Syst Synth Biol
DOI 10.1007/s11693-008-9018-z

COMMENTARY

Diffusion of synthetic biology: a challenge to biosafety

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Received: 5 June 2008 / Accepted: 20 June 2008

Abstract One of the main aims of synthetic biology is to make biology easier to engineer. Major efforts in synthetic biology are made to develop a toolbox to design biological systems without having to go through a massive research and technology process. With this "de-skilling" agenda, synthetic biology might finally unleash the full potential of biotechnology and spark a wave of innovation, as more and more people have the necessary skills to engineer biology. But this ultimate domestication of biology could easily lead to unprecedented safety challenges that need to be addressed: more and more people outside the traditional biotechnology community will create self-replicating machines (life) for civil and defence applications, "biohackers" will engineer new life forms at their kitchen table; and illicit substances will be produced synthetically and much cheaper. Such a scenario is a messy and dangerous one, and we need to think about appropriate safety standards now.

Keywords Biosafety · Synthetic biology · Biohackery · Safety standards

> "*My motivation is that years from now, anybody who wants to [can] dream up a useful biological system and pull it off, without having to go through this whole big research process to do it*"
> Drew Endy 2007[1]

> "*Some people would argue that we should not worry about that [spreading of the capability and technology of synthetic biology], that the best thing we can do is to spread this capability as widely as possible and then in some way I don't quite understand everything will be made safe. To my mind that's exactly the wrong way to go*."
> Malcom Dando 2007[2]

Background

Fast becoming one of the most dynamic new science and engineering fields, synthetic biology has the potential to impact many areas of society. Synthetic biologists use artificial molecules to reproduce emergent behaviour from natural biology, with the goal of creating artificial life or seek interchangeable biological parts to assemble them into devices and systems that function in a manner not found in nature (Benner and Sismour 2005; Endy 2005; Heinemann and Panke 2006; Luisi 2007; Serrano 2007). Approaches from synthetic biology, in particular the deliberate synthesis of complex, biological systems, have the capacity to change the way we approach many key technologies and biotechnology applications.

Knowledge on the design principles of biological systems becomes easier to understand, and fabrication capabilities are ever more powerful and ubiquitous. Tasks such as

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[1] Drew Endy is professor at MIT and co-founder of the Biobricks Foundation. For quote see: Bochner 2007

[2] Malcom Dando professor at the University of Bradford, UK, and an expert on the Biological and Toxin Weapons Convention. This quote stems from an interview carried out during the SB 3.0 conference in Zurich, June 2007, regarding proliferation, risk and synthetic biology. See full interview at: http://www.synbiosafe.eu/index.php?page=expert-interviews

sequencing or synthesizing DNA that some years ago had to be carried out at least by post-doc scientists can now be done by technical assistants or are outsourced to automated machines altogether. The increase in production capabilities for sequencing and synthesizing has already been compared to Moore's law in microelectronics (Carlson 2003; Carlson 2007a; Gibson et al. 2008). Advances in technological capabilities regarding synthesising and sequencing are accompanied by attempts to convert biology into a true engineering discipline with characteristics such as in silico testing of models, setting up hierarchies of abstraction, standardisation and interchangeability, and the decoupling of design and fabrication (Heinemann and Panke 2006). If successful these changes will further facilitate the rational use of biological systems. Also it will enlarge the circle of people who have the necessary skills to engineer biology. The iGEM student contest[3] for the design of genetically engineered machines, for examples, gathers undergraduate students from various disciplines including students from non-biological disciplines such as engineering or informatics. Its aim is to promote the use of standardized biological parts and to increase the number of useful parts in order to make it easier and more interesting to design novel and useful organisms. Diffusion of synthetic biology, in other words the easy access and the simplicity to use it, would automatically create an unprecedented biosafety challenge.

Newcomers and laboratory safety

Synthetic biology is a real interdisciplinary field, involving chemists, biologists, engineers, physicists or computer scientists. Some of those communities and practitioners of synthetic biology are generally educated in disciplines that do not routinely include formal biosafety training. As the growing interest in synthetic biologist attracts a number of non-biotechnologists to the field, the amount of newcomers untrained in biosafety rules increases as well. In a recent policy paper on synthetic genomics (Garfinkel et al. 2007) some governance options were presented that could help to targeting this phenomena:

- Include biosafety training as part of an interdisciplinary education in synthetic biology, dealing with risks and best practices as part of college and university curricula, critical for at least priming these newcomers to the safety challenges in synthetic biology
- Preparation of a biosafety manual for synthetic biology laboratories, distinct from those manuals already available
- Broaden Institutional Biosafety Committees (IBC) review plus enhanced oversight and/or enforcement

These, and other strategies may handle the possible problem related to the fact that many new researchers with a professional background other than biology are unskilled in the handling of (dangerous) biological material in the laboratory. These strategies are, however, practically useless if the newcomers are not working in a professional setting and are not accountable to a public authority, as is the case with so-called biohackers.

