules, cells like neurons and glial cells, neuronal networks, brain regions, etc. (Potter, 2007). This resulted in tremendous knowledge on the anatomy of the brain, on the way individual neurons process information and communicate with each other, on how the major sensory input systems collect and represent information and on how output systems (such as muscles, glands, etc.) are addressed. We also know which brain areas are active when we hear somebody talk, enjoy a piece of chocolate or feel nauseous. And we are unravelling more complex cognitive processes like learning and decision making. But reductionism has not helped in understanding how different neural mechanisms should be fitted together to generate function: *"Describing the brain as a zoo of lower level components and mechanisms (ion channels, synaptic function, neurotransmitter release, membrane properties and so on) does not guarantee an understanding of the system's behaviour or interrelationships between these components and the phenomenal world" (Pearce et al., 2005).*

So, as a consequence of neuroscience still being mainly a technology-driven and experimental science, the field is data-rich but still theory-poor (Rose, 2009). The reductionist vision of neuroscience has resulted in an enormous and important wealth of data at every level of the brain. In a review in Science, the well-known theoretical neurobiologist Karl Friston from the Wellcome Trust Centre for Neuroimaging emphasises the importance of a more theoretical approach within neuroscience. He argues that there is a need for better models in order to make more sense of neuroscientific data, and in the end to understand the brain better:

"In summary, the most promising avenues for the future may rest on developing better models of our data that complement and exploit the richness of these data. These models may well already exist in other disciplines (such as machine learning, machine vision, computational neuroscience, and behavioral economics) and may enable the broader neurosciences to access neuroimaging so that key questions can be addressed in a theoretically grounded fashion." (Friston, 2009: 403)

In the end, the ultimate goal for most neuroscientists is an overarching theory of the brain: understanding how the physical processes in our neurons turn into certain behaviours and a perception of the outside. The key to progress in understanding the brain will be a parallel development of new concepts on how to integrate the knowledge coming from all the disciplines involved in the neurosciences, from the molecular level to cell and system levels. So far there has been a lack of concepts on how to analyse such a huge complex system as the brain (Wadman, 2008).⁶⁰

4.1.1. The engineering approach

"Next to measuring nature, and making theories, there is also a third way to better understand the brain: building a system like the brain synthetically on computers", as one of our interviewees⁶¹ pointed out. Indeed, a genuine engineering approach for arriving at a grand theory of the brain seems to be emerging (see box 7). In the first editorial of the recently established Journal of Neural Engineering (2005), eight European neuroscientists make a case for neuroengineering as "the new renaissance in neuroscience". The editorial explains why neuroengineering is needed to meet the challenge of synthesising and interpreting the steadily growing data on the brain into one overarching brain theory: "Neuroengineering embodies a pragmatic, engineering methodology to understanding, representing, manipulating and augmenting the nervous system. It advocates understanding the brain through building physical implementations, sparing prejudgment on the conceptual basis or substrate of that implementation." The authors state that a neuroengineer explicitly asks himself the question: "Do we understand the brain sufficiently well to build and manipulate it?"

While our interviewee calls the engineering approach a "third way", Kevin Kelly – executive director of *Wired* – takes it further and describes engineering as something grounded in and part of "*the third culture*".⁶² The third culture is a new community of intellectuals who are not traditional scientists (first culture) or artists (second culture). According to Kelly, this community honours the scientific method while its goal is not seeking truth but novelty. In his article Kelly illustrates the third culture attitude in relation to the neurosciences as follows: *"In the third culture, the way to settle the question of how the mind works is to build a working mind".* This reflects more or less the same style of thought as the European neuroengineers demonstrated in the first editorial of the Journal of Neural Engineering. Furthermore, Kelly argues that third culture scientists prefer the engineering perspective since it leads to new findings much more rapidly in comparison to the theoretical approach: "*Creating new tools is faster than creating new theories, because tools lead to novel discoveries faster than theories do."*

Both statements of Kelly – understanding the mind through building one and creating tools not theories in order to gain understanding – actually stand for two approaches which can be discerned within the field of neural engineering: reverse engineering of the brain and forward engineering of the brain. We define the *reverse engineering* modus (see section 4.2) as the analysis of an existing system (i.e. the brain) in order to uncover its design principles by creating representations of the system in another form.

⁶⁰ Systems biology is, for example, such a discipline that systematically studies complex biological interactions.

⁶¹ We would like to thank our interviewees: Pim Haselager (Radboud University Nijmegen), Maartje Schermer (Erasmus Medisch Centrum), Wim Rutten (University of Twente), Kay Vogeley (Centrum für Neurologie und Psychiatrie Köln), Alexander Sack (University of Maastricht) and Karlheinz Meier (University of Heidelberg).

⁶² www.edge.org/3rd_culture/kelly/

The American National Academy of Engineering (NAE) – which recently proclaimed reverse engineering of the brain to be one of the fourteen grand challenges for engineering⁶³ – defines it as *"sophisticated computer simulations of the brain"*. We define *forward engineering* (see section 4.3) as the experimental testing of the newly discovered principles and mechanisms concerning the brain with physical implementations in the real world (i.e. the "new tools" Kelly is referring to). An important way of testing is through hybrid systems. With hybrid systems we refer systems that interface the brain with an artificial (mostly electronic) device that can manipulate or augment the brain – or the nervous system in general – including its sensory systems.

These two engineering approaches to the scientific endeavour of understanding the complexity of the brain and the mind are examples of the two mega engineering trends central to this report. Reverse engineering the brain, for example, is for the most part illustrative of technology becoming biology because this approach aims to mimic biology, in particular the brain, in both computer hardware and software. Main drivers behind this engineering approach have been Moore's law – the growing processing power of computers – and the progress in the nanotechnology (e.g. neuroimaging at nanoscale or nanoparticles functioning as neurons) and neurosciences (e.g. the discovery of spike based communication of neurons). Forward engineering the brain, however, is about biology becoming technology. The same combined progress in information technology (e.g. fast signal processing techniques), nanotechnology (e.g. smaller and better electrodes and sensors) and the neurosciences (especially in fundamental neurophysiological research) have enabled rapid development in engineering systems connecting the brain with electronic devices. What used to be science fiction is now scientific reality: the direct interfacing of the brain and/or the central nervous system with computers.⁶⁴

This chapter will elaborate on both neuroengineering approaches and reverse and forward engineering. Both can be subdivided into different approaches. When it comes to reverse engineering (section 4.2), we will pay attention to three different modelling approaches used in different research projects in the world, both large scale and smaller scale brain simulating projects.

- *Narrow reverse engineering*. This software approach is focused on rebuilding the brain and taking real life data as a starting point for developing virtual representations of (parts of) the brain (i.e. Blue Brain project, Connectome project).
- *Neuromorphic engineering*. This hardware approach is aimed at building better artificial intelligence or supercomputers through neuromimicry (i.e. SyNAPSE project, FACETS project, Brain in Silicon project and NOMFET project).
- *In vitro engineering*. This wetware approach is focused on studying the brain by using real life neurons in in vitro models like cultured neuronal networks.

⁶³ www.engineeringchallenges.org

⁶⁴ An important breakthrough in the field of forward engineering had to do with the capacities of the mammalian brain itself, however. Its high level of plasticity allows the adaption of its signals to communication over a limited number of channels (i.e. electrodes).

Box 7: Facts and figures on neuroengineering

Journals

Recently there has been an increase in newly published scientific journals in the area of neuroengineering.

- The Journal of Neural Engineering (first published in 2004)
- Journal of NeuroEngineering and Rehabilitation (JNER) (first published in 2004)
- Frontiers in Neuroengineering (first published in 2008).
- Neuromodulation (first published in 2009).
- Brain stimulation (first published in 2010).

Clinical trials

Another way to get an indication of the progress being made in – at least – forward engineering is by looking at the amount of starting, running or completing clinical trials within the forward engineering approach:

- Transcranial magnetic stimulation (TMS): 278 clinical trials
- Deep brain stimulation (DBS): 111 clinical trials
- Neurofeedback/biofeedback: 104 clinical trials
- Neurostimulation: 44 clinical trials
- Electroconvulsive therapy: 39 clinical trials
- Vagus nerve stimulation: 19 clinical trials

In comparison to the amount of clinical trials on psychotropic drugs, the amount of clinical trials in the field of neural engineering is still modest. Take for example antipsychotic agents (1424), antidepressive agents (1456) or tranquilising agents (2006) (source: <u>http://clinicaltrials.gov</u> mentioning mostly trials in the United States).

Economics

There are some economic reports on the market of 'neurotechnologies' as well. Some reports (e.g. from NeuroInsight) include psychopharmacology and others don't (e.g. Neurotech Reports). Neurotech Reports define neurotechnology as the "application of electronics and engineering to the human nervous system".65 The most important applications so far have been neural prostheses such as cochlear implants (annual sales at \$725 million in 2008, growing to 1.59 billion in 2012) and neurostimulators for the treatment of chronic pain. According to Neurotech Reports, the worldwide market for neurotechnology product are about \$3.6 billion in 2008 and will reach \$8.8 billion in 2012. The growing rate is supposed to be 20 to 30 percent in the next decade, far outpacing the market for cardiac devices. This growth is largely due to the continued growth and diagnosis of neurological and psychiatric disorders and conditions, amongst others because of demographic shifts in the aging of the population. According to the World Health Organisation (WHO), neurodegenerative disorders will become the world's leading cause of death by the year 2040, overtaking death caused by cancer and HIV/AIDS. Neurotech Reports predicts that the largest opportunity for growth in the market for therapeutic electrical stimulation products is at the rehabilitation of stroke patients. However, earnings for neurotechnologies are so far only 4% of the neuromedical market including psychopharmacology (NeuroInsight, 2008). Some of the largest companies in the neurotechnology field are: Medtronics, Cyberonics, Boston Scientific (neuromodulation), Cochlear, Advanced Bionics and Med-El (neural prostheses).

⁶⁵ www.neurotechreports.com

In the case of forward engineering (section 4.3), there are two approaches that use different technologies and have different goals. Both approaches can be done invasively as well as non-invasively.

- Neuromodulation. The goal of this method is to assist the brain (and/or mind) in functioning normally (again), or to augment the brain (and/or mind). Invasive technologies we will elaborate upon are electroconvulsive therapy, vagal nerve stimulation or deep brain stimulation (DBS). Non-invasive technologies are neurofeedback and transcranial magnetic stimulation (TMS).
- *Brain-computer interfaces (BCIs).* All efforts within this method are aimed at *restoring* brain or mental functions lost as a result of disease or trauma, or *introducing* new brain or mental functions. BCIs can both be done non-invasively (e.g. based on EEG) or invasively where electrodes to measure brain activity are put inside the brain.

In this chapter, psychofarmaceuticals are not considered as a way of forward engineering the brain. Neural engineering is like any other biomedical engineering field focused on solving design problems at the interface of living neural tissue and non-living constructs, therefore it excludes psychopharmacological drugs. This interpretation is underlined by the fact that all the neural engineering journals (see box 7) only incidentally publish articles on psychofarmaceutical research.

4.1.2. How to read this chapter

In this chapter, we want to explore to what extent an engineering approach within the neurosciences is indeed arising. Furthermore, we want to analyse whether within brain sciences we do witness that "technology is becoming biology" or "biology is becoming technology", or perhaps both. To what extent is biology being brought into the domain of technology and engineering through defining the brain in technological terms? In what sense can we say that neural engineering affects or even transforms the relation between biology and technology? What does it mean for our understanding of the human brain, the mind, consciousness and progress in the field of *artificial* intelligence?

We will try to answer the above questions by first going into the state of the art in research as well as already existing (clinical) practices in both reverse (4.2) and forward engineering (4.3). Obviously, there is much more to say on existing practices within forward engineering – talking about clinical applications – than in reverse engineering where artificial intelligence applications are still far off. We do not strive to be exhaustive in our descriptions of different neural engineering research projects and practices. We continue (section 4.4) with a description and discussion of the trends within EU sponsored neural engineering projects (within FP6 and FP7). What projects were carried out in the recent past and are currently conducted in Europe? To what extend is the engineering approach important within European sponsored research? And finally, we will focus on the ethical, legal and social aspects of neural engineering including possible impacts on existing European policy or the need for new European policy (section 4.5). The chapter ends with a discussion on the two engineering trends and on possible policy consequences.



Figure 3: Different neural engineering approaches

4.2. Reverse engineering of the brain

There are different levels of reverse engineering the brain. It all depends on what one thinks are crucial brain functions for different cognitive abilities. Different researchers therefore take different approaches to reverse engineering of the brain. For example, the Blue Brain project is focused on neurons as a basic unit and lacks the molecular level. The SyNAPSE project is focused on the neural network and misses the cellular level. Scientists working at creating a 'connectome' (i.e. a wiring diagram of the brain) concentrate on the wiring between the neurons. However, all three projects are attempts at large-scale modelling of the brain in order to figure out what makes a (mammalian) brain work the way it does, just like neuromorphic and in vitro models of the brain. In the end all three approaches are needed to come to a full understanding of the brain, as one of our interviewees said (for example, see the new FP7 project Brainscales which combines a software and hardware approach).

4.2.1. Narrow reverse engineering: rebuilding the brain Blue Brain project

Inspired by the Blue Gene project which helped out genetics through studying the molecular functioning of genes, the Blue Brain project was started in 2005 by IBM together with *Ecole Polytechnique Federale de Lausanne* (EPFL) in Switzerland. The main purpose is to build a physiological simulation of the mammalian brain. The first phase focused on reconstructing a single neocortical column, an elementary unit of the neocortex⁶⁶, at the cellular level.

⁶⁶ The neocortex is the outer layer of the brain and makes up of 90% of the cerebral cortex. It is involved in higher brain functions like language, sensory perception, conscious thought, etc.

To achieve this, an IBM supercomputer was used, consisting of 2000 programmed microchips, each of which acts like a real single neuron. The programming is based on existing ion channelling data: the basis of the way real neurons electronically communicate with each other. These data are derived from a robot that makes multiple recordings from different genetically engineered hamster cells under different physiological conditions.

Like genetics used information technology (IT) in the 1980s and '90s to study and model the human genome, neuroscience is employing IT as a tool for making sense of all the brain data. This first phase has been successful. The behaviour of the computer replicates with precision the cellular events in a neocortical column. The researchers are now planning to use more powerful computers to link such simulated columns together to form something that mimics a brain. The Blue Brain project has delivered the first bottom-up model of the brain grounded in empirical data, or in the words of chief scientist Henry Markram,

"there are lots of (functional) models out there, but this is the only one that is totally biologically accurate. We began with the most basic facts about the brain and just worked from there. The best way to figure out how something works is to try to build it from scratch" (Seed Magazine, 2008)⁶⁷.

The Blue Brain scientists explicitly state on their website that their project is *not* an artificial intelligence project: they are not trying to create a specific form of intelligence. The project is primarily designed to *understand* the brain and brain disorders. At the same time, they think it may well be possible that the project may be the first to deliver a true 'artificial intelligence' through this process of reverse engineering. Markram already has future plans to download the simulation of a complete rat brain into a robotic rat so that the brain has a body. *"The only way to really know what the model is capable of is to give it legs. If the robotic rat just bumps into walls, then we've got a problem"* (Markram, 2008).

The Blue Brain project is quite a prestigious project; some are even comparing the project to the Human Genome Project, but there is also some criticism. Some of the interviewees stated that the project depends too much on high performance traditional computers for their *numerical* simulations. They predict that, in the end, the conventional Blue Brain computers will not have enough power to simulate the complexity of a whole mammalian brain in all its details. Even Moore's law will not deliver the 500 petabytes of processing power Markram needs within ten years. Another criticism is that the researchers themselves are to judge whether the simulated neuronal column is actually working. But how do they know? They are building a fully detailed simulation without having any theory on how the brain works in principle. So the simulation might merely confirm the expectations the researchers already had.

Connectomics

Other approaches to reverse engineering the brain by using real life data are taken by projects trying to map a connectome: a complete circuit diagram of the brain. In comparison to the Blue Brain project, researchers are not imitating the cortex; they are trying to replicate parts of the brain⁶⁸. At Janelia's farm, chief scientist David Adler is working on a full-scale, three-dimensional wiring diagram of a fruit fly's brain. A machine shaves 50-nanometer slices off the top of a fruit fly's brain.

⁶⁷ http://seedmagazine.com/content/article/out_of_the_blue/

⁶⁸ There is a lot of competition between projects at three different universities in the emerging field of 'connectomics': the Howard Hughes Medical Institute in West Virginia (also called the Janelia farm), the Max Planck Institute for Medical Research in Heidelberg and Germany and Harvard's Center for Brain Science.

Then a scanning electron microscope (SEM) takes images of the brain slices at nanoscale⁶⁹, and these images are pieced back together by scientists to generate a 3-D virtual wiring diagram (Adee, 2008). Adler compares it to *"putting together a real-time traffic map of North America from high resolution satellite photos"*. He is hoping progress in machine learning or object recognition will help in automating the process of discriminating neurons, from synapses from axons, etc. The project is a combination of neuroimaging and histology. The storage requirements are huge. Hundreds of fruit fly brains have to be compared and the brain scan of one of them already racks up 1000 terabytes. Adler and other scientists working in the high speed brain imaging area count on Moore's law to aid them in their ultimate goal to produce such detailed brain images like Google's satellite views. There are also other obstacles, for example, extracting individual strands of neurons. Scientists at the Harvard's Center for Brain Science are using fluorescent proteins – providing 90 colours – for genetically engineering mice to track individual neurons and their connections to other neurons and muscles, etc. (Lichtman et al., 2009).

While these connectomics projects will help to make snapshots in time of the wiring of the brain, according to one of the interviewees it is merely a list of neuronal connections. According to some interviewees the field of connectomics does not teach us anything about the dynamics behind neuronal connections; the circuit diagrams are static and do not show how the connections change over time through learning processes driven by the outside world. In the end, the diagrams do not show any intelligence (and thus will not help to build novel intelligent systems).

4.2.2. Neuromorphic engineering: building supercomputers

The Blue Brain project and the field of connectomics aim to model the brain virtually, based on data on the communication of neurons in a real mammalian or insect's brain. Other reverse engineering projects are less interested in making 'software' – *numerical* simulating parts of the brain – but rather in actually building a brain-like hardware system: a *physical* simulation. They are focused on building chips and systems that mimic the neuron and synaptic structures of the brain or *certain* features of the brain like parallel processing or even neural plasticity. This field is also referred to as neuromorphic engineering; a field which started in the late eighties with work by Carver Mead who developed the first – fully analogue – silicon retina.

The aim of neuromorphic engineering is to combine the advantages of a computer (i.e. flexibility and programmability) with the advantages of the brain like low-power usage, fault tolerance (e.g. if you lose a couple of neurons it still works) and the ability to learn and adapt into a new computer architecture which is quite different from conventional Neumann computers. In other words, the researchers working in the neuromorphic engineering field are looking for a new computing paradigm. However, according to the European roadmap Neuro-IT (Knoll & De Kamps, 2006) written by the scientific field itself, a new neuro-inspired computing paradigm will still take long: *"In the short term, it is unlikely that such architecture will outperform conventional solutions, except maybe on the sensory periphery. But they could be the first step towards new high performance computing strategies and provide new insights into the working of the brain."* Internationally there are four neuromorphic projects which we briefly discuss here.

⁶⁹ FMRI is not useful here: the finest resolution of fMRI is approximately 1 cubic millimetre per voxel, which can already contain 300 million synapses.

SyNAPSE project

Towards the end of 2008, the Defense Advanced Research Projects Agency (DARPA) financed a research programme called Systems of Neuromorphic Adaptive Plastic Scalable Electronics (SyNAPSE) with 4.9 million dollars. IBM and Hewlett Packard and universities like Columbia, Cornell and Stanford are involved. The project is focused on both the software part – like the Blue Brain project – as well as on the hardware part. The difference with the Blue Brain project is that they are less particular about simulating a brain in all of its biological details. So far they have been able to build a 'cat scale simulation' of the brain consisting of 'point neurons' – a very basic mathematical representation of a neuron neglecting dendritic morphology. Basically it is a large scale simulation environment which can handle 147,000 processors or 144 terabytes of memory. According to chief scientist Modha, "despite being incomplete, the simulation is enough to offer insights into the brain's high level computational principles" (Ganapati, 2009). Besides the software, the SyNAPSE project also works on using nano-materials to build hardware like logic gates and transistors equivalent to neurons and synapses. This approach is similar to that of FACETS.

FACETS project

In Germany there is an EU funded project called FACETS: Fast Analog Computing with Emergent Transient States.⁷⁰ The researchers have created a silicon system designed to function like a human brain, "through recreating the neurons and synapses as circuits of transistors and capacitors, designed to produce the same sort of electrical activity as their *biological counterparts"* (Graham, 2009). So far they have developed a configurable neuron system existing of 200,000 neurons and 150 million synapses. The user can configurate it with special software called PyNN (i.e. a sort of Windows for a neurocomputing system). This programming interface improves the usability of the neuromorphic hardware for theoretical or computational neuroscientists. In their large scale system, the cell-based calculations are done using analogue models and communication across medium and long distances are made using digital (spike-time) coding. The most interesting part of such a system is that it is able to operate truly parallel like the brain does, instead of serial like conventional computers do. The current prototype can even operate (and learn) 10,000 times faster than the real human brain. Researchers claim that the system is able to mimic the brain's ability to learn much better than any other artificial cognitive system. Still, a disadvantage is that the system is hard to connect to external devices like laptops, etc. So far it is been used by different neuroscience research groups in Europe and the US in order to understand the information processing of the brains of different animals, including insects.

Brain in Silicon project

Researchers at Stanford University⁷¹ run a similar project like FACETS. They have also created a neuromorphic chip, claiming it to be far more efficient than software simulations of the brain. By using circuits with eight transistors, the researchers are emulating the characteristics of a neuron. They are in particular mimicking the ion-flow across a neuron's membrane with an electron-flow through a transistor's channel where the same physical forces are at work. The Stanford chip can simulate neural plasticity as well; it possesses an ability to form new connections. The Stanford researchers have put sixteen of these chips in an iPod sized device called Neurogrid that works as a parallel silicon neuron whose behaviour and connectivity are programmable.

⁷⁰ http://facets.kip.uni-heidelberg.de/

⁷¹ www.stanford.edu/group/brainsinsilicon/

It is just as fast as the 2048-processor Blue Gene rack – Neurogrid will simulate a million neurons in real-time – but it consumes a million time less energy and cost \$40,000, in contrast to the 2 million dollars that the Blue Gene computer of IBM costs.

NOMFET

In the French project NOMFET (Nanoparticle Organic Memory Field-Effect Transistor) at the Institute of Electronics, microelectronics and nanotechnology researchers are using nanotechnology to imitate a synapse.⁷² They have built an organic transistor that is able to chemically conduct an electrical pulse with golden nanoparticles (Alibart et al., 2009a. Alibart et al., 2009b). Before, traditional silicon chips have been designed to emulate brain behaviours, but this approach is limited because it takes at least seven silicon transistors (see Stanford's Neurogrid) to build an electronic synapse. Within the NOMFET or nanotechnological hardware approach in general, one needs only a single device. Because the NOMFET imitates facilitating as well as depressing synaptic behaviour, it exhibits short term plasticity. This property makes the electronic component capable of evolving as a function of the system in which it is placed. This way NOMFET opens the way to new generations of neuro-inspired computers, capable of responding in a manner similar to the nervous system. And, in general, the neuro-inspired nanochip can be made low-cost and they can work on flexible, plastic substrates.

All four projects have quite similar aims. The most important application of neuromorphic systems at the short term is within neuroscience itself. Or as stated on the Brains in Silicon website, "we are bridging the experiment-computation gap⁷³ by building an affordable supercomputer that works like the brain – one that can serve as a tool to investigate brain function – feeding back and contributing to a fundamental, biological understanding of how the brain works." In the long term, the compact, low-power neuromorphic intelligent systems could be used anywhere. "A brain on portable power", that is the ultimate aim of the Stanford group which recently teamed up with the SyNAPSE project. "Technology that emulates brain functions such as perception, sensation and emotion while using hardware and software of equivalent speed, efficiency, coherency and overall compactness" (Stanford, 2009).

4.2.3. In vitro engineering: cultured neuronal networks

Another engineering approach that captures the mechanisms underlying the brain is the wetware approach: in vitro, cultured or living neuronal networks. This approach can be considered reverse engineering as well, since it uses cell cultures of 'real life' neurons as a representation of the brain in order to reach two goals: to understand the information processing within (cultured) neuronal networks and to uncover the underlying principles behind neuronal learning, memory, plasticity and connectivity (Cohen et al., 2008). As one of our interviewees stated, *"it is a bottom-up approach to unravel neural codes and ultimately understand the brain"*.

The cell cultures usually consist of a couple of 100,000 neurons which are grown upon and thus connected to an input or output device such as a multi-electrode array (MEA), allowing two way communication between the researcher and the network (Fromherz, 2003). The spatial resolution of the microelectrode arrays is usually poor: about 500,000 neurons with a density of 2,000 neurons per mm² are placed on an array with 60 electrodes, and only the neurons on the electrode are monitored.

⁷² Within the EU funded project NABAB (Nanocomputing Building blocks with Acquired Behaviour), see www.nabab-ict.org.

⁷³ By this they mean the problem of not having enough computing power to analyse the existing experimental data on all levels of the brain at the same time.

In the near future researchers hope to be using chips – developed by ETH in Zurich – with 10,000 electrodes which will be able to monitor several times more neurons per mm². These chips have coatings with built-in carbon nanotubes that help to positively influence the adhesion between the electrodes and the neurons. The neurons are usually cultured, disassociated neurons from new-born rats which are widely available. Depending on the network (dense or sparse, large or small, etc.) neurons in culture produce spontaneous – and sometimes synchronised – activity just like in vivo neurons.

Besides resulting in fundamental knowledge about neurons and their networks, cultured neuronal networks can also be used in more mundane applications. For example, the in vitro neuronal networks can become a highly sensitive bio-sensing system for drug-screening applications. These systems show a good sensitivity to neuroactive-toxic compounds and reproducible results (Martinoia et al., 2005). The advantages are that they are non-invasive and permit the recording of neural activity for a longer period of time (i.e. hours up to months). They allow for a high throughput screening on network level while reducing the need for animal experiments (Chiappalone et al., 2003). According to one of our interviewees, the pharmaceutical industry like Solvay and Roche is very secretive about the developments in the field and are not willing to work with academic partners on it.

An application in the longer term might be for cultured neuronal networks to function as prototypes within the development of higher-brain prostheses (Fromherz, 2003). Hybrid (biological-electronic) systems composed of a network of human neurons connected to an artificial neural network (ANN) – in order to decode the information hidden in the neural response – and a minirobot may be the start of a non-invasive neurological prosthesis that can improve or substitute damaged brain function (Pizzi et al., 2009). So far, however, the control researchers have over cultured neuronal networks is limited. This is also an important obstacle in using living neurons as computing elements in tasks commonly solved by conventional silicon devices. With the EU programme NEST (New and Emerging Science and Technology) there has been such a project entitled 'Towards the neuronal machine'.

Another long-term application is to connect cultured neuronal networks to virtual bodies of animals ('animat'), robotic components ('hybrot') or real bodies of insects or mammals like rats. The goal is to use the system – called the embodied cultured network – to control a robotic or (animal) virtual body. For example, in case of a robot, the robot's input from proximity sensors is converted to electrical stimuli that are fed back into the cultured neuronal network within milliseconds (Potter, 2007). The main purpose of this research is to study different neuronal functions while the cultured neuronal network is receiving at least some sensory feedback. A European project, Neurovers-IT, focused on using cultured networks as a control system, recently concluded that this concept is not feasible for now. Though the project continues, its goal has been adjusted to gaining a better understanding of cultured neuronal networks and being able to teach them something.

We have already mentioned some disadvantages to using cultured neuronal networks in order to understand the brain: poor spatial resolution and limited control over the networks. Another frequently mentioned criticism especially by neuroscientists – who usually like to work with in vivo models – is the fact that in vitro cultured networks are living outside their natural environment which results in patters of abnormal behaviour. Finally, there is also the criticism that cultured networks on MEAs are only two-dimensional; the neurons are artificially kept 'flat' while in vivo they are three-dimensional networks with much greater connectivity.

4.3. Forward engineering of the brain

Forward engineering the brain, or constructive neural engineering, focuses on using knowledge on the brain discovered by reverse neural engineering and by 'traditional' neurosciences, in order to develop tools to support, manipulate or enhance the working of the human brain. As already stated in the introduction, forward neural engineering can be divided into two subdisciplines: neuromodulation and brain computer interfaces (BCIs).

4.3.1. Neuromodulation

The term *neuromodulation* originally refers to the release of neurotransmitters that stimulate groups of neurons. These neurotransmitters can themselves be stimulated or inhibited by certain drugs. Nowadays, neuromodulation also refers to *devices* that – often electronically – alter brain and mental functioning. While the *term* neuromodulation is relatively new, research and practices surrounding changing the functioning of the brain or the mind have been around for a long time. Since the 1870s, scientists have been trying to change the functioning of the brain with electrical modulation (Schwalb & Hamani, 2008). Nowadays, forward neuroengineering via (electrical or other) neuromodulation can be done in two ways: either non-invasively or invasively.

Non-invasive neuromodulation: TMS and neurofeedback

Non-invasive neuromodulation refers to devices that change the functioning of the brain from outside the skull. One technology that is used for non-invasive neuromodulation is transcranial magnetic stimulation (TMS). TMS influences the electrical activity of the brain; it is not exactly known how it works. TMS uses a coil placed on the outside of the skull. The coil produces changing magnetic fields which induce an electric field in the cortical (brain) tissue. TMS does not affect the whole brain; it can only affect the brain processes on the outside of the brain, three and half cm below the skull (Wagner et al., 2009).

TMS is both used in research and clinical applications. As a research tool, it can be used to simulate neuropsychological disorders in healthy people, also referred to as creating 'virtual brain lesions'. TMS is also important as a research tool in combination with fMRI because it can demonstrate the functional causality between a stimulus or certain behaviour and a certain brain area. FMRI studies only show associations between brain activity and a task or stimulus. With TMS, researchers can make causal inferences. If activity in an associated area is suppressed with TMS and the subject then has more trouble performing the task at hand, it proves that the brain area is involved in performing the task.

TMS as a clinical tool is much more open to debate. In clinical applications the generated electric pulses produced with the coil are alternated with pauses. A session will last for about twenty minutes. To produce lasting results, it is necessary to undergo TMS a number of times. This is called repetitive transcranial magnetic stimulation, or rTMS (Health Council of the Netherlands, 2008). A lot of applications for rTMS have been proposed and claimed. In 2008, a review by the Health Council of the Netherlands discussed which of these claims are (already) corroborated by scientific evidence. They concluded that positive effects have been shown for treatment of resistant depressions, and to a lesser degree also schizophrenic patients suffering from auditory hallucinations. Furthermore, they found a range of promising, though not yet proven future applications of rTMS, for conditions such as chronic pain, epilepsy, tinnitus, strokes and obsessive compulsive disorder, but a lot more research is needed. Amongst other things, the necessary strength of the magnetic field, how long the sessions should last, and how often they should take place needs to be established (Health Council of the Netherlands, 2008).

One of our interviewees mentioned that the research with cats and other animals points out that TMS positively influences brain areas that are "out of balance". Recently, TMS has also been considered as an enhancement tool. For example, this year, the second day of the TMS Summer School in London was especially focused on "brain stimulation to enhance sensory, motor and cognitive functions".⁷⁴ And one of our interviewees indicates that *"there is more and more work showing that TMS can clearly interact with brain plasticity and learning in a constructive way, boosting learning and memory consolidation, and helping in plastic recovery."*

Even though there is still a lot unknown about the efficacy of (r)TMS, there are already some commercial applications. After rTMS was FDA approved as a treatment for severe, treatment resistant depression, the American company NeuroStar started a series of clinics in the USA⁷⁵. In the EU, most of the legimate use of TMS is currently being done under research protocols approved by medical ethics board in hospitals and in the US, often under Investigational Device Exemption from the FDA. As a result, most of the clinical applications of TMS are not yet reimbursed by health insurance companies.

