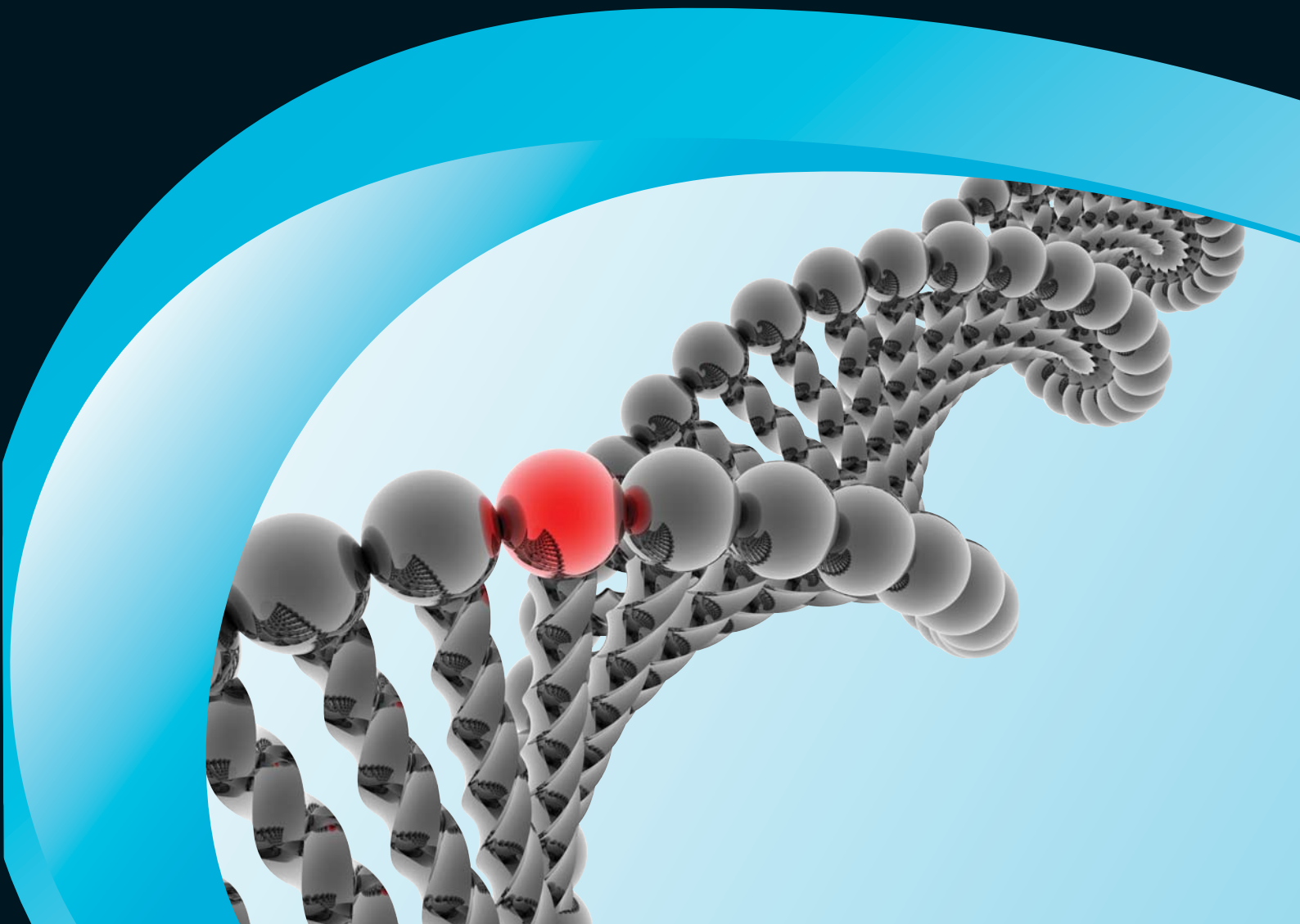
The Royal Academy of Engineering

Synthetic Biology:
scope, applications and implications



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Executive summary

The last half of the 19th century and the first years of the 20th century saw the development of technologies that would create the basis of wealth generation by means of major new industries – principally petrochemical, automotive, aviation and electronics. These developments helped create the modern world. Synthetic biology has the potential to create another raft of major new industries, the development of which is likely to have profound implications for the future of the UK, European and world economies. At this time of global economic uncertainty, the fostering of new wealth creating industries and technologies is a stated Government objective. At present, in the field of synthetic biology, the UK can demonstrate a competitive advantage in fundamental research, massive growth potential (as synthetic biology techniques mature and replace existing production techniques) and the realistic potential to being number one or two in the world. Synthetic biology is therefore a prime candidate for significant investment to develop UK capabilities.

While the UK can currently boast a strong global position in synthetic biology, maintaining this position is not a foregone conclusion. The US already leads the way with the US National Science Foundation's $16m funding of the Synthetic Biology Engineering Research Center (SynBERC) based at UC Berkeley, The Bill & Melinda Gates Foundation investment of $43m into medical applications of synthetic biology and the $500m Energy Biosciences Institute (led by BP and the US Department of Energy) - in which synthetic biology will have a significant role to play. This level of investment seems set to continue given that President Obama has recently announced his intention to support fundamental research in the United States through the economic downturn. The scale of US investment currently dwarfs British investment and consideration must be given to further significant UK investment. Failing to do so would risk the UK falling further behind the US and ceding our current position to other European or Far Eastern countries – who are also investing heavily in the field.

Synthetic biology, as a field, has developed over the last few years because of the confluence of a number of factors. There have been advances in biology, genetics and genome sequencing - coupled to the vast increase in the speed and storage capacity of computers and the internet. This has enabled researchers to understand living organisms in much more detail, both in terms of the individual molecules and at the system level. One of the key features of synthetic biology is the application of rigorous engineering principles to biological system design and development. The manipulation of DNA has now been possible for many years, but this has involved gene replacement on a case by case basis. By applying the engineering principles of specification, design, modelling, testing and validation, new biological devices and systems can be produced.

The coming together of engineering and biology that typifies synthetic biology means that it is, by nature, a multidisciplinary field of endeavour. Fundamental research requires collaboration between engineers, biologists, chemists and physicists, as well as social scientists and philosophers. As synthetic biology based techniques mature and start to move from the lab bench to commercial application, their scaling up to a level useful to industry will require collaboration with chemical and process engineers.

This report aims to define the term 'synthetic biology', review the state of the field and consider potential future developments and their likely technological, economic and societal impact. It will also attempt to assess the requirements for the development of the field and to identify key policy issues.

The following is a summary of the central themes and issues that the report has investigated, and the resulting recommendations.

Defining synthetic biology

We define synthetic biology thus:

"Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems."

This definition, while maintaining a certain level of simplicity, expresses the key aspects of synthetic biology. It is consistent with the views of most researchers in the field (both in the UK and abroad) and those of The Royal Academy of Engineering.

Synthetic biology strives to make the engineering of biology easier and more predictable.

Current activity and applications

There is considerable activity in a number of areas including health, energy, the environment, agriculture and applications in other industrial sectors.

A synthetic version of the anti-malarial drug artemisinin is being developed using synthetic biology methods. This makes it amenable to large scale industrial production - if successful, it will have a major impact on the treatment of malaria in the developing world. The cost of treatment should be low as the development of the drug is being funded by the Gates Foundation.

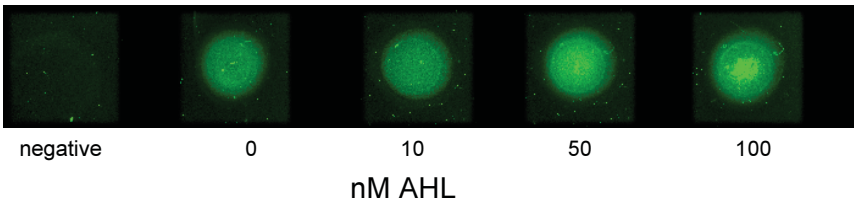


Figure 1: Fluorescent output from a UTI detector

In health, biosensors are being developed that can detect urinary tract infections (UTIs). When the device comes into contact with a UTI it triggers a response in one of its constituent proteins, which fluoresces. Because systematic engineering principles have been used in the design of the technology the sensor is capable of being readily adapted to detect other pathogens such as MRSA.

In the field of energy, synthetic biology is being used to develop far more efficient biofuels. These developments have the potential to alleviate current problems with biofuels – for example, competition for land use between energy and food crops. The current process of deriving biofuels from crops such as sugar cane or palm oil wastes about 90% of the biomass. Synthetic biology derived biofuels are being designed to use a much higher percentage of the biomass which will result in a significant increase in yields and the associated carbon savings.

Vision

Many commentators now believe that synthetic biology has the potential for major wealth generation by means of the development of major new industries, much as, for example the semi-conductor did in the last century, coupled to positive effects for health and the environment. In order to show how such developments might occur, the report gives a vision of the future in terms 5, 10 and 25 year time scales. (It is important to understand that any 25 year vision is, by definition, highly speculative.) Here are some snapshots from the 10 and 25 year visions.

10 year vision

- Routine and economically viable synthesis of large synthetic DNA sequences (genomes) to underpin synthetic biology applications.
- Synthetic biology techniques will be incorporated into biotechnology processes. This may involve the tuning of existing drugs to improve their therapeutic properties and to produce low or no side effects for the individual. A direct extension is likely to be the application of synthetic biology to the production of new drugs which are based on the known therapeutic properties of certain plants.
- The coupling of synthetic biology to tissue engineering. The biofabrication of accurate 3D scaffolds, to which cells attach. This has the potential to make engineered tissue of various kinds much easier to construct.
- More advanced biofuels (typically biodiesel and bio-aviation fuels) will be developed, with new synthetic biology based processes for fuel production in large quantities (equivalent to refining). An important aim will be to use as much of the current supply chain as possible in order to capitalise on the existing infrastructure.
- The reduction of CO_2 levels by the development of artificial leaf technology which is a synthetic version of the photosynthetic process.
- Synthetic biology techniques will be used to engineer new types of pesticides which are environmentally friendly by being very specific and have a natural life in the ground which is consistent with carrying out their function.
- The beginnings of the development of biologically based lightweight and very strong materials which will have direct application in the aircraft and automotive industries.
- A range of industrial standard biological parts will have been developed and placed in a professional register of parts. These will be incorporated into devices such as various types of counters. In addition, it is likely that over this period of time it will be possible to produce biologically based memory (the direct equivalent to computer memory). Once this stage has been reached, all of the components will be in place to produce biologically based microprocessors of different kinds. Like their electronic counterparts, they will begin to perform control functions applicable to living systems.