Biohackery, garage biology, do-it-yourself biology

The more biology becomes an information science the more computer software scenarios become possible within biology. It is little surprise that some people from the IT/engineering community aware of recent developments in synthetic biology foresee a development were computer scientists and/or hackers could turn their interest to biology (see: Hanson 2004; Counsell 2001; Anonymous 2003; Endy 2007). Also it is likely that in the future more and more people without a traditional education in biology or genetics (and probably even without higher education) will be able to manufacture biological systems. Synthetic biology could thus give rise to a new kind of hacker culture, the "biohacker". Biohackery means designing and manufacturing biological systems in an open way but without hardly any kind of regulatory oversight or enforcement in place. Although the number of such biohackers might be quite limited, it doesn't take a lot to become one and a few rather low-tech do-it-yourself DNA hacking documents are already available in the web.[4] Recently the do-it-yourself biology (DIY-Bio) online discussion group was launched[5] and motivated biohackers already held their first physical meeting in Boston, in May 2008. A young crowd of enthusiastic biohackers may well follow the example of the "Homebrew Computer Club" from the mid 1970s, and a true biohacker community might spark a wave of innovation unseen in cooperate research programs. Facilitating everybody to construct new life forms or biological systems, however, also creates an inherent biosafety (and biosecurity) risk. Imaging a world where practically anybody with an average IQ would have the ability to create novel organisms in their home garage

[3] The International Genetically Engineered Machine Competition, carried out by MIT and the Biobricks foundation. See e.g. http://parts.mit.edu/igem07/

[4] See e.g.: http://biohack.sourceforge.net/ This open, free synthetic biology kit contains all sorts of information from across the web on how to do it: how to extract and amplify DNA, cloning techniques, making DNA by what's known as oligonucleotides, and all sorts of other tutorials and documents on techniques in genetic engineering, tissue engineering, synthetic biology, stem cell research, SCNT, evolutionary engineering, bioinformatics, etc.

[5] See: http://groups.google.com/group/diybio/

without adhering to a professional code of conduct, filing a reporting system and lacking a sufficient biosafety training, is a thrilling thought.

It is true that there is a kind of informal code of ethics for the hacker community[6] that demands to "*be safe, do not damage anything, do not damage anyone, either physically, mentally or emotionally, be funny, at least to most of the people who experience it*". This hacker ethics, however, did not and could not prevent the tons of malware programmes out there in the worldwideweb. The more successful the attempts to program DNA as a 2 bit language for engineering biology become (Endy 2007) the more likely will be the appearance of "bio-spam, bio-spyware, bio-adware" and other bio-nuisances. An unrestricted biohackery scenario could put the health of a biohacker, the community around him or her and the environment under unprecedented risk. This scenario has not gone totally unnoticed in the biohacker community and some have started to show at least some interest in safety issues, asking e.g. "how to use a pressure-cooker as an autoclave" or thinking to obtain some lab safety videos.[7]

Illicit bio-economy

In contrast to a biohackery scenario that is driven largely by curiosity, another scenario enabled by the availability of this technology may involve illicit economic purposes. Among the potential applications of synthetic biology is the production of fine chemicals in a cheaper and easier way than it is done today (Ro et al. 2006; Keasling 2008). While most people would instantly think of pharmaceuticals, bioplastic or biofuels, the range of chemical products is not bound to moral norms. According to the United Nations Office on Drugs and Crime (UNODC), for example, some 200 million people, or 5% of the world's population age 15–64, have used drugs at least once in the last 12 months (UNODC 2005; UNODC 2007). Not to forget that the size of the global illicit drug market is substantial, with a value, measured at retail prices, higher than the GDP of 88% of the countries in the world (UNODC 2005). One of the flagship examples of synthetic biology is the production of anti-malaria cure artemisinin in engineered yeast (Ro et al. 2006). This production way is estimated to cut costs by a factor of 10 compared to the traditional way of production, namely plantation of *Artemisia annua* and subsequent extraction of its biochemical compounds. There is no reason to believe that full biosynthesis of currently semi-synthetic drugs such as heroine or cocaine, or fully synthetic amphetamine-type stimulants will not be possible and economically attractive using the toolkit of synthetic biology in the near future. Given, for example, that 2.8% of US adults are regular consumers of cocaine alone (UNODC 2005) the future illicit bio-economy could see some dramatic changes once the technology to manufacture metabolisms á la carte is out there.

