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Editorial

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Engineering biology: a key driver of the bio-economy

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Abstract: This study provides a relatively brief overview of the field of synthetic biology/engineering biology for the non-specialist reader. This is in line with one of the basic aims of the new journal *Engineering Biology* – which is to open up the field to a much wider audience than those currently engaged and, particularly, to people working in companies and disciplines whose technology may be relevant to the field. Consequently, the study contains some didactic material.

1 Introduction

It is now 8 years since the publication of The Royal Academy of Engineering (RAEng) Inquiry Report on synthetic biology [1]. Since the publication of the report much has happened. Back in 2009 there was still significant speculation about the potential of the field, e.g. in terms of economic and industrial impact. This view started to change in 2012 when the World Economic Forum, in Davos, voted synthetic biology as the second most important new area with major industrial potential. Subsequently, in January 2013, the British Government defined synthetic biology as one of its 'Eight Great Technologies'. More recently, the importance of the bio-economy has been recognised on both sides of the Atlantic – with the overall current bio-economy in the UK estimated to be around £150 billion, and increasing rapidly. It is now clear that synthetic biology will be a key driver in the growth of the bio-economy.

Many of the major industries of the twentieth century are based on a model which uses oil as its feedstock and synthetic chemistry for industrial processes and products. Synthetic biology provides an alternative model that uses a range of bio-based feedstocks to produce new industrial processes and products. These models are illustrated in Fig. 1.

In the RAEng Inquiry Report in 2009, synthetic biology was defined as: 'Synthetic biology aims to design and engineer biologically-based parts, normal devices and systems – as well as redesigning existing natural biological systems'. This definition, and slight variants, is still widely accepted internationally. What is interesting is the key phrase within the definition, 'design and engineer'. These terms are now seen as cornerstones of synthetic biology. In fact, synthetic biology is now often described internationally as engineering biology.

There are a number of factors which contributed to the emergence of synthetic biology at the beginning of this century. Principal among the background factors are the molecular and cell biology revolution (which has its origins M. Crick and Watson's seminal paper on the structure of DNA) – and the information and communication technology revolution (that has its origin in the invention of the transistor and led to the widespread use of digital computers, broadband telecommunications networks and the internet itself). More specifically, it was the technology behind the initial sequencing of the human genome (which culminated in the publication of the work in Nature, in 2001 [2]) that allowed the reading of DNA. Over the past 16 years the technology to read DNA has become fast, accurate and inexpensive – to a point where reading DNA is almost routine. A similar and equally important development has been the ability to write DNA chemically. Currently, there are a number of companies that write DNA to order. Whilst the accuracy is good, the cost still remains fairly high. However, this situation is likely to change in the near future with new technology coming on stream. The ability to read and write DNA quickly, accurately and cheaply could well have a similar impact on the world as the invention of the printing press around 1440 and is, arguably, the key factor in the development of engineering biology.

There are a number of other features that distinguish synthetic biology from earlier attempts to manipulate DNA (e.g. so-called genetic engineering). At the heart of synthetic biology is systematic design. This is based on the engineering principles of modularisation, characterisation and standardisation. A conceptual framework has been built around these principles (which are familiar to other fields of engineering), namely that devices are built from standard components and systems are built from standard devices. (The ability to characterise biological components will be covered in more detail later.) At a more fundamental level, an important part of the conceptual framework for the field is the concept of considering the biology in terms of systems and information (e.g. DNA as digital code). In their paper on the structure of DNA, Crick and Watson commented – 'It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material'. The structure of DNA, with its four bases, leads directly to the concept of digital biology.

Another key concept in synthetic biology is the design cycle. This is usually described in terms of the statement 'design, build, test, learn and correct'. The other concept that has emerged over the last few years is that the strategy for synthetic biology/engineering biology can be divided into two principal areas – platform (or foundational) technology and applications. Platform technology comprises technology that can be applied across a range of application areas. Such technology today includes information systems, registries of standard components (often called BioParts) and laboratory automation. Examples of application areas are fine chemicals, biomaterials, bio energy, biosensors and biocomputing.

