sagentia

Engineering solutions for synthetic biology

Biological engineering can be slow, expensive and uncertain. In this white paper, we explore the way that synthetic biology can borrow from the disciplines of other engineering sciences to make step changes improvements in speed and agility. It takes a look at microfluidics, biosensors, automated cell processing systems, software simulation tools and computer aided design.

By Nigel Whittle, VP Medical, Sagentia

A Sagentia white paper

Engineering solutions for synthetic biology

The world is facing a series of major challenges which could threaten the way we live our lives today. How will we satisfy the increase in the requirement for food (perhaps by up to 60% more than is needed today)? Then there is the growth in the demand for energy in the face of depleting resources. As the discovery of new medicines becomes increasingly challenging, we are also hit with the problem of the increasing prevalence of pathogens resistant to the drugs we have today. In principle we can use biotechnology to sustainably enhance crop yields, to efficiently convert non-food biomass into fuel and to engineer micro-organisms and plants into cost-effective producers of drugs. But biological engineering, as we currently practice it, can be slow, expensive and uncertain, requiring constant re-invention and re-iteration by academic and commercial research workers often operating in direct competition to each other.

New approaches to the world's problems

Other industries, such as electronics and high tech manufacturing, have employed the classical engineering cycle of 'design-build-test' to dramatically speed up product development and manufacture. Synthetic biology is an attempt to bring those same engineering principles into the field of biology, using *in silico* design, standardized construction modules and centralized production in so-called 'bio-foundries' to create new biological systems and organisms. This approach can be applied to all levels of biological complexity, from design and synthesis of novel genes, to modulation of interactions between elements, to multi-component systems - even whole cells. Behind this overarching ambition lies the need for us to improve and develop many areas of enabling platform technology: microfluidics, biosensors, DNA synthesis, automated cell processing systems, software simulation tools, and computer-aided design. Major technical challenges in each of these areas include the need to increase the versatility, scalability and robustness of the technologies, and the requirement to fully integrate and streamline individual processes in automated synthetic biology workflows.

Can micro-fluidics help with rapid prototyping?

The huge complexity of biological systems means that scientists are always coping with large numbers of samples, configurations, mutations, variants and other possibilities in each experiment. Microfluidic systems (or 'lab-on-chip' devices) can make biological experiments more manageable by working them up in miniature. Miniaturization allows us to precisely manage the flow of biological

elements in microscale devices, with the benefits of working with smaller samples, together with quicker analysis time and lower costs. Recent innovations in technology mean that it is also now possible to work with micro-droplets containing single cells, to conduct millions of PCR reactions simultaneously, to obtain transcriptomic data from individual cells, and perform mass-spectrometric analyses online. This should all mean a dramatic increase in the efficiency of biological research, making discovery of new drugs quicker, easier and cheaper.

However integrating such systems into synthetic biology workflows remains a daunting task, requiring specialist skills and a deep understanding of the physical processes and biological systems involved. Without this knowledge the challenges of multiplexing and scale-up will always limit the effective utilization of these innovative technologies

Meanwhile the goal of building more processes into a single device and replacing off-chip analyses wherever possible continues, with the objective of integrating complete synthetic biological workflows into microscale devices. We could then use such integrated microfluidics devices as rapid prototyping platforms for the discovery of novel therapeutics, or as new and improved biosensors.

Biosensors: streamlining analysis

The word 'biosensor' refers to a biological component that can recognize a specific analyte, and transduce this detection event to generate a quantifiable response, ideally one that can be converted into an electrical signal for processing or storage.

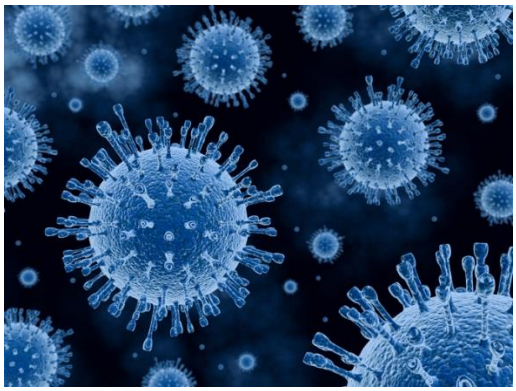
The artificial leaf

In 2016 a multi-disciplinary team led by Daniel Nocera, Professor of Energy Science at Harvard, announced the development of a system that produces liquid fuel from sunlight, carbon dioxide and water, dubbed 'the bionic leaf'. This process works at an efficiency of 10% using pure carbon dioxide, compared with natural photosynthesis which converts about 1% of solar energy into the carbohydrates produced by plants.