25 year vision

History shows that a 25 year vision is difficult to predict with any accuracy. Areas where it is expected that major progress will be made, may encounter hidden problems. Other areas of development, which currently seem impossible, could make major strides because of some unforeseen discovery or breakthrough. With that in mind, here are some examples of possible applications:

- Biosensors which permanently reside in the body to detect a particular type of abnormality, for example arterial disease. The biosensor will be part of a machine engineered by means of synthetic biology which then manufactures or releases a 'drug' to disperse the arterial plaque.
- Highly adaptive antibiotics. One of the problems with current antibiotics is that the bacteria which they are designed to kill adapt to the antibiotic, which then becomes ineffective. Synthetic biologically engineered antibiotics could be developed that monitor the adaptation of the bacteria they are designed to kill and modify their response accordingly.
- More advanced biofuels will be developed for different applications. Artificial enzymes are already used in the detergent industry. Synthetic biology will allow the development of enzymes which can break down a much wider range of biomass into useful forms. It should also be possible to develop plants whose whole biomass is readily convertible.
- Many products which are currently derived from petroleum, eg plastics, will be replaced by biologically engineered substitutes.
- The development of biologically based devices and systems which in the biological world perform as microprocessors and perform a range of control functions. This could involve signalling and actuators which replace or modify their natural equivalents, for example within the cell. Sophisticated biologically based interfaces which link biology to electronic systems, eg for cellular and intracellular monitoring in the treatment of diseases such as cancer.
- The establishment of rational and engineering-based synthetic biotechnology processes and protocols for the synthesis of fine chemicals, industrial-based enzymes and complex pharmaceuticals.

These applications may be achievable, but they need to be driven by a national strategy, with significant industry involvement. The strategy should include research and development which is directed at overcoming specific deficiencies in achieving set technical objectives – not dissimilar to the technology roadmap utilised in the IT sector.

Research and educational infrastructure

The development of synthetic biology is dependent on the establishment of an effective research and educational infrastructure. Such an infrastructure should be based on a group of leading research universities, but with close links to research groups in other UK institutions. There is a need to establish strong research and teaching centres which bring together expertise in engineering, physics and chemistry as well as biology. The same centres should provide high quality doctoral training programmes. Strong international partnerships, most notably with other groups in the EU, US and the Far East should be developed. This would also include sharing expertise in relation to educational programmes.

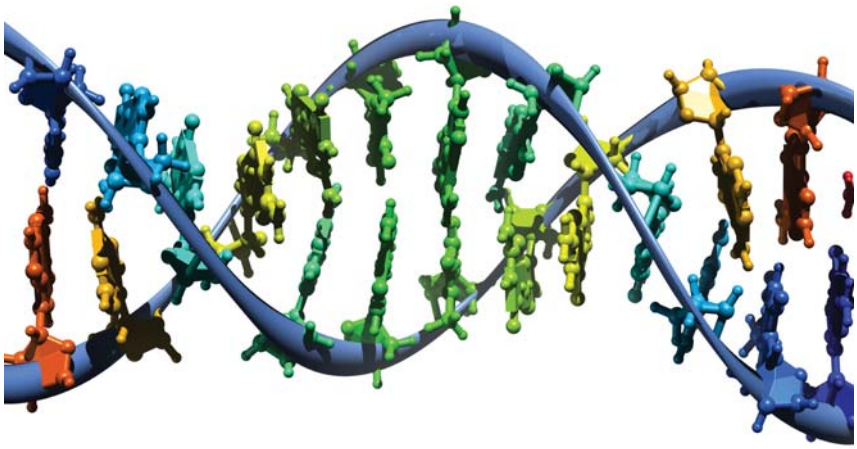
Societal and ethical implications

The development of synthetic biology brings with it a number of ethical and societal implications that must be identified and addressed. Key concerns are safety and security, based on the perceived risk of harmful organisms being released, either deliberately or accidentally, into the environment. In addition, issues surrounding intellectual property and control by multinational corporations must also be thought through. For some groups of people, synthetic biology could raise ethical questions pertaining to the creation of

novel life forms. These are crucially important issues that need to be addressed specifically and carefully. Throughout the inquiry, it was encouraging to find that individuals and organisations currently involved in synthetic biology are acutely aware of the need to consider these important issues. As well as an academic exploration of these issues by social scientists, ethicists and philosophers, early public dialogue is of the utmost importance to help promote listening and understanding of people's hopes, expectations and concerns.

Summary

Synthetic biology is destined to become of critical importance to building the nation's wealth. It has the potential to transform world industry in areas such as energy, health and the environment; to produce a new era of wealth generation; and create large numbers of new jobs. It is difficult to accurately determine the full economic impact of the field at this point; however, some idea of the scale of the industrial impact might be derived from comparing it to the development of synthetic chemistry in the 19th century, which is now central to the conversion of petroleum into a wide range of chemicals, as well as petrol, diesel, solvents and lubricants. Synthetic chemistry made possible the development of the pharmaceutical industry, as well as much of the food industry, detergents and plastics. In addition, synthetic chemistry is very important in semiconductor production - the basis of all transistors and, hence, all computers and integrated circuits. The potential impact of synthetic biology on the economy is likely to be as great, or even greater, than that of synthetic chemistry a century ago.



Recommendation 1
Strategic plan for the UK

1a: Developing the strategy
Synthetic biology has the potential to develop into a major new sector that addresses key global challenges while creating significant wealth and jobs for the UK. As such, it meets the criteria, as articulated by the Government, of being an appropriate area for focus, demonstrating a field where the UK already has significant advantage, with promising growth prospects and where the UK has the potential to become first or second in the world.

We believe that, in order for the UK to place itself in the best position to be a world leader in this sector, Government must begin the groundwork that would lead to a national strategy for synthetic biology. This undertaking should be a joint enterprise between Government and the national academies, along with input from other key organisations and individuals from academia and industry.

The development of the strategy, because of the multidisciplinary nature of synthetic biology, must cover a range of disciplines, principally engineering, life sciences and physical sciences, but also include the social sciences to put synthetic biology's development in a wider societal context. As well as bringing together the individual academic sectors involved, the strategy must begin to develop frameworks for regulation and the development of standards which will allow all researchers in the field, regardless of discipline, to work together in the most effective ways.

1b: Stakeholder engagement
The elements set out above cut across several Government departments. A strategy would enable appropriate policies to be put in place that acknowledged their interdependency. In the context of the current economic downturn, such a strategy would help ensure that the long-term nature and complexity of the development of synthetic biology would not create barriers and missed opportunities. It would also have the potential to shorten the time scale in which the sector could bear fruit by aligning the various elements involved and addressing any issues in an informed context.

In addition to the engagement of all the relevant Government departments, the strategy needs to be developed with the input and guidance of academia and industry. While the fundamental research that is currently being carried out in the field can be sustained by the pursuit of knowledge alone, as synthetic biology techniques mature, their development will become driven by the need to create applications and solve problems in industry. The involvement of industry in developing a strategy for synthetic biology will ensure that research becomes progressively more directed as it becomes more applied. This will ensure a more rapid and successful translation of research into commercial applications.

Recommendation 2
Training and research infrastructure

2a: Centres of synthetic biology
If the United Kingdom is to successfully compete globally in the field of synthetic biology, both industrially and commercially, a number of academic centres dedicated to the subject are required. These centres should be located within leading universities that have internationally competitive research in engineering and the physical sciences, and biology. They must be truly multidisciplinary, with the ability to carry out world leading research. Wherever possible, the centres should be based on universities with existing activity in synthetic biology in order to maximise UK capacity in the field at the lowest cost.

In addition to their research capacity, the new centres should provide teaching in synthetic biology. If the field develops as expected, there will be a pressing requirement for expert staff specifically trained to a high level. Synthetic biology requires a deep understanding of engineering and the complexities of the biological systems. It is envisaged that such training will be primarily at the postgraduate level. It is therefore proposed that the centres offer a doctoral training programme, similar to those which now exist in other fields, comprising a four year programme, for example, a one year MRes or MSc followed by a three year PhD.

2b: Funding requirements
Successful centres would require a critical mass in terms of researchers, facilities and equipment. Based on the model of comparable centres in fields such as nanotechnology and chemical biology, it is estimated that each centre would require funding in the order of £60m over a 10 year period. Given that the techniques involved are still largely at the pre-commercial stage, significant funding from central Government is likely to be required. But opportunities should also be sought for funding specific research projects through strategic collaborations, for example with industry and charities. The proposed centres are seen as an essential first step in developing new and expanding technology based industries, bringing with them a new wave of prosperity in the UK. As a guideline to minimum requirements, each centre would require capital costs of an estimated £12m, to be spent over the first three years, and a budget of £4m per annum to support a staff of approximately 30 to 35 researchers and administrators. In addition to this, the doctoral training programme would cost around £800k per annum (based on recruiting seven students per year at a cost of £40k per student).

As far as possible, existing resources should be redeployed by the host university and, after ten years, the centres should be progressively integrated into their host universities. Even so, it should be noted that such an initiative would represent a significant step change in the current level of funding for synthetic biology.

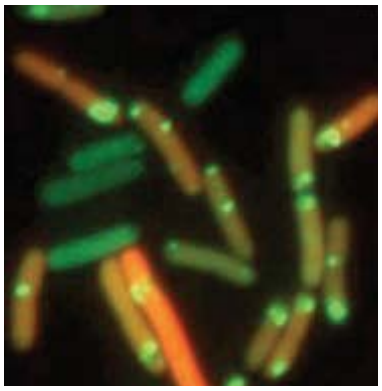
2c: Academic and industrial collaboration
There would need to be strong a and synergistic relationship between the centres. The centres would also need to be a focus of related activity in synthetic biology such as workshops and conferences, with effective networking to smaller centres in other universities and linked to international initiatives.

It is essential that the centres should seek partnerships with industry to ensure that projects of high national economic importance receive priority. This might mean developing and applying new techniques to existing industry, for example the biotech industry, as well as nurturing new and existing SMEs.

Recommendation 3
Societal and ethical implications

Synthetic biology research needs to be conducted in collaboration with social scientists and philosophers in order to raise awareness of the ethical and societal issues. This will also assist the development of mutually informative learning and fruitful research partnerships. Furthermore, an active and ongoing public engagement programme must be established which creates platforms for various stakeholders and publics to share their views on both the potential benefits of synthetic biology and their concerns as the technology develops.

This programme should be initiated and developed by the research community, in particular the Research Councils, using the existing public engagement infrastructure within the UK and its practitioner expertise. Involvement of policy makers, regulators and industrial players should be sought when appropriate. The need for the provision of training in public engagement theory and practice for scientists in the field is clear, in order that a baseline of understanding of the potential value of work in this area is achieved.



Chapter 1: An Introduction

1.1: What is synthetic biology?

Synthetic biology is seen as an emerging field which builds on the work in genetics and associated fields over the last few decades. Like most new fields at this stage of development, it is subject to a number of possible definitions. For the purposes of this report, the following definition has been adopted:

"Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems."

This is the simplest and perhaps the most widely accepted definition and, in addition, is consistent with the Academy's view of the importance of synthetic biology to the future of engineering, industry and the general economy.

Synthetic biology strives to make the engineering of biology easier and more predictable.