The modular approach to building devices and systems from standard components requires that the components are well defined. In synthetic biology, a device is usually created from a number of components. In their raw form, BioParts (components) comprise a section of synthetic DNA. When the synthetic DNA is placed in a cell, typically using a delivery device (e.g. a plasmid), the cell responds by producing something – proteins, which, ultimately, form the basis of, say, skin cells. The synthetic DNA is designed to have characteristics, which are anticipated, based on previous analysis, to be consistent with a particular human design.

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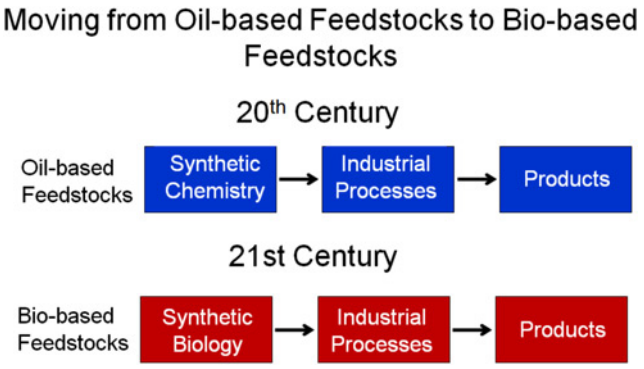


Fig. 1 *Alternative model that uses a range of bio-based feedstocks to produce new industrial processes and products*

In nature, the cell's DNA is already present and is used for this process. Under these conditions, the DNA and the cell naturally match. (In synthetic biology a cell is often called a chassis or host.) It is therefore essential to establish, for a particular type of cell and a particular species of the cell (known as the strain) how the cell will react to the synthetic DNA (or BioPart). In order to be able to produce a device, such as a biosensor (e.g. a biological device capable of detecting a certain type of bacterial infection); it is, therefore, essential to know precisely how the cell will react to the synthetic DNA. This process is called characterisation. In characterisation a series of detailed experiments are carried out to determine how a particular cell-type/strain will respond to a defined section of synthetic DNA. This is usually done by repeating experiments over several days to determine the reliability of the results. Once the BioPart has been properly characterised, the characterisation data, together with the information about the experiments, the protocols, the equipment used etc. (i.e. the Metadata) are placed in a special type of database called a registry, which is part of an information infrastructure. In a similar manner to describing electronic components, a significant amount of work has been carried out in producing datasheets for BioParts. Originally, such data sheets were limited to single page pdfs. However, today, datasheets are frequently electronic and comprise multiple pages that contain the data, the metadata, anecdotal data and information not contained under the first two categories.

The process of producing a device, such as a biosensor (real examples being the detection of bacterial infections and arsenic in groundwater) is achieved by a process which comprises a number of steps. The first of these is the design. Once a design has been determined, the device is constructed from a series of standard components (i.e. sections of DNA, BioParts, which have been fully characterised and reside in a registry). Currently, it is quite common for not all the standard components required for a particular design to be available. Under these circumstances, new standard parts have to be created. This is done using the characterisation process previously described. Once all the parts