The second method of non-invasive neuromodulation is *neurofeedback*. In neurofeedback, patients or clients have their own brain activity displayed in real time. The goal of this live feedback is to learn *how* to change your own brain activity in order to produce the desired brain activity, which results in different mental states. The brain activity can be monitored with electroencephalography (EEG), real time functional magnetic resonance imaging (rtfMRI) or near infrared spectroscopy (NIRS) and is usually presented on a monitor, but auditory feedback is also possible. The brain activity can be presented in the form of a game or task which gives immediate positive reward when the related task is executed correctly, for example through the display of a fire that becomes greater or smaller (Goebel, 2009: 35). Either technology requires the subjects to undergo 20-40 training sessions in order to learn how to adjust brain activity voluntarily. The subjects should be able to continue to alter their brain activity, even without the equipment present.

Neurofeedback has been studied as a treatment for different diseases and condition, but so far it has only been shown to be effective for ADHD (Arns et al., 2009) and autism (Kouijzer et al., 2009a; Kouijzer et al., 2009b). The treatment of (chronic) pain has shown some promising results (Jensen et al., 2009). More research is needed to establish if neurofeedback is indeed an effective and safe pain relief, for what types of pain it can be used, and how people can best change their brain activity. Other medical uses of neurofeedback currently studied include depression, epilepsy, anxiety, empathy and migraine.

Neurofeedback can potentially also be used for non-medical purposes, in other words, for human enhancement purposes. It has been suggested that neurofeedback could be a tool for improving cognitive performance (Vernon et al., 2003), or for learning to become more empathic or less afraid of spiders, in the case of people with mild arachnophobia (Goebel, 2009).

⁷⁴ See www.fmrib.ox.ac.uk/misc_events/tms-school-page.

⁷⁵ See http://www.neurostartms.com/Home.aspx accessed on 250710.

Christopher deCharms, a neuroscientist and owner of a company that develops novel MRI technologies, is very optimistic in his TED talk (2008)⁷⁶: *"This is not the matrix, you can only do this to yourself. You take control.* [...] *When you do, what do you want to control? You will be able to look at all the aspects that make you yourself, all your experiences."* In that same talk he refers to free will, joy, fear, pain, vision, brilliance, truth, love as cognitive capacities which in the future might be influenced by neurofeedback. Still, commercial uses of neurofeedback are more widely offered medically than for enhancement, although some companies have been offering it to sportspeople to improve their concentration skills⁷⁷.

Invasive neuromodulation: vagal nerve stimulation and deep brain stimulation

Vagal nerve stimulation (VNS) targets the tenth cranial (or: vagus) nerve. This nerve is located in the hindbrain and it is a major connection between the brain and the body; it has branches to and from the stomach and several other organs. The vagus nerve conveys for example information about the stretching of the stomach walls. VNS consists of an electrode that wraps around the left vagus nerve in the neck and a pulse generator generating an electrical current which, via the electrode, stimulates the vagus nerve. Because the electrodes are not placed deep inside the brain like in deep brain stimulation (see below), VNS has relatively few side effects (Albert et al., 2009; George et al., 2004). VNS has been developed for the treatment of epilepsy, but is also used for treatment-resistant depression. Theoretically, VNS could also be used for patient with severe obesity to regulate satiety signals transmitted to the central nervous system by the vagus nerve. More research into the use of VNS for neuropsychiatric disorders is being done. VNS is not a cure for those conditions, but can be an effective treatment. Like with TMS, the mechanism behind VNS is not known (Albert et al., 2009).

Deep brain stimulation (DBS) is a technique that also uses an electrical pulse to stimulate carefully selected areas of the brain. In surgery, two electrodes are implanted in the brain. Those electrodes are each connected with a lead and a single extension cord to a battery which is most often placed under the clavicle. The whole device is placed beneath the skull and the skin. The pulses generated by the battery can be programmed (by the doctor) using a remote control. Some patients also have a remote, with which they can change the settings of the electrical pulse and switch the device on or off.

Deep brain stimulation was originally developed to alleviate the motor symptoms (i.e. tremor) of Parkinson's disease. About 50,000 Parkinson patients have a DBS system implanted. Like vagal nerve stimulation, it cannot cure the disease, but it can improve the quality of life for patients for whom medication no longer works or who experience too many side effects of the medication.

A positive side effect of DBS was the alleviation of the depression that some Parkinson patients also suffered from. This led to research into the efficacy of DBS for psychiatric conditions. Trials are now being conducted for obsessive-compulsive disorder, severe depression, Tourette's syndrome and obesity. Recently, scientists have also started research into the use of DBS for patients in a minimally conscious state⁷⁸, by stimulating the thalamus. Furthermore, recent research on DBS for another degenerative disease – Alzheimer's – has started in Canada.

⁷⁶ http://www.ted.com/talks/christopher_decharms_scans_the_brain_in_real_time.html (accessed on 210710).

⁷⁷ www.brainclinics.com

⁷⁸ In a minimally conscious state a patient, after brain damage, is able to exhibit some, but very few deliberate behavioural or communicative responses.

The immediate cause of this line of research was the operation by surgeon Andres Lozana on a man with morbid obesity. While placing the electrode, it turned out that the appetite of the man was not suppressed; the electrode actually stimulated a very vivid recollection of a picnic the man had years ago. ⁷⁹ This illustrates the experimental phase DBS research and clinical applications are in, based on trial and error.

Alzheimer's and Parkinson's are both degenerative diseases that cannot be cured with DBS. DBS can only alleviate the symptoms, but the degenerative process continues and will reach a point where stimulation is no longer enough. Psychiatric conditions, on the other hand, are not degenerative by nature. Therefore the effects of stimulation might have longer effects for the patients.

DBS is a last resort treatment, as it involves brain surgery with all kinds of risks (such as bleeding and infection). DBS itself can also cause severe side effects, such as apathy, depression and speech problems. Also, increased rates of suicides and suicide attempts have been reported for Parkinson patients with DBS. These rates depend on the stimulated area, and range from 0.5% up to 4.3% of the treated patients (Voon et al., 2008). Furthermore, impulsivity and irresponsible and untypical behavior have been reported (see box 8). Most unwanted behavioral side effects of DBS will either disappear in different settings or when the stimulator is switched off. Unfortunately, damage done while on stimulation will not disappear.

Box 8 : Side effects of DBS – patients' stories

A man who was supposed to be treated for Parkinson's became manic and uninhibited after installation of a DBS system. He started spending lots of money, began an affair with a married woman and bought multiple houses that he couldn't afford. This uncharacteristic behaviour started after he had received a DBS device. When doctors switched his DBS off, he regretted what he had done, but he still chose to turn on the stimulator again – because he couldn't bear to live with his symptoms of Parkinson's. The consequence of this choice was that he had to agree (at the time that the DBS was switched off) to being checked into a psychiatric hospital if the device was reactivated (Leentjes et al., 2004).

During an experimental and unsuccessful treatment of OCD, a state of happiness was induced in a young woman. She was still behaving obsessive compulsively, but now feeling happy. Her psychiatrist, Damiaan Denys, switched off her stimulation because the surgery was not meant to make her feel happy, but to treat her OCD (Slob, 2007).

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⁷⁹ BBC News (2008), "Deep stimulation 'boosts memory'". http://newsvote.bbc.co.uk/mpapps/pagetools/print/news.bbc.co.uk/2/hi/health/7213972.stm

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The technology behind DBS is developing. At the moment, scientists are doing experiments using light-activated proteins to mark the neurons they want to stimulate. These lightactivated proteins make the treated neurons react to stimulation with blue light. The advantage of light over electricity could be that this activates neurons much more selectively than electrical pulses (Denys, 2009)⁸⁰. Since brain regions are vastly interconnected, electrical stimulation of certain areas also has consequences for brain activity in other areas. A more targeted stimulation might thus reduce the side effects. Another possible technological improvement will be longer lasting batteries or batteries that can be recharged through the skin to reduce or completely skip the surgeries for changing batteries. Because at this moment, batteries at most last three to five years before they have to be surgically replaced (Denys, 2009: 32). At the Philips Neurovation Symposium in Eindhoven in the Netherlands, psychiatrist Damiaan Denys said that the battery of a DBS system to treat OBS patients only lasts six to eight months. A third direction that research is exploring, is the development of electrodes that can record as well as stimulate neuronal activity, so that the system can monitor the particular brain area and give only the appropriate amount of stimulation (i.e. adaptive neural stimulation). The FP7 project BRAIN TOUCH – coordinated by IMEC in Belgium – is aiming to develop such a new generation of flexible Deep Brain Stimulation and Recording (DBSR) probes.

4.3.2. Brain computer interfaces

In this section, we discuss systems that can record brain activity in order to translate that activity into signals that control external devices like computers, wheelchairs or prosthetic limbs. This way, these systems are able to bypass conventional output systems like nerves and muscles. Collectively, these systems are called *brain-computer interfaces* (BCIs). BCIs process recorded activity in order to find activation patterns in the brain activity that correspond to the intention of the subject. That is, if somebody wants the system to do something, for example move the cursor; the device recognises that intent in the activity (Cincotti et al., 2008).⁸¹ BCIs are used to *"enable a new real-time interaction between the user and the outside world"* (Daly & Wolpaw, 2008).

There have been many developments in the field of BCIs in the last twenty years. The efforts are aimed at replacing, repairing or assisting brain or mental functions. The brain signals or brain activity used by BCIs can either be recorded outside the head on the scalp (non-invasively) or inside the skull and directly from the brain (invasively).

Non-invasive BCIs most often use EEG to record brain activity. EEG has the advantage (over invasive recording) that no risky brain surgery is required, but the signals recorded by EEG have less bandwidth than recordings from inside the brain. This means that EEG-based BCIs can probably only be used for tasks which require limited variety.

⁸⁰ See also:Medical News Today (2009), 'Scientists Use Optical Approach To Study Deep Brain Stimulation for Parkinson's Disease'. http://www.medicalnewstoday.com/articles/146503.php

⁸¹ A closely related field is neuroprosthetics, in which prostheses are implanted into the brain to aid brain function without using an external computer. Examples are retinal implants, which are being researched, or cochlear implants, which have already been used for some twenty years. There are also attempts to attach prostheses, such as artificial arms, to the remaining peripheral nerves in order to make them (more) functional.

For example, they will probably not be suitable for the (sophisticated) control of a prosthetic limb, but they can be used for (simple) computer cursor control, communication, and wheelchair control (Lebedev & Nicolelis, 2006). A recent experiment demonstrated that healthy volunteers could learn to drive a wheelchair quite well with EEG-based BCI, and it is expected that paralysed subjects can also manage this (Galán et al., 2008). Other non-invasive recording technology like fMRI – which can record signals much more precisely – are not yet suitable for everyday use. The scanners are too big, immobile and very expensive. There have been fMRI based BCI experiments though, for example the experiment where two users are scanned in two fMRIs and play a game of Pong in real time by altering their brain activity through neurofeedback techniques (Peplow, 2004).

The brain activity necessary to operate a BCI can also be recorded invasively from inside the skull, directly from the brain. This can be done in three ways: subdural⁸² (for example with *electrocorticography* (EOG or ECoG), in which electrodes are placed inside the skull but above the cortex), single neuron recording (with a small electrode), and multiple neuron recording⁸³ (with an array or grid electrodes). Compared to non-invasive recorded signals, there is less noise and loss of signal (caused by the signal having to pass through the skull). Unlike their non-invasive counterparts, they require surgery to either implant a recording array directly into the cortex or on the outside of the brain but inside the skull. Any brain surgery brings risks like haemorrhages, infections, etc. When the electrodes are placed on the brain with ECoG, this generates better signals than when EEG is used to record the signals. Apparently, the signal is so sensitive, so easy to control and requires such minimal training, that a sixteen year old effortlessly managed to learn how to play Space Invaders, a computer game, with it⁸⁴.

Once the brain activity has been recorded, it is translated via computer algorithms into the command the user intended to give. Each BCI has to be programmed to recognise the specific brain activity from the user. The user has to be careful that he or she always 'gives' the signal carefully, because otherwise the BCI might misinterpret it (Daly & Wolpaw, 2008). At the moment, errors in the interpretation of the intentions of the user are still a problem for the functioning of BCIs. This is mostly due to the noise or spontaneous brain activity - which may not be related to conscious mental activity at all - which is usually measured as well. Therefore the control of a BCI device usually takes a lot of training for the user, even more so for the non-invasive BCIs. It is not always the actual intention of the user which is measured. "It is the modulation by the user of cortical activity at a certain location after neurofeedback training. A small area of the cortex has artificially become an output channel for volitional conscious control" (Van der Togt, 2008: 207). For example, users are often trained to think about moving their foot to control the external device, like spelling a word on the computer. In short, the control methodologies so far have not been very intuitive. "Unintuitive control signal perception tests which are unrelated to the intended outcome make the interaction cumbersome and may result in subject's fatigue, loss of concentration and an increase in error rates" (Daly et al., 2008). Recently, researchers have been trying to use 'open tasks' for users in order to find more natural and well-suited brain signals as a control methodology. An important development question is whether the decoding of brain activity can be standardised across different users or whether each user is required to train and learn through neurofeedback on an individual basis.

⁸² That is underneath the dura (the membrane covering the brain) but on the outside of the cortex.

⁸³ A.K.A. single or multiple cell recording and single unit or multi-unit recording

⁸⁴ http://news.wustl.edu/news/Pages/7800.aspx accessed on 270810.

Currently, non-invasive as well as invasive BCIs are in the research stage, and not applied routinely. Many efforts are focused on helping patients communicate or have some control over prostheses or devices. Most research is directed at patients who are completely paralysed as a result of a high lesion of the spinal cord, patients who suffer from locked-in syndrome, or those who are in the final stages of the neurodegenerative ALS (which is one of the cause of a locked-in state (LIS) and a total locked-in state (TLIS))⁸⁵. For those patients, being able to communicate easier or exert some control over a computer, for instance, can contribute greatly to their quality of life (Daly & Wolpaw, 2008). Experiments with paralysed patients with ALS have shown that they can learn to communicate with BCI, provided that they have not entered the end-stage of the disease, the total locked-in state (TLIS). Once in TLIS, Birbaumer and Cohen (2007) hypothesise that the patient might lose "all contingencies between goal-directed thinking and intentions" and might therefore become unable to learn to communicate via BCI. It is unclear whether this is really the case, or whether patients might learn to communicate, perhaps via other brain activity, for example through metabolic activity measured via fMRI (Birbaumer & Cohen, 2007).⁸⁶ It is, however, something that needs to be researched.

At this stage, most of the experiments are not performed on human subjects, but on monkeys⁸⁷ (see also section 4.6 about animal experiments). There have been a couple of broadly publicised successes in humans (see box 9) which have raised the expectations of the general public. Unfortunately, expecting that locked-in patients will be able to communicate or that amputees will be able to use fully functional prosthetic arms via BCI on the short term is unrealistic. Or as one of our interviewees pointed out, for totally locked-in patients, brain computer interfaces are often not more or even less efficient than more traditional interfaces based on the blinking of the eyes. *"There has no been no 'killer application' for BCIs yet, like DBS does have with tremor control for Parkinson's."* He continued to say that in the short term, BCIs are only useful for few, small patient groups. But in the long run, there is a potential large group of patients in wheelchairs, for example, who will benefit from being able "to have their hands free".

⁸⁵ ALS (amyotrophic lateral sclerose) is only one of the possible causes of locked-in state or syndrome. Other possible causes include strokes or traumatic brain injuries. The difference between locked-in and total locked-in is that in the first state, patients still can blink their eyes (and communicate with their blinking). In a total locked-in state, patients have also lost the ability to blink.

⁸⁶ It is not yet clear what will happen when ALS patients, who have in earlier stages of the disease learned to communicate with BCI, reach the final stage of the disease. In order for the TLIS patients to be able to communicate via EEG-based BCI, it is vital that lack of control of the brain signals is not an inherit characteristic of the (untreatable and unstoppable) disease; otherwise all efforts towards EEG-based communication for ALS patients are in vain.

⁸⁷ Lebedev & Nicolelis (2006).

Box 9 : Matt Nagle

Perhaps the most familiar example of an invasive BCI is the case of Matt Nagle, whose story made headlines⁸⁸. Matt Nagle was paralysed from the neck down after a stabbing incident, yet three years later on he could control a computer cursor and a prosthetic hand. A neurosurgeon had implanted a so-called 96-electrode Utah Array on Nagle's motor cortex. This array was connected to a computer (outside of Nagle's body, of course). After a training period in which the computer had to learn what Nagle tried to achieve with what brain patterns, Nagle succeeded in operating a computer to open his e-mail, play simple games and open and close a prosthetic hand. This gave him back some of his independence. Nagle himself said about this new device: "*I can't put it into words. It's just wild*"⁸⁹. This is an encouraging result in this developing field. It means that the motor cortex can remain active when the spinal cord is lesioned and no movement is possible. But spinal cord injury and TLIS, discussed in the previous section, might have different effects on the brain, as Nagle was still able to communicate, for example.

Outside the medical realm, there is also research being done on BCIs, for example in the gaming world. Mattel's MindFlex – in which your 'concentration' makes a little ball float, or not – is one example. Another is by the American company Emotiv Systems, which developed a wireless 'neuroheadset' with sixteen sensors that can be used to control a computer game or a photo view programme, for example. There has been some debate on the Emotiv system though. Some neuroscientists think Emotiv's headset with 'dry' in stead of the usual 'wet' electrodes is actually more sensitive to muscle strains in the forehead than to the user's brain activity.

BCIs might in the future not be limited to use on this side of the moon, as ESA commissioned a report on the space applications of brain-machine interfaces⁹⁰. As an example they mention exoskeletons (wearable robot-suits designed to enhance ones strength) which can be controlled by a BCI. Another non-medical application could be in the field of monitoring cognitive workloads – for instance for pilots or air traffic controllers who have to interpret many different stimuli at the same time and perform the right actions based on that. It is thought that BCIs could help reach an information optimum with enough relevant information for the user to make a quick and goal oriented decision (Kohlmorgen et al., 2007). As with the medical applications, most of these professional or leisure applications are still in the early research stages and it is still questionable if these applications are feasible and even marketable. Most probably, especially in the short term, BCIs will not be able to surpass the human limbs as a more efficient output channel for the brain.

⁸⁸ http://news.bbc.co.uk/2/hi/5167938.stm ; http://www.nature.com/nature/focus/brain/experiments/index.html

⁸⁹ http://news.bbc.co.uk/2/hi/5167938.stm

⁹⁰ www.esa.int/gsp/ACT/doc/ARI/ARI%20Study%20Report/ACT-RPT-BIO-ARI-056402-Non_invasive_brain-machine_interfaces_-_Pisa_E_Piaggio.pdf

4.4. Engineering the brain in European research programmes

In this section we will give a brief analysis of European funded research projects which either has reverse or forward engineering of the brain as a goal. We went through the databases of both FP6 and FP7 to look for projects centred on one of the approaches to engineering the brain as described in section 4.2 and 4.3. The most important entries that we used were 'brain' (in FP6 418 hits and in FP7 303 hits) and 'neuro*' (in FP6 657 hits and in FP7 514 hits)⁹¹ and in order to check if we didn't miss any projects we used keywords like 'TMS' and 'DBS'. We also looked at projects from the European Science Foundation (ESF); we did not search for national funding activities on engineering the brain around Europe.

A detailed comparison of project subjects, aims and structures is beyond the scope of this project. However, we have tried to discover some trends in amounts of funding, framing and focus of the research projects over the years in the research projects funded in EU context.

4.4.1. Trends in FP6 en FP7

Table 4 shows that in FP7 there are only two more projects on engineering the brain than in FP6. Still, FP7 has not run the full four years that FP6 did (2002-2006). FP7 started in 2007 and will continue for seven years, until the end of 2013. When it comes to funding, the differences in neural engineering projects between FP6 en FP7 become more apparent.

Funding

In FP6, reverse engineering projects have received 28.86 million euro (for 13 project; 2.22 million per project) and forward engineering projects 31.03 million euro (for 20 projects; 1.55 million per project). In forward engineering projects on BCI and DBS, projects received most of the money (23.04 million euro).

In FP7, reverse engineering projects got less money than in FP6 so far: 23.82 million euro (but per project there was more budget: 2.98 million per project). The financial difference is due to the funding of one very large reverse engineering project in FP6: FACETS (described in detail in section 4.2) which got over 10 million euro.

The forward engineering projects in FP7 are better funded than in FP6; they received 47.76 million euro so far (for 27 projects: 1.77 million euro). Especially the projects on brain computer interfaces (BCIs) received a lot more funding: 34 million in stead of 11 million euro in FP6; three times as much. Also projects making use of TMS received more sponsoring: 10 million in stead of the 5.75 they got with FP6. That is almost two times as much. Deep brain stimulation (DBS) projects on the other hand, are much (six times!) less financed. This is due to a very large scale project in FP6 on DBS called NEUROPROBES which received nearly 10 million euro. This project combines – it is still running – technological partners (like IMEC), industrial partners (like Philips) and scientific partners to develop an "integrated tool that combines multiple functions to allow electrical as well as chemical sensing and stimulation of neurons". Their objective is, in the first place, to use such a multiple array for scientific understanding of cerebral systems, and in the second place, to thereby treat associated diseases.

⁹¹ Most of the hits turned out not to be relevant for our projects, since their main aim was not engineering the brain (but more oriented towards understanding the brain through genetic or neuroimaging studies for example).
In total, FP6 neural engineering projects obtained 57.71 million euro compared to 71.58 million euro in FP7. This is partly due to inflation rates, but one can safely state that neural engineering in general has become more fashionable in FP7.

Funding schemes

Most of the reverse engineering projects in both FP6 en FP7 are about modelling the brain in software. They are mainly funded within the themes IST (FP6: information society technologies) or ICT (FP7: information and communication technologies). Three of the FP6 projects trying to reverse engineer the brain are funded under the NEST (New and Emerging Science and Technologies) programme. These projects are operating at the scientific frontier and, for example, try to use biological neurons as computing elements (NEURO). Unfortunately NEURO has not been successful. Professor Vincent Torre involved in the project explains as follows: *"A major problem is that natural neurons have considerable noise which is absent in artificial neurons (as conventionally used in connection devices) and while each natural being can handle this noise, it has not up to now been possible to devise universal means of handling the noise." Besides the noise problem, no one – also not the NEURO project – has achieved succes at creating a stable source of neurons, on a cultivating medium.*

It might be that the wetware approach which had five projects funded in FP6 hasn't been succesfull overall since in FP7 only two wetware projects are sponsored. Budget has decreased as well: from 13.63 million euro to 7.8 million in FP7.

When it comes to forward engineering, there is an increase in projects on neurofeedback (from 0 to 3) as well as on brain-machine interfaces (from 7 to 13). Projects focused on or simply using transcranial magnetic stimulation (TMS) was and still is popular, but mainly as a research instrument (to create artificial lesions for example). TMS as a therapy instrument is only studied in one project in FP6 en in one in FP7. Also, neurofeedback is used in two out of three FP7 projects as research and not as a therapeutic instrument. For example, the project NEUROFEEDBACK describes neurofeedback as a "potentially important methodological innovation" for investigating causal links between brain activity and perception.

	n	Name of FP6 projects	n	Name of FP7 projects
		(including the action line		(including the action
	0	within FP6)	0	line within FP7)
Engineering the brain general	0	DEGLEVEN MOTION	0	
Reverse engineering	5		6	
Software				CONNECT (ICT)
		(MOBILITY) DAISY (IST)		BIOTACT (ICT)
		FACETS* (IST)		BRAIN-I-NETS (ICT)*.
				BION (ICT)*
Reverse engineering	1	FACETS* (IST)	2	BRAIN-I-NETS (ICT)*,
Hardware				BION (ICT)*
Reverse engineering	5	NEURONANO (NMP),	2	BRAINSTORM (ICT),
Wetware		NERBIOS (NEST), CILIA (IST),		SECO (ICT)
		NEURO (NEST), NEUROVERS-		
		IT (MOBILITY)		
Forward engineering	3	SENSORY MEMORY	0	
Neuromodulation/general		(MOBILITY), SOMAPS (NEST),		
		(MOBILITY)		
Forward engineering	0	(MODILITT)	0	
Neuromodulation/VNS	Ŭ		Ŭ	
Forward engineering	3	NEUROPROBES (ICT),	2	BRAIN TOUCH
Neuromodulation/DBS		DREAMS (NMP), MIND		(PEOPLE), CYBERRAT
		(MOBILITY)		(ICT)
Forward engineering			3 ⁹²	EMPATHICBRAIN
Neuromodulation/neurofeedback				(ERC),
				(PEOPLE), IIN-LAN
Forward engineering	10 ⁹³	NUMERICAL COGNITION	11 ⁹⁴	ITN-IAN (PEOPLE)*
Neuromodulation/TMS	10	(MOBILITY), NBNS (MOBILITY),		INSPIRE (ERC).
		STROKE AND LANGUAGE		SPINDLESINSCHIZO
		(MOBILITY),		(PEOPLE), NEUROTIME
		BRAINSPEECHSIGN		(PEOPLE), MEMORY
		(MOBILITY), BRAINTUNING		CAPACITY (PEOPLE),
		(NEST), BE-NEURAL		SEEING WITH
		(MOBILITY), CORTICAL MAPS		SOUNDS (PEOPLE),
		(MOBILITY), CISA (MOBILITY),		
		ENOUGH SLEEP (LSH),		(PEOPLE), C7 (PEOPLE),
		ABSTRACT (NEST)		GRASP-CN (ERC),
				HIVE (ICT)*
Forward engineering	7 ⁹⁵	SIMILAR (ICT), EYE-TO-IT	13	REHABCI (ICT), CLONS
Brain machine interfaces		(IST), MLFORBC I (MOBILITY),		(ICT), BCCI (ERC),
		MULTI-ADAPTIVE BCI		MUNDUS (ICT),
		(MOBILITY), MIND (MOBILITY),		DECODER (ICT),
		MAIA (IST), BRAINCOM		TREMOR (ICT), BRAIN
		(MOBILITY). BRAINROBOT		(ICT), TOBI (ICT),
		(MOBILITY)		BETTER (ICT), FUTURE
				BINCE (ICE),
				DENACHID (ICT) HIVE
				(ICT)*
			l	(101)

TABLE 4: neural engineering projects in FP6 en FP7

* Categorised more than once.

⁹² One project uses neurofeedback not for medical but for research purposes (i.e. NEUROFEEDBACK).

⁹³ One project uses TMS for medical purposes (TDCS, ENOUGH SLEEP) and nine for research purposes.

⁹⁴ Two projects are also network programmes (C7 and ITN-LAN) and one is focused on medical treatment (ITN-LAN).

⁹⁵ In one project (SIMILAR) BCI is part of the project.

Within the FP7 health theme – which is called Life Sciences and Health (LSH) in FP6 – surprisingly enough, only one forward engineering project is funded: ENOUGH SLEEP. This project aims to use TMS/EEG technology for discovering the basic mechanisms of sleep regulation and for therapeutic use. A large amount of the forward engineering projects – especially in FP7 – are not funded within the health theme but within the Information Society Technologies (FP6) and Information Communication Technologies (FP7) themes. This might be explained by the fact that most of the forward engineering projects have basic goals for research (e.g. TMS) or technology development (e.g. BCIs) and no therapeutic or enhancement objectives. Though in FP7, the projects on BCIs are much more geared towards therapeutic use. For example, think of neurorehabilitation (REHABCI), stroke (BETTER) and discrete motor learning (RENACHIP) rehabilitation, dizziness (CLONS) and tremor (TREMOR) suppression, upper limb support (MUNDUS) and the detection of consciousness in non-responsive patients (DECODER).

Large research programmes

The European Commission has been very committed to bringing the fields of IT and neuroscience together. There have been and still are some very large scaled programmes in this area. In 2000, within FP5, they started a network of excellence called nEUro-IT. This network aimed to complement and move beyond the well-established neuroinformatics or artificial intelligence (AI). Their goal was *"for IT to profit from neuroscience results to improve IT artefacts and for neuroscience to validate models or hypotheses with a better use of IT"* (Knoll & De Kamps, 2006).

The network also produced a roadmap of nEUro-IT development⁹⁶ - the latest version is from 2006 - meant to inspire future calls of FP6 and FP7. The roadmap describes eight grand challenges like the 'brainship' project (i.e. bidirectional BCIs), the bio-inspired hardware project, the factor 10 project (i.e. an artefact that autonomously grows its size, the aptitude of its sensorimotor skills and its cognitive abilities by a factor ten within ten months) or the constructed brain project (i.e. the simulation of an entire brain). Not all of these challenges have been materialised in FP6 or FP7 projects. Still the roadmap resulted in one large scale programme in FP6, a FET proactive initiative⁹⁷ called BIO-i3 with a budget of 20 million euro (aiming at "decoding brain processes and applying this knowledge for new information technologies") and two other FET proactive initiatives in FP7: BRAIN-ICT with a budget of 12 million euro (covering both "multiscale models of the information processing and communication in the brain" and "synthetic hardware implementations of neural circuits that mimic information processing in the brain") and Bio-ICT CONVERGENCE with a budget of 20 million euro (aiming to exploit the understanding of information processing and interpretation in biological systems like the brain in general). These three initiatives are grounded in the neural engineering approach - especially the reverse approach – and contain some of the projects mentioned in Table 4.

⁹⁶ See www.neuro-it.net.

^{97 &}quot;FET proactive initiatives aim at focusing resources on visionary and challenging long-term goals that are timely and have strong potential for future impact." See http://cordis.europa.eu/ist/fet. The proactive initiatives are either organised top-down (the European Commission provides the themes) or bottom-up (the FET Open Proactive Initiatives). Examples of FP7 projects from FES Open in Table 2: BION, BRAIN-I-NETS, CLONS, CONNECT and HIVE.

Conclusions

Since the beginning of this century, the European Commission has actively sponsored the convergence of the science and technology of neuroscience and information technology. There are and have been different large scale neural engineering programmes in the NEST/FET funding schemes with long-term horizons. Most of the accompanying projects are cutting edge technoscience projects centred on either reverse engineering the brain or developing BCIs. However, through desk research it is difficult to find out if these very challenging projects have been successful or not and it is not within the scope of this project to interview all of the involved scientists. From the limited amount of interviews we have done, it is, however, clear that the EU has an advantage over the United States when it comes to a well-established interdisciplinary research community on neuroscience and IT. This community is still largely absent in the US, although they are ahead in technology development, such as hardware components in neuro-inspired ICT. That's why in a recent application for the FP7 FET Flagship Programme (with a budget of 10 million euro per year, ten years long) the European neuro-IT community is advocating large investments in technology development.

It seems the European Commission is not funding many forward engineering projects for the development of neuromodulation technologies, like DBS, VNS, neurofeedback or TMS. In FP6 en FP7 together, neuromodulation projects got 33.5M euro funding.⁹⁸ Most of the funding went to TMS research; these projects are usually not about the development of TMS, but merely use TMS as a research instrument. Within the Health programmes in FP6 and FP7, there is no specific programme on neuromodulation, i.e. on ways to assist the brain to function normally again. This in spite of the fact that one of the aims of the EU Health programme is to develop *"innovative therapeutic approaches and interventions"* like gene therapy, regenerative medicine, etc.