1.1.1: Biological systems

In the context of synthetic biology, it is perhaps important to make some points about biological systems. Living systems are composed of a number of key components (cells, genes, proteins) that allow biological organisms to grow and replicate. Understanding how the orchestration of these components leads to the complex nature of cellular and physiological behaviour exhibited by living systems has formed much of the basis of biological and biomedical research over the last 100 years.

The research has resulted in the realisation that living systems operate at different scale levels: for example, from populations to individual organisms; and from the physiological level to the individual cell. Over the last 60 years our understanding has extended to the molecular scale. Today the functions of individual cells are known in detail - from individual biochemical reactions to metabolic pathways, gene regulation to the control of cell division and cell-cell signalling. This level of detail also extends to visualisation, where the macromolecular components such as proteins, sugars, lipids and nucleic acids that perform all of the necessary biochemical functions for cellular life can be imaged at atomic resolution.

The central tenet that underpins much of current molecular biology lies in the relationship between DNA, RNA and proteins. The genetic code (the DNA) instructs cells to produce proteins by translating the DNA sequence into an intermediary messenger RNA (mRNA) – this process is known as transcription. The mRNA is then translated into a polypeptide chain comprising a defined sequence of the 20 naturally occurring amino acids (a process known as translation) to produce proteins that carry out most of the cellular functions and activities within organisms. The revolution in molecular biology which has occurred over the last sixty years has been underpinned by parallel technology developments. Examples of such developments are: more and more powerful computers (including the widespread use of personal computers); the rise of the internet; powerful search engines (eg Google); and broadband networks. This has resulted in a massive explosion in data - including the genome sequences of hundreds of different organisms including the human genome - where the full complement of protein components can now be identified and studied.

These developments in biology have been accompanied by rapid developments in technology. Examples of such developments are: more and more powerful computers (including the widespread use of personal computers); the rise of the internet; powerful search engines (eg Google); and broadband networks.

1.1.2: Systems approach

The traditional approach to biological research has been to isolate a small number of biological components in order to understand their structure and function. The realisation that biological systems are multi-scale and multi-level has led to a deepening realisation that biological systems can no longer be studied using a reductionist approach. This approach assumed that single biochemical events resulted in single effects, in a simple cause and effect relationship. In reality, most genes, proteins and other components carry out their functions within a complex network of interactions, with positive and negative feedback loops that regulate their operation. Consequently, a single component (such as a gene) rarely specifically controls any particular biological function or disease, and conversely any given component may influence many different functions. Such a simple cause and effect framework posses severe restrictions on the ability to understand, manipulate and design increasingly complex biological systems. This realisation has led to the emergence of systems biology (which was the subject of a previous report by The Royal Academy of Engineering and The Academy of Medical Sciences[1]) which tightly couples 'state-of-the-art' biological measurements with sophisticated mathematical and computational modelling. This facilitates the understanding of how networks of interactions between the components of a biological system give rise to its observed properties. The systems biology approach allows the study of multi-scale, multi-level (including multi-cellular) organisms. One example of this approach has been the creation of accurate models for the human heart, by combining physiology with computer modelling.

Over the last decade, advances in molecular biology technologies have allowed researchers to manipulate, or re-engineer, DNA coding regions in many different organisms from bacteria, to plants, to animals. This has led to a revolution in molecular and cell biology – driven, primarily, by the genome projects. Animal models of human disease can be created, eg mice cancer models; cell-based systems can be manipulated to address fundamental biological problems, eg mutant yeast and bacterial strains; and organisms can be altered in beneficial ways, eg transgenic mosquitoes for the control of malaria. However, all of these approaches are primarily based on hypothesis driven questions - where researchers aim to address specific questions with often single and specific experimental solutions. By contrast, synthetic biology aims to establish a rational framework for DNA manipulation, based on the application of engineering design principles.

1.2: Relevant aspects of biological systems

Before considering how and why synthetic biology has developed as a subject, we must first review some of the basic properties of biological systems in order to familiarise ourselves with the key concepts.

1.2.1: Living systems

Over the long time period of biological evolution, living systems have developed and evolved using key fundamental mechanisms that distinguish them from non-living systems. All life forms are composed of molecules (proteins, lipids, sugars, DNA, RNA) that are, in themselves, non-living.

1. Systems Biology: a vision for engineering and medicine, Feb 2007

This has led to the conceptually difficult question - how could life have arisen from a collection of non-living molecules?

The origin and definition of life poses a number of questions. The widely accepted biochemical definition of life is that localised molecular assemblages are considered to be alive if they are able to continually regenerate, replicate and evolve. Regeneration and replication requires the living system to have the ability to import, process and transform molecules from the environment into cellular aggregates; whereas evolution requires heritable variation in cellular processes. Living systems have all the machinery to achieve these requirements. They store the instructions for life in informational chemical polymers (such as DNA and RNA) and they have metabolic systems that chemically regulate and regenerate cellular components - all of which are contained within a physical container. The totality of this is a living cell, the simplest form of life. More complex forms of life, like plants and mammals, comprise many cells working together in a coordinated and regulated manner - but at a different scale to molecular or unicellular living systems. The need to define living systems at different physical scales arises from the ability to visualise and interpret living systems at scales from near atomic resolution (10^{-9} m); to the sub-cellular (10^{-6} m); to the multi-cellular (10^{-3} m); to the whole organism (10^{-1} m). Such advances have been primarily driven by technology developments in imaging, resulting from interdisciplinary research involving engineers, physical scientists and life scientists.

One of the current challenges in bioscience is the need to integrate biological information from different physical scales, whilst simultaneously considering living processes as interconnected systems and networks. Systems biology is the attempt to meet these requirements; it is now driving research and thinking in life sciences.

1.2.2: Self-organisation

One key underlying process that has enabled primitive life to form is the ability of non-living molecules to self-organise[2] . The main chemical principle that allows such self-organisation is the ability of molecules to form non-covalent bonds, ie a type of chemical bond that does not involve the sharing of electrons. Such bonds are much weaker than covalent bonds and can be readily made and broken. For example, with just a few chemical building blocks (G, C, A, T), strands of nucleic acids can pair up to form large DNA or RNA molecules - allowing the storage and retrieval of information that is mediated though the formation and breaking of weak hydrogen bonds. The ability to break and reform non-covalent bonds is a key feature of living systems.

1.2.3: Noise

However ordered the appearance of living systems may be, the biochemical events that underpin such systems are in part random. This leads to the difficult question: how do living systems function and process information when the underlying molecular events are random?

This is beautifully illustrated when gene expression is measured in single living cells - as opposed to populations of cells[3] . However reproducible and regular cell population measurements are, single cells often show fluctuations and significant differences in gene expression - suggesting that the molecular events that underpin cellular physiology are in fact stochastic. It is now well established that cells exhibit significant noise in many biochemical processes. This has led to the proposal that noise is an important part of living systems. An

2. Lehn JM, Science 295: 2400-2403 (2002)
3. Elowitz MB et al., Science 297: 1183-1186 (2002)

example of this can be seen in the generation of errors in DNA replication that lead to mutation, which ultimately drives evolution. This does not fully explain how complex, robust and highly orchestrated cell behaviour is determined by random molecular events. However, living systems are not random - in fact cellular events are highly ordered and precisely regulated, despite the stochastic nature of the molecular events that underpin them. Since living systems have evolved to be highly robust in their behaviour, any biochemical noise within the systems is therefore tolerated as part of the living process[4].

1.2.4: Feedback and cell signalling

The regulation and control of biological processes is a major aspect of living systems that allows organisms to be responsive to both their external environment and internal physiological state. The use of feedback in biological regulation has a long history dating back to the work of Eduard Pflüger in the 1870s.

The concept of biological feedback has led to various theories and models of physiological homeostasis, pattern formation, metabolic flux and transcriptional self-repression. Underlying these models is a simple feedback loop, where an output from a process can be fed back to the input either positively or negatively. Feedback loops are fundamental processes in electronics and computing. Many signalling processes in biology have now been identified as being analogous to processes in engineering[5].

In biology, the concept of feedback is usefully applied to intracellular signalling systems that propagate specific cellular behaviour. In mammals, it is estimated that there are 3000 signalling proteins and around 50 secondary messengers (usually small chemicals that, together, build hundreds of cell-specific signalling systems). Many signalling molecules have upstream regulators and specific downstream targets which form part of a complex web of interactions, biochemical networks and pathways. These allow living systems to be responsive to their internal and external state. Within this complex network of signalling pathways there exist multiple feedback loops that result in biological outcomes such as oscillations, polarisation, robustness and bi-stability. Biological systems display a large variety of feedback loops including positive and negative, dual negative and dual positive, mixtures of both, and multiple feedback functions[6] .

1.2.5: Biological complexity

As illustrated above, living systems are often highly complex. The interdependent network of biochemical pathways, transcriptional circuits and spatial temporal signalling poses considerable challenges for researchers aiming to elucidate design principles of living systems.

However, the development of technology, such as high-throughput (rapid) DNA sequencing, is providing rich data sets. Many of the analytical and modelling techniques which have been developed in systems biology can be applied to synthetic biology.

1.3: The emergence of synthetic biology

Having reviewed some of the key concepts of living systems, the question of how and why synthetic biology has emerged as a discipline and what differentiates it from other related subjects will now be addressed.

4. Rao CV et al., Nature 420: 231-237 (2002)
5. Brandman O & Meyer T, Science 322:390-395 (2008)
6. Voigt CA, Current Opinion in Biotechnology 17: 548–557 (2006)

1.3.1: Why now?

The answer to this question lies in the confluence of three fields; biology, physical sciences and engineering. Sixty years ago two major building blocks were put in place. These were the publication of Norbert Wiener's book, *Cybernetics*[7] and the publication of Claude Shannon's work on information theory[8] .

In *Cybernetics*, Wiener established the mathematical basis for studying physical and biological systems. Wiener's work, and that of others, has resulted in a major area of engineering science called systems theory. This, coupled to signal processing methodology (another very important area of engineering), has been widely applied in a range of fields, including biology in the form of systems biology. For example, systems theory is used in the design and construction of aircraft control systems; information and telecommunication networks; and economics.

1.3.2: Developments in Information and Communication Technology (ICT)

Shannon's work established the basis of the information and communication revolution which has taken place over the last sixty years. The reason for this is that digital computers can only work with what is known as sampled data. In general, sampled data is uncommon in the natural world. Data tends to be continuous, that is it exists at all points in time over the period for which it is being measured. Shannon developed his sampling theory which allows data to be converted from its continuous form to its sampled form without loss of information and vice versa. Shannon's sampling theory is the basis of modern information and communication systems.

This sampling theory naturally leads biological research to produce large amounts of data requiring ever more powerful computers to analyse. As such, the rapid increase in the power and availability of computers is another important building block in the development of the quantitative techniques which underlie synthetic biology. Indeed, as data mining becomes increasingly intensive, the computational power that will be required for more sophisticated applications is likely to exceed the capabilities of local computers. Furthermore, the demand for computational operations involving data sources that may be distributed across many sites, where they are maintained and updated on a regular basis, is increasing - along with interactions between researchers working in different and often distant locations. Hence, high speed telecommunications networks and access to high performance computing are very important in modern biological research - and are an essential element in the development of synthetic biology.