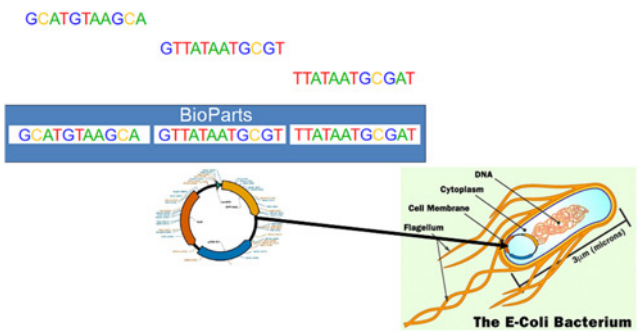


Fig. 2 *Steps in the process of producing a device such as a biosensor*

for the device (the gene circuit) are available they are assembled into an overall DNA sequence comprising a number of BioParts. The sequence is then inserted into a plasmid so that it can be introduced into the cell which will produce the device. This overall process is illustrated, schematically, in Fig. 2. Once the device is produced by the cell, a second level of characterisation is undertaken to optimise the design. This process implements the design cycle – design, build, test, learn and correct. Often, several iterations of the design cycle have to be undertaken before a satisfactory result is achieved – i.e. in this case a stable biosensor that works according to the design specification.

2 Laboratory automation and foundries

A key difference between synthetic biology as practiced at the time of the 2009 RAEng report and now is the widespread use of laboratory automation (e.g. robotics) and information infrastructures. Whilst it is true that it is still common for many 'wet labs' to use human operators to carry out laboratory procedures, in synthetic biology there is a major drive towards the comprehensive implementation of automation and information systems. An important, general reason for this is the large cohort of people involved in synthetic biology that come from engineering and computer science – where these approaches are common. More specifically, the practice of synthetic biology (engineering biology), particularly in relation to application projects and industrial translation, requires high levels of reproducibility. This, in turn, requires reliable, reproducible analysis and build processes – with minimal errors. This approach is common to many areas of engineering and advanced manufacturing – and involves the analysis of work flow. Consequently, in order to achieve these objectives, there is now a drive towards building Foundries.

Such Foundries are often referred to as DNA Synthesis Foundries. This can be misleading because the operation of a typical foundry comprises a multistage workflow – of which DNA synthesis is only one stage. The workflow is frequently based on the design cycle, described earlier. The Design Cycle includes design, modelling and assembly; build – DNA synthesis and sequencing, DNA optimisation and gene assembly; test – system characterisation, testing and trails; and produce – prototype build, scale up and production. Out of these stages (and their components), the one area which is typically not undertaken directly within the Foundry is DNA synthesis. Most people in the field believe that this is best done by specialist companies, such as Twist Bioscience. Foundries are important because in gene circuits, unlike their electronic equivalents, the order of the components (BioParts), indeed the components themselves, and the overall behaviour of the circuit (once placed in the cell) often cannot be predicted in advance. In practice, within the foundry, this problem can be overcome by creating multiple variations of the circuit (e.g. varying components and their order) in a parallel process.

3 Applications

The classic synthetic biology application story is that of artemisinin. In 1972, a Chinese scientist, Professor Tu Youyou, discovered the active ingredient for the cure of malaria in the annual wormwood plant (*Artemisia annua*) – for which she won the Nobel Prize for medicine in 2015. (It had been known for over 1000 years that the annual wormwood plant is capable of curing malaria.) Starting in the early 2000s, Jay Keasling led a project at the University of California, Berkeley, to produce artificial artemisinin, using sugar as the feedstock. Keasling and his co-workers perfected the ability to produce artemisinic acid synthetically. The process was initially developed by Amyris, a synthetic biology company located near Berkeley. Industrial scale production was undertaken by Sanofi – an Italian pharmaceutical company.

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In 2009, when the original RAEng Report was published, there were only a few examples of application projects in synthetic biology. There are now numerous examples, both industrial and academic. These projects fall into two categories: platform, or enabling, technologies; and application projects in areas such as biomaterials and healthcare. Within the limits of this paper it is only possible to give a few examples. In terms of platform technologies, one area of very significant importance is effective DNA synthesis (i.e. writing synthetic DNA chemically). Twist Bioscience, based in San Francisco, is an exciting company in this area. Founded in 2013, the company has attracted a large amount of inward investment because of its novel DNA synthesis technology. Two key features of the technology are a 10,000 well silicon platform, as opposed to the more traditional 96-well plate approach. (Each well in the plate can be considered to represent a different experiment.) The second key feature of the technology is the implementation of microfluidics. It is anticipated that when fully successful, from a production standpoint (over the next few months), the Twist technology will be capable of accurately producing large amounts of synthetic DNA to order – at vastly reduced cost.

