

EDITORIAL

Synthetic biology: promises and challenges

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Synthetic biology: another buzzword?

Life is evolving fast (at least in the first world) and the latest technological gadget becomes outdated even before we have learnt how to use it. In this respect, science is no exception. The new buzzword 'Systems Biology' entered the vocabulary of the scientific community only a few years ago. Now that every biologist is aware of it and almost everyone seems to be doing it, an even newer buzzword has entered the scientific arena, 'Synthetic Biology' (see as an example a sample of recent reviews on the topic, Benner and Sismour, 2005; Endy, 2005; Andrianantoandro *et al*, 2006; Heinemann and Panke, 2006).

We are still arguing about the true definition of Systems Biology, the more so since it became fashionable for the funding agencies and therefore any research project should include it in the proposal, and now we need to define Synthetic Biology and explain to the non-specialist what the difference is between the two. Is Synthetic Biology something really new or is it simply Biotechnology (another old and outdated buzzword) in new packaging? What are the achievements so far, what can we expect from it and are any biosafety dangers lurking ahead? How is Europe doing in this field compared with other countries? In this brief article we will attempt to provide some answers to those questions.

What is synthetic biology?

A consensus definition drafted by a group of European experts defined Synthetic Biology as follows: 'Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems, which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures—from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way' (Synthetic Biology: Applying Engineering to Biology: Report of a NEST High Level Expert Group). Clearly, an important aspect of Synthetic Biology that differentiates it from Systems Biology is the term 'Engineering' and 'Synthesis of novel functions'. Thus, while Systems Biology attempts to obtain a quantitative understanding of existing biological systems, Synthetic Biology is focused on the rational engineering of these systems. Following this definition, Synthetic Biology benefits from the knowledge drawn from Systems Biology

analysis, as well as from the conceptual tools developed in this discipline. Taking it to an extreme, Synthetic Biology is an engineering discipline and as such needs standard parts that can be put together using bioinformatic and simulation tools to build circuits that will introduce or modify biological functions. This would imply that only projects that involve the use of standardized parts (genes, proteins, circuits...) could be considered proper Synthetic Biology projects. In an ideal world, designing living systems for a practical purpose should be like redesigning a car to make it more efficient, or redesigning a computer with a faster processor. One would have the parts, the right software, the brains and the knowledge about the target system, and 'voilà!' a new bacteria that produces ethanol from water, CO₂ and light has been created. According to this vision, Synthetic Biology should be able to rely on a list of standardized parts (amino acids, bases, proteins, genes, circuits, cells, etc...) whose properties have been characterized quantitatively and on software modeling tools that would help putting parts together to create a new biological function. In this respect, it is encouraging to observe how fast the number of parts and circuits is growing at the MIT 'Registry of Standard Biological Parts' (<http://parts.mit.edu>), encompassing terms that will make any engineer happy (invertors, noise suppressors etc...).

However, life is not that simple. Although clearly a repository of well-characterized parts is a great idea, we should not forget about the daunting complexity of living systems, especially eukaryotes compared with prokaryotes. Thus, aside from the challenging task of having a repository of parts for different organisms (there is no guarantee that a part that works in *Escherichia coli* will work in *Bacillus subtilis*), we can never rule out the possibility that new emergent unexpected properties pop up when putting together parts that have been characterized in isolation or in a different context. Moreover, if we want to redesign a car, we already know the specifications of all its components, how they work together and how the car will behave under different conditions. This is obviously not the case for living systems, where even for the simplest of them we know very little (i.e., phage simplification by Chan *et al*, 2005). Tom Knight, a strong advocate of Synthetic Biology, argues that many problems regarding complexity can be overcome if we keep to key notions: the principles of hierarchical abstraction, modularity, standardization and flexibility, and define appropriate levels of abstraction in the description and design of biological systems. But the complexity of life continues to surprise us and even

concepts like the central dogma—one gene, one RNA, one protein—is becoming more and more eroded, with new discoveries in epigenetics, splicing, transcript analysis etc..., increasingly challenging our classical simplified view of gene regulation.

Thus, in my opinion, we should consider a more relaxed use of the term engineering in which the emphasis should be placed on the design and simulation of the new functions and properties, rather than on the standardization of parts. This does not mean that in the long run we should not aim for the equivalent of a DIN standard for Biological parts, but clearly we are not there yet. What is important and very much encouraging is that even without fully understanding how a living cell operates, we can still redesign it in a meaningful way. In a similar way that we can now design proteins with new functions, even if we do not yet fully understand how it folds and how it performs its function, it is possible to introduce new functions or modify existing ones in cells without a complete understanding of the system and without having a complete list of standardized components. This is probably possible because living systems are robust and can tolerate the introduction of foreign networks, which, with some tinkering, perform the intended function (Andrianantoandro *et al*, 2006).

