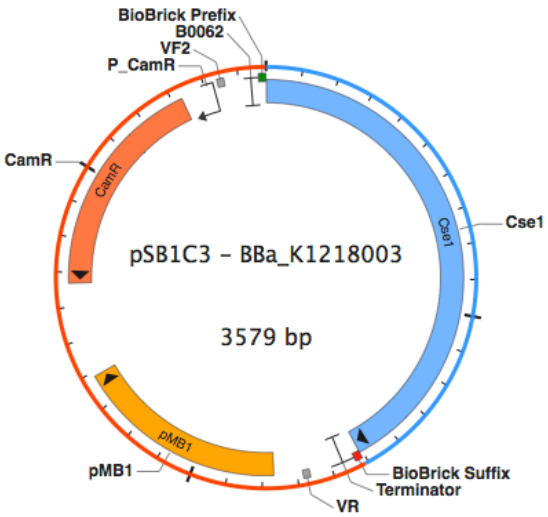
Standards for Synthetic Biology: the technical challenge and the power game

By Victor de Lorenzo and Markus Schmidt[1]

Standards are traditionally claimed to be one of the pillars of modern Engineering and as such they are also vindicated as one of the core tenets of contemporary Synthetic Biology –which is at the end of the day, looking at Biological systems through the eyes of an engineer (and deploy and engineering agenda on Biological objects). Standardization of physical assembly of DNA-encoded genetic parts was one of the first issues that the early pioneers of Synthetic Biology at MIT pointed as critical for the development of the field. This is still today one of the principles of the iGEM and its associated repository of biological parts. But soon after the issue was raised more than a decade ago, an avalanche of criticism followed: regardless of how one standardizes physical composition, the result is not a predictable functional outcome, as biological activities delivered by given DNA segments are context-dependent in practically all cases. Should we then give up robust design of biological systems with new-to-nature properties?



Example of information about plasmid design in the iGEM Registry of Standard Biological Parts (http://parts.igem.org/Catalog)

Shaping the field of SynBio for the future

A lot has happened since these discussions of the early 2000s on the feasibility of standards in Synthetic Biology. The need to get rid of context-sensitivity has led to an increased effort to develop orthogonal devices and even complete systems that are intended to work in a fashion minimally dependent and even autonomous of the biological host. These involve not only a suite of genetic patches and expression systems based on phage polymerases but also recoding and/or expansion of the genetic code. Also physical assembly of DNA pieces is no longer an issue owing to the ease of chemical synthesis and the onset of many procedures for composing genetic constructs which do not use restriction enzymes.

More importantly the debate on standards has gone beyond technicalities on DNA composition towards bringing up key fundamental questions of what else can and should be standardized. For example, how do we establish metrology, in other words how do we measure biological activities? And, along the way, non-technical issues were identified in order to benchmark good SynBio practices, including risk assessment methods.

At the same time, the growing awareness that SynBio can ultimately become a transformative technology has prompted a (mostly implicit) footrace on who will

succeed in establishing the rules and standards that will shape the field of SynBio for the future.

The power game

In reality, standards are not –have never been– merely neutral choices guided by technical efficiency. The establishment of and compliance with standards is a form of marking and expanding one's territory and ultimately exerting power. The etymology of the term *standard* reveals its military context of people following a banner (Anglo-French: e*standard,* German: *Standarte)*. The meaning of *all standing for the same* embodies two connotations.

1. The leadership that the followers recognize to the one holding the flag. There is thus an aspect of authority, solidarity and prestige that is also applicable to the scientific world. A standard proposed by someone in a top US University is likely to be more willingly accepted than one proposed by a Scientist of a not so well known University in the developing world, regardless of any intrinsic value that either proposition may have. As unfair as this may seem, it is the community of users who ultimately decides.