Research on ethical, legal and social concerns

Another interesting finding of our search through FP6 and FP7 is that there are no specific projects or subprojects – as part of larger technoscientific programmes – on ethical, social or legal issues (ELSI) of neural engineering. There has been only one specific project in FP6 on the brain sciences in general: 'Meeting of Minds: European Citizens' Deliberation on Brain Science'. Other technoscientific fields, like synthetic biology (e.g. SYBHEL or SYNTH-ETHICS) or nanotechnology (e.g. DEEPEN, NANOCODE or FRAMINGNANO), do have large ELSI projects. However, there are two larger programmes with the Science And/In Society funding schemes from FP6 and FP7 that touch upon ELS issues of neural engineering. These projects are not centred on the technology (like with nanotechnology and synthetic biology) but rather on the societal trend of human enhancement:

- ENHANCE (FP6). This project aims to reach a deeper understanding of the ethical and philosophical issues concerning the use of emerging technologies beyond the purpose of therapy, amongst others in the area of mood and cognition enhancement.
- ETHENTECH (FP7). The objective of this project is to substantially forward the ethical evaluation and public discussion on both neurological implants and human functional enhancement technology at large.

⁹⁸ BCI is the exception; these projects got 45.3M euro in both FP6 and FP7.

Another FP7 project worth mentioning is BIOSOCIETY. The social scientists working on this project want to provide a detailed description of the current impact on society of leading intellectual enterprises like neuroscience and molecular biology. However, it is not yet clear to what extent the project will concern societal impacts of the neural engineering approach. In the FP7 project HEALTHGOVMATTERS, there might be some research on the involvement of patients and professionals in the governance of computer implants within the realm of neurology.

A possible explanation of the absence of ELSI projects on neural engineering is that most of the neural engineering projects in both FP6 and FP7 are financed by – what is now called – DG Information Society and Media. This directorate-general has no specific directorate concerned with governance or ethics programming in the way that DG Research has the directorate Science and Society.

4.4.2. Trends in ESF projects

The ESF has initiated quite some large EUROCORES programmes on the brain (e.g. EUROSTRESS and Consciousness in a Natural and Cultural Context).⁹⁹ There is no programme specifically on neural engineering. Only recently, there have been two ESF research conferences on reverse engineering: a EU-US workshop in May, 2010 and in October 2010 there is a symposium entitled 'Functional neurobiology in mini-brains: from flies to robots and back again'. The ESF does support an initiative studying the social impact of the neurosciences. There is a research networking programme called the European Neuroscience and Society Network (ENSN). Most of their activities have to do with the ethical, legal and social issues concerning forward engineering of the brain, not reverse engineering.

4.5. Ethical, legal and other impacts of neural engineering

So far there has been little formal consideration of the implications of the rapidly growing brain research in general and neural engineering developments in particular. As was pointed out in section 4.5, there are no large EU funded research projects concerning the ethical, legal and social issues (ELSI) surrounding neuroscience or neural engineering for that matter. At the same time, there is no European policy on allocating a certain percentage of neuroscientific research budgets on ELSI research (as was the case with, for example, the international research collaboration on the Human Genome Project). The question is whether such formal consideration is needed. So far, the field of 'neuroethics' is developing quickly with a substantial amount of scientific literature having already been produced in this area, including specialised academic journals like AJOB/Neuroscience and Neuroethics. In addition, the Neuroethics Society¹⁰⁰ was recently founded (Illes & Bird, 2006).

In this section, we will explore the different ethical, legal and social issues surrounding neural engineering. Some issues might need further research or public deliberation; other questions might need policy action. It is important in this field of neural engineering, which is still in its infancy, to avoid the trap of "speculative ethics" (Rip & Nordmann, 2009). We continuously have to ask ourselves: is our knowledge of development of neural engineering "good enough to underwrite political efforts and ethical deliberation?" (Nordmann, 2006).

⁹⁹ Interestingly, calls for proposals for 2011 ESF Research Conferences on the topic of the brain, technology and cognition were quite successful. After mathematics (50%), they had a success rate of 42%.

¹⁰⁰ See www.neuroethicssociety.org.

Therefore, we will concentrate on the ethical, legal and social issues which are important on the short and mid term, and focus less on issues which may only come up in the long run.

	Short term	Mid term	Long term
Reverse engineering	 Increase in laboratory animals 	Animal brains as controlling devices	Machine consciousness
Forward engineering	 Increase in laboratory animals Mental integrity Informed consent Liability issues Regulating safety of invasive neuromodulation Regulating safety of non-invasive neuromodulation Bodily integrity Remote control issues 	Regulatory safety of neuromodulation for enhancement	 Mental privacy issues on brain reading Access to neuroimaging data of the patient

Table 5: Ethical, legal and policy issues of neural engineering

As the table already shows, the debate on the issues surrounding reverse engineering is much less developed than the debate on forward engineering. This can be explained by the fact that developments in reverse engineering the brain have been quite recent. What's more, research in this field is mostly long-term horizon research with no killer applications foreseen in the near future. Another reason for the absence of an ethical discussion on reverse engineering might be the indifference of the public towards the need for a debate on artificial intelligence. *"It seems to be taken for granted that benefits to society of intelligent artefacts are so obvious that critical review is unnecessary. This viewpoint must be challenged"* (Rosenberg, 2008: 369).

When it comes to forward engineering the brain, the situation is quite different. There, a variety of governance and ethical issues have already risen to the surface and have been hotly debated, although the debate has mostly stayed within the community of neuroethicists and to some extent that of neuroscientists. Most of the issues have not yet been addressed by policy makers or regulatory bodies, simply because it is not yet clear if regulation is needed or how it should be designed or implemented. In many cases, additional research has to be done in order to get the issues and their possible policy or political consequences clarified.

In this section we will give a description of the different ethical, legal and policy issues surrounding neural engineering as mentioned in Table 5. The issues we will address (e.g. safety, enhancement) may, at first sight, not seem very different from traditional bioethical issues, but the fact that they concern a field involved in both *engineering*, *neuroscience* and *information technology* does give them a different – more pressing – weight. We will explain this in the next subsection.

4.5.1. The ethics of neural engineering

The basic assumption that underlies most of the research described in this chapter on intuitive notions about the mind and the brain – which have by some been described as 'folk neuropsychology' (Rodriguez, 2006) – is that the human mind can be largely reduced to brain functions. Neuroscientists, and increasingly the general public as well, believe that the brain is a key and determinative factor of our personality. 'We are our brain', are often repeated words by neuroscientists. This view is contested by some philosophers of mind and others for being too reductionistic (see box 10). However, many of us, including most philosophers, agree that the brain at least constitutes some of the mind. This is hard to deny when deep brain stimulation and other interventions in the brain show that patients undergo personality changes after treatment (see box 8). Engineering of the brain raises questions on alterations of 'self' and 'personhood' that many people will feel uncomfortable with. Consequently, bioethical issues surrounding neural engineering may raise much more public concern than other more traditional medical technologies.

Engineering the brain involves engineering a very complex organ we still know little about. In fact, one of our interviewees - an expert on cultured neuronal networks - said, "engineering for me is instrumentalising and controlling neurons without a fundamental understanding of these cells." The same holds for other reverse engineering of the brain projects, like the Blue Brain project. One of their goals is to understand how intelligence and consciousness emerge while building the brain from the bottom up in silicon without having any knowledge or even a theory on either of them. Likewise, with forward engineering methods mentioned in section 4.3; scientists do not really know how TMS or DBS work, only that they work. At the same time, while experimenting with these neurotechnologies, they discover more about the workings of the brain and their clinical application possibilities. A nice example of this is the surgeon Andres Lozana who - while placing a DBS device to suppress the appetite of his patient with morbid obesity - found out that the electrode very strongly stimulated the patient's memory. Neural engineering is very much a discipline based on trial and error, because we still know so little of the brain, and on top of that, every individual brain of animals and humans is different. Consequently, neural engineering involves relatively more unpredictability and unforeseen effects than might be the case with other medical engineering research. Standardisation of neural engineering methods is therefore still very far off. This experimental nature of the field of neural engineering results in a wide variety of ethical and legal concerns.

The increasing convergence of neuroscience and information technology within the field of neural engineering has brought about the possibility of the 'translation' of neurobiological processes into digital information. Improved data processing, fast signal processing, better electrodes, etc., have all contributed to the growing possibilities of indirect (e.g. MRI or EEG) or direct (e.g. BCIs or DBS) interfacing of computers with the brain. It has opened up far reaching possibilities for analysing neuronal activity and ways of intervening in the brain through digital devices like neurostimulators, or connecting these devices to the brain. Because of the convergence of both fields – neuro and info – biology can actually become technology in the field of neural engineering. Introducing the digital information paradigm in the neurosciences is – just like in other medical fields – resulting in more control over biological processes; in this case brain activity. Naturally, the ablity to control brain activity amplifies existing ethical questions and regulations about physical integrity but also about mental integrity.

Box 10 : Philosophers on brain and mind

Among philosophers of mind, the consensus on the issue is not as unanimous as amongst neuroscientists and the general public. *What* the mind exactly *is* and *whether* it is identical to the brain, or whether there is another relation between mind and brain, has been hotly debated for decades.

Nowadays, few philosophers (and even fewer neuroscientists) embrace the position of dualism (i.e. the mind is made of a totally different substance than the body and the brain). Most philosophers and neuroscientists think that dualism raises a lot of hard questions that it cannot answer satisfactorily, such as how to explain the problem of mental causation¹⁰¹.

Most philosophers think that the mind can be explained by the brain (although not all believe that the mind is wholly reducible to the brain, see below). Still, the position that the mind consists of the same substance as the brain is not a problem-free position. Here, the problem of mental causation is an important one as well. Besides, if the mind and the self are completely constituted by the brain, then the idea of free will has to be discussed. If the brain constitutes the mind and the self with physical laws, then there does not appear to be much room for free will or rational, accountable agency. This could have far-reaching consequences, for example when it comes to legal responsibility. One of our interviewees, however, does not think the neurosciences are relevant for the subject of free will, for two reasons: "First, one important issue here is that "free will" or "freedom" does not come without causes and/or arguments. Hopefully, we always have more or less good reasons for what we are doing. So our decisions have a history that is based on the experience of a person and his or her considerations how to behave in a given situation. [...]. Secondly, the by far most underestimated and under-researched (in my view) aspect is the high degree of individuality, that has not been taken into account adequately. If we assume that we have something like 10¹⁰ nerve cells in each and every brain and something like 10¹⁴ connections between these nerve cells in each and every brain then the "connectivity" is much higher than the total population of our planet (roughly 7 x 10^9). If the connectivity between nerve cells is the relevant measure for "individuality" then the number of different "possible" brains by far exceeds the number of human beings on our planet. Another important issue here is neuroplasticity, you probably "never think with the same brain twice". So, I don't think we can live without the constructs of free will, etc."

The reductionist position can also result in an increased medicalisation, where neuroscientists place mental states like addiction, lack of concentration, etc., in the medical realm. Such medicalisation could lead to new forms of stigmatisation or may relieve individuals of a feeling of responsibility or feelings of guilt about their medicalised condition. Medicalisation could have far-reaching social consequences, ranging from children having to be medicated for being unable to concentrate 'enough', to the questions for the judicial system that are raised by advances in neuropsychiatry.

A third position which seems attractive to philosophers of mind, that mental states are only material in *some* way, is not without problems either. Here philosophers and neuroscientists have to explain how the mind has a biological underpinning, to which it cannot be reduced, and what the nonbiological part is and how it works. They, too, have to answer the problem of mental causation. So

¹⁰¹ There is the experience that mental states, like the decision to go to the gym right now, can result in behaviour, such as getting up and going to the gym. Yet, while the body is physical, mental states intuitively appear to be non-physical. But interaction between a physical and a non-physical substance is impossible. This is called the problem of mental causation.

far, the neurosciences have not been able to explain all the problems identified by the philosophers.

The questions raised by philosophers about the relationship between the brain and the mind are relevant for neural engineering. First and foremost, philosophers question the assumption that most neuroscientists work with, and thereby also the promises of their work. To what extent will we be able to influence the mind – for example when it comes to the treatment of psychiatric diseases – by manipulating the brain? Or, to what extent are we able to rebuild the mind by reverse engineering the brain? Secondly, the scientific and philosophical uncertainty as to *what* the mind is adds concerns to the problems surrounding forward engineering interventions in the brain. It is far from clear how engineering the brain will affect the mind and how people behave now and in the long term as a result of engineering it (see the two examples of personality changes in box 8). One of the concerns stems from the importance of our minds and brains for our lives, which is hard to underestimate. Experimentation with engineering the brain might be warranted in the case of severely ill people for whom other medical options have run out, but given the far from complete understanding of the brain, one must ask whether experiments on less than severely ill or even healthy volunteers should be allowed.

4.5.2. Reverse engineering

There are two ethical concerns which stand out when it comes to reverse engineering the brain: they concern laboratory animals (short and mid term) and conscious machines (long term). They are a consequence of the emerging trend of both technology becoming biology and biology becoming technology.

Laboratory animals

The concerns surrounding the use of laboratory animals in the field of reverse (and forward) neural engineering are twofold: there is a growing need for laboratory animals, but there are concerns regarding the use of the brains or neurons of animals to control electronic devices like we described in the section on cultured neuronal networks.

The most recent figures of 2005, supplied by the European Commission, showed that the total number of animals used for experimental or scientific purposes in the European Union has been 12.1 million.¹⁰² To what extent these animal experiments are related to neuroscientific experiments or neural engineering in particular is difficult to determine. However, there are statistics on the proportion of animals used for the study of diseases, which point out that human nervous and mental disorders make out 21.6 % of the total amount. This is quite a lot more than needed, for example, for studying human cardiovascular diseases (6%) or for human cancer research (12.6%), and even for studying animal diseases (19%). This may not come as a surprise, since basic neuroscientific research as well as neurological and psychiatric research has substantially increased over the years.

Especially nonhuman primates are needed – in 2005, 10,451 primates were used in European research – because parts of their brain, such as the visual system, for example, are highly similar to that of humans. Also for the understanding of the psychophysiology of Parkinson's, Alzheimer's, strokes and other neurological disorders, the assessment of therapies like deep brain stimulation and the development of invasive BCIs nonhuman primates are essential (Emborg, 2007).

¹⁰² This is the fifth report on statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union (2007).

When it comes to reverse engineering projects, the use of nonhuman primates and other animals is unavoidable according to scientists working in the field. One of our interviewees stated, *"when it comes to reverse engineering research all the input comes from biology, from animal experiments including nonhuman primates. Society is not very supportive of this research, especially not when it concerns future IT applications."* The very fact that we want to develop technology that is more like biology – in this case neuromorphic computers – leads to more animal experiments, because we need more knowledge of the brain in order to be able to mimic it. Critics state that *"the similarities between the various species of primates have led to the widespread use of nonhuman primates in psychological research, however, it is also this similarity which leads to the deep ethical concern over their treatment."¹⁰³ The report claims that advances in neuroimaging make it possible to study the processes involved in memory or perception directly in humans without using monkeys. However, a recent discussion in 2008 in the European Parliament on a possible ban on the use of primates has ended in favour of scientific research.*

Besides the ethical concerns about possible increases in animal experiments used in the neurosciences, including the neural engineering field, there are also some concerns about a shift in the instrumental use of animals. We are not only using animals to do research on – to study the brain and brain diseases – but also to do research with, i.e. using (parts of) animal brains for controlling machines like robots, as we have seen in the section on cultured neuronal networks. This shift is related to the emerging trend of biology becoming technology; researchers are instrumentalising animal brains and turn them into controlling devices, just like cell lines have been instrumentalised to do research (see Chapter Engineering the Body).

The resulting hybrids – half animal, half machine – question our interrelations with both animals and machines. The chapter Engineering Intelligent Artefacts elaborated on the ethical questions involved.

Conscious machines

A second concern which applies to the long term has to do with reverse engineering applications for developing advanced artificial intelligence with some form of consciousness. The premise underlying this vision – as expressed in the neuro-IT roadmap – is that "to build machines with real autonomy and adaptivity and a genuine capacity to interoperate with human beings, we need consciousness – a cognitive architecture that includes reflective control mechanisms akin to human introspection" (Knoll & De Marcs, 2006). Ethical issues concerning this so-called machine consciousness – such as an erosion of fundamental categories in our lifeworld and a growing insecurity about the sources of agency – will be addressed in the chapter Engineering Intelligent Artefacts.

4.5.3. Forward engineering

The underlying assumptions and characteristics of (forward) neural engineering – as already described in subsection 4.5.1 – result in different ethical and legal issues. In the first place, the assumption that changing the brain is changing the mind or the self, results in issues on integrity and informed consent. Secondly, the experimental nature of neural engineering results in issues of liability. And thirdly, the converging of the neurosciences with information technology – innate to neural engineering – leads to issues of safety, privacy, bodily integrity and control.

¹⁰³ See www.frame.org.uk/dynamic_files/foa_replacingprimates.pdf

4.5.3.1. Changing the self

Mental integrity

Neural engineering of the brain – especially with neuromodulation – is, in many cases, a form of behavioural engineering: it usually results in changing the behaviour of the patient. This is of course the purpose of the treatment: Parkinson patients lose their tremor and OCD patients are relieved of their compulsive behaviour. But many times, unexpected side effects of the stimulation come up: hypersexuality, depression, apathy, etc.; mainly caused by a bad position of the electrodes. However, side effects are not always a direct effect of the stimulation; they can also result in psychosocial problems because of the immediate and overwhelming effect of the treatment. The life of the patient is radically changing from one day to another.

The European Group on Ethics in their report on Ethical aspects of ICT implants in the human body (2005) is of the opinion that ICT devices should not be used to manipulate mental functions or change personal identity. *"The right to respect of human dignity, including the right to the respect of physical and mental integrity is the basis for this"* (EGE, 2005: 32). Later on in the report, they even propose to ban the use the ICT implants for changing identity, memory, self perception and perception of others. Clinical practice – with at least 50,000 patients having a DBS device and most of them experiencing some degree of personality change – has, however, overtaken the position of the EGE.

The banning of neural implants might be obsolete; it is still important to outweigh the benefits of the treatment to the possible personality changes a patient will be undergoing. *"Such a change would only seem legitimate, if behaviour and personality were abnormal, and if this abnormality was beyond the threshold"* (Berger et al., 2008: 246). This can be complicated, for example, when a patient's libido increases when the DBS device is on – which happens regularly – and the partner of the patient is not happy with it. According to one of the interviewees, in one such case the doctors replied that this was "normal sexual behaviour for a man and that she had to get used to it". But who is to decide what is normal behaviour? Specifying a normal or abnormal degree of sexuality or sadness, indifference, etc. or identifying 'real' improvements, for that matter, is not an easy task. It is possible to make generalisations when it comes to very different personalities? Although there are standard scales from psychology that can function as a guideline, a case by case deliberation of the possibilities of neurostimulation might be the best option.

Informed consent

Another issue which comes up in relation to personality changes is whether someone would still consent to his treatment with hindsight or – a more traditional bio-ethical question – if he is capable enough of giving informed consent beforehand. The STOA study Human Enhancement (2009) points out that it is unclear whether someone is fully capable of giving informed consent before being stimulated because of the severity of the person's suffering or because he is only able to think as himself after the DBS is activated (once the mind-crippling depression is relieved, for instance). But also for fully competent persons, it is still very hard to decide about a future as a 'different person'. It is unclear whether this should have consequences for the notion of informed consent. DBS is intended for use on severely ill patients, to relieve them of their symptoms, but DBS is not the only implantable device that can alter or help brain functioning.

When persons are suffering from ALS, the progressive disease that leads to a locked-in state (LIS) it is also not an easy task to get informed consent. And once the patient reached the TLIS¹⁰⁴ stage, it is completely impossible to ask the patient himself for consent (as that stage is defined by the absence of all means of communication). For patients in the LIS stage of ALS it is questionable to what extent they can make an informed decision, because the severity of the disease and the prospect of the TLIS stage ahead might influence their decision. Also, if a patient in the LIS stage of ALS already lost many ways to communicate, the question surfaces how reliable the signals are. Is it really understood what the patient intends to say? Questions surrounding informed consent both hold for treatment as well as research interventions (Haselager et al., 2009).

4.5.3.2. Experimental nature

Liability

The very experimental nature of forward neural engineering results in pressing concerns about liability. The procedure of placing electrodes in the brain is a question of trial and error, just like the settings of the neurostimulator. There is no way of standardising these procedures, simply because every brain is different. Every brain is customised from conception onward under the influence of genes and a biological and social environment. The results can therefore be quite unexpected. The persons giving the treatment psychiatrists, surgeons and other doctors – are especially worried about liability (Denys, 2010). If people change under the influence of or directly caused by the engineering of the brain, especially in the case of implants, who is accountable and legally responsible for the changes and the resulting behaviour? Take for example, the Dutch patient treated for Parkinson's with DBS who became manic and uninhibited, started spending lots of money and showed sexual promiscuity. Who was responsible for the debts he made? Or what if a patient commits a crime when his DBS system is switched on? The patient, the manufacturer of the implant, or the surgeon who implanted and adjusted it? Is the patient still himself when he is stimulated, even though he is showing behaviour they would never show when not stimulated? In the case of the Dutch patient, the patient himself – when he was not manic and mentally competent – chose to turn back on the stimulator. The doctors decided to do this after mature consideration, although they knew what the consequences might be. Consequently, a compulsory admission to a psychiatric ward was a very complicated legal matter.

The same liability questions come up with BCIs. Take, for example, a BCI used to direct a wheelchair. What if there is an accident with the wheelchair; it bumps into a child or a car. Who is responsible for the possible damage? Did the patient sent the right brain signal? Or did the BCI device malfunction? Was there a failure in sensors? BCI systems contain increasingly complex intelligence, which results in more autonomy for patients because they are less confined to a particular situation in which they can use the BCI. At the same time, the complexity leads to more unpredictability, and perhaps in the end situations where things could go wrong and liability questions could turn up. Liability questions in relation to forward neural engineering applications need further research and legal consideration.

¹⁰⁴ The difference between LIS and TLIS is that in LIS the patient can still move his eyes, and can therefore still communicate with blinking. In TLIS, the patient has lost control of all voluntary movements.

4.5.3.3. Converging neuro and info

Regulating safety of invasive neurostimulation

The market for neurotechnology, especially for neurostimulators for pain relief, chronic migraine, epilepsy, severe depression, etc., is growing rapidly. A market study by Neurotech Reports predicts sales worldwide from 3.1 billion US dollars in 2006 to 7.6 billion US dollars in 2010 (see box 7). All these invasive neurostimulators are categorised as (implantable) medical devices which can be introduced on the market without previous authorisation (EC Directive 1993/42¹⁰⁵), as opposed to pharmaceuticals which need preliminary market authorisation. It is then up to the manufacturers who are responsible for the performance and safety of their devices. Most of the neurostimulators do fall into a higher risk category of medical devices because they are implantable or invasive devices. This means that the conclusions of the manufacturers must be confirmed by an independent third party (i.e. Notified Body). This usually means that the devices will need some kind of clinical evaluation – which may include a clinical trial – before it can enter the market.

Nevertheless, nowadays, in the EU as well in the US, there is an ongoing discussion on whether the regulation on (invasive) neurostimulators as medical devices is stringent enough. The reason for this is that, in general, the regulations surrounding medical devices like neurostimulators are less focused on the protection of the patient, consumer or research subject as they are with pharmaceuticals. With medical devices, "the functioning of the market and the process of innovation have been taken into account to a greater extent, leading to a less restrictive regime" (Berger et al., 2008: 244).

In 2005, the European Group on Ethics (EGE) already argued that, in particular, *"implantable devices for medical purposes should be regulated in the same way as drugs when the medical goal is the same.* [...] *The EGE recommends that the European Commission should launch legislative initiatives in these areas of ICT implant applications"* (EGE, 2005). The majority of the 200 respondents of a public consultation (with industry, regulatory bodies, etc.) of the European Commission on regulation of medical devices, however, rejected this idea. The respondents did not want a larger role of the European Medicines Agency (EMEA) because they feared that *"the involvement of EMEA would represent a move towards the adoption of a pharmaceuticals-like regulation for medical devices."* ¹⁰⁶ Such an approach would – according to the respondents – lead to delay and higher costs for placing new devices on the market and would have an adverse effect on the small and medium size enterprises which make up around 80% of the market. The business model of the neurotechnology market is quite different from the pharmaceutical market. Small start-ups cannot afford large, randomised, controlled trials like large pharmaceutical companies can.

¹⁰⁵ In 2007, both directives on medical devices (93/42/EEC) and implantable devices (90/385/EEC) have been revised by the directive 2007/47/EC – which has been in force since March 21st 2010 – aiming to streamline the definition on medical devices. However, problems remain, according to the Commission on their website. "Experience indicates that the current system does not always offer a uniform level of protection of public health in the European Union. New and emerging technologies have challenged the current framework, highlighting gaps and pointing to a certain scarcity of expertise." http://ec.europa.eu/consumers/sectors/medical-devices/regulatory-framework/index_en.htm

¹⁰⁶ See summary of responses to the public consultation on http://ec.europa.eu/consumers/sectors/medical-devices/documents/revision/index_en.htm

Only recently in the United States, a consumer group has criticised the process by which the Food and Drug Administration (FDA) approves medical devices, especially neurostimulation devices (Hines et al., 2010). The group called Public Citizen, founded by the liberal American politician Ralph Nadar, published a report in which they state that the FDA process has led to the approval of products including brain stimulation devices for psychiatric disorders that have not sufficiently been proven effective. The report especially focuses on the approval of vagus nerve stimulation devices for the treatment of depression. The consumer group charges that the FDA allows lower approval standards for devices than for drugs. The lead author, John Hines, states in an interview that *"we don't see a justifiable reason for that distinction. Many of these devices are being used to treat disease, so it is hard to fathom why one wouldn't require the same level of rigor in approving them as is required for drugs."*

In conclusion, there is a discussion in the EU as well as in the US on changing the regulatory framework on medical devices, including neurostimulators. However, up till now there is no consensus on whether to force the regulations up to the level of pharmaceuticals or not. Within the EU, it is not clear yet to what extent the Commission is going to take the results of the public consultation round into consideration, or even if and when a revision could be expected.

The fact is that safety issues always remain. Even if clinical trials are required by the Notified Body before the market introduction, slowly developing and rare risks can simply not be detected in a trial which lasts a few months to, at most, a few years (Greely, 2005). One could argue that the monitoring of the long term effects of these technologies should be a centralised European or even international effort.

Regulating safety of non-invasive neurostimulation

So far we have mostly discussed the regulatory framework concerning invasive medical devices like neurostimulators, but what about non-invasive neurostimulation through TMS and EEG based neurofeedback? Both can be treated as medical devices according to EU directives and the FDA, but since they are considered less invasive, they can be evaluated in a lower risk category. One interviewee, however, questioned the non-invasiveness of TMS since TMS treatment can result in permanent changes in brain activity. "TMS although not physically invasive, can be mentally invasive in that respect." At the moment, TMS has only been approved by the FDA for severe depression, but only *after* approval did it prove to be effective in a large-scale randomised controlled trial (Hines et al., 2010). Neurofeedback therapy seems to be on the market without approval from a regulatory body. Some manufacturers are selling the equipment without registration and without stating which conditions their equipment can deal with. They purposefully stay away from such claims. Most companies do not have the money to get the approval for their neurofeedback equipment to treat ADHD, autism, chronic pain, etc. According to an American stakeholder organisation, no company will put up funding in the future as well since if they get approval for, e.g., neurofeedback for ADHD, they are opening up the market for their competitors, since the FDA considers all neurofeedback devices "substantially equivalent".¹⁰⁷ According to others there is also a lack of consensus on the efficiency and costs of neurofeedback in relation to psychopharmaceuticals.

¹⁰⁷ www.aboutneurofeedback.com/fda_guidelines.htm

Regulating the safety of neurostimulation for enhancement

Another concern in relation to regulatory safety - in the long term - is the use of (implantable) medical neurodevices for the purpose of human enhancement (i.e. off-label use). In section 4.3 we have described some possibilities in the future for the enhancement of cognitive capacities through neuromodulation technologies. It is not clear from the literature or the EC directives to what extent medical devices which have been introduced on the market for certain clinical purposes can also be used or even prescribed for enhancement purposes. Take, for example, the case of the deep brain stimulation for the OCD patient who – when stimulated – felt extremely much happier than before, although her compulsive behaviour did not diminish (see box 8). An important question here is: how much risk should we allow in a medical device that does not treat the disease but improves normal function? Normally, the safety risks are weighed in the light of the disease. If it were to weigh the risks against the health benefits of a medical device, it might require almost complete safety (Greely, 2005). Amongst the respondents of the public consultation there was broad support for the regulation of at least the implantable or invasive devices for - what they called - aesthetic purposes. "Most contributions from industry [...] stated that the Medical Devices Directives should not be opened up to devices that do not have a medical purpose in order to avoid derogation from the risk/benefit principle [...]. "108

Privacy

The consideration on privacy issues in relation to the collection of genetic data is rather well-established. For a couple of years there has also been a discussion among experts on privacy issues surrounding neuroimaging data. The concerns are not as pressing as some other problems, but they have to be addressed in the longer term.

First, there is the potential need for regulating `mental privacy'¹⁰⁹ or `cognitive liberty'¹¹⁰ when it comes to not yet mature applications of brain reading and lie-detection. However, if one assumes – as many do – that the brain is identical to the mind, then measuring brain activity comes close to measuring one's cognitive state or even thoughts. This makes the issue of privacy – in the long term – more urgent than with genetic data, since thoughts can be considered to be as central to our sense of self as our genes.

Neural engineering applications like BCIs or neurofeedback also collect neuroimaging data. In the future, DBS systems will be monitoring brain activity as well. Most of these data can not be deduced to actual thoughts; they are mostly imaging data of neuronal activity in the motor cortex. The privacy impact of motor data is, of course, much less than those of data on cognitive states which reveal certain preferences or lying. Still in the long term, it is important that that information about a patient's brain and mind cannot be accessible for others without permission, as the EGE warns in their opinion on ICT implants in the human body: *"Therefore, any type of ICT implant requires a strict preliminary evaluation in order to asses the privacy impact"* (EGE, 2005: 17). The EC directive on personal data protection should be applied here. This means that individuals have the right to determine what data about themselves is to be processed, by whom and for what purposes.

108 See footnote 45.

110 http://www.cognitiveliberty.org

¹⁰⁹ http://www.wired.com/techbiz/people/magazine/16-04/st_thompson

Another privacy concern in the long term is that the purposes of therapy, diagnostics and research might get mixed up. For example, in order to optimise the stimulation, DBS systems will also start monitoring and analysing brain activity. These large databases of privacy sensitive brain data of patients might be interesting for research, especially for comparing with other databases, and the interest of the patient might be overlooked; resulting in a situation that can be compared with the use of body material in biobanks for research (see Chapter Engineering the body). Usually, patients are only asked at the beginning if they object to the possibility that their material – or in this case data – is to be used for other purposes than it was collected for. And sometimes permission is not asked at all. The call for strict regulation on the usage of bodily material can be heard in different European countries (Boenink, 2009). It might be interesting to investigate whether the directive on personal data protection suffices for safeguarding the privacy of patients' brain data.

Bodily integrity

Forward neural engineering comes down to the hybridisation of man and machine. When biology is becoming technology and the arrival of neural implants like neurostimulators and BCIs result in so called 'cyborgs', the integrity of the body is at issue. How do we define the body and where do we draw the line between the artificial devices that do and those that do not belong to the body? Can we consider neural implants as part of the body and do they therefore fall under the protection of the integrity principle? When people start to think of their neural implants as indissolubly connected to their body and their identity, should their implants be legally considered as part of their body? This means that the moral and legal meaning of body and bodily integrity should be reconsidered (Schermer, 2009).

