Synthetic Biology – Do We Need New Regulatory Systems?**

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Summary

Synthetic biology (SB) is a new interdisciplinary field that aims to establish a systematic framework for the engineering of biological systems and cells to both address fundamental questions and provide new applications. The potential economic promise of SB is such that numerous countries are developing strategies for establishing SB in both academia and industry. Part of these strategies is the early inclusion of social scientists and policy makers, although there remains uncertainty as to how rapidly the field will develop and to what scale. Given that chromosome synthesis and assembly are now technically feasible, are new national and international regulatory and governance structures required? Can current and future SB research be accommodated within existing genetic modification (GM) regulatory systems and is self-regulation a suitable *modus operandi* for SB?

Current realities

Synthetic biology has been rapidly growing as a new research discipline since the early 2000s. However, while it is widely accepted by many researchers, funders, and policy makers that SB as a multidisciplinary approach aims to make the engineering of biological systems easier, there still remains confusion as to why this field has emerged now, despite enabling engineering work that has been ongoing for the past 20 to 30 years. The major drivers for the emergence of SB are the availability of complete genome sequences enabled by low-cost DNA sequencing, advances in bioinformatics, data mining and modeling, and the rapid development of cheap chemical synthesis of DNA. All of these strands now come together, which when combined with the development of an engineering framework, allows researchers to start thinking about designing biological systems and genetic circuits much like an engineer designs new electronic circuit boards. This powerful analogy results in complex biological systems being broken down into an engineering-like hierarchy of parts, devices, and systems where DNA forms the parts (termed 'bioparts' or 'biobricks') that when combined give rise to biological devices that together form biological systems. Current realities, however, do not allow such smooth transitions between the different hierarchies. For example, designing a biological system at the DNA sequence level does not guarantee that such a constructed system will perform as predicted in a living cell. This remains one of the key challenges of SB, although the rapid development of foundation technologies and frameworks for systematically engineering cells may allow this vision to become a partial reality in the next few years. One notable new project that illustrates this is the international consortium led by Jef Boeke of Johns Hopkins University to build the first synthetic genome for the budding yeast *Saccharomyces cerevisiae.* The project brings together international, public-funded researchers from the United States, China, India, and the United Kingdom, based on open-source and sharing of results, similar to the publicly funded human genome project. The success of the project will not only provide researchers with tools to study yeast biology but also provide a host cell that can be easily engineered using SB approaches for specific applications.

The current environment to achieve such a vision is formed from a number of important strands. Firstly, a developing SB academic community is emerging, driven in part by the continuing success of the International Genetically Engineered Machine (iGEM) undergraduate student competition. Secondly, government funding agencies around the world are targeting SB research for significant investment with the increasing realization that, as an application-driven field, there may be significant economic benefits to be realized. Thirdly, higher education institutes have responded to the new field by creating interdisciplinary teaching and research programs in SB. Finally, biotechnology, energy, and pharmaceutical industries are exploring how SB could accelerate their existing product pipelines

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as well as research and development. There is also an expanding and energized "start-up" culture in SB driven in part by iGEM and the youthful nature of the field. In summary, the current reality is that we are at the early stage of an exciting and developing interdisciplinary application-driven field, which aims to establish a legitimate engineering framework for biological engineering based in part on an open-source philosophy and the energy of youthfulness and optimism.

Scientific opportunities and challenges

Opportunities: The application areas that have been linked to potential SB solutions include energy and fuels, greener production of commodity chemicals, biomaterials (e.g., spider silk or bacterial cellulose), specialty chemicals and pharmaceuticals, protein-based bioproducts (e.g., enzymes), medical applications (e.g., biosensors, smart therapeutics, and tissue engineering), bioremediation solutions for pollution, biomining to increase yields from mineral ores using biological organisms, and engineering crops and soil organisms to increase global food yields. Although many of these opportunities have not yet been realized, by applying a systematic engineering approach to biological design, a series of platform technologies is emerging that will enable many different applications in the short and long term. Examples include new, efficient methods for rapid combinatorial DNA assembly; the rapid characterization of biological parts libraries and specific host cells (chassis) for SB; and the integration of modeling and computer-aided design (bioCAD) to aid biological design *in silico*. These platform technologies will inevitably lead to standardization as part of the field of SB that will accelerate the uptake of the technology both in academia and industry.