Biodefense

Biodefense has to be considered under the label of biosecurity, not biosafety. There are, however, also biosafety aspects involved. It is true that biodefense doesn't deal solely with synthetic biology, however, there is little doubt that such a powerful new technology goes unnoticed in the biodefense community. It is also worth remembering that one of the first viruses fully synthesized was the poliovirus and the 1918 Spanish infuenza pandemic virus (Cello et al. 2002; Tumpej et al. 2005; Sharp 2005). Since the 9/11 event the funding for work on biodefense has dramatically increased in the US. The US Government Civilian Biodefense Funding, between fiscal year 2001 and 2008 cost US tax payers more than 39 billion US$ (Franco and Deitch 2007). Even within the US there are many voices questioning this kind of allocation of resources. Klotz (2007) recently used basic risk assessment calculation to alert us to the imbalance in funding and effort between biodefense, "the overrated threat", and endemic infectious disease "the real killers". Anyway this issue is not solely restricted to synthetic biology, synthetic biology could only accelerate the ongoing situation.

The massive amount of money flooded into biodefense research, including construction of new biosafety level (BSL) 3 and 4 facilities in the US and extensive research with dangerous pathogens is prompting a safety risk to the increasing number of biodefense researchers and communities around BSL 3 and 4 facilities (see "newcomers"). The number of BSL-4 laboratories in the US, for example, has increased from 5, before 2001, to 15 in 2007. Also the number of BSL 3 facilities has risen to a total of 1,356 (GAO 2007). The conclusion on accountability of these BSL laboratories, presented by the United States Government Accountability Office, were particularly alarming saying that "*no single federal agency has the mission to track and determine the risk associated with the expansion of BSL-3 and BSL-4 labs in the United States, and no single federal agency knows how many such labs there are in the United States. Consequently, no one is responsible for determining the aggregate risks associated with the expansion of these high-containment labs.*" (GAO 2007).

[6] See: http://hacks.mit.edu/Hacks/misc/ethics.html or http://www.stevenlevy.com/index.php/other-books/hackers

[7] See protocol of the first DIYbio meeting: http://openwetware.org/wiki/DIYbio:Meeting_-_May_2008

Many new researchers, previously unexperienced in handling BSL 3 and 4 material are now working in biodefense research, and accidents in those facilities seem to happen more frequently than one would think (see: Hecht and MacKenzie 2005; MacKenzie 2007; GAO 2007; Sunshine Project 2007; Aldhous 2008).[8] Local communities are already uneasy and sometimes even protesting against new facilities (see e.g. Check 2006; Coleman 2006). Putting this altogether, there is no reason to believe that synthetic biology should not find its way into the biodefense R&D and into the increasing number of BSL 3 and 4 laboratories, with their not always so satisfying safety record, causing a notable increase in biosafety risk for laboratory workers, surrounding communities and beyond.

Safety for standardized bioparts

Research undertaken on standardized bioparts suggests that it could be possible to have—one day—a toolbox of bioparts that can be easily assembled to devices and systems. As R&D on standardized bioparts is continuing we will see more and more parts, devices and systems with different characteristics. If this concept proves to be successful it would mean a tremendous simplification in the design process of living organisms, so that even high school students could design their own pet bug (Dyson 2007). As more parts become available in the Biobrick registry, and as more people have general access to sequence specifications and DNA synthesis, the task of enforcement resulting from restricted access or practice will become increasingly untenable (Carlson 2007b). As with any toolbox, some combinations of parts, devices and systems could raise biosafety concerns, especially when emergent behaviour of novel biocircuits cannot be ruled out due to the lack of sufficient separation of functional units (such as in integrated circuits) and the skyrocketing number of possible interactions between those units.[9]

- *Parts*: There might be a need to think about safety standards when dealing with parts: Some parts could be more of a safety problem than others, so different safety categories could be invented for parts, and also for devices and systems.
- *Bio-circuits*: a combination of otherwise safe parts, may result in a gene circuit that exhibits characteristics that are not safe. Is there any way to include e.g. a safety check in bio-circuit design?
- "*Pimp my chassis*": a chassis[10] that is able to survive in the soil, e.g. for bioremediation purposes (Sayler and Ripp 2000; Cases and de Lorenzo 2005) has to be treated differently from a chassis that can only survive under certain laboratory conditions. Parts, device and systems that happen to extend the environmental range of a chassis, i.e. tolerance of a wider range of biotic and abiotic conditions, should be considered in a special safety category.

Working with parts, devices and systems in specific chassis organisms open up new safety and security challenges, not yet covered by current biosafety and security rules and guidelines. Although the idea of standardized bioparts is to outrule emergent properties, it is likely that not all emergent properties can be foreseen. Some emerging questions[11] are:

- *Different categories*: is it necessary to put parts, devices and systems into different safety or security categories?
- *Biosafety clearinghouse*: how can a safety issue be reported that was discovered in a certain bio-circuit and that was not foreseen (emergent) so other people can learn from that experience?
- *Provision*: how can safety and security aspects be integrated into the design process so the design software automatically informs the designer in case the newly designed circuit exhibits certain safety (or security) problems?
- *Design assessment*: do we need a new risk assessment tool to ensure safety (and security) of parts-based biocircuits?