Remote control

Some (implantable) devices, like DBS, can produce different results with different settings, and these settings can be changed via a remote control like any other IT device. An important question is, of course, who is in control of the remote control? The EGE is outspoken about the issue of the remote control: "The dignity principle prohibits transformation of the body into an object that can be manipulated and controlled remotely - into a mere source of information" (EGE, 2005: 33). At the same time, sometimes patients themselves control the remote. They are able to adjust the settings, which gives them a great deal of autonomy, especially since effects are so immediate and also reversible. For example, some Parkinson's patients have speech problems when stimulated. One patient therefore switches the system off when he has to give a lecture, resulting in his tremor coming back. But when the lecture is finished, he turns it on again (STOA, 2009). Applying the dignity principle mentioned in the Charter of the Fundamental Rights of the European Union should result in giving the patient as much autonomy in controlling the DBS device as possible. It may therefore be advisable to develop a benchmarking system that helps doctors decide when it is possible and desirable to give patients the remote control of their DBS device.

4.6. Conclusion

The field of neural engineering as described in this chapter consists of two quite different engineering subfields with separate scientific communities: reverse engineering of the brain and forward engineering of the brain. Reverse engineering tries to understand the design principles of the brain by building representations or simulations of parts of the brain in either software, hardware or wetware. The scientists involved are (computational) neuroscientists and bio-engineers, but also scientists with a background in artificial intelligence since one of the important aims of the field is the development of brain-based intelligence: computers that function like a brain – parallel, adaptive, low on power, etc – but have the advantages of being programmable. Forward engineering is about developing tools - mostly electronic devices - that support, manipulate or augment the brain. This subfield is very much part of the medical realm that includes psychiatrists, psychologists and surgeons, but bio-engineers and cognitive neuroscientists as well. An important similarity between the two subfields is that they are both strongly influenced by computer sciences and informatics. Without the current possibilities of the informatisation and digitisation of (recorded) brain activity, both subfields would not have progressed. Besides, the technology driven field of ICT that strives for the miniaturisation of microprocessors, sensors and electrodes - nowadays at cell level - has been very supportive to both subfields as well.

Reverse engineering

Reverse engineering the brain has attracted its share of criticism. It has been hard to imagine for many that building a brain bottom-up in software – based on the continuous monitoring of neuronal activity in animal models – without having a grand theory of how the brain works, can actually result in a working brain. However, progress has been made – especially by the Blue Brain project – and their mathematical model can successfully replicate the cellular events in a neocortical column composed of 10.000 neurons with 30 types of ion-channels and 30 million interconnections. The computational structure of the software actually does what the biological structure does. This is a perfect example of technology becoming biology. Markram, chief scientist of the Blue Brain project, says, *"every week the model becomes more biological. It is very much like a real bit of tissue."* The extent to which biology can be mimicked in all its details is not clear yet. Will a larger numerical brain model – which needs a lot more data processing power (i.e. 500 petabytes) than is available at the moment – actually develop cognitive abilities or even consciousness?

While the main aim of software simulations of the brain is to understand the brain and brain disorders and to give neuroscientists pieces of virtual nervous tissue to test their hypotheses and pharmaceuticals on, the hardware approach is aiming to build supercomputers. Progress has been made, also because the European Union has been generously sponsoring the field of neuro-inspired computing for several years now, mostly within larger cutting edge IT programmes. This has resulted in actual operating systems – although not widely used yet – and a well-established research community. Technology is slowly becoming biology here as well, but it will probably take years before there will be any killer applications for neuromorphic computing systems. More generally, the brain has been used already as an inspiration source for AI development, e.g. algorithms for speech recognition and machine vision systems.¹¹¹

¹¹¹ For example, in Eindhoven professor Bart ter Haar Romeny develops biologically inspired computer vision systems for computer aided diagnoses (e.g. to find tumours or polyps) based on the human vision system. His algorithms are based on the concept of the visual system as a multiscale imaging machine.

A much heard criticism on the cultured neuronal network approach within reverse engineering is that the cell cultures of real life neurons grown on a multi-electrode array are too remote from the natural situations of neurons. These models could therefore not help to fundamentally understand neuronal mechanisms. They can, in the future, be used as a controlling device for prostheses or robots or as a drug-screening device. The instrumentalisation of neurons of new-born rats for the development of prostheses or biosensing systems allows us to speak of biology becoming technology.

Forward engineering

Forward engineering of the brain is - in terms of killer applications - doing much better than the subfield of reverse engineering which is still in its infancy. Especially neuromodulation technologies for pain relief, chronic migraine, Parkinson's and epilepsy are emerging and responsible for worldwide sales of 7.6 billion US dollars in 2010. Also, noninvasive techniques like transcranial magnetic stimulation are slowly entering the market, e.g. for severe depression. While the progress in the development of psychopharmacologic drugs seems to be slowing down, neuromodulation devices are gaining momentum and are easier to introduce on the market. It turns out that electronically influencing brain activity can be much more precise than chemical interventions, although side effects can be much more severe as well. Still, this novel engineering approach to brain disorders has been more effective and has fewer adverse side effects than its predecessors which are (irreversible) lobotomies, being tranquilised completely and permanently, and (irreversible) ablations.¹¹² An important next step in the development of neuromodulation devices is the development of wireless devices. With clinical applications opening up, biology is indeed becoming technology in the sense that more and more people have and will have neuromodulation devices implanted in their brains or central nervous systems. When it comes to non-invasive neurostimulation through neurofeedback or TMS, this is, however, not the case.

While there are only a few EU sponsored research projects on neuromodulation, brain computer interfaces (BCIs) projects receive a lot more funding. This is probably because there still remains a lot of fundamental research to be done. No invasive BCIs have been placed routinely yet. They have only been placed in very small patient groups who are almost completely paralysed. Outside the medical realm, research on mostly non-invasive BCIs is done, for example in the gaming industry or in the army. But here as well, no killer applications yet. Invasive BCIs can be presented as examples of biology becoming technology in the same way as invasive neuromodulation can: it blurs the boundary between humans and machines.

Engineering perspective

It should not be forgotten that in large parts of neuroscience, engineering methods to understand the brain are not being used; instead, there are methods like observing nature (e.g. neuroimaging studies) or building theories (e.g. like in theoretical neurobiology). The neural engineering approach seems to slowly become more popular, just like biomedical engineering in general. Recently, there has been an increase in newly published scientific journals on neural engineering. However, no bibliometric or other analyses are available to support that the neural engineering approach is gaining momentum.

¹¹² Ablations are lesions created in the brain during surgery, permanently disrupting the functioning of that particular brain region.

The attractiveness of engineering the brain seems to lie in getting new findings much faster than through theoretical approaches. For example, Dharmendra Modha, working at the SyNAPSE neuromorphic project, says, *"the quickest and cheapest way to engineer mindlike intelligence into machines is to reverse engineer the structure, function and dynamics of the brain with its low power consumption and compact size"* (Friedman, 2009). This is the same style of thought as described earlier on as part of the third (engineering) culture in which scientists are not seeking truth but novelty. Likewise, in forward engineering, *"creating new tools is faster than creating new theories"* (Kelly, 1998). It seems that, because still a lot is unknown about the brain and the mind, serendipitous findings on brain activity in research on neuromodulation or BCIs are quite common. Side or unexpected effects of earlier attempts at neurostimulation have led to new research more often than not. It seems that neural engineering is partly about purposefully building unforeseen effects and unpredictable behaviour in order to stumble more rapidly upon new findings.

Ethical, legal and social issues

Since forward engineering of the brain has made much more progress in terms of applications than reverse engineering, it seems only logical that there has been more discussion about ethical and legal concerns on neuromodulation and BCIs. The debate on reverse engineering of the brain is still in its infancy; the most pressing issues concern the supposed increase in animal experiments (including animals with higher cognitive functions). This issue can be directly deduced to the trend of technology becoming biology where input from biology (i.e. animal brains) is very important in order to mimic it in technology. Other concerns in the long term are also related to technology becoming biology: will we be able to develop conscious machines and should we allocate a state of agency to these machines?

The issues concerning forward engineering are related to three specific characteristics of neural engineering: its experimental nature, its converging nature – neuroscience with information technology – and the fact that neural engineering is in many cases behavioural engineering which can result in personality changes. These three characteristics make the traditional bio-ethical issues involved more profound; in particular, mental integrity, informed consent, liability, regulating safety, privacy, bodily integrity and remote control issues. Therefore, it is remarkable that, unlike with emerging technologies like synthetic biology and nanotechnology, the EU is not yet funding any large ethical, legal and/or sociological projects in the neurosciences, or in neural engineering for that matter.

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5. ENGINEERING OF INTELLIGENT ARTEFACTS

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5.1. Introduction

Technical artefacts are becoming more lifelike in the sense that they are acquiring properties we used to associate with animals or humans. "Intelligence" is such a property which is by default assigned to human beings and not expected from technical artefacts. Designing artefacts like robots and avatars which have to prove their viability in human computer interaction and in human environments and social contexts require a concept of "intelligence", which addresses intelligent behaviour. This shift is reflected in the concept of situated or behavioural Artificial Intelligence (AI), which aims to increase the performance of technical artefacts which are situated by design (for purposes of communication or cooperation) in man-machine environments. Making *perfect* life requires in a sense perfectly aligned and adaptable artefacts with lifelike behaviour. In this chapter we distinguish between three different engineering approaches to achieving lifelike features of artefacts or "intelligent artefacts" (IA):

1) Engineering that aims to model and implement properties of living beings such as learning, adaptation to changing situations and autonomous behaviour, often relies on biological metaphors as guiding visions, for example "neural networks" or "swarm intelligence". But beyond biology, all behavioural sciences may contribute metaphors and guiding visions, e.g. the *Leitbild* (guiding vision) of a service robot as a "companion".

2) Artefacts meant to enter social relations require an interface which facilitates the manmachine relation. The engineering of lifelike behaviour at this point turns to emotional, affective and expressive qualities such as "body-language", expression of moods, etc. These cues are already more anthropological than just biological.

3) Human beings become a primary source for the extraction of neuro-physiological, physiological (i.e. biological), psychological, and social data (pulse, heart rate, facial expressions, illness, anxiety, stress etc.), which are used as input to increase the adaptability and lifelikeness of situated intelligent technical artefacts.

In the next section (section 5.2) we briefly sketch the history of Artificial Intelligence (AI) research to describe some lessons learned and we introduce – because of their relevance for the construction of intelligent artefacts - more recent paradigms of AI such as affective computing, ambient intelligence and situated AI. In this section we also discuss in more depth two types of IA, namely physical robots and "virtual robots" (software-agents, avatars) with their respective capabilities (autonomous acting, adaptation and learning) and shapes (anthropomorphic, zoomorphic or non-biological). The next section (5.3) focuses on European research, in particular within the 6th and 7th Framework Programme. Section 5.4 gives an overview of various social and ethical issues that might be raised by the development and use of various intelligent artefacts. The final section (5.5) concludes in what way and to what extent the engineering of Intelligent Artefacts should be on the research policy agenda. The analysis presented incorporates knowledge from external experts, all of whom have experience as coordinators of EU-funded projects in the field or have acted as European high-level experts.¹¹³

¹¹³ The authors wish to warmly thank the following experts who answered our questionnaire and shared ideas on the subject: Rafael Capurro (Karlsruhe, Germany), Cristiano Castelfranchi (Roma, Italy), Henrik Christensen (Atlanta, USA, and Stockholm, Sweden), Brigitte Krenn (Wien, Austria), Peter McOwan (London, UK), Sabine Payr (Wien, Austria), Giulio Sandini (Genova, Italy), Marc Schröder (Kaiserlautern, Germany), Nikola Serbedzija (Berlin, Germany), Guglielmo Tamburrini (Napoli, Italy), and Vincent Torre (Trieste, Italy).

5.2. State of the Art

There is no universally accepted definition of (human) intelligence. According to Sternberg, intelligence is "the ability to adapt to, shape and select environments["] (Sternberg in Wilson and Keil, 1999: 409-410). Research by one of the pioneers in the field, Spearman, suggests three types of information processes underlying intelligence: apprehension of experience, and education of relations and correlates. Alternative proposals, however, suggest the existence of multiple intelligences. Gardner argues for eight intelligences: linguistic, mathematical-logical, spatial, musical, bodily-kinaesthetic, interpersonal, intrapersonal and naturalist (Gardner, 1983).

This chapter does not deal with human intelligence, but machine intelligence or artificial intelligence (AI). It is important, therefore, to bear in mind that many terms used in AI are borrowed from science on human and animal intelligence and should be understood as analogies rather than as an exact equivalent. AI traditionally focussed on rational aspects of human intelligence which can be replicated sufficiently well on computers. Modern AI, also called situated AI, tends to focus on other aspects of human intelligence, such as those related to having a body, emotion and living and acting in complex social environments. But also the ability for social interaction and emotional skills has become more important within modern AI. Such a shift brings up new engineering challenges.

5.2.1. The Chequered History of Artificial Intelligence

Intelligent artefacts (IA) presuppose a possibility to engineer artificial intelligence. Since its establishment in the 1950s, the field of AI has experienced many ups and downs, both with respect to expectations and funding. A theme accompanying AI for most of its history is the controversy whether it is possible to fully understand human intelligence and replicate this on machines, eventually improving on human intelligence: "strong AI". The proponents of "strong AI" always have and still do play a big role in attracting media attention for AI and in creating high expectations. More modestly, proponents of "weak AI", seek to engineer machines which perform tasks with similar results as intelligent living beings. In both cases, the products of research result in computer programmes representing intelligent processes. The field of AI is influenced by the ever-changing scientific understanding of the concept of intelligence over time. In particular, advances in cognitive sciences have had impact on AI research. These include an intellectual transition from 'cold' to 'hot cognition' inspired by the development during the 1990s of a new approach towards AI, so-called situated or embodied AI.

Modern AI research history conventionally starts with the "Dartmouth Conference" in 1956, where John McCarthy proposed the name "artificial intelligence" for a study *"to proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it"*. Until the 1970s the field of AI was dominated by such a "symbol-processing" approach. Even then, Herbert Simon and Allen Newell claimed that with computers, the world already had machines with the potential to think, learn and be creative. Newell and Simon's programme, called the General Problem Solver (GPS), strengthened and popularised a belief in machine intelligence. In 1958 they famously predicted that, among other things, within the next decade a computer could defeat the reigning world champion chess player, discover and prove important new theorems and compose music of high aesthetic value (Simon and Newell, 1985: 1-10). Beating the world champion chess, however, took some forty instead of ten years: Even the best contemporary chess programmes still rely to a large extent on "brute force", i.e. the ability to compute a large number of options and their consequences in a very short period of time.

Another engineering approach to AI in the early 1950s was inspired by the model of the brain as a vast network of neurons and synapses (McCulloch and Pitts, 1943: 115-133). It was thought that the implementation of a model of the human brain describing brain cells and their communication with each other in terms of electronics in computers would lead to the emergence of artificial intelligence. An important assumption of this approach was that the activity of neurons had "all-or-nothing" character and could thus be modelled by binary programming (on/off or 0/1 states). In fact, empirical data now indicates that this is not the case. The most promising embodiment of the neural network approach was a category of machines known as Perceptrons (Rosenblatt, 1962).

At the end of the 1960s, faith in the feasibility of both approaches declined sharply. The neural network approach was criticised as a dead end by Minsky and Seymour Papert (Minsky and Pampert, 1969). The symbol-processing approach ran into severe practical and ontological problems. Simon himself conceded that for psychological theory, a distinction was required between so-called "cold cognition" - processes like reasoning, planning, perceiving, and deciding – and "hot" cognition - desire, feeling pain or pleasure, and having emotion (Simon, 1967: 29-39). One of the reasons for AI's failure at that point of time was the lack of sufficient computing power. Combinatorial explosion meant that all but trivial problems required immense computing time for their solution. There was also a need to create new types of logic for solving problems and for considering common sense knowledge and reasoning which humans acquire quite naturally through experience and learning. At the time, AI faced the paradoxical situation that it is relatively simple for computers to prove theorems or solve geometry problems, but difficult to accomplish rather trivial tasks such as recognising faces or crossing rooms (Moravec, 1988)¹¹⁴.

A first "AI Winter" with severely restricted funding for AI research lasted until roughly 1980. Around that time new hope arose with the appearance of so-called expert systems. The development of such systems was based on the belief that experts implicitly based their decision-making on a set of rules which could be explicated and translated into computer programmes. Additional impetus for AI in the US and Europe came from the announcement in Japan of the so-called Fifth Generation Project, a funding programme for machines that could carry on conversations, translate languages, interpret pictures and reason like humans. This period was dominated by attempts to "engineer knowledge" and to create massive databases of such things as commonsense knowledge. It also saw the revival of neural networks or connectionist systems with a seminal collection of papers published in 1986 (Rumelhart and McClelland, 1986). Commercially successful applications of neural networks have existed since the early 1990s with uses for optical character recognition and speech recognition. AI also achieved a number of successes enabled by long term exponential increase in computer power ("Moore's law"). One successful mainstream product of AI research is the "intelligent agent", a system programmed to perceive its environment and to take actions maximising its chances of success. Intelligent agents are put to use on the Internet, e.g. in search engines or recommendation systems, or in decision-making. However, AI as a whole failed to meet up with the extravagant expectations it had fostered itself. In particular, expert systems proved difficult to keep up to date and made grotesque mistakes when confronted with unusual problems. These and other problems led to a second AI winter in the late 1980s and early 1990s.

¹¹⁴ This is the so-called Moravec paradox as described by Hans Moravec (Moravec, 1988).

However, the late 1980s also saw the emergence of attempts within AI to tackle what Simon had called "hot cognition". One new approach to AI is known popularly as "situated" or "embodied" AI which is built on the notion of a "bottom up" accumulation of intelligence similar to that of the human child. Situated AI builds on the belief that a machine needs to have a body moving around in the world to display true intelligence. This approach sees intelligence as an emergent property. It gives "the evolutionary code full access to the substrate" and thus "the search procedure does without conventional human biases, discovering its own ways to decompose the problem - which are not necessarily those human engineers would come up with."¹¹⁵ A recent "Festschrift" on the occasion of the 50th anniversary of the Dartmouth Summer Conference reviewed AI's history and achievements (Lungarella, 2007). It signals a need for a new unifying view of intelligence, and beliefs that AI is gradually transforming from a heuristics-dominated science to a real, formal science (Schmidthuber, 2007: 29-41, 32). Most papers have a strong bias towards embodied intelligence. However, prominent AI researchers like Luc Steels, still argue for the physical symbol system approach and for the coexistence of several approaches side by side (Steels, 2007: 18-28).

Much AI research currently runs under names such as "cognitive systems", "knowledgebased systems" or "computational intelligence". In a paper for the EU High-Level Expert Group on Key Technologies, Daniel Andler describes cognitive science as "the interdisciplinary study of mind and brain, combining the concepts, methods and insights of large parts of psychology, neuroscience, evolutionary biology, linguistics, philosophy, anthropology and other social sciences, and formal methods from computer science, mathematics and physics" (Andler, 1995: 3). According to Andler, the contribution of each of these cognitive sciences is needed to achieve a full scientific understanding of the brain as "an integrated system supporting the entire array of mental functions". Fuelled by a continuous increase in computing power and advances in brain sciences, Andler believes it is only a matter of time until the functioning of the human brain will be fully understood and 'true' artificial intelligence can be realised (Andler, 1995: 9). An interdisciplinary endeavour to create conscious machines, thus, has become an integral goal of current cognitive sciences.

While not entirely belonging to AI research, "affective computing" (see also 5.2.3.2), which has been the subject of intensive research since the mid-1990s, is also of importance to IA. One application area of the results of research on affective computing is in the design and shaping of human-machine interfaces. The goal is for the machine to recognise emotions in its human user and to adapt its own actions to cope with these. By making computers and IA incorporating such computers adaptive and "user friendly", it is hoped to achieve greater acceptance of these artefacts (Picard and Klein, 2002: 141-169). Affective technology is also being used to research autism and to enable communication with persons on the autism spectrum (Picard, 2009). Similarly, results are being used in learning (Picard et al., 2004: 253-269). Finally, there are endeavours to endow computers and IA with emotional properties. Rosalind Picard, one of the leading researchers in the field, expresses her doubts about the possibility that computers could actually "have" feelings, but also notes that *"researchers have charged ahead with building machines that have several affective abilities, especially: recognizing, expressing, modelling, communicating, and responding to emotions"* (Picard, 2003: 55-64).

¹¹⁵ http://www.cs.brandeis.edu/~pablo/thesis/html/node22.html, accessed 10 March 2010.

Various interviewed experts pointed out the "as if" nature of affective computing: the artefact seems to recognise and exhibit emotions, but these are all the result of programming (see also 5.2.3.2, Box 12)¹¹⁶.

Finally, the field of "artificial life" (or, shorthand, "A-Life" aka "AL"), which evolved in the 1980s, needs to be mentioned here. Much as AI highlights the problematic concept of intelligence, "A-Life" highlights the concept of life (Boden, 2001: 37). "A-Life" research can be defined as an "interdisciplinary study of life and life-like processes that uses [...] three different synthetic methods. 'Soft' artificial life creates simulations or other purely digital constructions that exhibit life-like behaviour, 'hard' artificial life produces hardware implementations of life-like systems, and 'wet' artificial life synthesizes living systems out of biochemical substances" (Bedau, 2003: 505). The boundaries between AI and cognitive science on the one hand and "A-Life" on the other are contested (with cognitive scientists and AI researchers often characterising "A-Life" as a marginal subfield of their fields), but it is uncontroversial that they share common roots in cybernetics¹¹⁷. "A-Life" is of interest in the context of this project mainly for three reasons. Firstly, "A-Life", while for many years predominantly working with non-biological methods (such as computer simulations), has increasingly become "wet" which has led, for example, to the development of a subfield of synthetic biology, namely "proto-cell research" (see chapter 3) which was pioneered by "Alife" researchers. Secondly, "A-Life" researchers have joined forces with AI researchers who, having turned away from "classical" AI approaches, are working on embodied intelligence. Thirdly, we can see here one of the few examples of the trend of "biology becoming technology" in the area of intelligent artefacts: "animat" research - an area at the intersections of AI and "A-Life" focusing on animals - has also increasingly become "wet" in the last two decades and in this process started to integrate biology into technology, connecting, for example, neuronal cultures from rats with robots (see chapter 4).

In the following, we distinguish between two different types of intelligent artefacts (IA):

1) Robots, which can be sub-divided into anthropomorphic robots modelled on human beings and other types, such as zoomorphic robots modelled on animals, or even not modelled on any known being (5.2.2).

2) Software agents (also called "softbots") and avatars developed to improve humancomputer interaction and to mediate communication between humans (which will be discussed in section 5.2.3, focusing on lifelike agents and avatars on screen, or, to use a more general term, on computer-generated anthropomorphic characters).

¹¹⁶ The man-machine interface aspect of affective computing is also an essential element of ambient intelligence (AmI) and a necessary condition for making smart environments adapt to their inhabitants' changing emotional states and desires. AmI presents one of the central European visions on the future of the information society. It refers to a physical environment (ranging from the house you live in to public space) that is context aware, personalised, adaptive to and anticipating on user needs. According to Schuurman and colleagues "Ambient Intelligence literally means that people are surrounded by intelligent equipment. A smart environment not only knows that people are present but also who, and with what characteristics, needs, emotions and intentions. That is made possible by computers and sensors that – continuously or periodically – measure our physical functions, such as our blood pressure, muscle tension, heart rhythm or sugar level. Technology is becoming increasingly smaller and can, in principle, be incorporated anywhere: in appliances, in walls, in clothes or in our body. A smart environment can automatically respond to changing conditions, can give the user advice or transmit a signal to a contact person. An example is a sensor which observes that an elderly person falls, after which a care provider is automatically warned" (Schuurman et al., 2009). Intelligent living environments can be considered as IA. For example, the EU project Emergency Monitoring and Prevention (EMERGE) envisions an apartment that can be considered as a robot system (Seelisch, 2007). 117 Compare, for example, Bedau (Bedau, 2003), with Boden (Boden, 2001)

5.2.2. Robots

The term "robot" was derived from early 20th century literature (Čapek, 1920). It denotes machines that are apparently able to work independent of direct human control. There is currently no uniformly agreed definition of "robot", although the international standard ISO 8373 defines it as "an automatically controlled, reprogrammable, multipurpose, manipulator programmable in three or more axes, which may be either fixed in place or mobile for use in industrial automation applications." This definition refers to a typical industrial robot which exists in numbers of many thousands and has a single arm, is fixed and programmed to do a single task, such as welding or spraying automobiles. It is isolated from humans - often in a cage - for reasons of labour safety.

However, mobile robots are increasingly being designed for applications outside manufacturing. These must have the ability to acquire information from their environment and to adapt their actions according to this information. The following definition refers to technical aspects as well as the ISO Standard, but in a general sense,"robots are sensumotoric machines to extend the capabilities of human action. They consist of mechatronic components, sensors and computer-based control and guidance functions. The complexity of a robot can be clearly distinguished from other machines in terms of the higher number of degrees of freedom and the variety and scope of its forms of behaviour" (Christaller et al., 2001, p. 5)¹¹⁸. This definition also makes a direct connection to human activity and describes the basic components of a robot. A central element in all robots is provided by computer programming, usually based on research in "artificial intelligence". Other contributions are provided by electrical and mechanical engineering (together "Mechatronic"). However, these "technical" definitions are not valid for the current discussion of "autonomy" or even "intelligence" in modern robot systems. In contrast, Trevelyan concentrates almost exclusively on this one aspect, defining robots as intelligent machines that extend human capabilities (Trevelyan, 1999: 1211-1223).

In the following section we sketch some major, and to a large extent disconnected, developments in robotics. Robotics is a highly modular field of research which allows, by means of "intelligent programming", the combination of achievements in different subdisciplines of robotics.

5.2.2.1. Autonomy

If robots are to leave their "cages" and should become supportive in everyday and changing environments, this cannot be achieved through onsite programming by a robotic expert. A typical user is not a robotics expert and therefore not capable of detailed programming either. Robots therefore need to be autonomous in the sense that they are able to figure out their environment for movement, they need to identify tasks to do and they need a capacity for some decision making in order to fulfil a task in the best possible way. Most tasks for autonomous action can be realised by top-down programming.

¹¹⁸ One weakness in this definition lies in its distinction between robots and other, simpler machines. An automatic garage door has mechatronic components, a control unit and sensors, which, for instance, recognise the arrival of a vehicle or the presence of an object in the closing space. However, one would assume that the "variety and scope of its forms of behaviour" are insufficient to qualify it as a robot. In contrast, a modern passenger aircraft has a multitude of microcontrollers and actuators as well as a superior hierarchy in the area of control in terms of the autopilot. In this case, using the above definition, this would qualify as a robot, due to the higher complexity of the system.

The so-called "Robocup" competitions are popular benchmarks for the assessment of progress in the field of autonomous robots. The earliest and best-known is a football competition, of which the ultimate goal is described as follows: "By the year 2050, develop a team of fully autonomous humanoid robots that can play and win against the human world champion soccer team. "119 Obviously football is a fast sport with high uncertainties, requiring fast and robust decision taking in order to react to permanently changing situations. A later competition is RobCup Rescue, which is focused on disaster rescue: "The intention of the RoboCup Rescue project is to promote research and development in this socially significant domain at various levels involving multi-agent team work coordination, physical robotic agents for search and rescue, information infrastructures, personal digital assistants, a standard simulator and decision support systems, evaluation benchmarks for rescue strategies and robotic systems that are all integrated into a comprehensive systems in future"¹²⁰. Finally, there is RoboCup@Home: A set of benchmark tests is used to evaluate the robots' abilities and performance in a realistic non-standardised home environment setting. Here it is necessary for the robot to be able to navigate in dynamic and unknown environments, to view and recognise different things in changing light conditions, to manipulate objects and to interact with humans in a sensible way.

According to the visions of the developers and of funding agencies, healthcare and elderly care will be an important application area of future robot systems. This is also underlined by the results of our expert interviews. Five of the nine technical experts mentioned healthcare and assistive living at home as most relevant application fields. Additionally this is an area where close collaboration between professionals (such as care takers) and other people (such as elderly people or patients) become part of the cooperation. Through this health care is of specific interest from a technology assessment perspective.

In healthcare, R&D is being done on robots able to lift patients in and out of bed. Also, humanoid and animal-like robots (pet robots) are expected to be used as companions for the elderly or others who may feel the need for companionship. The appeal of these kinds of robots is thought to be partially due to their therapeutic qualities, resulting in a reduction of stress and loneliness among the elderly and infirm (Harper et al., 2008). Robots are being designed for household use as automatic vacuum cleaners, lawn mowers or floor cleaners.

There are already commercial applications in these areas which are generally called "robots", e.g. vacuum cleaners equipped with a multitude of sensors for control and able to autonomously clean living spaces without endangering inhabitants or breaking furnishings¹²¹, or robot animal companions for the elderly and infirm, such as the well-known seal robot Paro¹²², which is used principally for therapeutic purposes. These examples are not particularly sophisticated with respect to the existing visions of "IA", although they might appear as "intelligent" to some users and are marketed as robots.

Robots in elderly care focus on the wellbeing of patients by supervising medical data and functioning as communication tools. In both professional care facilities and at home, elderly or handicapped people are normally lusty enough to live without permanent personal supervision by a care taker. However, the problem occurs when the "abnormal" situations appear. Robots are proposed for closing the gap between autarky of patients and permanent care taking.

122 http://www.parorobots.com/

¹¹⁹ http://www.robocup.org/organization-of-robocup/

¹²⁰ http://www.robocup.org/robocup-rescue/

¹²¹ For example: http://www.irobot.com/de/home_robots_roomba_tech.cfm

This is, for example, how GeckoSystems (USA) advertises its service robot "CareBot" which measures and stores vital data of the patient and submits them to the personal physician. It is also able to remind patients to take their medicine. Since it is equipped with a screen, a camera and a microphone, remote control and supervision via Internet are also possible.

The German Fraunhofer institute for production engineering and automation (IPA) has developed Care-O-Bot III which, in a way, blurs the distinction between assistant and carer. This robot supports the mobility of patients by assisting in walking and it is able to grab objects with precision, using three very tactile fingers on a robot arm. Care-O-Bot is also provided with communication equipment and participates in the support of needy persons, as assistant and carer in one.

5.2.2.2. Adapting and Learning

If robots are to be put into the position of carrying out actions in specific service sectors and different contexts, then they must be able to adapt themselves in some fashion to different contexts of action if their services are to be helpful, particularly where these contexts are complex. In the process, the robot must be able to learn.

This begins with its perception of the environment via sensors, continues with the planning of actions on the basis of this sensory data and leads finally, if one assumes that the robot does not always restart from the beginning, to learning – adaptation to the context of action. Here, strict top-down programming no longer seems possible (see below). The *"ability to learn on the basis of on-line perceptual (also proprioceptive) data and act on the basis of past experience"* and the ability for *"social behaviour and situatedness"* were mentioned by interviewed experts as specific areas in which breakthroughs are required for the advancement of the whole research field.

If we consider how humans learn, for instance through parental explanation, copying siblings, or by trying something out, then it becomes obvious that trial and error is an integral part of learning. When a person perceives something that is worth learning, they take the next opportunity to try it out. If the trial is successful, what has been learned is validated; if the trial fails, it is questioned.

In robotics research, the central significance of trial and error is taken into account. The most recent research projects place the experimental (XPERO, 2006) or playful (BCCN 2006) nature of learning at the centre of their research strategy. Yet this thought is not new (Mjolsness/DeCoste, 2001; Weng et al., 2001), and it is also a central aspect of the famous robot system "Cog" developed at MIT, which is designed to learn "like a child" from the people around it (Brooks/Stein, 1994; Brooks, 1997). To permit this experimental, playful type of learning, artificial neural networks are used¹²³. Artificial neurones are combined to exchange signals with one another. Incoming signals are transferred over a weighting factor to the output signals. The "training" of the artificial neural network then reflects the variations in the weightings (Decker, 1997: 12ff).