Technical challenges: As stated above, SB aims to apply engineering principles to biological systems but there are significant technical challenges to achieving this. For synthetic biologists, it is important to realize that although living cells are not electronic circuit boards, they do utilize many regulatory elements in their decision-making processes which mimic the behavior of human-defined electronic components (e.g., genetic switches that act as logic-like inverters), but at a biological time scale of seconds to minutes. Cells can also use sensors (e.g., small molecule inducers) to activate transcription of specific genes or environmental sensors (e.g., light) that activate specific gene networks or cell-cell communications systems that signal between cells. Cells are thus exquisitely evolved to sense and adapt to their living environments and have genetic circuits that encode these functions. It is these circuits that synthetic biologists are now adapting for different applications As we begin to fully understand the function of single cells at a systems level though experimental and mathematical modeling (which is the aim of systems biology), our ability to predictably intervene in such systems will be significantly increased. It is important to note that similar situations exist in other fields of engineering, such as with semiconductors (e.g., transistors), where physicists and engineers have worked for many years to obtain optimal performance. It is also interesting to consider naturally occurring DNA-encoded functional modules like bacterial operons, where biological context and complexity have been already encoded within the DNA sequence through evolution. The challenge here is to correctly interface such modules, which again requires a systematic approach.

Societal challenges: One interesting aspect about the developing field of SB has been the early engagement and exchange among social scientists, scientists, and engineers. The cynical view is that synthetic biologists are trying to prevent an unfavorable public reaction to their work and thus by engaging with social scientists, they can somehow achieve a level of acceptability through professional scrutiny. This is a very simplistic and incorrect view and a more realistic assessment is that SB is a research field that requires and encompasses the interdisciplinary work of social scientists. It is perhaps obvious that to create a vision of engineering biology based on SB, the final outcomes will rightly be open to public questioning.

Policy issues

- Although humans have been carrying out genetic manipulations for centuries through selective breeding, and more recently through modern molecular biology techniques, it is clear that the scale and vision of SB require a reassessment of the public value. Much progress has been made in public dialogues around SB primarily in the U.S. and U.K., and these activities need to continue, perhaps with even greater vigor and responsiveness. It is important to note that at least in the U.K., all publicly funded researchers in SB must have social scientists as collaborators and co-investigators on any SB project. The overall aim is to integrate social scientists and scientists/engineers at the early stage of project development and the term "responsible research innovation" used to describe this is being discussed widely. If society in general does not see any real and/or tangible benefit to the adoption of SB technologies, then the field will be in real danger of fizzling out before it has started.

- SB poses a number of key policy issues around regulation and governance, in particular whether existing international regulations are sufficient to govern this emerging field or whether new policies and/or structures are needed. This is a difficult question, as any newly emerging technology with transformative potential has by inference some unknown outcomes. The main issue is whether national and international regulatory structures currently in place are sufficient to govern access to DNA synthesis capabilities, encompass large-scale genome engineering, monitor the environmental release of synthetically engineered organisms, and oversee the synthesis and potential design of human chromosomes.

- In relation to the U.K., there are already significant GM regulations in place that cover most of the current SB research within contained laboratory facilities. The regulations are implemented locally as part of a government licensing system, with every GM and/or experiment using biological material formally registered (locally) and approved before commencement. The formal registration form covers areas such as Risks and Control Measures, Personal Protective Equipment and Hygiene, Waste, Maintenance, Training, Emergency Procedures, Access, Occupational Health, Containment Level, and GM class. In terms of GM release, another rigorous set of regulations is already in place, with each project requiring, in effect, government approval.

- Whilst I feel that the U.K. system has the right balance of regulation (although under continual review), I am concerned that the scale, scope, and potential of SB internationally leads to the need for global forums, agreements, and perhaps even governance standards for SB. This should not only include government-funded research and companies (often global), but also public activities like do-it-yourself biology and service provider companies (e.g., DNA synthesis). Such forums should also include all stakeholders and be transparent at all levels. I would argue that because SB is at an early stage of development but rapidly growing and evolving, there is an urgent need to develop international forums, which can also evolve and change as the field develops.