1.3.3: Developments in biology

There have also been major developments in biology over the last sixty years (some of which are directly associated with the work of Norbert Weiner, as described in the previous section). A good starting point for a discussion of the developments in biology is the publication in April 1953 of Jim Watson and Francis Crick's paper on the structure of the double helix[9] . At the 50th Anniversary Celebration of the publication of their paper in April 2003, Lord May, the then President of the Royal Society, described Watson and Crick's discovery as "probably the most important scientific discovery of the twentieth century". There are very good reasons for this statement as, without question, their paper triggered the molecular biology revolution. There are many milestones in terms of this revolution, but a few can be singled out. The first is

7. Weiner N: Cybernetics or control and communication in the animal and machine. MIT Press, Cambridge, MA. (1948)
8. Shannon C, Bell System Technical Journal, Vol. 27, pp. 379–423, 623–656 (1948)
9. Watson JD & Crick FHC. Nature 171: 737–738 (1953)

proof of the existence of mRNA by Sidney Brenner and colleagues in 1960. This was followed in 1961 by a paper by Sidney Brenner and Francis Crick in which they described how DNA instructs cells to make specific proteins. In 1973 techniques were developed which allowed the transfer of genes to bacterial cells in order to reproduce and generate multiple copies. In 1977 Fred Sanger and Walter Gilbert independently developed a technique for reading the DNA chemical bases, ie DNA sequencing. This discovery resulted in the large international project (which occurred during the 1990s) to carry out the initial sequencing of the human genome. The initial publication of the sequencing of the human genome was published simultaneously in *Nature and Science* in 2001[10] .

In a lecture approximately two years after the publication in *Nature*, Francis Collins, the Director responsible for the Human Genome Project within the National Institutes of Health (NIH), stated that "the initial sequencing of the human genome would not have been possible without the extensive use of ICT and computers". This statement encapsulates how the development of the fields engineering, physical science, ICT and computing on the one hand, and biology on the other, has resulted in a situation today where the confluence of these fields has produced the new discipline of synthetic biology.

1.3.4: The relationship between systems biology and synthetic biology

Systems biology aims to study natural biological systems as a whole, often with a biomedical focus, and uses simulation and modelling tools in comparisons with experimental information. Synthetic biology aims to build novel and artificial biological parts, devices and systems. Many of the same methods are used and as such there is a close relationship between synthetic biology and systems biology. But in synthetic biology, the methods are used as the basis for engineering applications. The basis of quantitative systems biology lies in the application of engineering systems and signal theory to the analysis of biological systems. This allows the *definition* of systems in terms of mathematical equations. Once a system, or part of a system, has been described in this way, then synthetic biology allows the reduction of the system to biological parts (bioparts) whose function is expressed in terms of input/output characteristics. These characteristics are then presented on a standard specification sheet, so that a system designer can understand the functional characteristics of the part. The parts are then entered into an inventory. The parts defined in an inventory (or registry) can then be combined into devices and, finally, into systems. Tolerances are built into the design of any engineering part, device or system to compensate for imperfections in the manufacturing. Bioparts tend to have wider tolerances than standard engineering parts, so biologically-based devices are designed to accommodate such features. Hence, synthetic biology incorporates the classic reductionist method whereby complex systems or processes are built from defined parts and devices. This means that if a biologically based system is being developed, it is developed on the basis of standard parts and devices which form part of a reference repository or registry.

1.3.5: The Engineering design cycle and rational design in synthetic biology

A key aspect of synthetic biology, which differentiates it from genetic engineering and current biotechnology approaches, is the application to biology of techniques which are normally used in engineering design and development. The essence of this approach is to define the specification of the

10. International Human Genome Sequencing Consortium, Nature 409: 860–921 (2001) and Venter JC, Adams MD et al., Science 291 (5507): 1304-1351 (2001)

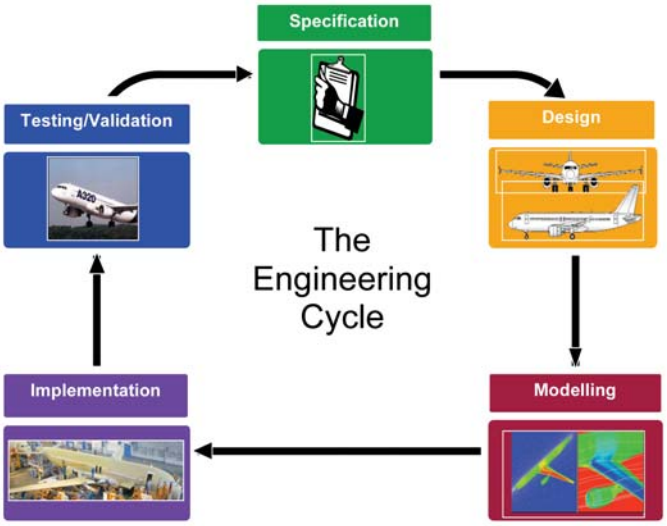


Figure 2: The engineering cycle[11]

part, device or system that is required and to develop a design which meets these specifications. Hence, in engineering, systems are normally built from standard devices, which in turn are built from standard parts. The standard parts and devices are all fully characterised and may be used in the design of multiple systems. (This is very different from, say, genetic engineering where specific genes are modified to overcome, for example, a medical problem such as cystic fibrosis.) This overall approach is part of what is known as the engineering cycle; this is illustrated in figure 2 above.

Referring to figure 2, it can be seen that the specification step is followed by a detailed design step. One of the key differences between design today and that of the past is the ability to undertake detailed computer modelling. This is also true in synthetic biology. Comparisons are often made between the difficulty of designing biological systems and the design of electronic devices, such as transistors, sixty years ago. The difference today is the wide availability of large amounts of computer power, which makes it possible to carry out detailed computer modelling. This means that the expected behaviour of the part, device or system under development can be simulated in detail. The next stage in the cycle is implementation. In synthetic biology this normally means modifying synthetic DNA and inserting it into an E. coli cell or some other chassis. The next stage on the engineering cycle, testing and validation, is particularly important in synthetic biology because it is the response to the insertion of modified bacterial DNA which determines whether or not the specification and the design have been properly realised.

Another key aspect of the engineering cycle approach is that the development of a part, device or system can involve a number of iterations of the cycle with each iteration refining the design and its implementation. Engineering systems such as the A320 Airbus shown in figure 2 are based on standard devices which are built from standard parts. In synthetic biology the field of electronics is sometimes used as a conceptual model. Taking the example of a simple audio amplifier, this would be designed using standard resistors, capacitors and transistors. The designer would have a set of specifications for the amplifier and look up manufacturers' handbooks (today, probably on the web) to find component parts which meet the exact specifications which are required for the design. What is important here is to understand that a great deal of time

11. Kitney RI, Freemont PS & Rouilly V, Synthetic Biology, IET vol 1, issue 1.2: 68-70 (2007)

and effort will have been devoted by component manufacturers to produce parts which exactly matched their specifications. In fact, it is common in engineering for a number of manufacturers to make and sell parts which exactly match the same specifications. It is important to note that the designer

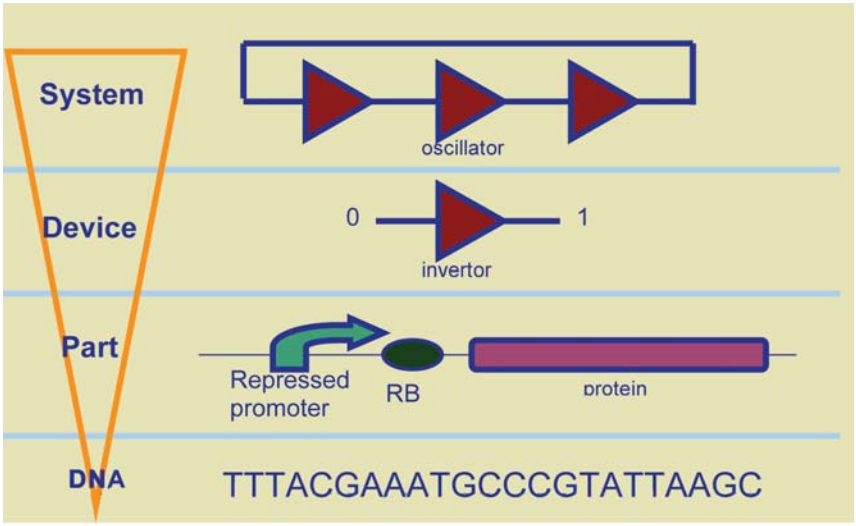


Figure 3: Building a system from standard parts

of the audio amplifier would not question for a moment that a commercially available part exactly matches its specification. Once built, tested and validated, the audio amplifier becomes a standard device built from standard parts – with its own specification sheet - the same approach applies to standard parts and devices in synthetic biology.

Taking this whole approach one step further, now suppose that the objective is to build a simple radio. Radios basically comprise three standard devices, a radio frequency, or RF stage; an intermediate frequency, or IF stage; and an audio stage (the audio amplifier). Hence, the aim would be to build the radio from three standard devices: the RF stage, the IF stage and the audio amplifier. It may well be the case that each stage is manufactured and supplied by a different manufacturer; but, because they are all standard, it is possible to connect the three stages together to form the radio. This is a very powerful approach and is routinely applied to the building of most engineering systems - because it does not require everything to be designed and built from scratch. The challenge in synthetic biology is to apply these approaches in engineering biological systems. See figure 3.

1.3.6: Bioparts

The overall approach described above is also the basis of how biological parts, devices and systems are created in synthetic biology; hence the use of the terms bioparts. A biopart is a modular biological part which is designed so that it can be easily combined with other parts. Ultimately, the aim is to produce a range of standard devices (built from standard parts) which can be used in standard systems. An example is the development of a standard biologically based NAND gate. Such devices have already been produced, but are currently not very stable or reliable. In electronics such devices are the basis of counters, calculators and computers.

The biopart standard provides a framework where parts can be re-used in various applications to achieve the specific function intended for the device. The behaviour of any biopart component is described on a data sheet

comprising a set of parameters and performance characteristics. A specific combination of parts, in the form of a device, is then modelled prior to physical assembly of parts, to ensure correct functionality.

This approach of using standardised bioparts has been led by the BioBricks Foundation[12], a not-for-profit organization founded by engineers and scientists from MIT, Harvard, and UCSF. Information about the bioparts or BioBricks™ is stored on a Registry of Standard Biological Parts[13] run by MIT which is available to the public free of charge.