¹²³ Next to "connectionism" (Matthias, 2004: 178) quotes also "reinforcement leaning", "genetic algorithms" and "genetic programming" as examples for creating "autonomous" agents and contrasts them with symbolic "expert system" like programmes, in which "the knowledge of expert systems are stored inside the system in the form of explicit, distinct, quasi-linguistic symbols. They can be inspected at any time and, should need arise, be corrected".

An artificial neural network thus represents a signal input-output unit which does not admit any possible interpretation of its internal processes: "In artificial neural networks, the symbolic representation of information and flow control disappears completely: instead of clear and distinct symbols we have a matrix of synaptic weights, which cannot be interpreted directly anymore" (Matthias, 2004: 181). Matthias notes that the same is true for further learning algorithms and deduces from this that there is a gap as to who is responsible for the actions of learning robots.

5.2.2.3. Shape Matters

The shape of the robot might be of less relevance as long as the robot is able to fulfil the tasks it was built for. While some of the experts interviewed for this project see the human-like shape as simply needed, others argue that a human-like shape is not helpful at all. Most of the experts argue that the shape of the robot should refer in a sensible way to the tasks to be fulfilled by the robot (see box 11). However, a human-like shape might give cause to higher assumptions about the robots capabilities.

A technical argument to build human-like or humanoid robots is that our every day environments are optimised for the human (adult) body. If a robot needs to climb stairs it needs legs. If it needs to work in a kitchen all the cupboards are located in the range of an average size human body including the length of the arms. The doors are in a shape for the human body and a "head" including the camera system and the microphones simplifies the recognition of humans by the robot since humans are trained to look in and speak in the direction of each others' faces.

Box 11: Expert Views on Anthropomorphisation

Question: Anthropomorphisation is a controversial subject. On the one hand anthropomorphisation of artefacts such as robots and avatars seems to be highly required. [...] On the other hand, even if technology is not humanoid or provides only some rude cues, people will interact with technology by anthropomorphisation, and it will take a conscious effort for people not to anthropomorphise. What is your opinion on the need for and the benefits of anthropomorphisation when designing IA?

[1] "I do not subscribe to the assumption that artefacts need to be human-like for achieving sensible interaction. From our project's data, we can already conclude that people shift effortlessly between anthro- or zoomorphising and machine-ising."

[2] "I think anthropomorphism is essential to *understand* how we can design intelligent artefacts (at least if we are interested in "human intelligence"). [...] As Calvino said, 'our imagination is anthropomorphic' and this is something we lodged deep in our perceptual, emotional and motor system."

[3] "It will be necessary in some cases (systems and interactions) but not in all cases. [...] Sometimes anthropomorphisation is just for marketing."

[4] "To me the aim of anthropomorphism is to simplify interaction with humans. The content should be able to keep the promises of the packaging, so to say. Where that is violated, people become very upset: for example, interactive voice response systems claiming that 'you can talk to me like to a human operator' but then fail miserably to satisfy a customer request induce anger and aversion."

[5] "It is needed and should be supported."

[6] "For some applications it makes a lot of sense [...], such as ease of interaction, but there must be a clear distinction as there is a risk of confusing the boundary and the capabilities of humans and the machine which can also have serious ethical consequences."

[7] "Anthropomorphisation is not needed in most applications. Games and entertainment are important exceptions, though. [...] The recommendations of the ETHICBOTS project were to make the distinction human-machine as clear as [...] and as often as possible."

[8] "Anthropomorphisation can be user-friendly but also user deceptive. This is not a question of the product itself but of the situation in which a product is used/misused. Throughout the history of technology, there are periods in which machines were designed to look more like living beings and/or humans and other periods in which there was a strong difference that made them look more like technical artefacts."

[9] "The important issue in studying anthropomorphisation and realising lifelike or human-like artefacts is to better understand presuppositions humans make in their communicative interactions. This kind of understanding is necessary to develop successful human-agent communication. [...] We need [...] to experiment with building artefacts that are as human-like as possible for research purposes, in order to find out what is the minimum of anthropomorphisation required for successful communicative and collaborative interaction between humans and specific kinds of artificial agents."

There is an additional argument with respect to the abovementioned modern learning algorithms. "Learning like a child" presumes that a human being takes care of the robot and spends some time with it in order to function as a role model for learning. This is the idea of social (or sociable) robotics. The Personal Robots Group at MIT Lab writes:

"Robots are an intriguing technology that can straddle both the physical and social world of people. Inspired by animal and human behaviour, our goal is to build capable robotic creatures with a "living" presence, and to gain a better understanding of how humans will interact with this new kind of technology. People will physically interact with them, communicate with them, understand them, and teach them, all in familiar human terms. Ultimately, such robots will possess the social savvy, physical adeptness, and everyday common sense to partake in people's daily lives in useful and rewarding ways".¹²⁴



Figure 4: Humanoid Robot. Source: http://www.sfb588.uni-karlsruhe.de/

Others, such as Hiroshi Ishiguro (see figure 5), emphasise that humanoid robots should look like humans in detail ("android" or "gynoid" robots). Only then could they become companions accepted by humans.

¹²⁴ MIT Lab, Personal robots group; http://www.media.mit.edu/research/groups/personal-robots, n.p.



Figure 5: Hiroshi Ishiguro & Geminoid. The robot Geminoid was developed by ATR Intelligent Robotics and Communication Laboratories. Source: rubra Ars Electronica 2009, http://www.ejournal.at/Artsite/ishiguro/android.html

The question "how humanoid", for example, service robots should look like is answered controversially. Some developers (e.g., Fraunhofer IPA) avoid human-like shapes for such robots in order to avoid an overestimation of their capabilities. Others prefer such shapes¹²⁵ since it allows cooperation and learning by imitating movements of humans.

One article at an EU research news website raises the question why we remain "*fascinated*" by "*the allure of the mechanical friend, the humanoid robot*", although robots can take "*any shape or form*" and with the "*explosion*" in European research and development (R&D) "*for every imaginable robot application, there are dozens of completely different designs*" (CORDIS, 2008). The article concedes that, at first blush, humanoid robots "*do not necessarily make a lot of sense*", since "*they are seriously difficult to design and implement*", and could be seen as "*an extravagance, given that a robot can be any shape that will allow it to best perform its function*." However, humanoid robotics do play an important role in European research, and, as the article argues, "*not just because they look cute*." As main reasons for R&D in this area, the article mentions (i) that this kind of R&D will "*advance the field as a whole*", (ii) that such robots are expected to function in a world designed for humans, serving, e.g., as companions for elderly people and children, and finally it mentions (iii) the growing importance of this field, particularly in Japan and the USA.

Swarm robots can be taken as a kind of opposite to humanoid robots. Each "member" of the swarm is optimised for a certain task and for collaboration with other swarm robots. As already mentioned in the case of football playing and rescue robots, the collaboration between robots is a very interesting task for robotics research.

¹²⁵ See the work and visions of SFB588: http://www.sfb588.uni-karlsruhe.de/textdateien/English%20Version/goals_frame.html. See also Fig. 1.

Robots with complementing capabilities can refer to each others sensor data, call each other for different tasks to do and inform each other about certain actions to do. In the EU project IWARD (Intelligent Robot Swarm for Attendance, Recognition, Cleaning and Delivery), the aim is to develop swarm intelligence for the robots. Each robot in the swarm can act autonomously but simultaneously maintains contact with all other robots. The capabilities of the swarm are expected to far exceed those of the individual robots. The implementation area for these swarms is the hospital environment. Possible tasks are "find doctor", "call nurse", "clean ward" and "direct visitors". The mobile robots, however, will also recognise if a patient falls down and needs help (Schlegel, 2007; Schlegel und Thiel, 2007).

Swarm building is closely related to cooperation between robots and between robots and humans. When two humans cooperate, the corresponding action is agreed, for example, against the background of a categorical imperative that everyone (at least the two in the current situation) should behave accordingly in this specific situation. The negotiation about the best action to take is a necessary condition for successful cooperation. In the cooperation between humans and advanced robots would exist, in contrast, a tension between the ethical inadmissibility of the instrumentalisation on the one hand and the achievement of the corresponding goals of cooperation on the other – a crucial issue for robo-ethics and also for technology assessment.

5.2.3. Agents and Avatars

5.2.3.1. Autonomy and Lifelikeness

AgentLink, the European Commission's IST-funded Coordination Action for Agent-Based Computing¹²⁶, defines agents as follows: *"Put at its simplest, an agent is a computer system that is capable of flexible autonomous action in dynamic, unpredictable, typically multi-agent domains"* (Luck et al., 2005: 11). These authors hold that agents represent the most important new paradigm for software development since object orientation. The areas in which multi-agent systems are expected to become indispensable are Grid Computing, Semantic Web, Web Services, Peer to Peer, Ambient Intelligence, and "autonomic computing" (for the latter, see below). The new paradigm in which computer components interact is obviously inspired by general systems theory and in particular by knowledge about social systems.¹²⁷

Looking at research challenges, AgentLink distinguishes between the agent level, the interaction level, and the organisational level, in the following way: The Agent-level is concerned with individual agents and has been the primary focus of artificial intelligence for a long time. Today, research is focused on the higher levels: Technologies at the interaction level are concerned with communications between agents - for example, technologies related to communication languages, interaction protocols and resource allocation mechanisms. Research and development in this field is drawing on knowledge from disciplines such as economics, political science, philosophy and linguistics. At the top organisational level are technologies/techniques related to "agent societies" as a whole. Here, issues of organisational structure, trust, norms and obligations, and self-organisation in open agent societies are paramount. Again, many of the questions have been studied in other disciplines - for example, in sociology, anthropology and biology (Luck et al., 2005, p. 29). Learning technology is clearly important for open and scalable multi-agent systems, but it is still at early stages of development:

¹²⁶ This chapter draws, first of all, on the work of AgentLink as it presents a view of the field, which is based on the input of many experts (Luck et al., 2005).

¹²⁷ The term "socionics" is sometimes used to address the field of Distributed Artificial Intelligence making use of knowledge from sociology for multi-agent systems (Malsch, 2007).
"Reasons for this can be found in the fundamental difficulty of learning, but also in problems of scalability and in user trust in self-adapting software. In the longer term, learning techniques are likely to become a central part of agent systems, while the shorter term offers application opportunities in areas such as interactive entertainment, which are not safety-critical" (ibid., p. 36).

In the field of autonomous agents, another vision called *autonomic computing* is worth mention. In a metaphorical way, this vision refers to the autonomic functioning of the human central nervous system.¹²⁸ Autonomic computing is an approach to self-managed computing systems with minimal human interference. It is to be seen in the context of computational "self-* systems" (e.g. self-awareness, self-organisation, self-configuration, self-management, self-diagnosis, self-correction, and self-repair), involving interactions between autonomous entities and components. The key message to be drawn from this vision is that it shares many of the goals of agent-based computing, and agents offer a way to manage the complexity of autonomic systems (cf. Luck et al., 2005, p. 24). It is however not a case of "biology becoming technology" as the reference to the human central nervous system merely serves as a metaphor. Looking at systems research, however, we see that *autopoiesis* as a common denominator for biological as well as social systems is currently turning into a guiding vision for software development.

In this section, focus lies on computer-generated lifelike characters developed to advance human computer interaction and to mediate communication between humans. More specifically, we refer to lifelike software agents (softbots) and avatars, which combine "virtual embodiment" with further capabilities to simulate lifelike properties normally assigned to humans.

Computer-generated anthropomorphic characters are referred to as "agents" when they autonomously interact with users and as "avatars" when they represent users in computer games or virtual reality (Gong and Nass, 2007: 163-193). Although the border between software agents and avatars is blurring, it is worth explaining the difference. Russell and Norvig give the following definition of an agent: "An agent is anything that can be viewed as perceiving its environment through sensors and acting upon that environment through effectors. ... A software agent has encoded bit strings as its precepts and actions" (Russell and Norvig, 1995: 31). Examples given are a software agent designed to fly a flight simulator for a 747 and another one designed to scan online news sources and to show interesting items to customers (Russell and Norvig, 1995: 36). But software agents may also receive input from the outer worlds by sensors, e.g. a camera or a microphone serving as preceptors, and they may receive input through ongoing interaction with users.

Independent of the type of input an agent receives and independent of the application being offline or online¹²⁹, common to all agents is that they are designed to accomplish a specific goal and to fulfil corresponding computational tasks. The tasks can be manifold and may imply a high level of "cold cognition".

¹²⁸ Researchers of IBM first introduced the concept in 2003 (Kephart, 2003: 41-50).

¹²⁹ The most ambitious vision of the semantic web envisages personalised intelligent software agents, which answer natural language questions and perform tasks for users on the "Internet of services". The idea of having an agent that can reliably search for information is still largely a vision rather than a reality. This topic has already been dealt with previously by Böhle and others (Böhle et al., 2008: 40ff).

Graphically "embodied conversational agents" (ECA) engaging in conversation with humans are an important case in point. Nowadays we often find virtually embodied agents at the interface of online services that are programmed for specific tasks, such as guiding a user through a help-system of a software application, answering questions of a shopper at an online-shopping system, helping a reader find his or her way through an online library system, acting as real estate agent, a virtual educator and so forth.¹³⁰



Figure 6: Chatbots. The screenshot above is taken from a video in which two chatbots are engaged in conversation, Fake Kirk and A.L.I.C.E., two of the more advanced chatbots: http://www.youtube.com/watch?v=Lr7qVQ3UoSk

In contrast, avatars are related first of all to communication in virtual environments and gaming worlds. Bailenson and Blascovich define avatars as "perceptible digital representations whose behaviours reflect those executed, typically in real time, by a specific human being" (Bailenson and Blascovich, 2004: 65). Avatars are different from Online Identities, a term referring to all information available about a specific person on the World Wide Web (e.g. in social networks such as Facebook or MySpace, in chat rooms or on personal homepages). However, as Avatars let users define appearance, attributes and characteristics which may correspond more or less to their self-image, an Avatar can also be considered a part of the online identity of a person. Communication between humans mediated by avatars is of course different from usual telecommunication via e.g. videoconference and has rightly but still vaguely been termed "transformed social interaction" (Bailenson et al., 2004: 428-441).

While Avatars may first of all serve self-expression and communication purposes in virtual worlds, software agents may serve primarily as front end to sophisticated computer applications, e.g. to an expert system or a semantic web application. Nevertheless there is convergence between virtual embodied agents and avatars, because both function as digital communicators. In computer games we find both types already side by side (Lim and Reeves, 2010: 57-68).

¹³⁰ The website chatbot.org provides an inventory of chatbots, virtual assistants, conversational agents and other virtual agents with reference to about 565 of them (as of June 2010); http://www.chatbots.org/

The EU-funded project CyberMotions (cf. http://www.cyberemotions.eu/) may serve as a further example of where the distinction between Agent and Avatar is already hard to draw. The project focuses on the role of collective emotions in creating, forming and breaking-up e-communities. It concentrates on the issue of how to support and maintain the emotional climates of security, trust, hope, and freedom in techno-social communities and how to prevent or resolve conflicts within them. Data on human emotions and their influence on the structure of sustainable cooperative communities will be collected from the blogosphere, newsgroups and Internet discussion forums and compared to computer simulations based on active agent models. Finally an artificial agent shall be built to help assess the emotional states of the members of e-communities and to act as cyber adviser in e-communities. This cyber adviser may appear as a distinct intelligent artefact, but it may also present itself as just another human participant, who may, for example, cool down a debate when it gets too emotional (e.g., hateful).

A particularly interesting future issue is the potential merger and combination of Agents, Avatars and Online Identities. On the one hand Softbots will be designed to become artificial personalities, on the other hand humans will create computer-generated characters which incorporate their personal profile and resemble their outer shape. Softbots may thus turn into "virtual Doppelgangers" able to communicate and to perform tasks.

5.2.3.2. Adapting and Learning

Both *physiological computing* (including neuro-physiological computing) and *affective computing* exploit the human body, i.e. biology, in order to improve the adaptation capabilities of interactive computing systems. In a very particular and individualised way, biology is becoming part of technology. These computer applications learn by analysing the physiological and emotional state in which the users are in a given session.

In the case of physiological computing, a person's physiological state is sensed and measured in order to improve the adaptation capabilities of computing systems, and, in the case of affective computing, the affective state of a person is used as a resource for adaptation. In the first case, more or less unconscious processes of the human body (biology), which were usually measured and revealed in medical settings only (a suffering patient and a trustworthy physician), are now used to increase the adaptability of computing. In the second case, indicators of emotions and other affects spontaneously displayed (voice, posture, facial expression, gesture) conveying social meaning are used to adapt computer applications and their interface. The different concepts to be introduced in this section are shown in Figure 7.





Figure 7: Affective Computing and Transformed Social Interactions. Source: The authors reproduced graphic elements of MIT (Malatesta et al., 2009: 53-70).

Turning first to *physiological computing* (including neuro-physiological computing), which started in the 1990s, we should remind ourselves that the human body is chemical, electrical, mechanical, thermal and magnetic in nature. Physiological computing aims to transform bioelectrical signals from the human nervous system into real-time computer input – not for medical purposes alone – but as an input source for interactive systems¹³¹. To achieve this, physiological sensors are used. To give some examples:

- Electroencephalogram (EEG) can be used e.g. to monitor the state of alertness.
- Electromyograms (EMG) can be used to inform about the activity of a muscle; e.g. the activity of the muscle of the eyebrow corresponds to pleasant and unpleasant stimuli.
- Electro-oculogram and pupillometry provide information about visual attention.
- Blood pressure may indicate a state of challenge or stress.
- Electrodermal activities react to audio and visual stimuli (music, violent pictures, erotic stimuli).

Based on the real-time measurement of psychophysiology, the system's functionality and its user interface are modified. This is called *biocybernetic adaptation*. Biocybernetically adaptive systems use the changing psychophysiological state of the user in order to change its own functionality and/or appearance. An example given by Allanson and Fairclough is the detection of a user's fatigue indicated by a long duration of eyeblinks to which the system responds by an increase in font size.

¹³¹ The following information is mainly taken from Allanson's pre-existing overview (Allanson and Fairclough, 2004: 857-878).

The authors also envisage the use of physiological computing for computer game design. Games are intended to challenge, engage and stimulate the player, but the optimal level of challenge may vary considerably with respect to a particular person, and among players. Psychophysiological input is meant to provide a source of real-time adaptability for computer games, adjusting the game difficulty dynamically in order to maximise user engagement.

Physiological computing is closely linked to *intimate computing* where intimate knowledge about a person is made available to a computer, which is able to process it and to react on this input. Computers that "have knowledge" about the user are supposed to interact more appropriate with human being, e.g. in the case of *wearables* (computers close to the body equipped with sensors to measure intimate information).

Affective computing (see also 5.2.1) has been defined by MIT's Rosalind Picard as computing that relates to, arises from, or influences emotions.¹³² The engineering tasks sensing and recognising affects as well as understanding and modelling affects - are visualised by MIT in Figure 8. Affective computing goes beyond physiology, particularly analysing voice on the one hand and visual cues such as facial expression, gesture and posture on the other hand. Furthermore, conversational knowledge and knowledge about social rules and habits (politeness, etc.) are taken into account.¹³³ To introduce knowledge - in general unnoticed - about a user into a computing system is also one of the basic ideas of affective computing. In e-learning, affective computing could be used to adapt the presentation of a teacher avatar when the student is frustrated, pleased or bored. In gaming applications it is already possible to scan the expression of the face of the gamer and transport the same expression real time onto the face of his or her avatar. An interesting example stemming from game development is Project Natal, where a human being in front of a screen makes gestures and movements to which a computer-generated anthropomorphic character responds with gestures and facial expressions.¹³⁴ Health care is a specifically targeted application field. At MIT, researchers are working on an "Interactive Social-Emotional Toolkit" (iSET) designed to help children with disorders linked to sensory processing, such as autism, understand emotions in other people.¹³⁵

One direction of affective computing has been termed *persuasive computing*.¹³⁶ Persuasion can be understood as the attempt to shape, reinforce, or change behaviours, feelings, or thoughts about an issue, object or action. In many cases persuasion will require motivation. Persuasion requires intentionality and as computers do not have intentions, a computer qualifies as a persuasive technology only if those who create distribute, or adopt the technology do so with intent to affect human behaviour. Persuasive games are one technology.¹³⁷ field pervasive The application of game "America's Army" (http://www.americasarmy.com/), "the official U.S. Army Game", is an interesting case in point, set up with the intention to recruit young Americans for the army.

¹³² MIT is one of the research centres with a focus on affective computing, as the more than 50 projects in this very field may prove; see: http://affect.media.mit.edu/projects.php.

¹³³ Malatesta et al. (2009) provide a good, terminologically differentiated introduction to "affective intelligence" (e.g. concerning the differences between emotion and feeling and between emotions and preferences; see p. 54-59). For a very detailed classification of emotions based on the work of Goleman, see also Martinez-Miranda and Aldea (Martinez-Miranda and Aldea, 2005: 323-341).

¹³⁴ See the corresponding video "Meet Milo" on YouTube at: (http://www.youtube.com/watch?v=HluWsMIfj68&feature=related: Meet Milo),

¹³⁵ For works on autism and on anxiety respectively, see Khandaker (Khandaker, 2009: 37-39) and Sharry et al. (Sharry et al., 2003). A general discussion on artificial agents for psychotherapy is presented by Hudlicka et al. (Hudlicka et al., 2008: 60-64).

¹³⁶ For the following definition, see Fogg (Fogg, 1995: 225f).

¹³⁷ For a discussion of persuasive games, see Edegger (Edegger, 2008: 41-55).

Another visionary trend in computing of IA which builds on affective computing is *social relationship computing*. These relationships are envisaged as long-standing. Benyon and Mival, members of the EC funded Companions project, hold that *"it is possible to design artefacts that will enable people to develop relationships with them"* (Benyon and Mival, 2008: 3661). To achieve this, *personification technologies* will have to be developed:

"Personification technologies enable intelligent interaction with people in terms of speech and language, gesture and other forms of touch, and nonspeech audio. They are believable, intuitive, and convivial conversational partners. They are autonomous and personality rich. They will be sensitive to emotion in speech and will be capable of demonstrating emotional/affective behaviour through speech" (ibid, 3658).



Figure 8: Engineering Affects (Malatesta et al., 2009: 60).

Box 12: Expert Views on Affective Computing Research

Question: Typically, researchers treat the affects or emotions displayed, and the internal and external state and behaviour of a computing machine with the reserve or proviso "as if". Notwithstanding, the claim often goes much further, turning the "as if" into real properties of the computing systems. For instance, R.W. Picard, pioneering affective computing, envisages "building computers that have emotions", and C. Nass and S. Brave, pioneering voice interfaces, envisage people and computers speaking with one another (not just talking at and listen to). What is your opinion about the vision of computers having emotions, understanding, and consciousness?

[1] "Picard only speculates [...]; I haven't met any researcher beside her who goes beyond the "as if" or even would like to do so. [...] A machine does not need to "have" emotions to engage in what a human takes as a real conversation, and it is an open question to what degree it even has to simulate human-like emotional states to do so. The difference between the two is enormous, like building a computer that plays chess 'exactly as' a human does vs. [one] that simply plays good chess [...] (the latter approach has been much more successful). The 'vision' that is stipulated in this question [...] is quite arguably non-existing and does not deserve more serious discussion in this general form."

[2] "[M]ost of the research [...] is assuming that emotions can be distinguished 'just' by measuring the exterior displays (e.g. of the eyes), while I believe we recognise emotions because we had emotional experiences ourselves. [Accordingly], a machine may have to be designed with emotions, [with the] ability to express emotions in a proper way. Still don't know how... :-(..., but I guess emotions are the doors to consciousness."

[3] "In my view the relevant aspect for the societal impact of technology is the "as if" - the machine must be able to act in ways that humans find natural and convincing: a good simulation, but a simulation. The aim to build cognitive architectures that embed emotion-like elements [...] is to be clearly distinguished. Where sensors are integrated with appraisal mechanisms [...], benefiting 'survival' of a research robot [...], that is about the machine 'having' emotions, at least structurally. [...] Personally I have trouble imagining that a machine will ever be able to have that, but this is a philosophical question."

[4] "Emotions are fuzzy categories and we are used to expect 100% precision from computers. [...] Again, we need first to make the machines that can diagnose and react to human emotions before we start thinking having machines with their own emotions."

[5] "Why do you think the ambition of research in affective systems is unclear? If you ask [...] Picard she has a clear view. She would like to understand affective mechanisms to be able to replicate them in systems. Affect is an important part of social interaction and if we are to design systems for natural interaction they must have a component of affect."

[6] "There is no model of the mechanisms underlying emotion, understanding, and consciousness which can be duplicated into machines. I guess that the "as if" provision will be in place for a long time to come. And the main research efforts and (limited) achievements of affective computing are mainly in the direction of computers interpreting human emotions from an analysis of their physical correlates."

[7] "I see the problem more on the human side: reducing our emotions to computation we are restricting their realm that goes far beyond what a subject feels 'inside him/herself' as something

apparently disconnected from the ways he/she experiences his/her being-in-the-world. Feelings are forms of world-disclosure."

[8] "The difference [...] between [...] having emotions as opposed to making use of emotion constructs is at some point a philosophical question and dependent on the emotion theories under discussion. In my point of view, it is even more a bio-physiological question as human emotions are related to bodily feelings of bio-physiological processes such as feeling a flap in one's stomach [...]. [T]here is no direct equivalent for computers. Rebuilding human physiological processes would be simulation again. Currently it is unclear what having emotions could sensibly mean for computers, and what would be good reasons for developing computers that have emotions instead of computers that make use of emotion models at various levels of processing as mentioned above."

Summing up the expert opinions we received (see Box 12), we can contend that without doubt, the recognition and diagnosis of the emotional states of users are the main strand of affective computing. The next, more ambitious claim, that computing systems should be able to express emotions in man-machine interaction, is already less clear and regarded an open question. The most ambitious claim that computers should or may "have" emotions is still very controversial and mostly rejected. A strong argument – not only put forward by the philosophers we interviewed – is the insight that emotions are rooted in bio-physiological bodily processes, which cannot be replicated by machines, and an understanding that "feelings" are closely connected to the way humans experience their being-in-the-world and that feelings are forms of world-disclosure.

5.2.3.3. Social Performance Matters

The design of Softbots and Avatars raises again the question about how much "anthropomorphisation" is best. Research tells us that "shape" is not such important, while social performance matters, and most important for social performance are communication capabilities, and in particular language.

People anthropomorphise when interacting with technology. Apparently people use the same rules and heuristics in this kind of interaction as they do when interacting with other people¹³⁸. Anthropomorphisation, as theologian and robot researcher Anne Foerst puts it, *"is the initial and natural response to anything we interact with; it takes a conscious effort not to anthropomorphise"* (Foerst, 2009: 188). Peter Fuchs, a renowned German sociologist, convincingly argues that language (even in the form of written text) is at the heart of anthropomorphisation, because language irresistibly affects consciousness and opens up for communication (Fuchs, 1991: 1-30). As language occupies consciousness, it is probably the main vehicle to get people engaged in man machine interaction (1991, p. 16f). Chatbots beginning with ELIZA¹³⁹ and PARRY¹⁴⁰ were simple text-based human-computer interfaces (Wilks, 2007: 927-928), but even at this stage attractive for humans to communicate with and about.

140 PARRY was authored by the psychiatrist Kenneth Colby to simulate a paranoid human, complementing ELIZA.

¹³⁸ Sociology is recently giving more importance to the interaction of humans with non-humans (including machines). For an overview, see Cerulo (Cerulo, 2009: 531-552). There are many intricate problems when trying to match the use of terms like "interaction", "social actor" in HCI-research with their use in sociology.

¹³⁹ ELIZA was a simple conversation system emulating a Rogerian psychiatrist. Although it was based on quite simple pattern-matching algorithms, it was seen by some as having passed the well-known Turing Test to determine the existence of intelligence. This caused ELIZA's author, Joseph Weizenbaum, to question the validity of the Turing test.

Although exchange of text is still very common in man-machine communication, anthropomorphisation by language has made a significant step forward with voice interfaces. We learn from Nass and Brave that as a result of human evolution, humans are automatic experts at extracting the social aspects of speech (Nass and Brave, 2005). Humans have become "voice-activated with brains that are wired to equate voices with people". Again we learn about the irresistibility of language: "Listeners and talkers cannot suppress their natural responses to speech, regardless of source" (2005: 4) using the same parts of the brain to act with machines as with other humans. Hence the extraordinary importance of voice interfaces in the context of affective computing.

Drawing on the empirical knowledge of Symbolic Interactionism (Erving Goffman), appearance is not as important as performance, because a "persona" is constructed through social performance and relates identity to social behaviour rather than appearance (Morie and Verhulsdonck, 2008: 365-372). This concept of "persona" hints at the importance of "personality" when designing Softbots and avatars. Krenn et al. state: *"The incorporation of personality is indispensable for modelling lifelike agents"* (Krenn et al., 2004: 4). The argument is that "personality" conveys coherence, consistency, and predictability to the computer as social actor. Therefore engineers aiming to improve the performance of Softbots and Avatars will probably go for personification technologies.

5.3. Relevance to European Research

In the following section, we provide some information and expert views on the funding of intelligent artefacts R&D in Europe, and on Europe's position in the world in this regard, particularly concerning the field of robotics.

R&D in the field of what we have termed "intelligent artefacts" (IA) is clearly a booming field in Europe as well as in other parts of the world. In general, Europe's position in IA research, in particular with regard to robots, is seen as strong. EU officials working in relevant funding agencies and EU researches have characterised Japan, the Republic of Korea and the USA as the most important competitors in this field. The East Asian competitors appear to be very strong in non-industrial robot applications and particularly leading in the entertainment field.

It might be of interest how non-European experts view the field. In the case of robotics, one instructive example is a 2006 study by a panel of the U.S.-based World Technology Evaluation Center (WTEC), sponsored by the National Science Foundation, the National Aeronautics and Space Administration, and the National Institute of Biomedical Imaging and Bioengineering of the U.S. Government (Bekey, 2006). The WTEC panel also sees robotics as a very active field worldwide. The experts point out that Japan, Korea, and the EU invest significantly larger funds in robotics R&D for the private sector than the U.S. does, that in the U.S. as well as in and other parts of the world there are numerous start-up companies in robotics, and that venture capital appears to be available.

In the panel's view, the U.S. currently leads in areas such as robot navigation in outdoor environments, robot architectures (the integration of control, structure and computation), and in applications for space, defence, underwater systems and some aspects of service and personal robots. Japan and Korea lead in technology for robot mobility, humanoid robots, and some aspects of service and personal robots (including entertainment), and Australia leads in commercial applications of field robotics, particularly in such areas as cargo handling and mining, as well as in the theory and application of localisation and navigation. The experts hold that Europe leads in mobility for structured environments, including urban transportation, and also has significant programmes in eldercare and home service robotics. In their view, the U.S. lost its pre-eminence in industrial robotics at the end of the 1980s, so that nearly all robots for welding, painting and assembly are now imported from Japan or Europe. Moreover, the panel thinks that the U.S. is in danger of losing the leading position in other aspects of robotics as well. The EU and countries such as Korea are characterised as better performers than the U.S. in terms of the amounts of funding for robotics R&D as well as of funding strategies.

The experts interviewed for our project likewise named Japan, USA and Korea as the most important non-European countries in this area. One expert stated that EU researchers are very well connected and pointed out that R&D in this field is highly internationalised. Some experts mentioned Germany, Italy and the UK as EU Member States that are particularly advanced in this field. One expert argued that the EU should have a long-term perspective (10-15 years) in the field of cognitive systems and warned against projects and objectives with a three-year perspective.