A second company of interest in terms of platform technology, is London-based, Synthace. The company has developed what they describe as an operating system for biology, Antha. The operating system enables building a workflow using a number of Antha elements – that can be connected together in different software configurations. The technology is capable of high-level implementation of the synthetic biology design cycle – with a facility to import BioParts from a range of sources using different standard data formats. A key element of the technology is the ability to optimise designs through computer modelling.

The optimisation of host-organisms is another rapidly developing area. One example of this is DuPont. The company is working on the optimisation of enzymes to break down agricultural waste in the production of biofuels. Waste is an important area in the application of synthetic biology. Currently, the UK is, effectively, saturated in relation to landfill waste and it is seen as a major negative factor from an environmental standpoint. However, from the synthetic biology standpoint, landfill is an important source of feedstocks. If developed properly, landfill waste, coupled to synthetic biology technology, could represent a very significant industrial and environmental gain. Two examples (of many) are: (i) the ability to turn landfill biomass by heating (gasification) into syngas – and then, through synthetic biology, using special types of bacteria to manufacture new products (Nottingham University); and (ii) the technology to turn landfill plastics into the raw material of new products, which are produced using biodegradable plastic (Imperial College, London). On the theme of recycling, LanzaTech is an interesting company. Founded in New Zealand, but now with a US base, LanzaTech has perfected a process for capturing industrial exhaust gases (principally carbon dioxide and carbon monoxide). These gases represent carbon waste and waste energy (and are damaging to the environment). The LanzaTech process employs bacteria to process waste gases to produce bio ethanol and industrial chemicals. The company uses an anaerobic bacterium (*Clostridium autoethanogenum*) to produce ethanol from carbon monoxide through a process which the company calls 'syngas fermentation'.

Oxitec and Medicago are two examples of healthcare applications companies According to Oxitec, over 1 million people die from mosquito-borne diseases, such as Dengue Fever, every year. Oxitec has developed technology, through synthetic biology, that modifies the male mosquito's genome to make it, effectively, sterile. When these males mate, the offspring do not survive to adulthood and the mosquito population declines. (The decline is rapid because the life cycle of the mosquito is relatively short.) The second example of healthcare applications relates to two companies working on new technology for vaccines. The first is Prokarium, a UK biopharmaceutical company who are using synthetic biology to develop oral vaccines. Their oral vaccine delivery system, Vaxonella, simulates the human immune system. The company is currently developing an oral chlamydia vaccine. The second company is Medicago. In England, in excess of 6 million working days are lost each year due to flu. In 2015, in the UK, the flu vaccine was ineffective because a new strain was detected in Australia in March – it takes around 9 months to produce 10 million doses of a flu vaccine, using current methods. Work on a little-known plant virus (cowpea mosaic virus) at the John Innes Centre in Norwich has resulted in the ability to rapidly multiply the virus in greenhouse plants. The new method uses the machinery of a modified version of the virus to produce a non-infective viral shell, called a virus-like particle or VLP. Genetic information from the human flu virus is then used to place influenza proteins on the surface of the VLP. The method is now being produced commercially by Medicago, a Canadian company based in Québec. The company says that, in contrast to current methods of vaccine production, which can take several months before vaccine production is started, with the new technology vaccine production can begin 2 weeks after the target flu virus is identified.

The bio-based feedstocks/synthetic biology can be applied more generally to chemical production – resulting in an alternative approach to the production of, for example, solvents, resins, polyvinyl chloride and nylon. This can be achieved through processes based in synthetic biology which use lignocellulose waste (plant dry matter) of various kinds and industrial gases (e.g. CO_2).