1.3.7 Potential areas of application

This section provides a brief overview of some potential areas of application (this is covered much more comprehensively in Chapter 3). Synthetic biology could revolutionise a number of fields of engineering. The field of materials is one example of a potentially important area of the application. Here, synthetic biology involves the harnessing of biological processes (on an industrial scale) to produce new materials. In many areas of industry, for example the aeronautical industry, there is a need to use materials that are very strong but, simultaneously, extremely light. In aircraft design, if it were possible to significantly reduce the weight of the aircraft there would be immediate and major improvements in fuel consumption. The understanding and manipulation of the biological processes that control the production of such materials could result in the synthesis of a whole range of new materials. This would significantly change and invigorate several industrial sectors such as civil engineering, aeronautical engineering and the automotive industry. Biologically based biosensors and control systems are another important area. Biological AND and NAND gates have now been produced, these will form the basis of such devices and systems. Biologically synthesised devices may be operationally many thousands of times slower than their electronic equivalents, but this may be an advantage if such devices are to be used to monitor biological processes where the time constants of the devices match the environment in which they are operating.

1.3.8: Parallels with the historical development of synthetic chemistry

In the 19th century, chemists learned how to synthesise compounds that had hitherto only existed in nature. For example, in 1856 William Henry Perkin was able to produce synthetic quinine from benzene derived from coal tar. This led to Perkin's patent in 1856 entitled Dyeing Fabrics. A dye works was established in 1858 in North West London to produce a synthetic dye and one year later English fashion observers named the new purple dye mauve. Another example of the rise of synthetic chemistry was the synthesis of Aspirin by Felix Hoffman at the Bayer Company in Germany in 1897. The subject was extended in the 20th Century to the development of plastics and other materials, which now find extensive use in most industrial sectors. One can consider aspects of synthetic biology as following this historical development path in that synthetic biology industries of the future will be able to harness the natural diversity and mechanisms of biology and biological systems to produce the biomaterials, chemicals and products of tomorrow.

1.3.9 'Bottom-up' approaches in synthetic biology

Another school of research in synthetic biology is the 'bottom-up' approach . In this approach, researchers using chemical approaches aim to build synthetic cells and biological systems from scratch using chemical components that are not necessarily natural but mimic the properties of natural molecules and

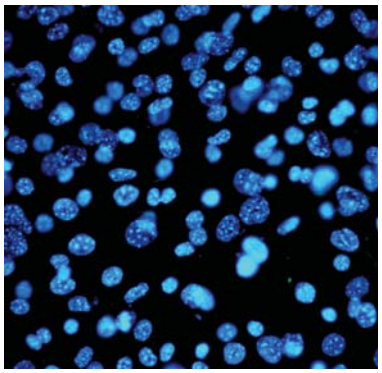
12. http://bbf.openwetware.org/
13. http://partsregistry.org/Main_Page

macromolecules. While these studies are challenging, they are at an early stage of development in that such synthetic cells will be relatively simple compared with the complexity of natural living systems. The development of self-replicating protocells[14] will undoubtedly address fundamental issues on the origin of life and will lead to alternative design strategies for synthetic biology applications, overlapping closely with the construction of minimal cells (Section 2.2.3).

The development of self-replicating protocells[15] will undoubtedly address fundamental issues on the origin of life and will lead to alternative design strategies for synthetic biology applications, overlapping closely with the construction of minimal cells (Section 2.2.3).

14. Szostak JW et al., Nature 409: 387-390 (2001); Rasmussen S et al., Science 303: 963-965 (2004); Luisi PL et al., Naturwissenschaften 93: 1-13 2006

15. Hanczyc MM & Szostak JW, Current Opinions in Chemical Biology 8: 660-664 (2004)



Chapter 2: Fundamental techniques in synthetic biology

2.1: Technological enablers

In the previous chapter the basic concepts of living systems and the developments in traditional fields of research which have led to the emergence of synthetic biology were reviewed. This chapter will discuss the fundamental techniques and technologies that underpin synthetic biology and which are the focus of current research in the field.

Despite the emergent nature of synthetic biology, there is already considerable research activity within both the academic and commercial arenas. It may be asserted that there are three key technological enablers that have facilitated the emergence and rapid development of synthetic biology - these are: computational modelling, DNA sequencing, and DNA synthesis.

2.1.1: Computational modelling

Synthetic biology approaches the design of engineered biological systems through the engineering cycle (see Chapter 1). Modelling of the design, to predict system performance prior to fabrication, is an important component of synthetic biology. Synthetic biology is therefore similar to systems biology, in that both rely heavily on computer modelling of biological processes. In systems biology, modelling of whole biological systems is undertaken in order to obtain a better understanding of the complexity of biology for the purposes of analysis. Synthetic biology can therefore be considered at one level to be the application of certain systems biology techniques to the construction of new biological parts, devices and systems. Synthetic biology will consequently benefit from the significant investment made in systems biology in the UK, eg BBSRC Systems Biology Centres. Current and future advances in the modelling of the interactions of molecules and systems will serve to drive progress in the complexity of designs implemented in synthetic biology – for example, how DNA encodes the information needed to sustain and reproduce the cell. Recently, multi-scale models of gene regulatory networks have been developed that model the complete set of bio-molecular interactions in gene regulatory networks, ie transcription, translation, regulation, and induction. This work helps to guide the design of synthetic systems. Commercially available software currently caters for the needs of the systems biologist, but there is a need for an integrated design environment (IDE) for the synthetic biologist, similar to computer aided design (CAD) systems developed for other branches of engineering.

The quantitative measurement of biological parameters is an essential part of the accurate specification, design, modelling and validation of synthetic biological devices and systems. For example, discrepancies between the behaviour predicted by a model and actual measurements may identify shortcomings in current biological control hypotheses and shed light on the malfunction of synthetic systems.

To close the circle, synthetic biological systems may prove especially useful in substantiating hypotheses regarding natural biological systems; if a functional system can be built in another organism then the hypothesis on which the design is based is likely to be sound. In the future, technologies which allow many parallel, even single cell, and time-dependent measurements, will be especially powerful for synthetic biology.

2.1.2: DNA sequencing

The 'reading' or sequencing of DNA is the second key enabling technology for synthetic biology. DNA comprises four bases. These always pair in groups of two - T with A and G with C. In many ways the bases can be thought of as two sets of different magnets where the north pole of magnet type A is only attracted to the south pole of the same magnet type. A single pairing of, say, T with A is called a base pair (bp). Hence, the genome of a particular organism is said to comprise so many base pairs. The entire content of DNA for a particular organism is called its genome – this contains complete instructions for constructing any type of protein, cell, tissue, organ, etc. For example, in humans every cell contains the complete human genome (with the exception of gametes). The sequencing of entire genomes of numerous organisms has provided a wealth of information regarding the chassis within which synthetic biologists seek to construct functional devices. (Chassis are the environments into which synthetic DNA is placed – see section 3.2.3 below.) Additionally, sequencing is used to verify that engineered sections of DNA or possibly even whole organisms have been fabricated correctly[16]. Rapid, inexpensive sequencing can also facilitate the detection and identification of novel systems and organisms. This approach is exemplified by the trawling of the oceans for valuable marine organisms yet to be discovered.

Commercial activity and available technologies in this area are well established as a result of the significant investments made within the context of the race to sequence specific key genomes, ie The Human Genome Project.

2.1.3: DNA synthesis

Once a genome has been sequenced, the next step may be to 're-write', or synthesise, all or part of the genome. There are a number of cases where the genome of an organism has been entirely synthesised. In 2002, Cello and co-workers at State University of New York, Stony Brook, synthesised the poliovirus genome (7,741 bp) from its published sequence, producing the first synthetic organism[17] . This feat was achieved only after some two years of painstaking work. In 2003, the genome of the bacteriophage ΦX-174 (5,386 bp) was assembled in just two weeks by a team at the J. Craig Venter Institute[17] . In 2008, Hamilton Smith and co-workers again pushed forward the boundaries of synthesis with their reconstruction of an entire 489,000 bp synthetic genome of the bacterium, *Mycoplasma genitalium*[19] .

The customised synthesis of DNA is a key enabling technology for synthetic biology. There is significant commercial activity surrounding the supply of DNA constructs in the 100 – 1,000 bp range. A device in synthetic biology may be, for example, constructed by combining bioparts which already exist in a registry of parts and new bioparts which have been designed for the particular device. Alternatively, the combined bioparts may be synthesised directly as a single sequence of DNA rather than constructed from bioparts. A small number of companies worldwide currently offer such a service; none of these are in the UK. Synthesis capacity has shown a steady increase in the last decade. There has been a concurrent fall in cost to less than $0.55 per base pair, depending on sequence length and composition. At present, a technological barrier to progress in synthetic biology exists in terms of the cost and speed of fabrication of synthetic genetic sequences. To enable the cycle of specification, design, modelling and validation, discussed above, to be commercially viable, with a reasonable time frame and cost, there is an urgent need for new

16. Gibson DG, Benders GA et al., Science 319 (5867): 1215-1220 (2008)
17. Cello J, Paul AV & Wimmer E,Science 297 (5583): 1016 (2002)
18. Smith H O, Hutchison CA, Pfannkoch C & Venter JC, Proceedings of the National Academy of Sciences 100 (26):15440-15445 (2003)
19. Gibson DG, Benders GA, Andrews-Pfannkoch C, Denisova EA, Baden-Tillson H, Zaveri J, Stockwell TB, Brownley A, Thomas DW, Algire MA, Merryman C, Young L, Noskov VN, Glass JI, Venter JC, Hutchison CA 3rd, Smith HO, Science 319 (5867):1215–20 (2008)

technologies that are capable of routine, very rapid, ultrahigh-fidelity, DNA synthesis. The need for the routine large scale synthesis of DNA will become an increasing obstacle as the ability to design ever larger genetic devices and systems becomes a reality. Technically, the current methodology uses phosphoramidite-based oligonucleotide synthesis of small oligonucleotide fragments and self-(sub)-assembly of dsDNA (double strand). The final assembly of synthetic DNA constructs are generated using standard molecular biology techniques involving plasmid vectors and bacteria. This latter step is currently rate-limiting and attempts to automate this process are currently being sought. This technology is likely to fail as the size of the DNA sequences increases. A somewhat similar situation has occurred in the microchip industry but the technology has, over many years, kept pace with demand. There is no reason to believe that this will not also be the case in DNA synthesis.

A related technological challenge lies in the ability to successfully transfer large DNA segments, even whole genomes, into populations of cells. In prokaryotic (eg bacterial) cells, circular plasmids (ie circular genomes) of tens of kilo base pairs may be routinely transfected (ie transferred) into cells. Whole chromosomes present a much greater challenge. This problem is particularly difficult in eukaryotic cells (eg mammalian cells) where DNA is linear and specifically modified (methylation) and, in general, genomes are larger. For synthetic genome transfer, these massive DNA molecules may have to be packaged using molecules such as histones (the chief protein components of chromatin) that act as spools around which the DNA winds. Using this method, the DNA can be placed in the cell's nucleus without damage. The other major challenge in genome transplantation is to understand the role of DNA methylation and histone modifications. These modifications directly affect gene activity and such modifications may play key roles in activating transplanted (genomes).