EU funding in IA research mainly takes place by means of funding activities on the theme 'Information & communication technologies' (ICT) of the FP7 programme 'Cooperation'. However, R&D in the area of IA, in particular the development of robots¹⁴¹, are also funded in activities on several other themes of the programme 'Cooperation', such as 'Space' and 'Nanosciences, nanotechnologies, materials & new production technologies', as well as in the other FP7 programmes (e.g. funding by the European Research Council in the programme 'Ideas' and the Marie Curie Actions in the programme 'People').

At the heart of EU funding of IA research and development are the activities on 'Cognitive Systems, Interaction, Robots'. This is both (i) the name of one of seven so-called 'ICT challenges' defined in the ICT work programme under FP7 and (ii) the name of unit E5 of the Directorate E ('Digital Content and Cognitive Systems') within the 'Information Society and Media' Directorate General. An important role in the area of IA is also played by the Directorate F ('Emerging Technologies and Infrastructures') with its two 'Future & Emerging Technologies (FET)' units. The funding on "future and emerging technologies" (FET) is one of the additional funding schemes in the ICT programme besides the seven 'ICT challenges'. When preparing FP7, the EU (and the European technology platforms, in particular) identified three major technological challenges in the field of ICT, one of them being the engineering of context-aware and easy-to-use ICT systems that self-improve and self-adapt within their respective environments. For this reason, the fields of cognitive systems, robotics and interaction, which were already funded together in FP6, remained priority research topics. However, IA R&D is also significantly funded in the context of other 'ICT challenges' (in particular 'Independent living, Inclusion and Governance', where projects on service robotics are funded in the context of 'ICT and ageing').

Given this background and the broadness of our definition of IA, a quantitative analysis of funding activities is difficult. However, some information on the amount of funding and its relative relevance can be provided: According to information from the EU, more than 120 projects of R&D in the areas of cognitive systems and robotics were funded since 1998, with a total funding sum of more than \notin 400 million (and with 90 of these projects still running at the end of 2009). On the other hand, it is planned that in FP7 (2007-2013) about \notin 9 billion will be spent for the ICT theme as a whole. In the scheme "future and emerging technologies" (FET), in which investments of about \notin 800 million will be made in FP7, \notin 900 million were spent between 1998 and the end of 2009.

¹⁴¹ The mainly academic European Robotics Research Network (EURON), which was founded in 2000 and was supported by the European Commission for eight years, and the industry-driven European Robotics Technology Platform (EUROP) are increasingly cooperating, a trend which is financially supported by the EU as well.

These numbers suggest that R&D in the area of IA is an important area within the EU's future-oriented funding activities on emerging technologies and on the necessary basic research. Seen at large, however, the funding of R&D on IA accounts for only a small fraction of the funding on ICT, let alone of FP7 as a whole.

Remarkably, EU funding often focuses on R&D that aspires to combine the various strands of R&D on IA. In FP6 and when preparing its activities in FP7, the abovementioned unit (E5), which deals with cognitive systems and robots, stated that research will be funded into systems (computers, robots, and other manmade creations) that have cognitive functions normally associated with people or animals and which exhibit a high degree of robustness in coping with unpredictable situations. These artificial cognitive systems (ACS) were characterised as being at the junction of the cognitive, ICT, and natural sciences (see figure 9).

Sketching the related 'ICT challenge' ('Cognitive Systems, Interaction, Robots'), the following goals were defined:

- I. In the real world, ICT systems should be able to respond intelligently to gaps in their knowledge and to situations that have not been specified in their design.
- II. They should be able to exhibit robust and versatile behaviour in open-ended environments, give sensible responses in unforeseen situations, and greatly enhance human-machine interaction.
- III. Robots should understand their environments and their users while operating either fully autonomously or in cooperation with people in complex, dynamic spatial environments.
- IV. Artificial systems should understand and control material and informational processes, e.g. in industrial manufacturing or public services domains, for instance through real-time information gathering and interpretation in natural or artificial environments.
- V. Finally, these systems should allow for rich interactions using all senses and for communication in natural language and using gestures, and they should be able to adapt autonomously to environmental constraints and to user needs, intentions and emotions.

According to the abovementioned unit E5, a new approach is needed for these purposes, namely a rethinking of the way we engineer systems:

"As we aim to get machines to exhibit performance capacities that resemble those of humans or animals, inspiration and insights will be borrowed from bio-sciences, social sciences and humanities. This may include the study of new computational paradigms derived from models of natural cognition. In some domains the exploration and validation of the use of new materials and hardware designs is strongly encouraged. Engineering progress will crucially depend on advancing our scientific understanding of what both natural and artificial systems can and cannot do, and how and why."¹⁴²

¹⁴² See http://cordis.europa.eu/fp7/ict/programme/overview2_en.html (n.p.)



Figure 9: Artificial Cognitive Systems (ACS): at the junction of the cognitive, ICT, and natural sciences. Source: http://cordis.europa.eu/fp7/ict/cognition/home_en.html

A number of EU-funded projects can serve to further exemplify the trends towards the combination of various IA technologies, and towards a kind of convergence of life and technology. These projects include, but are not restricted to the following FP6 and FP 7 projects: BEAMING, COMPANIONABLE, COGNIRON, COSY, E-SWARM, HUMAVIPS, IMMERSENCE, INDIGO, LAMPETRA, LIREC, MINDRACES, NECA, NEURO, NEUROCHEM, ORGANIC, PRESENCCIA, REFLECT, SEARISE, SEMAINE, SERA, SIMILAR, SPARK I and II and VERE. The spectrum includes

- I. diverse R&D activities on socially accepted, "emotionally intelligent" and anticipatory IA which communicate in a way similar to humans, take into account their mood and intentions, and can also serve as long-time companions for humans (either as physical robots or in virtual forms, or even as companions which can take both forms¹⁴³)
- II. a number of projects on the fusion of the human body with virtual or physical surrogates by means of immersive "virtual reality" technologies and of brain computer interfaces ("remote body ownership", "body substitute illusion")
- III. a wide range of biomimetic projects (e.g., the use of biological neurons as computing elements, a system inspired by the human visual system which could be used for the observation of large crowded public spaces or of individual activities within restricted areas, and the development of bioinspired artefacts for chemical sensing, for performing neuroscientific studies related to goal-directed locomotion, and for finding innovative solutions for high-performance artificial locomotion)
- IV. a wide range of "pure" robotics projects, including some R&D activities on robots that can mimic human body language or use other (e.g., audiovisual) technologies for a more effective interaction with humans.

¹⁴³ The project BEAMING also focuses on flexible embodiments, but not on companions. It aims to produce a new kind of virtual transportation, where a human can be physically embodied (e.g. as a robot), interacting with life-sized people who may be thousands of kilometres away.

5.4. Ethical, Legal and Societal Aspects

In this section, ethical, legal and societal aspects (ELSA) of 'intelligent artefacts' (IA) are explored in some detail. Moreover, we briefly deal with some related, mainly long-term policy issues.

ELSA of the scientific and technological fields relevant for the creation of IA are already quite widely studied and discussed, under such labels as 'robo-ethics', 'A.I. and society' and, more generally, 'information ethics'. However, as Rosenberg states, while biologists *"must explain, why research on cloning, for example, will have long-term benefits, such concerns rarely arise in AI. It seems to be taken for granted that benefits to society of intelligent artefacts are so obvious that critical review is unnecessary. This viewpoint must be challenged [...]" (Rosenberg, 2008: 369).*

In fact, quite a few discussions about ELSA of robotics and AI revolve around highly visionary scenarios in which the potential usefulness of IA is not questioned in principle, but debated against the background of a possible future rivalry between humans and intelligent machines. Other topics of the discussion, some of them less visionary, are, for example, the embedding of ethically derived principles into the programming of intelligent machines, the question of 'rights' of intelligent robots and other IA (in analogy to human rights and animal rights) and, finally, social, psychological and legal implications of a further penetration of intelligent artefacts into everyday human life and society (including military uses).

In the following, we will not discuss the whole spectrum of the thematic, but instead focus on such topics that appear to be highly relevant with regard to our notion of 'technology becoming biology' or lifelike. This notion relates to the tendency that technologies are becoming more lifelike in the sense that they appear to acquire properties that were formerly associated only or mainly with living organisms, such as self-organisation, selfhealing and cognitive functions. More and more artefacts display certain forms of 'intelligent' behaviour, such as machines detecting aggressive human behaviour or robots using emotional elements of human communication to interact with humans. Progress in the field of anthropomorphic (aka 'humanoid') and zoomorphic robots has already been remarkable and thus raises questions concerning socio-psychological and other aspects. Programmes mimicking human behaviour or human identity in digital environments also belong to such instances of technology becoming lifelike. These technologies obviously raise legal and security aspects, and they may also have socio-psychological relevance. More generally, it can be argued that new IA can contribute, in the context of ambient intelligence and pervasive computing, to the construction of an encompassing 'second nature'; a new environment in which humans, in certain respects, slowly become as dependent on as they have been (and still are) depending on our natural environments. Thereby the lifeworld increasingly becomes a target of engineering. This tendency as well as R&D in such fields as affective computing may also increase the impacts of computer sciences and robotics on our view of human and non-human life, for instance with regard to the widespread use of machine metaphors for the description of humans, of parts of the human body or of human faculties. Last but not least, developments in the field of brainsemiconductor hybrids, which are also discussed in chapter 4, do not only build on a tradition of lifelike (e.g., animal) models in AI research (e.g., "animats") and in the research in the (non-biological) field of 'artificial life', but they are presently transgressing the boundaries between the organic and the inorganic in a way that has added to the encompassing tendency of a blending of life and technology.

5.4.1. Ethical and Legal Aspects

In the following, we discuss ethical and legal aspects of IA, with a special view to robots and including a number of upcoming social issues.

How to Treat a Robot

The goal to replace human action, and to a lesser degree animal action, with robotic action is the main developmental driver in the field of robotics. Much of the abovementioned research and of the discussions on 'robo-ethics' focuses on this aspect.

From our specific perspective, the underlying assumption that robots can act or function like, or at least in ways similar to, human beings is the most important aspect. While a possible replacement, for example, of mules by new robots as beasts of burdens in rough terrain¹⁴⁴ appears to be ethically irrelevant or at least largely unproblematic, the use of robots for military attacks or violent police operations is a wholly different issue. One can ask here if we would like to, or even need to programme 'ethics' into a robot which could allow it to be even more 'ethical' than a human would be (who may lose his temper and act irrationally aggressive). In any case – and not only with regard to military and police uses – safety and legal liability issues have to be systematically taken into account, and precautions and regulations are needed.



Figure 10: BigDog. Source: http://www.bostondynamics.com/. To see BigDog in real action, go to http://www.youtube.com/BostonDynamics.

¹⁴⁴ The quadruped robot BigDog is, if we trust a video by its producer (who developed the robot on behalf of the U.S. military), one of the most impressive examples of such new artefacts (see Figure 5.7).

On the other hand, it is already quite vividly discussed if intelligent robots and other IA should be granted some kinds of rights, similar to human rights and animal rights. We would, however, argue that, for the present moment at least, any restrictions on how to use an intelligent artefact should be based on assumptions and reasons which relate to the consequences of this use for human or other living beings. As long as machines do not suffer and are not self-conscious, "abusing", damaging or destroying them do not in themselves constitute ethical problems. It becomes a problem only if these actions imply a violation of the dignity of humans (or perhaps animals), or if by using an intelligent artefact a human being or animal is in fact treated in an unjustifiable way.

When applied to the cooperation between humans and artefacts, Kant's formula of humanity says that a human being in this cooperation should not be instrumentalised, i.e. used solely as a means to achieve an end which is external to him or her. This formula of humanity is widely accepted in ethics today. The absolute validity that Kant claimed for it is, however, disputed by consequentialist and particularly by utilitarian positions. They accept restrictions of the autonomy and dignity of individual persons under certain conditions, if they can be justified by super ordinate and more extensive considerations of utility (Christaller et al., 2001: 124). Analogously, the target group of the formula of humanity in utilitarianism is not categorically determined but introduced via interpretations of the concepts of interest and feeling. This makes it possible to take the feelings of animals into account. The applicability of the formula of humanity is thus not restricted only to humans and could in the future be extended to advanced IA.

Anthropomorphism

Anthropomorphic robots raise additional ethical and legal issues. The popular image of robots has been strongly shaped by visions and early exemplars of such artefacts. Today, some of those robots appear astonishingly similar to humans. This tendency to become more lifelike is intensified by the rise of anthropopathic robots and affective computing. In this context we are faced with the question of how to design a robot in a way that humans are willing to interact with it, in order to enable the robot to learn something. The humanlike (or, for that matter, animal-like) shape, culminating in android or gynoid robots simulating emotions, can become relevant (Breazeal, 2002). One important challenge raised by anthropomorphic robots is the question of how to deal with the use of such robots for the simulation of abuse or murder of human or other beings. Are we going to accept, as long as it is kept private, that owners of anthropomorphic or zoomorphic robots use them to simulate sodomy, rape, torture, murder, or pederastic sexual abuse? (Whitby, 2008: 326-333). Whitby argues that "[i]t may be that there are classes of users – for example children, or those with known psychiatric disorders that morally we should protect from the possibilities offered by the technology. The fact that [...] we have already allowed a high degree of violent abuse in the context of computer games is not an argument for continuing to do so" (Whitby, 2008: 330). He believes that we need to begin this discussion now. In his view, an ideal result would be clear guidance on what, if anything, is on the list of unacceptable activities enshrined in the relevant professional codes and maybe eventually in law regarding the public use of anthropomorphic robots (if it is not part of a theatre performance or similar activities).

Liability

Already a core issue in ELSA research on robotics is the question of liability. The implementation of a learning algorithm entails that even the robot manufacturer is no longer in a position to predict the robot's actions if the latter has been in a new context of action for some time and has "learned" there.

One might argue that the manufacturer is not liable if he did not design the robot for use in certain contexts, but this would imply that he has to warn against use in untested contexts – which is to an extent contrary to claims made about learning robots. Christaller et al. argue that in cooperation between "man and robot", man is at the top of the decision-making hierarchy (Christaller et al., 2001). This results in immediate demands to the organisation of the man-machine interface. The responsibility gap in learning robots that was diagnosed by Matthias (2004) is handled in connection with liability for damages caused by robots. The gap in responsibility arises between the robot manufacturer, who is an expert on robots and who implemented the learning algorithm, and its owner, who uses the robot in a particular context of action and who as a rule is not a robot expert. On the one hand, we have the ethical argument that – even with learning robots – man's role as the determining decider in the cooperation must be guaranteed, and on the other hand there is the legal argument that it is equally necessary to guarantee how responsibility is divided between the robot's owner and its manufacturer. This results in a recommendation for action regarding the technical equipping of learning robots: i.e., that

"[i]t should be possible to distinguish learning robots from non-learning ones since the liability for damages between manufacturer and owner is influenced by the employment of learning algorithms. [...] It is recommended that the learning process be transparent for the robot owner and for third parties. In this connection it can be of assistance to install a non-manipulable black box to continuously document the significant results of the learning process or the sensory impulses" (Christaller et al., 2001: 220).

It is clear that this technical solution for an ethical-legal problem represents a significantly greater technical challenge than the mere integration of a "confirmation" button and a recorder. The robot must be able to communicate to the robot owner what he suggests to be learned. If this communication were to take place, for instance, in text form on the robot's screen, then the robot would have to phrase a text in which it describes an observation, formulate a hypothesis on the basis of this observation, and finally develop a suggested explanation and procedure for action, which would then be learned. The robot would have to develop a well-founded if-then statement and pass it on to the robot owner – but such if-then statements, e.g. those used in expert systems (Decker, 1997: 10ff), are not available in experimental learning algorithms. From the way in which, for example, individual neurons can weigh their incoming signals, it is impossible to draw conclusions about actions in concrete contexts of action.

We asked the experts interviewed for this project if they think that the responsibility gap identified by Matthias can be bridged by cautious and thoughtful engineering (responsibility design, including learning), by liability provisions enshrined in contracts, or by other provisions. While one expert dismissed the question as too futuristic to be fruitfully answered at this point in time, the majority of experts voted for a mixed approach. One expert argued that risks can be reduced with careful engineering, but not eliminated – as is the case with the risks of using other artefacts. This expert argued that we will probably need to develop a new concept of liability, similar to the ones we have for our children or for our pets. We would need a mix of safe engineering, shared responsibilities and social awareness. In a similar vein, another expert stated that on the one side we will need new norms, practices and laws, depending on the degree of autonomy of those systems ("will they (...) be like domestic animals? like slaves?"), and on the other side, it will be necessary to incorporate responsibility, commitments, conventions, institutions, order, powers, and even emotions, ethics and punishments within the IA norms. The comparison with parental responsibility for a child's actions was made by two other experts as well. One of these experts added that companies will be held responsible for the actions of their systems even if those systems work with some level of autonomy.

The other expert holds that design principles are very important, for example, a design should make sure that a human can always "pull the plug" if necessary. Still another expert emphasised that *"to say that a machine can be made morally and/or legally responsible when things go wrong is nonsense."* All the more important would be to enhance the safety of machines. Finally, one expert argued that there are no foreseeable ethical and legal responsibility problems that cannot be addressed on the basis of current ethical and legal frameworks – and that this is the case with many other new and emerging technologies where the demand for interdisciplinary approaches as well as the social (rather than the individual) burden of responsibility will grow.

Emotional Bonding

In the case of affective computing, we have to keep in mind that emotional bonding with pet animals and, to a certain degree, with machines such as cars is already a widespread phenomenon in modern societies. However, advanced anthropomorphic and zoomorphic robots with anthropopathic and affective qualities might raise new ethical challenges. Up to now, social scientists have shown little interest in broadly surveying people's attitudes and behaviour toward nonhuman 'interactants'. This is slowly changing and questions are asked about how individuals envision and interpret nonhumans in interactive settings (Cerulo, 2009: 531-552). This corresponds to the vision of a "companion" establishing long-term relations with humans; a companion which is conceived as an agent or "presence" that stays with the user for long periods of time, developing a relationship, "knowing" its owner's preferences and wishes and communicating with him or her primarily by using and understanding speech. If we want to maintain a rather strict line between humans and machines, we might want to protect, for example, young children in their interactions with advanced IA. Arguably, children are more inclined to animism than the average adult in modern societies, and if these robots are going to mimic human or animal behaviour in more and more sophisticated ways, this may lead children to put these machines on a level with human beings or animals. It appears to be a crucial question if we allow the use of 'companion' robots in the case of people who may not be able to fully understand their mechanic and instrumental character, such as children and mentally handicapped elderly people. Maybe the notion of 'informed consent' would have to play a central role here, too. Moreover, one could argue that today's therapeutic or toy uses of zoomorphic robots camouflages the delegation of basic duties (the care for children and for the elderly) to machines, a tendency which in the long run could put into question the civilised and humane character of our societies. We may also ask if a possible heavy use of robotic or "virtual" intelligent and emotive artefacts may amount to an addictive behaviour in humans. As long as we do not know more about the effects of close bonding of children with such artefacts, we may also face legal challenges, for example if such children develop psychological disorders that cause deviant or criminal behaviour later in their lives. On the other hand, affective computing might turn out to be beneficial in learning environments, for therapeutic purposes (e.g., in the case of autism), for the (subjectively felt) quality of life of elderly people, and for creating more lifelike and emotive computer games.

Box 13: The ETHICBOTS Project on Ethical Aspects of Intelligent Artefacts

The EU-funded ETHICBOTS project, which looked at ethical aspects of AI, robotics, softbots and prosthetic and human enhancement technologies, summarised its findings on legal and regulatory issues as follows: While there is still a need for regulations in the field of prosthetic and enhancement technologies, "a vast number of regulations can be applied with regards to artificial agents (robots and software agents), although there are no regulations dealing explicitly with neither autonomous robots nor autonomous software agents" (Capurro et al., 2007: 43f). The authors argue that major issues with robots as well as with software agents are connected with "the possibility of direct or indirect forms of tele-presence, which raise concerns about moving into a surveillance society and a 'panopticon Europe'", although these kinds of techniques "may also be used to protect privacy." They also stated that we are confronted with a paradox in a potential major application of IA in the future: if developments serve the goal of increasing and realising the rights of old-aged or disabled people, these technologies are at the same time an intervention with their fundamental rights which must be justified and which confronts them with the danger of discrimination.

Privacy

Last but not least, privacy issues are raised by new and emerging IA, for example in the case of security services using face and posture reading systems in order to sense stress from a distance. With regard to all IA, it also needs to be ensured that the data and information required to make these artefacts adaptable to the preferences, needs and wishes of individual human users will not be misused for other purposes. If this is not taken care of, we will most probably have to deal with serious problems regarding 'informational self-determination' and the 'right of privacy'. In the case of computer-generated personalities, new questions may arise with regard to such problems as identity theft and to new forms of identity management in general. Both, physiological computing and affective computing are also fields where biology is becoming part of technology in a very particular and individualised way. Medical data might be increasingly used in non-medical contexts, and human emotions could be deeply embedded into the technical world.

5.4.2. Broader Societal and Policy Aspects

In the following section, we discuss some broader societal aspects of intelligent artefacts (IA). This includes the question of how to balance short-term with long-term perspectives of the field, with a special view to policy-making, and the notion of "technology becoming biology". The question of how to balance shorter-term perspectives with longer-term perspectives is related to such issues as expectation management, the highly visionary aspects of the field, and its public image – and thus also relevant in the policy context. Here we also present views of the experts interviewed for this project.

Broader Societal and Cultural Aspects

With regard to biomimetic (aka 'bionic') R&D, which has led to the rise of zoomorphic and anthropomorphic robots, we may also ask how our views of the corporeality of animals and humans, and thereby of life, might be changed in the long run. As in such fields as synthetic biology (see chapter 2), life could progressively be seen as 'being' technology. Interestingly, in "artificial life" research, which can be deemed a segment of cognitive science (where it overlaps with neuroscience and biological engineering), animal neurons or whole animals are used for controlling machines.¹⁴⁵ Some researchers connect cultured neuronal networks (taken, for example, from rats) with robotic devices and have shown that such brain-semiconductor hybrids can, for example, control a flight simulator (see chapter 4). At least one researcher in this field (Steve M. Potter of Georgia Tech) has characterised these creatures as "semi-living animals". Other researchers as well as artists connect living insects with robotic machinery, in order to let the former control the latter. While some observers hold that such a research raises techno-ethical questions, it could also be argued that the use of animals, including their perceptive and cognitive faculties, is an age-old human activity - which does not become problematic when advanced technoscientific means are used (Meyer and Guillot, 2007: 1395-1422). Seen from another perspective, however, these hybrid embodiments of intelligence raise new questions with regard to our interrelations with both animals and machines. Humans have defined themselves since time immemorial by marking their difference to animals, and since early modern times, machine metaphors have become crucial for human self-understanding and the understanding of other living beings. If animats are now slowly leaving the "virtual" world, fundamental changes may occur regarding the significance of the triad humananimal-machine.

The abovementioned vision that advanced IA will become ethical agents and carriers of rights, considered on a par with higher mammals or even with humans, may also fundamentally affect our human self-understanding. While humans might thereby lose some of their uniqueness, they would, on the other hand, act as the creators of their new partners or rivals – a fascinating topic which has already been explored in fiction and science for a very long time now. When it comes to the vision of an AI with an intelligence that exceeds that of humans and at the same time operates autonomously, self-organises and self-optimises, some people predict that there will be a so-called 'singularity': a runaway chain reaction of machines capable of building even better machines, in the course of which machines may replace or enslave humans, or, more optimistically seen, become our real partners and help us to exist eternally (as minds uploaded on machines) and to conquer outer space. These quasi-religious, techno-eschatological visions may change our views of what it means to be human and of the human destiny.¹⁴⁶

More realistically, we can ask in which way and to what extent our appreciation of interaction with other humans, and thereby our anthropological assumptions and our societies, might be changed if we would regularly interact with anthropopathic robots or with highly sophisticated programmes that are able to adapt to our moods and needs. Here we need to remind ourselves that our societies and self-understanding as humans might not be changed fundamentally merely by highly advanced IA which could interact with humans in such areas as child and geriatric care or military and police actions. Other, less powerful IA (including programmes), if widely used and interconnected, could also have significant impacts on society and the human condition.

¹⁴⁵ See, for example, Bakkum et al. (Bakkum et al., 2007, 130-145).

¹⁴⁶ For these visions, see the overview in the recent STOA report by Coenen et al. (Coenen et al., 2009). For a discussion of the political challenges in this context, see also Section 5.4.2.1 (in this chapter of the report).

In a report of an EU expert group on converging technologies¹⁴⁷, it is argued that the better, smaller and more deeply embedded sophisticated technology will be, the less we will notice our dependence on it or even its presence. The new artificial environment will constitute a 'second nature' which will challenge traditional boundaries between nature and culture and might also dramatically alter our sense of responsibility for the world we live and act in. Together with other technologies relevant for ambient intelligence, IA may thereby contribute to profound changes in our sense of reality and responsibility. We still appear to be quite far away from a ubiquity of IA in 'real life'. However, some of such changes are foreshadowed in virtual environments. In online shopping, chatting or computer game worlds, for example, it can already happen that we deal with hidden or discreetly embedded AI or that we do not know whether we are informed by or interact with humans or intelligent agents.

How to Deal with Short-Term and Long-Term Perspectives

But how can policy makers, stakeholders and society at large make sure that their approaches to IA are realistic? This is a question of the right balancing of shorter-term and longer-term perspectives. The AI researcher Noel Sharkey has argued that decision makers as well as scientists engaged in academic discussions often tend to focus on a "mythical" version of AI, popularised by science fiction, and less on "real" AI (Martin-Jung, 2008: 18). Likewise it could be argued that it makes sense to focus on the more realistic developments concerning IA rather than on visions of a kind of artificial life as the result of a sudden and surprising development or otherwise at some point in the distant future. This view is, for example, shared by the 'AAAI 2008-09 Presidential Panel on Long-Term AI Futures' which was organised by the president of the Association for the Advancement of Artificial Intelligence (AAAI).¹⁴⁸ The panel expects AI research to have great positive influences in many realms, including healthcare, transportation, education, commerce, information retrieval, and scientific research and discovery. The experts of the AAAI panel are, however, overall sceptical of the radical views expressed by futurists and science-fiction authors, relating, for example, to the prospect of an intelligence explosion as well as of a coming "singularity", and also of the large-scale loss of control of intelligent systems. Nevertheless, there was a shared sense that additional research would be valuable; research on methods for understanding and verifying the range of behaviours of complex computational systems for minimising unexpected outcomes. The panel suggested outreach and communication to people and organisations about the low likelihood of the radical outcomes and for the need to educate people outside the AI research community about the promise of AI for enhancing the quality of human life in numerous ways. According to the panel, one of the shorter-term issues is the development of methods for enhancing privacy while enabling people and organisations to personalise services. Other shorter-term opportunities include investments in methods that enhance interactions and collaborations between people and machine intelligence and the support of fluid transitions between automated reasoning and human control. According to the panel, the latter includes developing methods that make machine learning and reasoning more transparent to people, for example, by giving machines the ability to better explain their reasoning, goals, and uncertainties. It was argued that AI methods might one day be used to perform relatively deep and long-term learning and reasoning about individuals and organisations and then perform costly actions in a sophisticated and potentially secretive manner.

148 For the following, see Horvitz and Selman (Horvitz and Selman, 2009).

¹⁴⁷ High Level Expert Group on "Foresighting the New Technology Wave": Converging Technologies. Shaping the Future of European Societies (Rapporteur: A. Nordmann). Luxembourg: Office for Official Publications of the European Communities 2004.

Among the experts of the AAAI Panel there was a shared sense that it would be wise to be vigilant and to invest in proactive research on these possibilities. Proactive work could include new efforts in security, cryptography, and AI research in such areas as user modelling and intrusion detection directed at this potential threat, in advance of evidence of criminal efforts.

If we look at the expert answers to our questionnaire, we see a rather broad spectrum of views regarding the question of longer-term and shorter-term perspectives: One researcher, for example, vehemently argued against highly speculative, far-reaching visions and against "science-fiction" notions of AI. In a similar vein, one ethicist argued that 'the Singularity' and other trans/posthumanist scenarios of new intelligent species (such as cyborgs or a fully autonomous AI which is intellectually superior to humans) are often nothing more than a "hype", fuelled by "(unprofessional) journalism". However, this ethicist also believes that "[t]he symbiosis between human lives and technologies will become ever more extensive". One researcher perceives "a strong integration between technology and body" and between "technology and mental activity", where both will make the boundaries between life and technology "much more fuzzy, not just practically but theoretically speaking". This researcher emphasises: "I believe in artificial 'creatures' and in artificial real 'intelligences'." The same researcher also thinks that both a merger of humans with machines and the creation of fully autonomous IA which are intellectually superior to humans will happen. This expert also pointed out that the old Gramscian dictum that we need a pessimism of reason, but an optimism of will, is also true with regard to our political and societal handling of IA: we would have "to see" and "understand the possible consequences and dangers, while driving and orienting the process towards human wellbeing" by means of an inclusive social shaping of the relevant technologies and a constant deliberation which is not restricted "to engineers, to scientists, to businessmen, or to politicians". Another ethicist does not believe that the abovementioned "utopian/dystopian questions" are realistic, but points out that "they might have an impact" similar to the impact of "literature or science fiction" - the question is "not whether technological artefacts of whatever kind might become like natural ones, but what kind of differences we want to create and for what purposes: artificiality is about differences not identities." Still another expert, a cognitive scientist, believes "on a personal level" that "human intelligence" is due to the neuronal substrate, which is essentially computing". As "we better understand how this computational framework in the brain operates we can better approximate it in other forms of computational substrate, e.g. electronics." This expert emphasises, however, that this will probably not lead to a civilisation dominated by IA or to a post-human era: "As this progresses I believe we will blend with the technology rather than be dominated by it."

Most of the interviewed experts, albeit not all of them hold that post-human scenarios are merely science-fictional, believe in a future merger of humans and technology. Also a majority of the experts emphasised that the ethical and societal implications of IA should receive more attention, in order to be able to steer the development in a direction which is beneficial for society. One expert emphasised that the short-term and long-term prospects of IA should seriously be discussed, in terms of a "constant" and participative discourse on the area's ethical and political implications: *"This cannot be delegated to engineers, to scientists, to businessmen, or to politicians!"* One may add here that policy makers could stimulate or initiate such a discourse.

Is Technology Becoming Life?

We have also asked the experts interviewed for this project what they think of the claim that technology can in fact become life, or at least indistinguishable from life in many respects. Again, there was an interesting diversity of viewpoints. While one expert said that one would need to write a book about this question and that "it is simply too broad and general(ising) for a questionnaire", all the other experts provided answers. One sceptic stated that the most significant impact can for the time being only be a new understanding of humankind. Another expert believes that the boundary between natural and artificial systems is going to become less clear in the future, pointing to developments in the fields of prosthetic technologies and robotics. In a similar vein, one answer was that we will slowly get closer to developing a kind of artificial life: "society will have time to adapt to this change and see these advances as a way to support our abilities so that we can extend our productive and active life." Still another expert thinks that IA soon will have a significant impact due to body and behavioural monitoring in the areas of health assistance, sport and psychotherapy. One of the interviewees emphasised: "I believe in artificial 'creatures' and in artificial real 'intelligences'." Another respondent pointed out that new technologies have already fundamentally changed social networks and modes of communication and believes that the historical trend, a beneficial blending of life and technology, will continue. Still another respondent emphasised that, for the time being, technology is influencing life, although it should be vice versa. On the other hand, one expert told us that the challenges in emotion-oriented computing are "so dramatic, so tremendous, so basic, that I cannot imagine a real risk of humans mistaking technology to be 'living'." In the view of this expert, "the key issue" probably is "that in order to competently interact socially and emotionally, technology would need to have so much knowledge about social customs, cultural norms, world knowledge, and the capability to identify tiny deviations from a norm as potentially highly informative, that the realism in interaction will remain highly limited for many years to come." In a similar vein, one interviewee pointed out that some visions of early AI research had been naïve and that today too much emphasis is placed again on "wild" speculations.