It is also important to differentiate Synthetic Biology from Biotechnology. Thus, improving the production of a certain metabolite by tinkering with some of the components of a metabolic network will fall within the realm of Biotechnology. On the other hand, the introduction of several exogenous enzymes in an organism to produce a new compound will fall within the scope of Synthetic Biology. Similarly Systems Biology and Synthetic Biology should be differentiated. While both disciplines consider modeling and simulation as important tools, Systems Biology aims at the quantitative understanding of natural biological systems, and not at the engineering of new functions, or properties. Of course Synthetic Biology benefits enormously from Systems Biology studies, since engineering of a biological system requires at least some understanding of it. On the other hand, Systems Biology benefits enormously from engineering concepts applied to network components (e.g., switches, amplifiers and control elements) and network properties (e.g., robustness and modularity), and such studies have provided invaluable insight into module behavior, while abstracting the details of molecular interactions (Di Ventura *et al*, 2006).

Synthetic Biology can operate at every level, from proteins to organs. Thus, we could consider the 20 amino acids as the standard parts, protein design algorithms and protein structure databases as the simulation and bioinformatic tools, and the resulting newly engineered macromolecule as the new biological function. A similar analogy could be performed at higher levels, with genes and their regulatory transcription factors being the standard parts, cell-modeling software and databases the simulation, and bioinformatic tools and the resulting modified cell representing the new biological function.

Why has Synthetic Biology become so popular in the last 3–4 years? Various groups had engineered synthetic genetic circuits 7 years ago, before the use of the term Synthetic Biology became so widespread (Becskei and Serrano, 2000; Elowitz and Leibler, 2000; Gardner and Collins, 2000; Gardner *et al*, 2000; Becskei *et al*, 2001). Since these publications, we

have witnessed an explosion of designed new genetic circuits in bacteria and eukaryotes, although in the majority of the cases without a practical application (see next chapter). Probably, there are three main reasons for this. The first one is the success in designing and engineering small circuits that could produce complicated behaviors (see examples in Di Ventura *et al*, 2006), which suggest that biological systems are quite robust and easily tolerate the addition of new components which could operate in a 'context-independent' manner. The second reason is the incredible developments of DNA synthesis technologies that have taken place in this period (Bügl *et al*, 2007). These developments have been quickly adopted by DNA synthesis companies, or are the basis for new companies. Thus it is affordable now to synthesize your favorite gene instead of cloning it, and if you have the budget, a small virus can be assembled simply using the information stored in a genome database (Tumpey *et al*, 2005). Although we have not seen so far widespread use of this technology in Synthetic Biology, it opens the way for thinking big and for aiming at the design of very large and complex circuits. This 'think big' mood has been very recently boosted by the demonstration that it is possible to replace the genome of one organism by another (Lartigue *et al*, 2007). Finally, the creation by the MIT of the 'Registry of Standard Biological Parts' (<http://parts.mit.edu>) has also added to the expectations and hype in the field.

Fundamental versus applied synthetic biology

Although I will contend that many groups have been doing for many years what we call now Synthetic Biology (the most obvious example is Protein Design), it is in the last few years that we have seen an increasing number of publications reporting on synthetic circuits of increasing complexity (see Andrianantoandro *et al*, 2006 for a recent review). Having said this, it is important to mention that in the great majority of the cases the designed circuits have been assembled without using standard parts and involved some serious tinkering of the components (Andrianantoandro *et al*, 2006; Di Ventura *et al*, 2006). Thus, the discipline is still in its infancy and one can hope that in the future the concept of standardization, parts etc... will be applied more widely.

Aside from this and if we except metabolic engineering and protein design, the majority of the Synthetic Biology advances realized in recent years have been achieved purely '*in vitro*' (Isalan *et al*, 2005), or in microorganisms involving the design of small gene circuits for 'fun', that is, without a direct practical application, although scientifically very exciting (see Benner and Sismour, 2005, #12; Endy, 2005; Andrianantoandro *et al*, 2006; Heinemann and Panke, 2006 for recent reviews). An interesting example of a larger system that has been redesigned is the refactoring of the T7 bacteriophage (Chan *et al*, 2005). These studies have offered fundamental insight into biological processes, like the role and sources of biological noise, the existence of biological modules with defined properties, the dynamics of oscillatory behavior, gene transcription and translation, or cell communication (Andrianantoandro *et al*, 2006). Thus, in the same way protein design has offered

fundamental insight into the fields of protein folding, stability and function, Synthetic Biology contributes to the fundamental understanding of biological processes.