2.1.4: Yields

In practice, it has been found that it is unrealistic to expect standard yields of synthesised DNA to be greater than 99.5% error free, unless some costly precautions are taken (which increase the product price substantially). The theoretical final length product yield based on the 99.5% coupling yield can be calculated using the equation: yield (%) = (0.995^{length})x100. From this formula it can be shown that the yield falls from >90% for a 20 bp; 60% for a 100 bp; and 35% for a 200 bp. Yield for a 1000 bp is only marginally above 5%. Yield is dictated by a number of side (or secondary) reactions taking place during the synthesis.

In practice, the yield is often lower than that theoretically calculated. This is due to problems with the multi-stage synthesis process. Again, conceptually, these problems are similar to those in the microchip industry and require development work on new techniques – which is ongoing.

2.1.5: Future trends in modern synthesis

In the 1980-90s, the area of DNA synthesis was driven by the promise of new and efficient therapies. This approach was based on producing a range of modifications to the nucleic acid bases. The main objective was to develop modifications that would make the modified DNA more stable to *in vivo* conditions. In the near future it is likely that the trends in DNA synthesis will involve very small volumes and synthesis steps carried out in parallel such that large pieces of DNA (>10^6 bp) could be routinely synthesised and assembled *in vitro*. The ability to produce large pieces of synthetic DNA in a reliable, cheap

and quality assured way will not only impact on synthetic biology research but will also affect all experimental molecular biology where the need for cloning and DNA plasmid assembly will be made redundant.

2.1.6: Large scale DNA (oligonucleotide) synthesis

There are currently six different methods for depositing spots of long chain DNA sequences onto an impermeable solid support. These include separate synthesis and further immobilisation; synthesis using photolithographic masks either with or without standard DNA synthesisers; synthesis using a multi-channel synthesiser; electrochemical control of spatial synthesis; and inkjet synthesis. Photolithographic methods can produce 40 bp. Ink-jet printing, on the other hand, is capable of producing a very high quality sequences (oligos) of impressive length (60-70 bp probes are commercially available), and much longer oligos (120 bp and longer) have been synthesised.

2.1.7: Potential for innovation and microfluidics

On a micron-scale, common liquids like water have very different behaviour to our understanding of them in everyday experience. This length-scaling effect is illustrated by the Reynolds number (R_e) of the system, which represents the ratio between inertial and viscous forces that act when fluid moves past an object. At high R_e (>1000, eg when mixing milk in a cup of tea) inertia dominates, whilst at low R_e (<0.01, associated with many microfluidic systems with applications in synthetic biology) viscous forces dominate. Under these latter conditions, fluid movement shows no inertia (and hence comes to an abrupt stop when driving forces are removed). This raises the possibility of accurately controlling the dispensation and movement of fluid at the micro scale – thus controlling fluid dispensation precisely, spatially and hence temporally, confining reagents to the parts of a chip being used for synthesis or assembly.

The requirements imposed by synthetic biology on the synthesis of DNA sequences is the ability to quickly produce large quantities of long double-stranded DNA fragments, typically at the nano- or picomol level, preferably at a reasonable cost. The recent progress in combinatorial chemistry, automation, robotics and microfluidics allows for highly parallel microscale synthesis of a very large number of oligonucleotides.

The processing of sections of DNA (oligonucleotides) may from now on be more effectively carried out using microfluidic systems. For particularly sensitive experiments, a Polymerase Chain Reaction (PCR) based purification step for long sections of DNA (long base pair oligonucleotides) can also be incorporated into this format. On chip PCR has been demonstrated in the 1990s by deMello[20] . The method will probably be used for oligonucleotides longer than 60 bp, as the 50 bp seem to work without any purification.

2.1.8: Lab-on-a-chip

A lab-on-a-chip (LOC) is a device that integrates one or several laboratory functions onto a single chip. The synthesis integration of the process for long sequences and their assembly may be achieved by bringing disparate microfluidic processes together on the same chip. The challenges of removing by-products that may inhibit synthesis and of the precise assembly of larger sequences may in the fairly near future be realised by micro-droplet technologies. In this method, partitioned nanolabs, comprising droplets containing sequences, are combined through controlled fusion.

20. Kopp MU, deMello AJ & Manz A, Science 280: 1046 – 1048 (1998)

The current price for sequencing a human genome is around $1m (per 3 billion base pairs). This translates into $1 per 3,000 base pairs. With the prices of sequencing falling steadily over the recent years (and $1,000/genome looking more achievable than ever), it may soon become possible to achieve large scale synthetic sequences that have been cost-effectively proof-read prior to their incorporation into host organisms (chassis). It is important to note that many modern innovative techniques, currently under development, are aimed at developing sequencing systems which are capable of operating in a chip based format - which is compatible with other technology (such as concentration annealing ligation systems).

Analysis of the current trends in oligonucleotide chemistry suggests that in the near future development of methods for direct cost-effective chemical synthesis of hundred to thousand base pair oligonucleotides, required for synthetic biology experiments, looks unlikely. It seems that the way forward may be in relying upon reasonably short (50-70 bp) oligonucleotides. These can be synthesised (often without a need for purification), processed, annealed, ligated and, possibly, also proof-read in a highly parallel format. This should be possible with relatively small scale, low cost equipment which is already available (such as ink-jet printers from Agilent), in combination with yet to be developed microfluidic devices.

2.2: Additional tools in synthetic biology

In addition to the three core technologies of modelling, DNA sequencing and DNA synthesis, there are a number of other technologies, techniques and approaches which are important to the development of synthetic biology. The following section provides a review of these and related issues.

2.2.1: Chassis

A significant challenge to engineering in biology is the inherent complexity of the cells in which the modified DNA, ie the biopart, is embedded in order to produce the desired device or system. It is important that the synthetic device or system is either decoupled from the metabolic processes inherent to the viability of the cell or does not adversely affect these processes. One approach to this problem is to simplify the chassis by reducing the genome and hence the complexity of the chassis. Researchers adopting this approach draw inspiration from refactoring, a process used to streamline computer software without affecting functionality. Prof. Drew Endy (Stanford University) and his group have done some preliminary work on refactoring the bacteriophage T7[21]. Oligonucleotides harvested from a photolithographic or inkjet manufactured DNA chip combined with DNA mismatch error-correction allows inexpensive large-scale changes of codons in genetic systems to improve gene expression or incorporate novel amino-acids.

The synthetic DNA is optimised for the functionality within the chassis – which is the host for the reaction to take place, whether it is a simple biological switch, an oscillator or a biosensor. The chassis is often referred to as the 'hardware' in synthetic biology and the synthetic DNA as the software. By far the most common chassis in use today is *E. coli*. However, there are a number of other natural chassis in use. The most common are listed below, with a brief explanation of each type and an example of their use. In order to successfully use a particular chassis, it is essential to understand in as much detail as possible how it will behave to the presence of synthetic DNA circuits. A key point to understand is that, by definition, chassis are living organisms whose response to the injection of synthetic DNA may be difficult to determine. In

21. Chan LY, Kosuri S & Endy D, Molecular Systems Biology 1:2005.0018

addition, for a given set of tasks one type of chassis may perform better than another. One recent example of this is described in the paper published in Science by the J. Craig Venter Institute[22] . This involved the synthesis and reconstruction of a simple bacterium *M. genitalium* which comprises 589,000 bp. The bacterium was sequenced and then reconstructed. The DNA sequence was divided into cassettes of 24,000 bp and the cassettes were sent to gene synthesis companies (principally Blue Heron and GeneArt) for synthesis. What is important to understand is that the data sent to theses, gene foundries was purely alphanumeric. The cassettes were then synthesised and the DNA returned to the Venter Institute. The cassettes were then reassembled in one eighth and one quarter whole genome sections using *E. coli.* However, it was found that the half and whole genome could not be reconstructed in *E. coli.* The Venter Institute scientists discovered that the final reconstruction could be carried out successfully in yeast.

2.2.2: Examples of natural chassis

Listed below are a few of the most common chassis currently in use. As synthetic biology develops the number and type of chassis will inevitably increase as a wider range of applications are catered for.

- ***Escherichia coli:*** a bacterium which is normally found in the lower intestine of warm blooded animals. Because *E. coli* can be grown easily and has relatively simple genetics which can be easily manipulated, non-infective lab-strains can be constructed and it is one of the most common model organisms used in molecular biology. At this time, it is also the most common chassis used in synthetic biology.
- ***Bacillus subtilis****:* a non-pathogenic bacterium which is frequently found in soil. Like *E. coli, B. subtilis* is easily manipulated in relation to genetic changes. It is therefore quite widely used in a range of laboratory studies. It is sometimes used in the place of *E. coli* because certain of its properties are more amenable to some specific forms of genetic manipulation related to synthetic biology (DNA circuits can be easily integrated into the *B. subtilis* genome).
- ***Mycoplasma:*** a bacterium which does not have a cell wall. In terms of synthetic biology, the most well known form is *M. genitalium.* This is because (as described above) it was the bacterium which was synthesised by the Venter Institute. Because *Mycoplasma* tends to be unstable, it is not normally used as a chassis in synthetic biology.
- **Yeast:** there are large numbers of species of yeast. The species which are mainly used as a chassis in synthetic biology are *Saccharomyces cerevisiae.* Yeast is widely used in molecular biology, particularly in relation to research on the eukaryotic cell, which links directly into human biology. Yeasts are used as a chassis in synthetic biology and appear to be (under specific circumstances) able to accommodate larger sequences of modified DNA than *E. coli.*
- ***Pseudomonas putida:*** whilst it is sometimes used as a chassis in synthetic biology, its use is nowhere near as common as *E. coli, B. subtilis* and yeast

2.2.3: Minimal cells

As described above, one of the key problems with using natural chassis is achieving adequate control in biological synthesis. An alternative approach to the use of natural chassis is to create minimal cells. The basic concept behind this idea is to produce a cell which has the minimum number of components required to support biological synthesis from synthetic DNA circuits or

22. Gibson DG , Benders GA et al., Complete Synthesis, Assembly, and Cloning of a Mycoplasma genitalium Genome. Science Express (24 Jan 2008)

genomes, whilst being as simple as possible in order to achieve adequate control of its function[23] .

Figure 4 shows a minimal cell containing biological macromolecules and pathways proposed to be necessary and sufficient for replication from small molecule nutrients. Referring to the diagram, it can be seen that compared to a natural cell the internal structures are greatly simplified.