Conclusion

A rarely mentioned challenge for the safe and constructive development of synthetic biology is the ongoing diffusion of the technology, knowledge and capabilities beyond the professional biotechnology community. This would, first of all, involve engineers and computer scientists, but later on this will include also other groups beyond the academic

[8] E.g. failure to report to CDC exposures to select agents by Texas A&M University (TAMU); power outage at CDC's new BSL-4 lab in Atlanta, Georgia; and a release of foot-and-mouth disease virus at Pirbright in the United Kingdom. (GAO 2007; Sunshine-Project 2007)

[9] In theory a relatively small number of 20 bioparts may result in up to 20! (20*19*18*…*2*1) or about 10^{18} possible interactions making it difficult to calculate all interactions and completely outrule emergent behaviour with the current approach. See discussion on the Biobricks Standard mailing list: http://biobricks.org/pipermail/standards_biobricks.org/2008-February/000033.html and http://biobricks.org/pipermail/standards_biobricks.org/2008-May/thread.html

[10] A chassis is a kind of minimal cell that can be used to incooperate bio-parts, -devices and -systems.

[11] These safety questions have previously been posted by the author at the biobricks standardisation mailing list, see: http://biobricks.org/pipermail/standards_biobricks.org/2008-February/date.html

and professional circle such as hackers and school kids, and maybe even less benign individuals and organisations active in the illicit knowledge based bio-economy. Finally the massive support and growth of the (US) biodefense research community and their activities also raise some serious safety issues, both for the biodefense workers and the surrounding communities. The growing repositories of the biobricks foundation dealing with standardized bioparts also opens particular biosafety questions that need to be addressed as more and more people start to use them.

Synthetic biology could well be the next industrial revolution defining the 21st century, and if so it is absolutely necessary to consider the implications of its diffusion, well before they materialize and devise possible strategies to minimize safety risks (NSABB 2006, 2007; Schmidt 2006; Tucker and Zilinskas 2006). There is, however, no silver bullet to solve these complex issues, and righteous prohibition is not an option if we want to harvest the benefits of synthetic biology. And of course a cornucopian anything-goes mentality isn't the answer either. Some scientists argue that certain key technologies in synthetic biology (such as synthesis of DNA) will eventually be controlled by fewer and more efficient companies, automatically creating bottlenecks for regulation and licensing (Bhattacharjee 2007; Bügl et al. 2007). Such a development can be compared to the electronic industry where nowadays only a handful of companies produce computer chips.[12] This economic and technological concentration process would on the one hand easily solve the problem of out-of-control experiments, but on the other hand would limit the "democratic domestication" of biotechnology (Dyson 2007). (Promoting safety and security standards you might find yourselves unintentional aligned with people with vested interests in the monopolisation of key technologies in synthetic biology.)

> *"Domesticated biotechnology, once it gets into the hands of housewives and children, will give us an explosion of diversity of new living creatures, rather than the monoculture crops that the big corporations prefer. […] The final step in the domestication of biotechnology will be biotech games, designed like computer games for children down to kindergarten age but played with real eggs and seeds rather than with images on a screen. […] These games will be messy and possibly dangerous. Rules and regulations will be needed to make sure that our kids do not endanger themselves and others."*
>
> Freeman Dyson 2007[13]

There is, however, no ready-to-use recipe or toolbox we can apply to minimize the risks of a biotechnology that one day could be so easy to use that everybody can design their own organisms. Failing to address the challenges posed by diffusing the technology, knowledge and capabilities of synthetic biology, might ultimately lead to a situation where we cannot go back and close "Pandora's box". We should better start to think about it now.

Acknowledgments The work was fully supported by a grant from the European Commission's 6th framework programme under the category "New and Emerging Science and Technology" for the project "SYNBIOSAFE: Safety and Ethical Aspects of Synthetic Biology", contract 043205. The author wish to thank Helge Torgersen, Nikola Biller-Andorno, Agomoni Ganguli-Mitra and Alexander Kelle for thoughtful conversations and comments on the paper. The author declares that he has no conflict of interest.

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[12] See e.g. interview with George Church, professor at Harvard Medical School at: http://www.synbiosafe.eu/index.php?page=expert-interviews

[13] Freeman Dyson has spent most of his life as a professor of physics at the Institute for Advanced Study in Princeton. This quote is from "Our Biotech Future", The New York Review of Books. Volume 54, Number 12, July 19, 2007. See: http://www.nybooks.com/articles/20370

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