This is not to say that Synthetic Biology has no exciting future as an applied discipline. A successful example has been the production of terpenoid compounds in *E. coli* (Martin *et al.*, 2003) and *Saccharomyces cerevisiae* (Lindahl *et al.*, 2006; Ro *et al.*, 2006) that can be used for the synthesis of the anti-malaria drug. In other cases, important steps have been achieved toward practical applications. For example, an extensible RNA-based framework has been developed recently for engineering ligand-controlled gene-regulatory systems, called ribozyme switches, that exhibits tunable regulation, design modularity, and target specificity and could be used, for example, to regulate cell growth (Win and Smolke, 2007). Another interesting example is the construction of *E. coli* harboring designed plasmids that invade cancer-derived cells in a density-dependent manner under anaerobic growth conditions (Anderson *et al.*, 2006, 2007). There are also promising future applications in the field of Bioenergetics, living vectors for gene therapy, chemical factories, bioremediation etc, but still the discipline needs to deliver and, importantly, concrete and significant applications of Synthetic Biology should be achieved within the context of a bona fide engineering discipline involving rational design with the smallest amount of tinkering.

As I mentioned above, the majority of the work performed in Synthetic Biology has been more in what we will call Basic Science than in Applied Science (with the exceptions mentioned). However, this could change rapidly. Nowadays it is possible to synthesize *de novo* a small virus, to replace the genome of one bacterium by another and to make large chunks of DNA coding for elaborate genetic circuits. Software tools to simulate large networks are available, and we can use the entire panel of omics technologies to analyze the engineered microorganism. It is quite obvious that all these technologies will improve further in the incoming years and the day is not too far when we will be able to synthesize a large eukaryotic artificial chromosome. The repository of parts will increase in complexity, number and reliability of circuits available for different species. So it is quite conceivable that in 10 years we will be able to fully redesign or make new cells, bacteria or viruses. However, it appears that major efforts are still needed to reach these ambitious objectives. Listening to the talks given at the Synthetic Biology 3.0 conference in Switzerland (<http://www.syntheticbiology3.ethz.ch>), it seems that only a minority of projects relied on a rigorous engineering approach as defined by the MIT groups responsible for the parts repository. Also, the majority of the projects were centered on developing new experimental and computational tools, using synthetic biology to understand how organisms work or to generate minimal cells, but few examples were shown of fully developed practical applications.

Biosafety, ethical and technology transfer aspects

Although we are far from it, Synthetic Biology could open the way to engineer living systems a similar way as we design new

dishwashers, cars, computers or planes. The same way that engineering has improved our quality of life, but also has created sophisticated bombers, tanks or the atomic bomb, Synthetic Biology could be used for good or bad. We can expect huge benefits as a result, but also—as with any other important advance in science—there are risks. One obvious one is related to the accidental release of redesigned organisms. This concern is in fact similar to the current Biosafety problems associated with genetically modified crops, the use of engineered microorganisms to enhance production of desired targets etc..., and therefore are well taken care of by current policies in the matter. The main concern in Biosecurity arises however from the possibility that rogue states or terrorists organization re-engineered microorganisms, or living systems with the purpose to harm. Although this seems scary, it is not yet so simple to create a new pathogenic organism and to release it in an effective way. There are indeed many unknowns in what makes a pathogenic organism virulent in the environment compared to the laboratory. Thus, it needs to survive against competing microorganisms and escape the immune response of the host. These hurdles and the engineering challenges they currently represent may however be overcome in some near future by further advances in science and we need thus to keep vigilant.