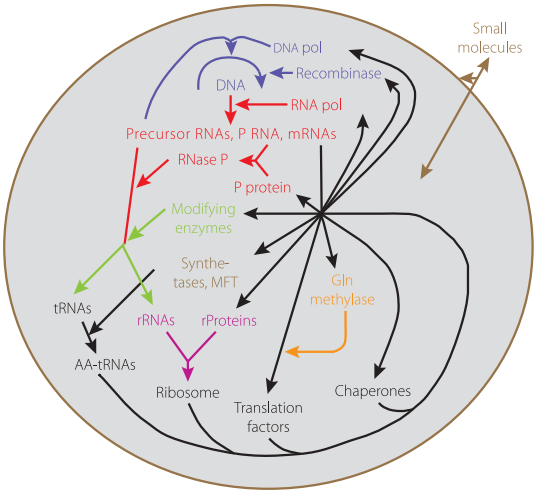


Figure 4: A minimal cell[24]

2.2.4: Cell free

For certain applications of synthetic biology there is now a developing trend towards using a cell free approach. The basic point of using a bacterial chassis is two fold. The first reason is to provide hardware which is capable of reacting to and supporting the process defined by the synthetic DNA. The second reason is that they provide a natural energy source. As previously stated, the big problem with using bacterial chassis is the inability to control the process, ie whilst a particular process is defined by the synthetic DNA circuit the end result may be different to that predicated and there may be unexpected side effects. As already explained, one approach to overcoming this problem is to develop minimal cells. The cell free approach uses a different strategy, where only biochemical extracts containing the components necessary to operate the synthetic DNA circuit are employed. This offers improved control of synthetic biology devices as non-specific effects due to the presence of the living system have been removed. The difficulties involved in this approach are that the cell free environment may prove to be unsupportive of the biochemical process which is required and may, in fact, be toxic to the process. Secondly, there is the difficulty of providing a suitable energy source. Nevertheless, if a cell free approach can be used for specific applications, it has a number of major advantages relating to the ability to undertake process control and scaling up of the processes. This is a classic problem in biotechnology research. An example which encapsulated this concept (but is not directly applicable) is the discovery of penicillin. Whilst penicillin was effective in the laboratory, it took a great deal of time and effort to get to the point where it became possible to manufacture it in a viable industrial process.

23. Forster AC & Church GM, Molecular Systems Biology 2:1-10 (2006) and Luisi PL, Ferri F & Stano P, Naturwissenschaften 93: 1-13 (2005)
24. Forster AC & Church GM, Molecular systems biology 2: 45 (2006)

2.2.5 Orthogonal circuits and new genetic codes

The engineering framework of synthetic biology will allow the specification and design of new complex biological circuits which would be implemented in living chassis. However such circuits will need to work against a background of the normal biochemical networks of the chassis. Given the interdependence of biological networks and possibility of non-specific interactions between the new circuit and existing (natural) circuits, the issues of robustness, performance and reliability become highly relevant. However these can be addressed by constructing minimal chassis to limit complexity and non-specific interactions as well as newly designed circuits that operate orthogonal to the normal biological systems.

Over the last 10 years, a number of laboratories have been investigating the possibility of extending and re-defining the genetic code. In biological systems the genetic code is firstly decoded by RNA polymerases (reading DNA to make mRNA) and then ribosomes (reading mRNA to make proteins). The latter stage involves the highly regulated and specific recognition of triplet DNA sequences or codons (3 bp) by the ribosome that encode for single amino acids that are linked together to form proteins. Recently, the intricate molecular details have been elucidated by protein crystallography where 3D atomic resolution structures describe the chemistry and specificity of DNA transcription and mRNA translation[25]. This has allowed researchers to create modified polymerases that can insert non-natural base pairs into mRNA and modified tRNA /aminoacyl t-RNA synthetase base pairs that can recognise either non-natural codons or a new genetic code defined by four base pair sequences rather than three[26] . These studies lead to the possibility of designing orthogonal DNA circuits that would be independent and distinct from natural circuits and could only be decoded by the modified polymerases, tRNA/aminoacyl t-RNA synthetase pairs and evolved ribosomes[27] . A new genetic code of 4 bp sequences would allow synthetic biologists to design circuits that would be insulated from the natural systems much like electronic components in circuit board.

2.3 Standards

Central to the understanding of international standards is the concept of the biological continuum, ie the hierarchy of the human organism comprising:

Systems » Viscera » Tissue » Cells » Proteins » Genes

The challenge facing researchers is to gather data at each of these levels in such a way that the information can be stored and understood by anyone working in the field. Given that this covers objects comprising orders of magnitude from a metre down to a nanometre and involves researchers from a variety of disciplines such as medicine and bioengineering, the challenge is considerable. Standards fulfil this role by laying down strict formats, procedures and protocols for handling, storing, displaying and transferring the data and metadata. However, no single standard is able to cover the whole of the continuum. Associated with the various standards are mark-up languages, eg XML, PDBXL, which manipulate the data for display purposes and ontologies (shared vocabularies) that allow concepts and semantics to be shared across elements of the biological continuum and enable the entire scientific community to integrate the data efficiently.

25. Bushnell DA et al., Science 303: 983-988 (2004); Nissen P et al., Science 289: 920-930 (2000)
26. Anderson JC et al., Proc. Natl. Acad. Sci. USA 101: 7566-7571 (2004)
27. Neumann H et al., Nature Chemical Biology 4: 232-234 ((2008); Ghadessy FJ et al., Nature Biotechnology 22: 755-759 (2004)

The starting point for each standard is the hardware, or modality, used to collect the data. This can range from MRI scanners at the system and viscera scale, down to X-ray crystallography and microarrays at the protein and gene level. The data therefore ranges from images at the larger scale down to alpha-numeric code at the small scale. For display and comparison purposes, the mark-up language is then able to convert the data into a 3D representation of the object in question. Ultimately, all the images and data are stored in a digital repository (normally associated with a particular standard) that can be accessed by researchers in the field and understood via the related ontology.

Over time, various standards have been developed that deal with certain parts of the biological continuum. The most widespread and well-established of these is the DICOM standard (Digital Imaging and Communications in Medicine) that covers scanners operating at the systems and viscera level. Such scanners, almost without exception, conform to the DICOM standard and by doing so, medical images produced by different imaging modalities and manufacturers can be integrated into a common health care environment.

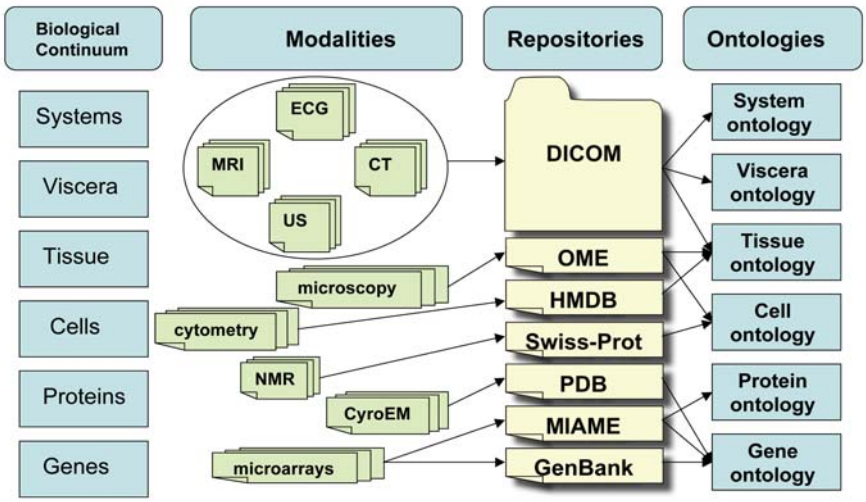


Figure 5: Schema for Standards and Interoperability

Beyond this, a number of alternative standards are being developed as indicated in figure 5. This is especially true at the molecular and genetic levels which have seen rapid advances since the completion of the Human Genome Project.

The development of synthetic biology will rely heavily on standards. In practical terms it is unlikely that in the foreseeable future any form of universal standard will be developed across the entire biological continuum. Consequently, it is necessary to develop a schema for the incorporation of existing standards and their development within an overall framework based on the concept of the biological continuum. The key to this is to link the various modalities and standards at the various levels of the continuum via ontologies. This will provide a holistic approach to research on the whole biological continuum. Standards are an essential aspect of all engineering systems; ensuring compatibility and safety in a global manufacturing base. As synthetic biology develops, an effective global standard will be crucial and familiarity with it essential for all involved in the industry. What is needed is an international standard for bioparts similar in concept to DICOM. Currently, a number of different standards are being developed in tandem with the various biopart repositories which will ultimately result in a single recognised international

standard. The US-based not-for-profit BioBrick Foundation have established a number of working groups to develop technical standards for synthetic biology, eg BioBrick construction and assembly and standard tests for measuring the regulation of BioBrick functions (standard promoter test-kit). The BioBrick Foundation is also promoting the free and open source sharing of BioBricks within synthetic biology[28], an area which has major implication commercialisation and future intellectual property. Direct involvement in developing such a standard by the BSI would greatly enhance the UK's profile in synthetic biology and enable emerging UK synthetic biology companies to compete on the global stage.

28. http://openwetware.org/wiki/The_BioBricks_Foundation:Standards/Technical

Chapter 3: Applications of synthetic biology

3.1: Introduction

The ultimate goal of synthetic biology is to develop commercial applications that will benefit society, ie to design and build engineered biological systems that process information, manipulate chemicals, fabricate materials and structures, produce energy, provide food, and maintain and enhance human health and our environment. The aim of this chapter is to summarise current activities in both academia and the commercial sector to develop such applications, give examples of the type of potential applications and to look forward to the applications synthetic biology might provide in the future.

As a result of the emergent nature of synthetic biology, concrete examples of its application are relatively small in number. Perhaps the most cited example of a successful synthetic biology project is the work of Prof. Jay Keasling (UC Berkeley) and co-workers in engineering yeast to produce artemisinic acid, the precursor for artemisinin, an anti-malarial drug[29] . A second example of the application of these technologies is the work of Dr Chris Voigt and co-workers (UCSF) on re-engineering the Type III secretion system of *Salmonella typhimurium* to secrete spider silk proteins for which there are a range of potential applications that relate to the production of light and extremely strong materials which can be woven.

There is, however, an ever increasing body of work regarding proof of concept studies which support the robust engineering approach to modifying biological systems. An important difference between synthetic biology and conventional genetic engineering is that there is a major emphasis on developing foundational technologies that make the engineering of biology more straightforward and reliable. Good examples of engineering in synthetic biology include the work of Prof. Tim Gardner and Prof. Jim Collins (Boston University) to produce an engineered genetic toggle switch[30]. *E. coli* has been engineered to become light sensitive and express fluorescent protein - this produced a photographic 'lawn' of bacteria. In a further iteration the quorum sensing mechanics of the bacteria were modified such that the lawn became an edge sensor only expressing protein at the boundary of a light/dark region.

3.1.1: Location of current synthetic biology research

The majority of activity within the field of synthetic biology up until about 2005 took place in two principal geographical clusters on the East and West Coasts of the United States. However, since then there has been expanding interest and activity in the UK, with one or more other examples in the rest of Europe, eg ETH Zurich, although the level of investment is small compared to the US. Activity in Asia is also expanding rapidly with Japan in particular focusing on artificial cell technologies. In addition, the number of Chinese teams participating in the iGEM competition (see section 3.1.3) has grown significantly during 2007 & 2008.