2. The other aspect is not bottom-up, but a mere top-down issue of influence and political / economic advantage. From the British Empire telegraphic network to today's computer operating systems, standards have reached every aspect of our society and are the basis of global industrial production. By making (if not imposing) choices about them, countries, companies, institutions, or platforms ensure their prevalence over alternatives. There are many stories to illustrate this: Napoleon imposing the metric system in his conquered European territory. Edison and Westinghouse extensively fighting over US public support in the alternating-direct "war of currents". In more recent years the high definition optical disc format war between Blu-ray Disc versus HD DVD represented an industry dispute between competing companies. In some cases, standards also prevent commercial competition while in others they are accused of fostering a neoliberal globalization agenda.

A long way to go yet

While such *non sanctus* aspects of standards are not on the radar for most SynBio practicioners, the subject is often discussed in nearly every meeting in the field –without practical results thus far.
There is a general sentiment that the level of knowledge right now is not sufficient to address standards in Biological design with the same rigour as electric or civil engineering does. There have indeed been partial advances in metrology and proposition of operating systems in living organisms, but most standards proposed thus far have not made it beyond very limited communities of users. There is still a considerable *wander in the wilderness* that the SynBio Community has to go through before reaching the Promised Land of full-fledged standardized Biology!

EU lagging behind in SynBio standardization

In the meantime there is a remarkable (and worrisome) difference in the interest of the US and EU agencies on the issue at stake. The American National Institute of Standards and Technology NIST, belonging to the United States Department of Commerce, has been very proactive in bringing together a great number of US synthetic biologists from academia and industry by means of specialized workshops and follow up networking. Along the lines discussed above, their agenda includes both to get things done through a solid research program and –not the least, to establish an early leadership of the US on whatever development may come later. In contrast, no EU level-related agency or stakeholder on standards has expressed thus far the slightest interest in becoming involved in the SynBio standardization process. Every proposition to develop a European Institute of Biological Standards that could team up and compare with US initiatives has been ignored, ridiculed or turned down (with the stand-alone 4-year EC research project ST-FLOW being the only exception). This means that when the field will be ripe to deliver, Europe will once more react to what others have already done, having lost out on a window of opportunity to a partnership with our US peers that would still be possible now. But do not only blame Brussels bureaucracy. The EU-based SynBio Community is both mesmerized by the awesome (and quick!) progress made in the US, and engrossed on the difficulties of merely scientific bottlenecks. By focusing only on scientific bottlenecks we may gain more knowledge, but will altogether lose any chance of being global players in the bioeconomy that will be brought about by SynBio.

Not in vain we Europeans proud ourselves of producing the best local gourmet food, the one left to the momentous inspiration of a chef, while we often disdain the multi-billion business of franchised, standardized food. Setting standards is not only a decision between quality and quantity, but it is the basis of a successful bioeconomy and a flourishing society. Science needs freedom to operate, but as European society longs for a knowledge-based Bioeconomy we cannot ignore the risks of simply signing up heteronomous standards after they have been developed by others!

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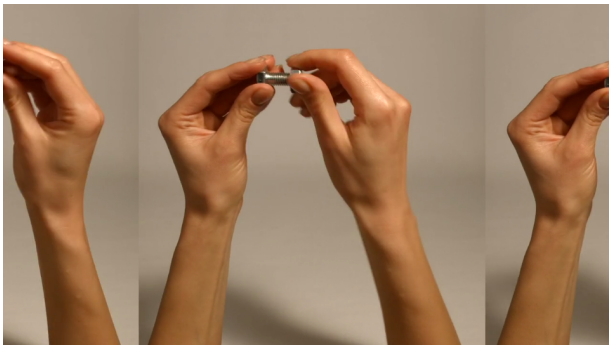
[1] *Victor de Lorenzo is Research Professor in the Spanish National Research Council (CSIC), where he currently heads the Laboratory of Environmental Molecular Microbiology at the National Center for Biotechnology*
Markus Schmidt works in the area of technology assessment of novel bio-, nano- and converging technologies, such as synthetic biology.

Biofaction Austria produced a short film about Standardisation processes in Synthetic Biology. The film shows:

- why standards are so important in synthetic biology,
- what should be standardized,
- who are the people driving this process, and
- what this all means for society and the environment.



The video can be watched at https://vimeo.com/147433019