The device uses solar electricity from a photovoltaic panel to power the chemistry that splits water into oxygen and hydrogen gasses. Pre-starved R. eutropha bacteria are then added to the system, where they use the hydrogen as a food source, combining it with CO_2 from the air to produce alcohol fuels. In principle the bacteria can be engineered to generate more complex hydrocarbon molecules, including those currently obtained from fossil fuels. The team have already used the system to synthesize isobutanol, isopentanol, and PHB, a bioplastic precursor.

http://science.sciencemag.org/content/352/6290/1210

The biological component may be either a structural protein (such as an antibody, as used in many optical biosensors), or an enzyme (such as the glucose oxidase system used in most blood glucose monitors). We can even use more advanced systems such as living cells as biosensors, utilizing binding to a specific cellular receptor to induce a reporter gene response, for example in the detection of toxins in ground water or food substances. It is not difficult to envisage the practical applications of biosensors that are capable of a whole range of rapid and accurate biological analyses. They have the potential to provide cheap, accurate and efficient molecular tests that could significantly reduce the time required to diagnose diseases. The impact of such tests might be especially relevant in developing countries, particularly where public health has been threatened by emerging diseases such as Ebola or the Zika virus.



However a major problem is the requirement to allow such tests to work in different and potentially hostile environments, requiring a robustness that is not commonly associated with biological systems. Recent advances in freeze drying and subsequent reconstitution of cellular components[1] have gone some way to demonstrating how these problems can be overcome. However applications such as wearable analytic biosensors for continuous patient monitoring are still faced by a whole range of technical barriers, in addition to concerns over cost and complexity.

Modelling complex systems

The complexity of biological systems means that we are becoming increasingly reliant on *in silico* modelling and detailed analysis of system interactions in order to effectively design biological systems to achieve specific outcomes. We can then utilize these software tools to more fully characterize and optimize specific pre-determined genetic elements before final synthesis.

There is a proliferation of software tools and computational methods that already exists to support different aspects of the synthetic biology workflow, such as optimizing DNA assembly, simulating interactions within gene networks, or accessing information from databases. Importantly, most of these tools allow straightforward exchange of detailed genetic designs in standardized file formats or support display of genetic designs using standard visual motifs. However we have not yet achieved the objective of enabling routine design and construction of novel synthetic

[1] https://www.ncbi.nlm.nih.gov/pubmed/26807940

biology systems. This is largely due to the inherent complexity and 'noisiness' of such systems, so that computational models of biological systems can only currently provide a qualitative understanding. Assembling simple standardized modules into systems of increasing complexity is then hampered by the large number of unknown interactions within those systems.

We will clearly need further developments in the technology, perhaps in fields such as Computer Aided Design (CAD), and in Systems Biology (which attempts to understand the network of interactions within biological systems) in order to overcome the challenges associated with this inherent complexity.

Progress through collaboration

Synthetic biology has become a high priority science in many countries, and the field is evolving an internationally collaborative structure, with organizations such as the EraSynBio Network linking research groups in the USA and Europe. In the UK SynbiCITE has been set up as a national center to accelerate and promote the commercial exploitation of synthetic biology research and technology. One outcome of this collaborative effort has been the development of standardized biological parts, such as Biobricks[2], which allows real 'plug-and-play' operations in synthetic biology.

As the science has matures, we have seen an increasing interest from the commercial sector, including major biotechnology companies such as DuPont and Novozymes, and energy corporations such as BP and Abengoa. There has also been an explosion in start-ups, with North America now home to nearly 200 Synthetic Biology companies, backed by private investment of $830 million in 2016 alone.

Towards integrated, automated workflows

Since the elucidation of the structure of the DNA helix in 1953, the fundamental biochemical components that comprise living systems have been identified and extensively characterized by research workers. This reductionist approach has been hugely effective in developing a detailed understanding of how the separate components of complex biological machinery work.

Today we see the development of a new 'bottom-up' approach, a synthetic biology in which novel biological systems can be designed and built in a rational and coherent manner, through the use of a forward-engineering design cycle. Indeed, biological engineers have already created synthetic biological systems that can be used for applications in bio-sensing, bio-energy, bio-remediation and medical therapeutics. This approach now has the potential to further transform our economy and our lives, with major industries such as energy production,

[2] http://parts.igem.org/Main_Page

crop production and healthcare being amongst the first to benefit from this exciting new technology.

About Sagentia

Sagentia is a global science, product and technology development company. Our mission is to help companies maximise the value of their investments in R&D. We partner with clients in the consumer, industrial, medical and oil & gas sectors to help them understand the technology and market landscape, decide their future strategy, solve the complex science and technology challenges and deliver commercially successful products.

Sagentia is a Science Group Company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has six offices globally, two dedicated, UK-based R&D innovation centres and more than 350 employees. Other Science Group companies include Leatherhead Food Research, Oakland Innovation and OTM Consulting.

T. +44 1223 875200 | info@sagentia.com | www.sagentia.com