Two experts fundamentally criticised our project's central question – namely whether technology will in fact become life(like). One of the experts thinks that this question is unimportant: crucial would be instead what kind of differences we want to create and for what purposes. In the view of this interviewee, *"artificiality is about differences not identities."* Finally, one expert pointed out, with reference to robotics, brain-computer interfaces and other technologies, that the *"symbiosis between human lives and technologies will become ever more extensive."* Responding to the more radical notions of a blurring of the boundaries between life and technological underpinnings of these visions, and what are the relevant philosophical conceptions of life in this context?

5.5. Conclusions

In the following, we will not try to summarise the broad variety of results of our analysis, but instead focus on our central question: do the developments in the area of intelligent artefacts (IA) indicate that technology is becoming life?

We have seen that in various world regions, including a large part of Europe, R&D in the area of IA is significantly funded and several of its strands appear to be booming fields. We have to keep in mind, however, the chequered history of artificial intelligence (AI); a research field which is highly vulnerable to hype.

One could argue that this is also true for the whole area of IA, be they virtually embodied, such as agents, or physically embodied, such as robots. Opinion makers as well as policy makers should be aware of the risk of overhyping the fields in question, and one should not lose sight of what is the real core of the R&D activities which are relevant for the area of IA: The main aim of these activities is to make users feel "more comfortable" with the technology, which is designed for the express purpose of providing support to humans. Progress in this direction is being made, but the perhaps more appealing idea, at least for the public, is the building of machines that have emotions or truly act in an autonomous way. Although there clearly are tendencies to blur the distinction between life and technology in the area of IA, we should keep in mind that in most cases - even when it comes to highly visionary perspectives - we are not dealing with artefacts that "really" become "biology"; we are dealing with artefacts that have lifelike properties or features. Accordingly, as one of the experts emphasised, we will primarily have to deal with two questions regarding this trend: what are the scientific and technological underpinnings of the relevant visions, and what are the relevant philosophical conceptions of life in this context?

There are, however, exceptions and qualifications to be made with regard to these conclusions: 1) Some boundaries between life and technology will probably be increasingly blurred due to the further integration of life-like artefacts in our ("online" and "offline") daily life. 2) There are, in fact, some examples of a physical blending of biology and technology in the realm of IA, such as the abovementioned animats. 3) More and more artefacts are designed biomimetically and thereby not only acquire (often strangely) familiar, lifelike features, but, in fact, amount to a kind of techno-zoology.

With regard to the ethical, legal and societal aspects of IA, we can identify at least two major trends: 1) An erosion of the fundamental categories of the lifeworld ('*Lebenswelt*') appears to take place, or at least a radical reconfiguration of their interrelations. This relates, for example, to our notions of machines and animals, to our interrelations with machines and animals, and, last but not least, to our concepts of intelligence and to the embodiments of intelligence. 2) There appears to be a growing uncertainty concerning the sources of agency which today can, above all, be observed in virtual environments, but may in future encompass a 'real life' pervaded by responsive, adaptive and anthropopathic technology. Human agency can become indistinguishable from machine agency.

These two major ELSA trends bring along a whole range of ethical, social and also legal implications. Both trends reflect what we have termed 'technology becoming life', inasmuch as technology is either merged with biological entities or substances, or technology becomes integrated in our social interactions and environments in a way that produces uncertainty about the sources of agency, rendering invisible differences between human and machine action. It is fascinating to see that R&D in the area of IA, sometimes even explicitly, aims to create technologies which blur subjective perceptions of reality and the boundaries between the natural and artificial, between life and technology. These efforts, in which various strands of IA research converge, could lead to a multi-layered reality in which actors, switching between physical and "virtual" embodiments, are not easily identifiable as either human or artificial.

At EU level, ELSA issues of IA are dealt with to a significant degree, but not in an encompassing way. What is more, the public societal dialogue on these issues has not yet developed in a satisfying manner. Although there are many noteworthy EU-funded and other activities on IA and a significant degree of mass media interest in them, a gap appears to remain between the techno-scientific developments in this area and public dialogue about it.

Crucial issues, such as the question of how far we want to integrate future machinic 'actors' in the lifeworld (e.g. in the case of eldercare or in the learning and living environments of children) and how far we want to "embed" human emotional aspects in our sociotechnical infrastructure (e.g., in the case of the Internet), have not been systematically and broadly discussed. Thus, there appears to be a need for a public dialogue in which core issues of the expert discourse on IA (such as risk and liability issues associated with the integration of more and more non-industrial robots in everyday life) are discussed in a broader perspective, which includes such aspects as our fundamental understanding of the place of human beings and artefacts in our societies.

If we look at the developments and tendencies that have been sketched and discussed in this chapter, the following general conclusion can be drawn: Potentially intelligent, situated artefacts will progressively become parts of our "real" and "virtual" daily lives. It is precisely in this sense that technology is becoming life, and most of the ethical, societal and political challenges raised by the technologies in question, as well as the many new options in man-machine interaction, result from this embedding in our societies and in the lifeworld.

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6. CONCLUSIONS

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The previous chapters have described the state of the art of four prosperous bioengineering fields: engineering of the body and the brain, and engineering of intelligent and living artefacts. The chapters analysed to what extent the various strands of research within those engineering fields are currently being supported by the Framework Program of the European Commission. In addition, the chapters provided an overview of the different ethical, legal, and social aspects related to the abovementioned bio-engineering fields.

To structure the description and analysis of the four bio-engineering fields and the societal issues they raise, we have used the trends or metaphors "biology becoming technology" and "technology becoming biology" as a conceptual lens. In the introduction we argued that the trend "biology becoming technology" implies that engineers and scientists increasingly look at living organisms in mechanical terms. The trend "technology becoming biology" implies that engineers, like self-healing and cognition, into technology. This final chapter aims to complete this intellectual exercise. Section 6.1. reflects on the broad terrain of bio-engineering that is being developed and how this fundamentally broadens the bio-debate. Section 6.2. deals with the ethical, legal and social aspects involved in this discussion. The chapter ends with some concluding remarks.

6.1. Bio-engineering in the 21st century

This section discusses to what extent the trends "biology becoming technology" and "technology becoming biology" capture many developments within the four bio-engineering fields we have mapped. We then reflect on how these two megatrends impact the way of doing science, in particular the role played by engineering. We show that "biology becoming technology" and "technology becoming biology" constitute two different types of engineering approaches to science. Finally, we will clarify that bio-engineering in the 21st century presents and promises both new types of interventions in living organisms, including human bodies and brains, as well as the development of new types of bio-, cogno- and socio-inspired artefacts. We conclude that these envisioned new technical interventions and artefacts radically transform and broaden the bio-debate.

6.1.1. Biology becoming technology - and vice versa

The four fields of bio-engineering described in this report – engineering of the body, of the brain and of intelligent and living artefacts – show many R&D activities that either illustrate the "biology becoming technology" trend or the "technology becoming biology" trend (see Table 6). This section provides an overview thereof.

Bio-engineering field	Biology becoming technology	Technology becoming biology
Engineering of the body	Molecular & regenerative medicine	From repair to regenerative medicine
	• Biomarkers	
	Gene therapy	
	Tissue engineering	
	Stem cell therapy	
Scientific goal	<i>Molecular medicine</i> Understanding metabolism as genetic and molecular information processes	<i>Regenerative medicine</i> Understanding the cell as a building block of life
	Regenerative medicine See right column	
Engineering goal	<i>Molecular medicine</i> Developing new medical diagnostics and therapies to manipulate the cell	<i>Regenerative medicine</i> Controlling the cell's power of growth (reproduction) and differentiation for medical therapies
	Regenerative medicine See right column	
Engineering of living artefacts	"Top-down" synthetic biology	"Bottom-up" synthetic biology
	Whole genome synthesis	Minimal genomes
	• Enhanced metabolic engineering (GMOs)	• Synthetic (proto) cells,
	Minimal genomes	Xeno-organisms (chemically modified organisms)
Scientific goal	Understanding the metabolism of cells	Understanding the origin of cellular life (evolution)
Engineering goal	Engineering cells into custom-made chemical factories	Engineering (non-existing) life forms
Engineering of the brain	Forward engineering of the brain	Reverse engineering of the brain
	Neuromodulation (TMS, neurofeedback, VNS, and DBS)	 Narrow reverse engineering (software),
	 Brain-computer interfaces (BCI), including animat research (using animal neurons as controlling device) 	 Neuromorphic engineering (hardware),
		 In vitro engineering of cultured neuronal networks (wetware)
Scientific goal	Understanding how the (non-) diseased brain works and its relation to cognition and behaviour	Understanding how (parts of) the brain work including consciousness
Engineering goal	Developing brain diagnostics and therapies to support or manipulate brain functions, and brain-computer interfaces	Building supercomputers
Engineering of intelligent artefacts	Persuasive computing & animat research (see above)	Artificial intelligence (classical & situated) & Affective computing
Scientific goal	Understanding man-machine interaction	Understanding intelligence
Engineering goal	Developing computers and artefacts that can affect social behaviour	Engineering learning artefacts that make (autonomous) decisions, behave "as if" they are emotional and social

Table 6 An overview of R&D activities within four bio-engineering fields

6.1.1.1. Biology becoming technology

The "biology becoming technology" trend is illustrated by molecular medicine, regenerative medicine, "top-down" synthetic biology, forward engineering of the brain and persuasive technology.

Top-down synthetic biology

Synthetic biology ranges from the attempt to radically modify existing organisms all the way to the design of life from scratch. Torgersen, Schmidt and Kastenhofer (chapter 2) make a distinction between "top-down" and "bottom-up" approaches in synthetic biology. The "top-down" approach illustrates the "biology becoming technology" trend, because it builds on conventional biotechnology, which aims to genetically modify existing living organisms. An example is enhanced metabolic engineering, which aims at engineering a micro-organism into a machine that delivers a specific chemical product.

Engineering of the body

According to Hüsing and Geesink (chapter 3) both molecular medicine and regenerative medicine illustrate the "biology becoming technology" trend. Molecular medicine tries to understand and develop means to treat diseases at the molecular (including genetic) level. The field of regenerative medicine increasingly uses bodily material to engineer body functions. Here biology is becoming technology.

Forward engineering the brain

Van Keulen en Schuijff (chapter 4) show that the brain sciences illustrate both trends. Reverse engineering of the brain illustrates the "technology becoming biology" trend (see below). Insights into the brain, partly discovered by reverse engineering of the brain, may be used to develop tools to support, manipulate or enhance the working of the (human) brain and consequently behaviour. Such forward engineering of the brain falls within the trend "biology becoming technology".

Forward neural engineering can be divided into two sub-disciplines: neuromodulation and brain-computer interfaces (BCI). Over the last decades, various invasive and non-invasive ways of (electronically) altering mental functioning have gradually entered medical practice (i.e. neurostimulation). Besides, (non-)invasive BCIs have been developed in order to relate activation patterns in the brain with certain intentions of the patient. So far, invasive BCIs have only been tried out in a few, almost completely paralysed patients and animals. So-called animat research experiments with animal neurons as a computer to control devices, e.g. a flight simulator, is a radical form of BCI, where the distinction between the brain and the computer – and therefore the distinction between "biology becoming technology", and "technology becoming biology" – vanishes.

Persuasive technology

In chapter 5, Böhle, Coenen, Decker and Rader describe that some intelligent artefacts are expected to be able to display "human" emotional, affective, social and expressive qualities, with the aim to influence human attitudes and behaviour on an emotional, (sub)conscious level. This part of affective computing is called persuasive computing. Such persuasive technology can be seen as a kind of non-invasive form of forward engineering of the brain, and thus falls within the trend "biology becoming technology".

6.1.1.2. Technology becoming biology

The "technology becoming biology" trend is illustrated by the shift from repair to regenerative medicine, "bottom-up" synthetic biology, reverse engineering of the brain and the engineering of living artefacts.

From repair to regenerative medicine

When seen from the perspective of the tissue engineer, developments within the field of regenerative medicine can also be described as "technology becoming biology". Namely, the shift from repair to regenerative medicine is guided by a wish to increase the ability to engineer and use bio-inspired materials and materials (e.g. genes, cells) directly derived from the human body. Mimicking nature is seen as the best possible way to not just repair or replace failing human body parts, but to regenerate these parts and their functions altogether. We can witness a development from artificial and synthetic organs to hybrid artificial organs, and the long-term ideal of constructing a completely biologically derived organs. Moreover, human derived (stem) cells and tissues could be modified and (re)programmed in such a way as to take over bodily functions and replace defective parts (such as genes) on the spot. Here the technology to intervene in the body is becoming biology. It is hoped that the synergy between molecular and regenerative medicine will lead to new tools, like gene therapy, (stem) cell therapy and tissue engineering, for a medical intervention at the cellular or molecular level.

Bottom-up synthetic biology

The "bottom-up" side of the synthetic biology spectrum represents the "technology is becoming biology" trend. Researchers that aim to build proto-cells and/or xeno-organisms start from chemical building blocks (that may go beyond the chemistry found in nature) to design and construct novel life forms. Torgersen et al. underline that the top-down and bottom-up approaches are not mutually exclusive. For example, the minimal genome research shows a clear hybrid since it radically alters an existing micro-organisms by replacing its entire genome by a fully synthesised (minimal) genome that has been built from scratch in the laboratory.

Reverse engineering of the brain

Reverse engineering of the brain nicely illustrates the "technology becoming biology" trend. This field tries to understand the design principles of the brain by building representations or simulations of (parts of) the brain in either software (narrow reverse engineering), hardware (neuromorphic engineering) or wetware (in vitro engineering of cultured neuronal networks). The famous Blue Brain project presents an example of the software approach and attempts to build a software simulation of the biological structure and activity of the brain of a mammal. So-called neuromorphic engineering aims at building supercomputers by mimicking certain features of the brain like parallel computing or neural plasticity. In vitro engineering of cultured neuronal networks presents a third research strand. Besides, for fundamental research on the brain, cultured neuronal networks may be applied as highly sensitive bio-sensing systems for drug screening, or, in the long term, even as controlling devices (e.g. animal neurons – semiconductor hybrids).

Engineering of intelligent artefacts

Böhle et al. (chapter 5) present engineering approaches for developing intelligent, life-like artefacts, such as physical robots, smart environments and software agents, also called software "bots" or "softbots". The long-standing endeavour to construct artificial intelligence (AI) links to the "biology becoming technology" trend. AI always aimed to design and construct artefacts that display some level of autonomous behaviour, because they are able to learn and adapt to changing situations. In this respect, the arrival of "situated" or "embodied" AI is relevant. While for classical AI reasoning and behaviour can be reduced to clean algorithms, the new AI approaches hold that behaviour is embodied, embedded and situated in the real world. Affective computing starts from a similar assumption and aims to improve the interaction between human beings and artefacts. For this goal artefacts have to 'understand', connect with and influence human beings on a social and emotional level. Tools are built to measure and respond to (neuro-) physiological, psychological and social data of human beings. This is so-called (neuro-) physiological computing.

6.1.1.3. R&D funding by the European Commission

The European Commission actively stimulates R&D projects that fit within both megatrends. With respect to "biology becoming technology," the European Commission, mainly within the thematic area "Health", strongly sponsors the development of molecular and regenerative medicine. The involvement of industrial partners in all related projects suggests that research is oriented towards future commercial applications. The European Commission, however, is not funding many forward engineering activities that focus on the development of neuro-modulation technologies. For the European Commission, the importance of synthetic biology has been comparatively high over the last years. Research focuses on strengthening metabolic engineering ("top-down" synthetic biology).

With respect to "technology becoming biology", "bottom-up" synthetic biology, like protocell research and chemical synthetic biology, gets only limited attention. Since the beginning of this century, the European Commission, in particular DG Information Society and Media, is very actively stimulating the convergence of neuroscience and information technology. Most cutting edge projects centre on developing intelligent artefacts, reverse engineering the brain, and developing brain-computer interfaces (BCIs).

6.1.2. Bio-engineering and science

"The effect of concept-driven revolution is to explain old things in new ways. The effect of tool-driven revolution is to discover new things that have to be explained." (Freeman Dyson 1997: 50-51)

The development of both megatrends is enabled by a close interaction between science and bio-engineering. To indicate such a close cooperation and the blurring of the boundaries between pure and applied science, engineering and society, the term *technoscience* is regularly used (Latour, 1987). This subsection explores whether the nature of the relation between science and bio-engineering within the trend "biology becoming technology" differs from the nature of that same relation within the "technology becoming biology" trend. To do that, we use Dyson's (1997) insight that there are two kinds of scientific revolutions: those driven by new concepts, like the advent of quantum mechanics, and those driven by new tools; he gives the example of the use of X-ray diffraction by Watson and Crick to unravel the structure of DNA. This section investigates to what extent and in which precise way the two bio-engineering trends are driven by new tools or new concepts. We first explain that both trends are driven by a specific engineering concept of life, which enables two tool-driven ways of doing science.

6.1.2.1. A new engineering concept of life

Whereas Descartes looked at living organisms in static and mechanistic terms, engineers nowadays are mostly guided by another engineering concept of life: life as an information processing system (Van Est, 2010). Norbert Wiener, the founding father of cybernetics, was one of the pioneers of the so-called *digital control paradigm of life*. He described animals and machines alike as information processing systems that constantly move from acting to sensing the environment to comparing the feedback with a certain goal, and then back to acting in order to achieve that goal. This new scientific way of looking yielded the hypotheses that machines could be built that would act with purpose, and that life itself could be looked at and studied as an information processing system.

The cybernetic view of life thus presented a new way of understanding nature, which in turn created a need for new tools to deconstruct life as an information processing system. Besides, it also provided an alternative tool-driven route to studying nature, namely by rebuilding nature, and experimenting with artificial nature (see 6.1.2.2). This subsection illustrates the influence of the computational view of life and looks at molecular medicine (as an example of "biology becoming technology") and intelligent artefacts ("technology becoming biology").

Molecular medicine

Both synthetic biology and molecular medicine are guided by the digital control paradigm of life. The unravelling of the DNA code in 1953 caused a breakthrough for the computational view on life (Kay 2000). The potential of reprogramming life was first opened up in the 1970s through the invention of recombinant-DNA technology, and then fully captured during the 1980s by two visions: systems biology and artificial life. Molecular medicine directly fits in with the systems biology vision. The Human Genome project is the showpiece of systems biology. The Human Genome project was as much a high-tech project aimed at developing tools for automatic sequencing of DNA as it was a scientific endeavour to understand the human genome. In the wake of genomics, molecular medicine is expected to elucidate the underlying information and mechanisms of disease processes, and apply this information in medicine.

Engineering of intelligent artefacts

The endeavour to engineer intelligent artefacts is also influenced by the computational view of life. Building intelligent artefacts has, for a long time, been guided by a rational-cognitive approach to intelligence and attempts to make a "top-down" model of the physical world in abstract symbols. New AI approaches, like situated and social AI, are led by the conviction that all behaviour is guided through interaction with the world, and thus is "embedded, embodied, situated". Still, situated and social AI follow the digital control paradigm of life, because they assume that social interaction and emotions can be digitally recorded and modelled into a physical or virtual robot. Such an assumption guides new research questions and trajectories. Building a 'social' and 'emotional' artefact requires a deep understanding of not only the physical but also of the social and cultural context that the artefact has to act in and interact with. Thus, here the aim to engineer intelligent artefacts leads to new scientific research questions.

6.1.2.2. Two tool-driven approaches to science

Bio-engineering in the 21st is driven by the digital control paradigm of life, and new tools for science. These tools - like computers, biomarkers, DNA synthesisers, electronic microscopes, functional MRI - are used to discover new things about life. The trend "biology becoming technology" is defined by such tool-driven science, in which engineering delivers the tools to investigate nature. "Technology becoming biology", however, is driven by a distinct type of tool-driven science. In this case, engineering provides the experimental tools, but also the object of scientific study. This engineering of new technological entities, which mimic living nature, forms a new 'bottom-up' way of doing science. This engineering approach to science is aptly summarised by Feynman's famous quote: "What I cannot construct, I do not understand". In Science, Kevin Kelly (1998) signalled the arrival of this new way of doing science, which was not primarily about carefully setting up controlled experiments, but especially about creating insights through "trying to create an artificial reality, an artificial life, and artificial consciousness". Here a kind of second artificial nature – a parallel technological world, as Kelly names it – is being engineered, physically or virtually, to foster scientific understanding of the world. This subsection illustrates both tool-driven types of doing science, by looking at the field of engineering of living artefacts and the brain.

Engineering of living artefacts

Synthetic biology illustrates that science is driven by an engineering perspective, but also that engineering itself has become a scientific method. Synthetic biologists promote a prime role of engineering in unravelling and (re)designing metabolic processes. Torgersen et al. (chapter 2) aptly explain that in the field of synthetic biology, *"engineering becomes science, and scientific insights drive engineering while, at the same time, scientists need engineering to gain insights."* Synthetic biologists promote an engineering perspective to make genetic engineering into a 'real' engineering discipline. In addition, the engineering view is also seen as a "bottom-up" way of doing science, a new strategy to acquire a deeper understanding of life. This is exemplified by Venter's minimal genome project, which aims to foster scientific understanding of various fundamental characteristics of life. What is the smallest set of genes that life needs? But at the same, a microbe with a minimal genome is expected to be an ideal platform for a cell-factory system. Here, doing science and engineering an industrial product have become undistinguishable activities.

Engineering of the brain

The brain sciences have been collecting a lot of information about different parts of the brain, but they still lack concepts to deal with the complexity of the whole brain. Forward and reverse engineering of the brain can be seen as pragmatic ways to deal with alack of theory. These two approaches exemplify two different tool-driven research routes. The classical route of tool-driven research is presented by the (top-down) forward engineering approach which puts the brain on the rack. Here engineering delivers the tools to study the brain. This approach is not guided by a precise theoretical understanding of the brain. The scientists and doctors that experiment with TMS or DBS don't know how these techniques exactly work. Instead, they discover things by trial and error, through learning by doing. Here, acquiring scientific knowledge about the brain – at least when human patients are concerned – coincides with the application and development of new therapies. Reverse engineering of the brain presents a second tool-driven approach.

Its promoters think that their efforts will lead to discoveries faster than the development of new theories. In chapter 4, Van Keulen and Schuijff quote Kelly (1998) who states that *"the way to settle the question of how the mind works is to build a working mind"*. Analogues to the minimal genome project, the effort to reverse engineer the brain to promote scientific understanding coincides with the application-driven effort to build an artificial brain (cogno-inspired supercomputer).

6.1.2.3. Recognising life's special characteristics

Bio-engineering in the 21st century is guided by a specific engineering concept of life. This digital control paradigm of life enables two types of tool-driven science. With regard to "biology becoming technology", the role of engineering is to give science the experimental tools to reveal to mankind the secrets and laws of nature. "Technology becoming biology" is guided by an even more intricate relationship between science and engineering. Here, engineering provides the tools to build an artificial nature, which can be used as a model to study nature. The arrival of these two engineering approaches to science can partially be understood as a pragmatic way to deal with the dynamic complexities of living organisms and social processes.

But more fundamentally, it also presents recognition of the special characteristics of life itself, like its complexity, flexibility, autonomy and emerging properties. As Weber explains, *"in the age of technoscience, the dimensions of becoming, the possible and the unpredictable are of central concern and at the heart of a new techno-rationality that does not represent the living as dead material"* (Weber, 2010: 27). Life as a complex scientific object, thus, has lead to an intimate relation between science and engineering. In addition, we may conclude that, in the meantime, the boundaries between experimenting and intervening with nature, and constructing living and intelligent artefacts for acquiring knowledge or for the market, are also being blurred.

6.1.3. Bio-engineering and the bio-debate

The trend "biology becoming technology" presents and promises a range of new types of interventions in living organisms, including human bodies and brains. The trend "technology becoming biology" presents and promises many new types of artefacts, as it aims to emulate certain lifelike features in and through technology. This section gives an overview of these new types of interventions and artefacts, and analyses how the increased bio-engineering capacities will fundamentally broaden the current bio-debate.

6.1.3.1. New types of interventions in living organisms

The foregoing chapters show a myriad of new bio-engineering ambitions with regard to influencing and rebuilding organic life. Society is already accustomed to, although not always at ease with, re-making the living world with the aid of technology. In the second half of the 20th century, all kinds of bio-tech inspired and IT-inspired ways of intervening with living organisms have been put in practice. Since the 1950s, artificial pacemakers are used to regulate the beating of the heart. Since the 1970s, gene technology is employed to genetically modify E. coli bacteria in order to produce insulin to treat diabetics. The introduction of GM food on the market during the 1990s led to much debate. GM animals, like mice, rats and fish, are being used on a massive scale in laboratories all over the world. The foregoing chapters show the possibility of an enormous expansion of the types of interventions in living organisms. Table 7 gives the reader a quick overview.

With regards to biotechnological interventions, synthetic biology aims to bring genetic engineering to the next level through its ambition to standardise and automate the reengineering of micro-organisms. But also in the field of engineering the human body, all kinds of new diagnostics and therapies are promised. Think for example about the development of gene therapy or the futuristic idea of genetically enhancing sperm cells with artificial chromosomes. Other new forms of interventions in the body, like tissue engineering and stem cell therapy, use living materials often derived from the body it aims to repair.

But information technology, too, offers increasing numbers of ways of intervening in living organisms. Hybrid artefacts are created that mix cells, insects, and animal brains with semiconductors. For humans, smart pills are being developed that monitor diseases and deliver medicines within the body. Also, the brain is rapidly coming up as a new area of IT-inspired interventions. We are moving from the artificial pacemaker of the heart into the era of the artificial pacemaker of the brain. New brain therapies include the use of electrodes put into the brain. The result is regularly described by the term human cyborg.

Living organism	Bio-tech based interventions	Info-tech based interventions
Micro-organism	Extreme genetic engineering (synthetic biology)	Cyborg cell, cell on a chip
Insect, animal		Insect/animal brain – semiconductor hybrid
Human body	Genetic modification (gene therapy, use artificial chromosomes in gametes), stem cell therapy	Smart e-pills
Human brain	Stem cell therapy	Brain computer interfaces (BCIs), (non-)invasive neuro-modulation, persuasive technology

 Table 7
 New bio-tech and IT-based ways of intervening in living organisms

6.1.3.2. New bio-, cogno- and socio-inspired artefacts

Traditional engineering is about building nonliving artefacts, like cars and bridges, by means of nonliving material. Our study shows various new engineering ambitions to build intelligent artefacts and living artefacts from components that are all nonliving. We also encountered examples of so-called hybrid artefacts consisting of both nonliving and living components, like animal brain – semiconductor hybrids. Table 8 presents an overview of various types of new (envisioned) artefacts.

Synthetic biology includes the aim to build a proto-cell – a living artefact – from scratch, i.e. from nonliving material. Engineering a microbe with an artificial minimal genome presents a hybrid artefacts, built out of living and nonliving components. Other hybrid artefacts can be found based on the engineering of living material derived from insects, animals or humans. Examples are cultured neuronal networks, or animal-brain semiconductor hybrids. Bodily materials of humans are employed to engineer tissues, hybrid artificial organs and stem cells.
In particular, reverse engineering of the brain and the field of robotics are indicative of engineering ambitions to create artefacts that show intelligent behaviour. Reverse engineering of the brain aims to build supercomputers through both wetware (neurocomputer) and hardware approaches. Böhle et al. (chapter 5) explain that new robotics moves away from the rational-cognitive approach (with its computational theory of mind) towards biologically, neurologically and emotionally inspired approaches. Engineers aim to build physical robots and softbots that are capable of learning, making autonomous decisions and performing adequately in complex social environments.

Source of inspiration	Bio-inspired	Cogno-socio-inspired
Micro-organism	Proto-cell	
	Minimal genomes	
Insect, animal	Cultured neuronal networks	Animalistic robot (e.g. Paro), avatar
	Hybrid artefact: animat	Neurocomputer
Human	Biopharmaceuticals	Humanoid robot, avatar
	Engineered tissues (hybrid	AI robots and softbots
	materials with living ingredients)	Social robots
	Stem cells	Ambient persuasive technology
	Hybrid artificial organs	

Table 8	New types of bio-	. cogno-, an	d socio-inspired	artefacts
	New types of blo		a 30010 mispirea	ancoracio

6.1.3.3. Fundamental broadening of the bio-debate

The scientific ambition to understand the living world has become intimately connected to the engineering ambitions to both intervene in living organisms and our social world as well as to construct lifelike artefacts. These ambitions, if only partly fulfilled, would increase the hybridisation of the living and nonliving world, through ways of intervening in human bodies by means of engineering bodily material, interventions in human brains, hybrid artefacts which consist of a mixture of nonliving and living components, and artefacts that get lifelike features.

This (anticipated) broad field of bio-engineering is fundamentally broadening the biodebate. Next to gene tech interventions, the societal aspects of info tech interventions in the bodies and brains of animals and human beings will take a centre stage position in the political and public debate. Besides "biology becoming technology", the "technology becoming biology" trend is expected to lead to debate more and more. In the following section, we sketch the contours of such an enlarged ethical and political debate.

6.2. Bio-engineering the 21st century

This section reflects on the various ethical, social and legal aspects involved in the four bioengineering fields described in our report. Again, the trends "biology becoming technology" and "technology becoming biology" structure our analysis of the societal meaning of bioengineering in this century. First, we will look at the hypes, hopes and fears that surround these two trends, because they form the 'spiritual' drivers of both the funding of research as well as the societal debate about it. Next, we will describe the state of the art of the societal debate and social reflection on the various developments. Finally, we will clarify how the trends "biology becoming technology" and "technology becoming biology" challenge both familiar social, legal and ethical issues, as well as the fundamental concepts – like life, body, mind, technology – we use to make sense of our world.

6.2.1. Hypes, hubris, hopes and fears

"I was concerned that parliamentarians - particularly in the House of Commons have been convinced that it was just a matter of a few years before we would be able to transplant stem cells and cure a lot of neurological disorders, like Alzheimer's disease, for which I think it is going to be a hugely difficult problem and probably completely insoluble by stem cells." Lord Winston, President of the British Association of the Advancement of Science (quoted in Amos, 2005)

All four fields of bio-engineering share imaginative and speculative long term visions, and are prone to hypes and guided by both high hopes and fears (see Tables 9, 10 and 11; under "speculative long term perspective"). We will first look at the "biology becoming technology" trend, represented by molecular medicine, regenerative medicine, forward engineering of the brain, and synthetic biology. The hopes and fears surrounding the "technology becoming biology" trend are illustrated by reverse engineering of the brain, and the engineering of living artefacts.

6.2.1.1. Biology becoming technology

Synthetic biology

The spectacular long term view of synthetic biology and creating artificial life attracts a lot of media attention. Synthetic biology promises to radically reduce the complexity of genetic engineering by standardising the design and construction processes of such living machines. Time will tell whether this assumption will come true or not. Like Torgersen et al. argue: *"The important factor is time: what appears science fiction today may turn out to become reality in a not too distant future, giving rise to ethical questions that are not fundamentally new but gain in salience."* However, normally it takes a considerable amount of time from the emergence of a new research field to introducing the first applications on the market. High expectations raised by synthetic biologists, however, may help turn synthetic biology into a hype, with unrealistic plans and timescales (Mampuys and Brom, 2010).