To address all these issues, different bodies, agents and organizations have started lively discussions to see what will be the best ways of minimizing the risks associated with Synthetic Biology (Bhutkar, 2005; Church, 2005; Check, 2006; Tucker and Zilinskas, 2006). Propositions ranging from self-regulation of the scientists to government-imposed regulations have been put forward. One major concrete concern refers to the purposely design of pathogenic strains taking advantage of the recent improvements in DNA synthesis (Bügl *et al.*, 2007). This has resulted in the proposition of different actions (discussed on the Internet site of the US synthetic biology (<http://pbd.lbl.gov/sbconf/> and http://syntheticbiology.org/SB2.0/Biosecurity_and_Biosafety.html) (Bügl *et al.*, 2007), mainly centered around the use of efficient software that could allow DNA synthesis companies to detect orders aiming at synthesizing possible pathogenic genes or organisms. However, with the current technologies, it is easy to imagine that dangerous genes or pathogens could be split into small inconspicuous oligonucleotides ordered via several dozen companies dispersed all over the world and that could be assembled in a third-party laboratory. Thus, Biosecurity in Synthetic Biology remains an open question. Both in the US and in the EU several forums for discussion and documents regarding Biosafety have appeared (<http://www.etcgroup.org/upload/publication/602/01/synbioreportweb.pdf>; <http://www.jcvi.org/research/synthetic-genomics-report/>; Rathenau Institut <http://www.rathenau.nl/>; http://openwetware.org/wiki/Synthetic_Society/Community_Organization_and_Culture). In the case of the EU, some research projects have been funded to analyze the impact and safety problems of Synthetic Biology in Europe (SYNBIOSAFE, <http://www.synbiosafe.eu>; SYNBIOLGY, 2005, <http://www2.spi.pt/synbiology/>). It is important that European governments and scientific bodies think in advance about all the open questions now that the public yet is not aware of Synthetic Biology. Learning from the

backlash that genetically modified plants created in Europe, we should think well in advance the answers we will offer to society.

Aside from the safety problems, we cannot forget the Ethical issues centered about the complete engineering of new living forms or the redesign of existing species. Even if these types of activities do not, in principle, pose an immediate danger in terms of Biosafety or Biosecurity, they can be seen as ethically problematic by part of the population, since it will be akin to playing God. We are not yet there and there is still probably some time before we can start thinking of the use of synthetic biology for the improvement of certain features in target species and logically the possibility of doing it in humans. Clearly all of these possibilities need to be contemplated and clear rules should be established, like we have done for human cloning. While designing a new living system for scientific purposes is not expected to raise major ethical concerns, the potential of redesigning human beings clearly needs to be analyzed from an ethical point of view. Perhaps the 'playing God' aspect could be more problematic in the US, while in Europe the redesign of living organisms could be perceived as a major cause of concern.

Europe versus USA

The immense potential of Synthetic Biology should now hopefully be obvious to the reader. How well is Europe doing with respect the world in this emerging field? (We recommend the interested reader to visit the Synbiology website at <http://www2.spi.pt/synbiology/> to get more information on this topic.)

There have been several serious studies looking at the number of publications in the field per country (Europe/North America Comparative Assessment available at <http://www2.spi.pt/synbiology/>). Although we always need to take those numbers with caution, since European groups often do not label their field of research with the latest buzzword and therefore might be underrepresented, the numbers speak for themselves: up to September 2005, 64% of the publications in the field were from US laboratories, versus 24% from Europe, with the immense majority of those articles that are published in high-impact journals originating from the US.

This situation could change since the EC has taken an active role through its Pathfinder program, financing several projects in Synthetic Biology and European funding agencies have included the topic in their new financing plans (see SYN BIOLOGY report).

Regarding European companies working in this area, the majority are DNA synthesis companies that make large DNA fragments (for example Febit Synbio or GENEART in Europe), and small spin-offs from universities and research groups, the majority of which are, once again, located in the US (see <http://www.etcgroup.org/upload/publication/602/01/synbioreportweb.pdf>). More recently, some companies (i.e., Amyris) have appeared in the area of Biofuels, aiming at redesigning microorganisms for efficient fuel production from plants. As in the previous case and although there are European companies working in biofuel production, the Synthetic Biology companies are mainly starting in the US.

Why are we lagging behind the US? Perhaps it is due to a general problem in Biology research and the way Europe has structured its research. In particular, Europe will need to take more and bolder initiatives in funding and building new institutes to create the necessary critical mass, and should raise its ambition for starting novel research areas. Competitive European groups in areas related to Synthetic Biology definitely exist, mainly amongst the very top EU institutes, where the system is more flexible and excellence is actively pursued. But these few world-class laboratories are usually small, scattered and in many cases have just entered into the field of Systems Biology and, therefore, do not have the capacity to fully embark into Synthetic Biology. As in many other fields, if Europe wants to stay competitive, we will need a major overhauling of the system, promoting excellence, flexibility and young investigators with new crazy projects. In this sense the European Research Council (ERC) initiative may represent a decisive step forward.

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