4 The future

How will synthetic biology/engineering biology develop over the next few years? The field is now moving to a point where industrial translation is becoming a key driver of the field. Industrial translation requires the deployment of engineering. Standards also need to be developed in order to interface the new technology with industrial processes. Two technical standards (i.e. SBOL and DICOM-SB) are already being developed. Once the technical work has been completed, these will need to be formalised by standards bodies, such as the BSI – and NIST in the USA. At a more strategic level, the drive is towards high-level design. As observed at the beginning of this paper, design and engineering were at the core of the 2009 RAEng report and are still central to synthetic biology. The difference today is that we now have many of the tools and techniques necessary to undertake high-level design. How will this be achieved? The design process will initially occur in the dry lab. Beginning with a basic design, a set of specifications will be defined and a more detailed design developed. The next stage is to determine and analyse a number of candidate gene circuits to realise the design. The analysis will determine whether or not the appropriate BioParts already exist in a registry somewhere in the world. If some of the BioParts do not exist, then new parts will need to be designed and built. This process involves DNA synthesis, part characterisation, testing and validation. Once all the appropriate parts have been made available, the next stage comprises detailed computer modelling to determine and optimise the operation of the device. The process now moves to the wet lab, where the device is assembled. Detailed testing and validation is then undertaken, and, if necessary, parts of the cycle repeated until the device is working optimally.

As described earlier, much of this work will be carried out in the near future within a DNA synthesis foundry. In one respect this represents a key area of development in the field of engineering biology, namely the introduction of more and more automation. This is an absolute requirement, along with the development of technical standards, for the successful industrialisation of biology. As previously stated, the last few years have seen the introduction of more and more liquid handling robots into the wet lab. The foundry concept represents the logical extension of this approach. It is already apparent that foundries are essential for improving reliability and reproducibility to the levels required for industrialisation. Once the foundry approach is established it will then be possible to add to this business process management

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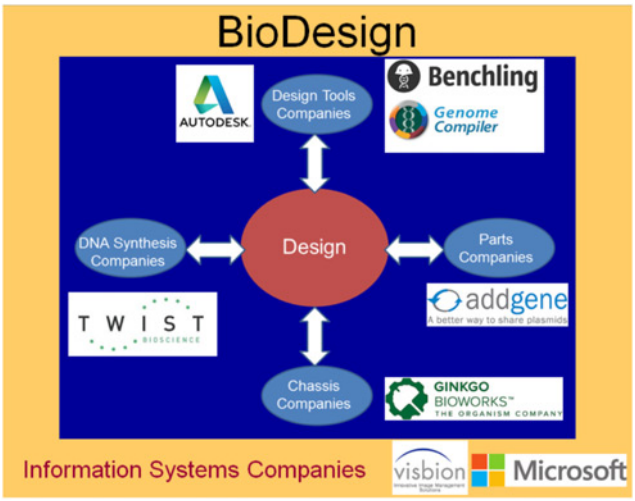


Fig. 3 *Specialist company ecosystem*

technology and optimisation techniques to improve bio design and its implementation. The goal is to undertake bio design at a higher level in the dry lab with automatic translation into the wet lab via bio automation systems. One of the trends in engineering biology, and an important differentiator from standard biology, is the increasing shifting balance from the wet lab to the dry lab.

The other key area of bio design is the development of a specialist company ecosystem. This is directly comparable with the automotive industry where companies, such as BMW, are increasingly reliant on specialist, high precision engineering companies to produce components for the cars. A similar trend is developing in the field of engineering biology with the development of the bio design ecosystem; this is illustrated in Fig. 3, which shows that at the heart of the ecosystem is design. This process is valid by a number of specialist companies, including design tools companies, parts companies, chassis companies and DNA synthesis companies. As shown in Fig. 3, a range of such companies already exists (here, only some examples are given).

As pointed out in a number of international reports, the bio-economy in a number of countries (e.g. the US and UK) is one of the fastest growing scientific and technological fields. It is predicted that the engineering of biology will have major impact in many areas of the bio-economy and beyond.

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