Molecular and regenerative medicine

Regenerative and molecular medicine create futuristic applications, ranging from genetic modification of gametes or embryos through the use of artificial chromosomes to artificial meat and wombs. Such applications will be hopeful for some, but plain scary for many others. The state of the art, however, looks far much mundane and illustrates that the above futuristic visions are far away from being realised in the short or medium term. In 2005, Lord Winston, the president of the British Association for the Advancement of Science, admitted that the potential benefits of embryonic stem cell research have probably been oversold to the public (see quote above). He argues that some of the huge uncertainties in developing cures for degenerative disorders need to be emphasised in the debate.

Currently, gene therapy and cell therapy are slowly moving closer to clinical applications. However, safety issues have to be thoroughly addressed. In particular with respect to gene therapy, the fact that several patients died because they developed severe immune reactions, has slowed down progress seriously and has dampened expectations in this field. One of the recurrent themes is that research leads to new insights, but at the same time and maybe even at greater speed, new complexities are unravelled. Science is confronted with a complexity paradox. For example, the Human Genome Project elucidated all kind of puzzles – only 23,500 genes, 'junk' DNA – that showed that life is not a straightforward computing machine, as many promoters of the digital control paradigm of life might have expected.

Forward engineering of the brain

From a public perspective, forward engineering of the brain may be one of the most sensitive research areas, since it concerns influencing people's personhood. Future visions include cognitive enhancement, but also outside manipulation of the brain by others. Although little is known of how particular neuro-modulation techniques work, the field of forward engineering the brain already presents a huge emerging global market. This has led to a discussion in the United States and Europe on whether the regulatory framework on medical devices, for introducing neuro-stimulators on the market, still suffices.

6.2.1.2. Technology becoming biology

Reverse engineering of the brain

In contrast, reverse engineering of the brain and social reflection on it are currently in their infancy. The speculative vision that accompanies these attempts is a future possibility for engineering a conscious machine. Since the brain is one of the most complex systems known to mankind, the attempts to reverse engineer the brain has met with a lot of scepticism from other scientists. Like with synthetic biology, only the future can tell whether it is possible to re-engineer the brain.

Engineering of intelligent artefacts

History shows that the field of engineering intelligent artefacts is very vulnerable to hype. Throughout history, 'strong' AI has always competed with 'weak' AI for media attention and funding, and periods of high hopes alternated with times of severely restricted research funding; so-called AI winters. Currently the field is experiencing a new revival through the inspiration of new heuristic paradigms, such as situated AI and affective computing (so-called social AI).

To a large extent, the 'strong' AI version explains the field's vulnerability to hype. Today's version of strong (classical) AI is represented amongst others by Ray Kurzweil, who predicts the arrival of machines with superhuman intelligence – so-called technological singularity – is near. With strong (nouveau) AI, future expectations refer to machines that feel emotions, instead of machines that act 'as if' they have emotions, and moral machines that can make ethical decisions. The reality of AI, however is far more mundane. Böhle et al. (chapter 5) warn that "policy makers should be aware of the risk of overhyping the field in question, and should not lose sight of what is the real core of the R&D activities." According to the authors, the real R&D core is guided by 'weak' AI and not the spectacular future visions that are predicted by strong AI. This advice also seems to apply to the three other fields of bio-engineering.

6.2.2. Towards an ELSA agenda of bio-engineering

The four case studies show an impressive list of ethical, legal and social aspects related to the four fields of bio-engineering. In this section, we will describe how the trends "biology becoming technology" (see Tables 9 and 10) and "technology becoming biology" (see Table 11) evoke discussions about how familiar regulatory issues – like safety, privacy, informed consent and bodily integrity – are challenged by new developments in science and technology. Moreover, these two trends challenge some of the central concepts we use to categorise reality (Swierstra et al., 2009). We will finish this section by describing how the European Commission currently stimulates debate and reflection on bio-engineering.

6.2.2.1. Towards an ELSA agenda of "biology becoming technology"

This section provides an overview of an ELSA agenda of "biology becoming technology". We will discuss ethical, legal and social aspects related to "top-down" synthetic biology (see Table 9). For the time being, this type of bio-engineering is basically about altering the genetic make-up of micro-organisms. Moreover, we look at the ethical, legal and social aspects of three bio-engineering fields that aim to medically intervene in humans, the body and the brain: i.e. molecular medicine, regenerative medicine and forward engineering of the brain (see Table 10). We describe how these bio-engineering terrains challenge current regulatory practices and fundamental concepts.

Issues challenging current regulatory practices

"Top-down" synthetic biology

"Top-down" synthetic biology brings up various societal issues: safety, security, intellectual property and governance. The debate on synthetic biology follows in the footsteps of the discussion on GM micro-organisms. In contrast to the GM food and GM animals debate, the debate on GM micro-organisms has never really raised much public controversy. Van den Belt (2009) expects that as long as synthetic biology only deals with microbial life, this scenario will not change. Still, genetically modified micro-organisms have raised complex regulatory issues, like safety, security and intellectual property rights (IPR). Current biosafety regulations assume that engineering starts with a parent organism. "Top-down" synthetic biology does not challenge that idea in a fundamental way ("bottom-up" synthetic biology does, see below). The fact that synthetic biology presents a form of 'digital biology' does challenge the way bio-safety and IPR are regulated nowadays. With respect to IPR, a basic question is whether this should be guided by the culture of the pharmaceutical industry (heavy patenting, which sometimes reaches the limits of practicality) or by the culture of the software industry (with open and shared forms of access). Bio-security is about how to control the proliferation of dangerous micro-organisms and knowledge and skills. The extra risks that stem from DNA synthesis challenge the current regulatory practice.

Table 9: ELSA of "biology becoming technology" (part 1): "top-down" synthetic biology

"Top-down" synthetic biology			
Challenging regulatory issues			
•	Safety		
•	Security		
•	Intellectual property (digital biology)		
	• Patenting versus open or shared access		
Wit	h regards to governance		
•	ELSA research integrated within EU Framework		
•	New engineering		
•	Public awareness is low		
Gradually changing fundamental categories			
•	Relationship between biology and technology, material and information		
•	Reductionism: life as an information-processing system, life as a construction kit		
•	Democratisation of genetic engineering (do-it-yourself synthetic biology)		
Speculative long term perspective			
•	Micro-organisms as standardised chemical factories		
•	Artificial animal and human chromosomes		

Molecular medicine

Research in molecular medicine depends on the existence of well-functioning and wellregulated biobanks, which collect bodily material and health related information. The regulation of biobanks should strike a proper balance between the need for medical research and the donor's right of self-determination. This implies that the gathering of bodily substances and personal medical data must be subject to the donor's informed consent. Molecular medicine is inherently reductionistic, because it sees disease primarily as a molecular event, steered by genetic factors. To counterbalance and complement this myopic view on disease, R&D into environmental and lifestyle factors is needed.

Over the past two decades, the cost of the testing of genetic traits has decreased exponentially. It is expected that this trend will lead to the sequencing of an entire human genome in one day at costs between 1000 and 100 dollars (Singer, 2008). High-throughput genomic techniques make it urgent to re-examine established ethical and legal concepts (privacy, confidentiality and informed consent) that guide the current research and genetic testing practice. At the moment, genetic testing is mainly confined to analysing a few genes, mostly related to rare monogenic hereditary diseases, and guided by medical staff specialised in genetics. Some principles that guide genetic testing today are: right of selfdetermination and the idea of genetic exceptionalism (including the principle of informed consent and the right not to know one's genetic status, and genetic counselling before and after testing). Cheap techniques to test genetic traits will severely challenge this practice and the ethical and legal principles that guide it. Hüsing and Geesink (chapter 3) warn policy makers about a near term avalanche of new biomarkers that need to be sufficiently validated before being brought to the market. The authors also note that the availability of information about genetic factors that contribute to cognitive traits, psychological behaviour and sexual orientation, may be used for selection; before birth (pre-implantation diagnostics, or prenatal screening) but also during our lifetime (e.g. higher education, sports career).

Regenerative medicine

The use of bodily material for medical research and applications has proved to be an ethically and politically very sensitive topic. Human dignity prevents human bodily material to be used in a pure instrumental way, as things or artefacts. Bodily material, ranging from brain-dead bodies to leftover embryos in fertility clinics, has an explicit moral and politically negotiated legal status. In general, the policy challenge is to prevent the exploitation of people as sources of cells, tissues or organs. Guiding principles are informed consent and transparency. The FP7 Framework also does not give research funding for the creation of embryos for research or stem cell procurement and human productive cloning. The moral status of human embryos created from artificial gametes may be one of the most sensitive topics for debate in the future. For now, the collection, engineering and trading in bodily material has already become a substantial market. An important question that policy makers need to address is to what extent bodily material can be treated as goods. A complex set of issues play a role here: intellectual property rights and the moral issue of whether we should allow the "patenting of life", to what extent should we allow competition between public and private organisations, shift from an altruistic donor system towards a commercial system based on donor compensation, the (cross-border) trade of bodily materials, and the danger of exploiting desperate poor people.

Forward engineering of the brain

Van Keulen and Schuijff (chapter 4) explain that the ethical, legal and social issues related to the forward engineering of the brain result from three characteristics. First of all, neural engineering may lead to personality changes, and thus may imply behavioural engineering. Second, this type of engineering is based on the convergence of neurology and IT, that is, the digital control paradigm of life. These two aspects combined with the experimental nature of forward engineering lead to a list of traditional bio-ethical issues: safety, informed consent, mental and bodily integrity, remote control issues, liability and privacy.

Neural engineering of the brain is a drastic medical treatment because it may change the behaviour of the patient. Both in the EU and US there is a debate on whether the regulation of (invasive) neuro-stimulators as medical devices is stringent enough. There is a complaint from patient groups that the current regulation neglects the protection of patients. Along this line of reasoning, the European Group on Ethics (2005) argued that implantable devices for medical purposes should be regulated in the same way as drugs when the medical goal is the same. The notion that non-invasive devices might still be mentally invasive raises the question whether non-invasive medical devices indeed lead to lower risks, as current regulations suggest. Another safety concern relates to the use of neuro-stimulation for the purpose of enhancement.

Self-evidently, neural engineering needs the informed consent of the patient. In some cases, like severe depression or a locked-in state, it can be questioned whether patients are physically or mentally reasonably capable of giving informed consent beforehand. In the case of the engineering of the brain, informed consent is guided by the principles of bodily integrity and mental integrity. Based on these principles, the European Group on Ethics (2005) argued that ICT devices should not be used to change mental functions or personality traits. The fact that the settings of some implantable devices, like deep brain stimulation, can be remotely controlled, raises an important question with respect to mental integrity: who is control? Van Keulen and Schuijff recommend the development of a benchmarking system to help doctors decide in what situations it is possible and desirable to give patients control over their own brain settings. Another issue related to bodily integrity is the question whether neural implants should be legally considered as part of the body.

Molecular medicine	Regenerative medicine	Forward brain engineering				
Challenging regulatory issues						
Collection and use of genetic information (anticipate whole genome sequencing) • Safety and efficacy of treatments • Informed consent: • open-consent approach • genetic counselling • Privacy: confidentiality of medical information • Biobanks	 To prevent exploitation of people as sources of cells, tissues and organs Safety and efficacy of treatments Informed consent: obligatory or presumed Bodily integrity: moral and legal status of bodily material Bodily material as goods Intellectual property rights ("patenting life") Commercialisation, donor trade 	Concerning treating brain diseases and preventing misuse • Safety and efficacy of (non-) invasive neuro-modulation (for enhancement) • Informed consent • Mental and bodily integrity • Remote control • Mental privacy • Neuroimaging data giving clues about cognitive state • Privacy impact of brain implants • Brain Databases • Liability issues				
Gra	dually changing fundamental categor					
 Blurring borders health and illness Self-management of health Genetic reductionism (life as an information-processing system) Attitude towards start of life 	 Body as a resource of tradable material Body as a construction kit Attitude towards end of life 	 Technology as integral part of the body Person extends beyond the body (remote control) Transparent brain 				
Speculative long term perspective						
 Human enhancement (anticipate artificial chromosome) Biobanks as knowledge base for selection and enhancement Moral status of human embryos created from artificial gametes 	Human enhancement	 Cognitive enhancement External control of brain activity 				

Table 10:ELSA of "biology becoming technology" (part 2): molecular medicine,regenerative medicine, and forward engineering of the brain.

The experimental stage of neural engineering leads to many unintended side-effects, like psychosocial problems, which may change the life of the patient. This makes the issue of mental integrity even more problematic. Nevertheless, for many patients the benefits seem to outweigh the risks. The experimental nature of neural engineering, however, causes doctors who give the treatment to worry about liability issues. Such liability questions need further research and legal consideration.

Van Keulen and Schuijff believe that, in the long term, the issue of mental privacy might become just as important as genetic privacy. The underlying assumption is that, as the technology evolves through time, measuring brain activity will come closer to measuring one's cognitive state or even thoughts. In that case, all kinds of neural applications that collect neuro-imaging data might endanger the mental privacy of patients. The European Group on Ethics (2005), therefore, pleads for a privacy impact evaluation of ICT implants. Analogues to biobanks, also the privacy of patient's brain data stored in large brain-databases should be safeguarded. One important question is whether the current EU directive on personal data protection suffices to deal with these upcoming privacy issues.

Challenging fundamental categories

The way we view the world is mediated through culturally defined concepts and classification schemes. These schemes jointly make up what the well-known anthropologist Mary Douglas (1966) named our 'symbolic order'. This symbolic order literally orders or structures our way of living, thinking and judging by drawing boundaries, and making fundamental distinctions for instance between life and death, natural and artificial. According to Swierstra et al. (2009: 214) *"Technological innovation is an important cause of change and as such of 'symbolic confusion'."* Below we describe how the trend "biology becoming technology" challenges some of the fundamental categories we nowadays use to understand ourselves and the world we live in.

"Top-down" synthetic biology

It was described above that synthetic biology is guided by the digital control paradigm of life. This engineering field considers and reduces life to an information-processing system. In this way, life, at least on the level of microbes, is seen as a construction kit. Moreover, the aim is to create easy translations between the virtual world in which the life process is modelled and the material world of living organisms. This blurs the basic distinction between biology and technology, and the material and information. The standardisation and automatisation of the genetic engineering of micro-organisms also raise the question of whether genetic engineering will always stay an activity only mastered by highly educated scientists and engineers or whether genetic engineering will be democratised and turn into a do-it-yourself type of synthetic biology.

Molecular medicine

Molecular medicine changes the meaning of health and illness. Sickness is no longer solely connected to visible and for the patient noticeable symptoms, but it becomes a phenomenon at the molecular level. This offers the possibility of diagnosing disease before the symptoms of disease have revealed themselves to the 'non-sick' patient. But even more, molecular medicine can reveal predictive information on individual health risks. Certain diseases then change from something that happens (fate) to people actively having to prevent it from taking place. Health becomes a personal responsibility, and a product of self-managing a healthy lifestyle. Finally, molecular medicine provides information that may be used to select people, during life, but also even before life starts. This would have an influence on our attitude towards the start of life – e.g. do we accept it as a gift, or do we want to specify the genetic features of newborn children – but also on the way we judge people. Do we want to be judged based on our genetic make-up?

Regenerative medicine

Regenerative medicine challenges the way we look at our own body and at other humans. This scientific approach views the body as consisting of parts that can be replaced and repaired. The body, in that sense, becomes a kind of technological artefact; the body as a construction kit. Looking at the body as a repairable machine will also change our views on the finiteness of our lives. Our bodies not only present a construction kit, but also the resources or building blocks for repairing or reconstructing the body. Such awareness may change our views on our bodies and other human beings. Do we want to be looked at in terms of a commodity?

This is aptly expressed by Scheper-Hughes in *The Last Commodity*, which deals with the (illegal) organ trade: *"The ethical slippery slope occurs the first time one ailing human looks at another living human and realizes that inside that other body is something capable of prolonging or enhancing his or her life"* (Scheper-Hughes 2008: 40-41).

Forward engineering of the brain

Forward engineering of the brain introduces technology into the brain, which challenges the distinction between mind and matter; nature and technology. Should we consider the electrode that stimulates the brain of a Parkinson patient as an integral part of his body or even his mind? All kinds of techniques to image and influence brain functions challenge the idea of the brain as a wholly isolated and impenetrable black box. Do we want our brains and thoughts to be transparent for other people? Engineering of the brain also extends the brain beyond the body and opens up the possibility of remotely controlling it.

6.2.2.2. Towards an ELSA agenda of "technology becoming biology"

This section gives an overview of the ethical, legal and social aspects which are challenged by the "technology becoming biology" trend (see Table 11). This implies that we will reflect on ELSA of engineering of intelligent artefacts, reverse engineering of the brain, and the A-Life ambition to "bottom-up" engineer artificial life (cf. Bedau and Parke 2009). After describing how these bio-engineering terrains challenge both current regulatory practices, we will give an overview of some fundamental concepts that are challenged by the "technology becoming biology" trend.

Challenging regulatory practices

Reverse engineering of the brain and "bottom-up" synthetic biology

The debate and ethical reflection on the reverse engineering of the brain and "bottom-up" synthetic biology mirror the state of the art of the science, which still is in a very early stage. One of the issues concerns the safety of artificial life and its risk assessment. In the case of genetically modified organisms, safety regulations are guided by long term experience with the behaviour of parent organisms. In the case of artificial life, there is no longer a parent organism to compare with. The question then becomes how the risk assessment should be set up. Reverse engineering projects rely on the use of non-human primates. In contrast to the use of non-human primates for medical research on neuro-degenerative diseases, societal support for their use for future IT applications seems very questionable.

Engineering of intelligent artefacts

The development of intelligent artefacts has a much longer history, and so has the debate. To increase the applicability and acceptability of intelligent artefacts in various social contexts, like the home, hospital, or battle field, engineers aim to build artefacts that can learn on the spot, look like humans and/or animals, and show social and emotional behaviour. In order to incorporate lifelike features into artefacts, like robots, these social practices have increasingly become a target for engineering. This engineering tendency to blend our social life with technology raises new challenges with regards to familiar issues, like privacy, informed consent and liability. And it also brings up relatively new issues, like how to deal with the increasing intimate relationship between artefacts and people. In the remainder of this subsection we will focus on the societal issues related to learning robots and anthropomorphic robots.

According to Sharkey and Sharkey (2010), the embodiment of robots and their lifelike appearance is unique to robots, and this is in need of closer scrutiny because of its social consequences. First, these features may enable these artefacts to get "closer" to human beings in all sorts of ways. Privacy is a well-known IT related issue. Affective computing techniques, like facial coding and posture reading systems, however, pose new types of privacy issues. Who may use these techniques, in what kind of situations, and should people be informed about it (informed consent)? In addition, robots and softbots with a lifelike appearance may be able to persuade people to hand over sensitive private information. Finally, these types of intelligent artefacts often depend on the personal knowledge of various users. How do we prevent such information from being stolen (identity theft)?

The existence of anthropomorphic and zoomorphic robots also raises questions on whether we will accept their owners to use them for the simulation of abject violent behaviour, such as rape, torture or sexual child abuse. Whitby (2008) pleads for a public discussion right now. He would like to see a list of activities of which their development is unacceptable, a list which may influence professional codes of conduct or laws regulating the use of anthropomorphic and zoomorphic robots. Such lifelike robots with affective qualities also raise new ethical issues with regard to emotional bonding and the automatisation of some basic duties, like taking care of children or elderly people. A first question is to what extent we will employ robots to take over such basic duties. A follow-up question is whether we allow the use of 'companion' robots in case of people who may not fully understand their mechanical and instrumental character, like children or people with dementia. The principle of informed consent plays a role here.

Böhle et al. (chapter 5) notice that the development of physical and virtual robots makes it increasingly hard to distinguish between human and machine agencies. This raises liability questions. The use of situated AI for enabling robots to learn requires a new perspective on liability issues, because a robot's ability to learn entails that the manufacturer cannot longer predict the robot's actions. Matthias (2004) talks about a "responsibility gap" with respect to damages caused by learning robots. This leads to a discussion among experts whether current ethical and legal frameworks are able to deal with such a new situation. Some experts think current frameworks are sufficient. Others argue for a new concept of liability, similar to the ones we have for our children or pets. They propose a mix of safe engineering, shared responsibilities and social awareness.

Table 11:ELSA of "technology becoming biology": engineering intelligentartefacts, reverse engineering of the brain, and "bottom-up" engineering of livingartefacts

Engineering intelligent artefacts		Reverse engineering of the brain	"Bottom-up" engineering of living artefacts		
Challenging regulatory issues					
Related to (semi-)autonomous robots and		New types of animal use	Safety: 'Unfamiliarity' with		
sof	ware agents	• Increase in laboratory animals	existing organisms		
•	Safety	Animal brains as controlling			
•	Liability: uncertainty about sources of agency	devices			
Related to anthropomorphic/social robots					
•	Privacy and informed consent				
•	Simulation of friendship: emotional bonding				
•	Simulation of violent behaviour (rape, torture, murder, child sexual abuse)				
Related to governance		Related to governance	Related to governance		
•	At EU level ELSA are not dealt with in an encompassing way	 EU (DG Information Society and Media) is not funding ELSA 	Need to start debate		
•	Gap between techno-scientific developments and public dialogue	projects on neurosciences or neural engineering			
	Gradually	changing fundamental categories			
•	Hybridisation of real and virtual life	Brain as a construction kit	Blurring of natural and		
•	Symbiosis between humans and technology	Wet computers	living		
•	Arrival of a second nature		New forms of life		
•	Views on corporeality of animals and humans		Life as a construction kit		
•	'Raising' machines to become responsible 'autonomous' actors				
Speculative long term perspective					
•	Need for or fear of ethical robots/moral machines	Machine consciousness	Artificially created novel forms of life		
•	Machine intelligence superior to humans (singularity)				

Challenging fundamental categories

Also the trend "technology becoming biology" challenges various fundamental concepts we use to categorise reality. Böhle et al. (chapter 5) signal that the engineering of intelligent artefacts gradually erodes fundamental categories of the lifeworld ("*Lebenswelt*"). The vision of conscious machines, which is included in the Neuro-IT roadmap, assumes that there will be machines with real autonomy and adaptability and a genuine capacity to cooperate with human beings, and that such machines need consciousness. Reverse engineering of the brain might be a way to develop a machine with some sort of consciousness. New artefacts, such as brain-semiconductor hybrids that can control a flight simulator, raise new questions with regard to our relation to animals and machines.

Besides, new artificial environments challenge traditional boundaries between nature and culture and may alter our sense of responsibility for the world we live in. Most of the experts interviewed also expect a further symbiosis between human lives and technology; between our bodies and technology; between the virtual and physical world; between human and machine intelligence. Reverse engineering of the brain and "bottom-up" synthetic biology exemplify these tendencies. The former aims at building a brain. Here the brain is regarded as a conscious machine, which can be built. With its attempt to create artificial life, "bottom-up" synthetic biology treats life as a construction kit, and blurs the boundaries between the natural and the artificial, and between living and nonliving material.

6.2.2.3. Stimulation of the bio-debate by European Commission

In the former section, the contours were sketched of an ELSA agenda for a debate on bioengineering. Here we describe to what extent the European Commission stimulates reflection and debate on bio-engineering, that is, on "biology becoming technology" and vice versa.

The debate on "biology becoming technology"

The Human Genome project was the first large scale R&D project that was accompanied by research on the ethical, legal and social aspects of genomics. At the beginning of this century and partly in reaction to past problems with agricultural biotechnology, so-called ELSA research became mainstream in Europe with the arrival of nanotechnology. Torgersen et al. (chapter 2) argue that scientists in the field of synthetic biology seem to be particularly sensitive to the social implications of their work. This is reflected in the research programs of the European Science Foundation and the European Commission. In both cases, various research activities that deal with philosophical and ethical implications, safety and security, governance and regulation, and so on, are being funded.

EU funded research projects in the field of molecular and regenerative medicine are not accompanied by ELSA research. However, applicants must address potential ethical issues related to the used methodology and possible applications in their proposals. It is not always clear, however, what the impact of this requirement is. Besides, the FP7 ethical framework excludes three areas of research from funding: human reproductive cloning, intentional germ line modification (unless related to gonad cancer) and the creation of human embryos for research or stem cell procurement.

The lagging debate on "technology becoming biology"

As indicated above, the convergence of neuroscience and IT is very actively strived for by DG Information Society and Media, by funding research on intelligent artefacts, reverse engineering of the brain, and brain-computer interfaces (BCIs). Böhle et al. (chapter 5) argue that important ELSA aspects of research related to the development of intelligent artefacts are already widely studied under such labels as robot ethics and information ethics. Despite the fact that the field of neuro-ethics is quickly developing, Van Keulen and Schuijff (chapter 4) note that there are no large EU funded ELSA research projects surrounding neuroscience or neural engineering.

Van Keulen and Schuijff explain that DG Information Society and Media, which funds most of the neural engineering projects, has little institutionalised attention for the governance and ethics of information technology. Whereas DG Research has a directorate Science in Society which focuses on the governance of emerging technologies, DG Information and Media lacks such a specialised directorate. In contrast to the life sciences, the benefits to society of intelligent artefacts seem to be taken for granted. As a result, critical review is regarded unnecessary. According to Rosenberg (2008: 369), *"this viewpoint must be challenged"*. Van Keulen, Schuijff and Böhle et al. agree on this matter, especially because information technologies are converging with the life sciences. Concerned about the current "gap" between developments in the field of intelligent artefacts and the public dialogue about it, Böhle et al. advise the European Commission to deal with societal issues of information technologies in a more comprehensive fashion.

6.3. Safeguarding human dignity in the 21st century

"Progress in science will bring confusion and misery to humankind unless accompanied by progress in ethics." (Haldane, 1923)

This study tried to come to grips with the new technology wave that is expected from the convergence between nanotechnology, biotechnology, information technology and cognitive sciences. For this purpose we studied four bio-engineering fields: engineering of living artefacts (chapter 2), engineering of the body (chapter 3), engineering of the brain (chapter 4), and engineering of intelligent artefacts (chapter 5). To describe these engineering terrains and reflect on their societal meaning we used the metaphors "biology becoming technology" and "technology becoming biology" as conceptual lenses. Our study confirms the existence of these two megatrends and their transformative social and political character. The European Commission is challenged to assume fullfledged responsibility for the anticipatory governance of the new technology wave in order to safeguard human diginity in the 21st century.

6.3.1. Bio-engineering in the 21st century

The "biology becoming technology" trend is illustrated by molecular medicine, regenerative medicine, "top-down" synthetic biology, forward engineering of the brain and persuasive technology. The "technology becoming biology" trend is illustrated by the shift from repair to regenerative medicine, "bottom-up" synthetic biology, reverse engineering of the brain and the engineering of living artefacts.

The European Commission actively stimulates both megatrends. However, with respect to "biology becoming technology", the European Commission is not funding many forward engineering of the brain activities. With respect to "technology becoming biology", in particular DG Information Society and Media is very actively stimulating cutting edge projects that centre on developing intelligent artefacts, reverse engineering of the brain and developing brain-computer interfaces (BCIs). "Bottom-up" synthetic biology, like protocell research and chemical synthetic biology, receives only limited attention.

Bio-engineering in the 21st century is driven by the digital control paradigm of life and new engineering tools. One the one hand, using these experimental tools leads to new data and insights that ask for scientific explanation. Next to this our study reveals a second, new type of engineering approach to science, in which scientific experimentation with nature is replaced by the scientific inquiry on virtual and physical models of nature. That is, the search to understand nature becomes the science of engineering artificial nature.

Finally, the "biology becoming technology" trend implies and promises a strong increase in the types of interventions into living organisms, including the human body and brain. The "technology becoming biology" trend embodies a (future) increase in bio-, cogno-, and socio-inspired artefacts, which will be applied in our bodies and brains, and/or intimately integrated into our social lives. These (anticipated) new types of interventions and artefacts present a new technological wave that is driven by NBIC convergence, broadening the existing bio-debate fundamentally.

The debate on genetic engineering has already broadened over thelast decade from microorganisms, plants and animals to include human beings. Besides genetic interventions, the societal aspects of info-tech interventions in the bodies and brains of animals and human beings will take a centre stage position in the political and public debate. Besides "biology becoming technology", the "technology becoming biology" trend, in which information technology also plays a central role, is expected to lead to various controversial issues. The next section describes how the European Commission is challenged to anticipate the new technology wave, which has the potential to radically broden the bio-debate.

6.3.2. The European Commission's governance challenge

A good starting point for discussing the societal meaning of the new technology wave is through realising that all four fields of bio-engineering share imaginative and speculative long term visions. Related to this, these fields are prone to hypes and guided by high hopes and fears. Within the "biology becoming technology" trend these visions include total engineering control over micro-organisms and human enhancement. The visions within the "technology becoming biology" trend speculate about the future possibility to build living and intelligent artefacts. These visions refer to the ultimate engineering dream of being able to construct novel forms of life, machine intelligence superior to humans, machine consciousness, and moral machines. Policymakers should be aware of the risk of being spoon-fed by these spectacular future visions and overhyping the field in question. But they also need to acknowledge that these speculative visions already have a real impact on the way we steer science and technology and discuss and regulate its societal meaning. On the one hand, the dreams of engineers provide hope for a better future. On the other hand, bio-engineering in the 21st century induces the fear that human dignity is under pressure in various ways.

Our study shows the transformative social and political character of the trends "biology becoming technology" and "technology becoming biology". These bio-engineering trends are slowly but surely blurring the boundaries between science, engineering and society, between living and nonliving, between sickness, health and enhancement, technology and nature, and between human and machine intelligence and agency. These shifting categories cause uneasiness within society because they challenge various fundamental concepts we use to understand the world we live in and to define what it means to be human,. In order to safeguard human dignity, policy makers are confronted with a vast collection of ethical, legal and social challenges. Almost all described bio-engineering fields, which range from molecular and regenerative medicine to forward and reverse engineering of the brain, "top-down" and "bottom-up" synthetic biology, and the engineering of learning and/or anthropomorphic robots and softbots, challenge current regulatory practices. New types of interventions in the human body and brain force policy makers to anticipate on new issues in the field of safety, privacy, bodily and mental integrity, and informed consent. New bio-, cogno-, and socio-inspired artefacts also lead to new safety, privacy and liability issues, and questions regarding the limits to animal use and the simulation of friendship and violent behaviour.

The broad challenge of safeguarding human diginity, prompts the European Commission to assume fullfledged responsibility for the anticipatory governance of this new technology wave in a way that truly reflects its transformative character. A crucial first step is to acknowledge that the bio-debate is no longer solely guided by the life sciences, but by NBIC convergence. Our study shows that the attention for ethical, legal and social issues differs across the different bio-engineering fields. There already is a strong awareness within the European Commission that developments in biotechnology and nanotechnology can lead to controversial political and regulatory issues. The European Commission seems to pay less attention to the governance of information technologies and their convergence with cognitive sciences. The fact that science and society issues are treated differently for different fields seems to relate to the fact that the research in these fields is commissioned by different DGs. For example, DG Research has a special directorate Science in Society of DG Research, which explicitly focuses on the governance of emerging technologies. DG Information Society and Media, which very actively stimulates the convergence of neuroscience and information technology, needs to pay more attention to the ethical, legal, and social aspects of information technology. For this, it is crucial to acknowledge that the benefits to society of information technology can not automatically be taken for granted. Such awareness is already growing within the IT industry. For example, Harper et al. argue that "the bottom line is that computer technologies are not neutral - they are laden with human, cultural and social values. We need to define a new agenda for human-computer interaction in the 21st century - one that anticipates and shapes the impact of technology rather than simply reacts to it" (Harper et al., 2008: 57). It is important that the European Commission takes advantage of this trend and further stimulates it. We may conclude that NBIC convergence induces the European Commission to take a more prominent, integral and pro-active role with regards to stimulating reflection and public debate concerning the role of bio-engineering in Europe in the 21st century.

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