In the United States, the East Coast cluster is mainly centred around Boston and includes the research groups of van Oudenaarden & Knight (MIT), Weiss (Princeton), Silver, Forster & Church (Harvard) and Collins (Boston University).

The West Coast cluster is mainly centred around the Bay Area and includes the research groups of Arkin, Bustemante & Keasling (UC Berkeley), Voigt & Lim (UCSF), Endy and Smolke (Stanford), and Sauro (Washington).

29. Ro D-K, Paradise EM, Ouellet M, Fisher KJ, Newman KL, Ndungu JM, Ho KA, Eachus RA, Ham TS, Kirby J, Chang MCY, Withers ST, Shiba Y, Sarpong R & Keasling JD, Nature 440: 940-943 (2006)
30. Gardner TS, Cantor CR & Collins JJ, Nature 403: 339-342 (2000)

In the United Kingdom activity is mainly centred around Kitney and Freemont (Imperial College); Elfick, Tyers and French (University of Edinburgh); and Haseloff (University of Cambridge). Additional activity is also noted at the universities of Glasgow, Manchester, Portsmouth, Sheffield, Leeds, Liverpool, Newcastle and Cardiff that indicate increased interest in the field.

In Europe particularly active groups may be identified at ETH Zurich (Panke, Stelling), Paris (Jaramillo), Barcelona (Serrano), Israel (Bennenson, Shapers)

3.1.2: Current research activity in the UK

The research at Imperial College, to date, has focused on a number of areas including a Lotka-Volterra oscillator which can be controlled in terms of frequency and amplitude; a biologically engineered device for detecting urinary tract infection (infector detector); a bio fabricator; and fundamental work on biologically based logic gates. Researchers at The University of Edinburgh have produced an arsenic detector, principally for use in detecting arsenic in drinking water in developing countries. They are also actively researching approaches in cellulosic biomass degradation for biofuel applications and are involved in work considering strategies for decoupling engineered functionality from a cell's intrinsic processes through the exploitation of synthetic organelles. Cambridge University has largely been involved in synthetic devices related to plant biosciences. All of these examples use a synthesis-from-scratch approach.

3.2 Research funding

In the UK, research funding comes principally from the Research Councils and, in particular, the Engineering and Physical Sciences Research Council (EPSRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). The Royal Society has a strong interest in synthetic biology and, although they do not currently fund any activity directly, they have set up a Synthetic Biology Policy Coordination Group[31] . This group, made up of relevant stakeholders from Government, funding bodies, academia and NGOs, aims to track and stimulate policy activities and processes to encourage the responsible and responsive development of synthetic biology (although it should be noted that this group is not designed to produce the national strategy called for in Recommendation 1 of this report). The Wellcome Trust is also interested in synthetic biology. The Trust held a workshop in November 2008, with participants from the UK, Europe and the US. All the funders have a variety of mechanisms (eg responsive mode, programme and personal awards including fellowships) available for investigators to apply to, if they want to undertake synthetic biology research.

BBSRC identifies synthetic biology as one of ten research priorities[32] which are applicable across all aspects of funding, eg responsive mode, research initiatives and studentships. EPSRC has also made strategic provision by prioritising synthetic biology in responsive mode within the Material, Mechanical and Medical Engineering Programme[33] . The Research Councils also support a much larger volume of relevant research in areas such as bioengineering, systems biology, nanotechnology and informatics.

In addition, EPSRC has funded a Science and Innovation Award designed to build capacity in synthetic biology and four Research Councils have worked in partnership to establish a number of research community networks, details of both these activities are given below.

31. http://royalsociety.org/page.asp?id=7388
32. http://www.bbsrc.ac.uk/funding/priorities.html
33. http://www.epsrc.ac.uk/ResearchFunding/Opportunities/ResponsiveMode/Signpost/Engineering.htm

3.2.1: Research centres

Synthetic biology has been identified by EPSRC as a strategically important research area with its funding, through their Science and Innovation Awards, to Imperial College and London School of Economics for a Centre for Synthetic Biology and Innovation. This award, totalling £8m over five years, will fund a new and innovative research centre with the aim of establishing a strong research base in synthetic biology, coupled to a full educational and training programme.

The centre is being established within Imperial's Institute of Systems and Synthetic Biology (IoSSB), which is located on Imperial College's South Kensington campus with close links to LSE's BIOS Centre (centre for research and policy on social aspects of the life sciences and biomedicine). It will create three new lecturer positions as well as associated post-doctoral and administrative posts.

The principal aim of the centre will be to identify the main challenges that need to be addressed in the field of synthetic biology and establish research clusters involving multiple institutions to tackle these challenges. To this end, the centre will host a number of meetings and workshops with a strong international dimension and set up a Visiting Professor scheme. Ultimately, by the end of the award period in 2014, it is expected that the centre will be actively engaged in a rapidly expanding industrial sector in terms of intellectual property, spinout companies and collaborative research.

3.2.2: Research networks

In a joint initiative between BBSRC, EPSRC, the Arts and Humanities Research Council (AHRC) and the Economic and Social Research Council (ESRC), with funding totalling £970k, seven networks in synthetic biology have been established. The aim of these networks is to develop a cohesive, cross-disciplinary community of researchers from the biosciences, engineering and the physical sciences as well as the social sciences and humanities. Each network has a specific focus, details of which are:

- *Synthetic Components Network: Towards Synthetic Biology from the Bottom Up.*
  Led by University of Bristol (Professor Derek Woolfson)
- *Standards for the Design and Engineering of Modular Biological Devices.*
  Led by University of Edinburgh (Dr Alistair Elfick)
- *A Synthetic Biology Network for Modelling and Programming Cell-Chell Interactions.*
  Led by University of Nottingham (Dr Natalio Krasnogor)
- *From Robust Synthetic Biological Parts to Whole Systems: Theoretical, Practical and Ethical Challenges.*
  Led by University of Oxford (Professor Antonis Papachristodoulou)
- *SPPI-NET: A Network for Synthetic Plant Products for Industry.*
  Led by Durham University (Professor Robert Edwards)
- *The UCL Network in Synthetic Biology.*
  Led by University College London & Birkbeck College (Professor John Ward & Dr Irilenia Nobeli)
- *MATEs - Microbial Applications to Tissue Engineering: An Exemplar of Synthetic Biology.*
  Led by University of Sheffield (Professor Phillip Wright)

These networks should help to overcome some of the difficulties of developing such a new and interdisciplinary subject. They will allow researchers to overcome language and terminology barriers, establish productive partnerships and stimulate ideas - thereby establishing an effective critical mass of researchers in synthetic biology from across all the necessary disciplines. Their continued support, in both financial and administrative terms, is to be encouraged.

3.2.3: International activities

The Research Councils are also involved in a number of international activities including:

- **EU NEST Pathfinder Initiative in Synthetic Biology**[34]: The goal of the EU NEST Pathfinder Initiative is to stimulate forward-looking cross disciplinary research to demonstrate the key principles as well as to generate the tools and parts to progress the field of synthetic biology in Europe. Eighteen projects were funded with total EU investment in the region of 25M Euros. One of these projects was **Towards a European Strategy for Synthetic Biology (TESSY)**[35]. The main activity of the initiative was the development of a European roadmap for synthetic biology. Both BBSRC and EPSRC have engaged with the TESSY process.
- **ESF EUROCORES in Synthetic Biology (Euro-SYNBIO)**[36]: The European Science Foundation's EUROCORES activities support large scale multinational collaborative research programmes. BBSRC and EPSRC are among the 18 funding agencies from 14 countries supporting Euro-SYNBIO's recent call for outline proposals. The two Research Councils have made a commitment of £2m towards the call.
- **EPSRC-NSF New Directions in Synthetic Biology**[37]: EPSRC and the US National Science Foundation (NSF) held an interactive five day workshop (sandpit) in Virginia, USA in spring 2009. The aim of the sandpit was to stimulate thinking in promising new, or currently underdeveloped, areas of synthetic biology. As a result, EPSRC and the NSF have allocated up to £5.5m to support a number of potentially transformative, transnational research projects.

3.3: The economic importance of synthetic biology

The economic and industrial potential of synthetic biology is enormous. The last half of the nineteenth century and the first years of the twentieth century saw the development of technology which would form the basis of wealth generation via the great industries of the twentieth century – petrochemical, automotive, aircraft and electronics. The second half of the twentieth century saw the dawn of the information age – high performance computers which are widely available, advanced telecommunications, and the rise of the internet. These developments created the modern world. We are now on the cusp of the development of major new industries based on synthetic biology (coupled to systems biology) and this emerging area should be drawn to the attention of the UK's Technology Strategy Board. These developments will have profound implications for the future of the UK, European and world economies, as well as the environment and medicine.

34 ftp://ftp.cordis.europa.eu/pub/nest/docs/5-nest-synthetic-080507.pdf
35. http://www.tessy-europe.eu/
36. http://www.esf.org/activities/eurocores/programmes/eurosynbio.html
37. http://www.epsrc.ac.uk/CMSWeb/Downloads/Calls/SynBioSandpit.pdf

3.3.1: Commercial applications in synthetic biology

The table below lists the major areas, and associated applications, where there is either commercial activity or collaboration between industry and academia in synthetic biology. A list of companies currently active in the field and their specific area of interest can be found in appendix 3.

Health	Energy	Environment	Agriculture	Other Industry
Cell counter Biological sensors Disease diagnosis Disease fighting Controlling signs of ageing Custom drugs Tissue engineering	Bio power units Biofuels Enzymes Artificial leaf	Emissions sensors Spill/chemical/ radiation detection Biodegradable packaging Stronger/lighter materials	Starch synthesis New seed products Bioenergy feedstock Agro-fuels Optimised food production	Biological computers Digital/bio converters Logic gates Switches/oscillators Cleansing biofilms Responsive materials, eg oil Nano particle production Bioremediation Biofabrication

3.4: Future vision

The contents of this section are a projection based on current evidence and the opinions of the working group; by definition, it is not based in fact but is instead a best estimate. As with all new fields, it is important to see things in a fresh light. For example, an opinion is sometimes expressed regarding biologically based counters and computers – this is normally along the lines of "even if it were possible, why would we ever want such devices when their electronic equivalents are infinitely faster and always will be?" One answer to this question is that, at best, electronic devices will always require an interface to the world of biology; whereas, biologically based devices are part of that world. A simple example is the distinction between the worlds of analogue and digital devices.

Biologically based devices and systems produced by the techniques of synthetic biology will be used to monitor biological processes, where the time constants (which may be very long) match those of the environment in which they operate. In addition, they are likely to be driven by power supplies which derive their energy from the surrounding environment. Natural biological organisms often operate in environments which would be totally inhospitable to their electronic counterparts; for example, under extreme pressure at the bottom of the ocean. Another example is the development of intracellular sensors - it is difficult to imagine how these could be achieved using even the most advanced electronics. In terms of sophistication, the eye is a perfect example – in nature there are numerous examples of different types of eye, eg humans, fish and insects, which are optimised for different conditions.

The example of the analogue and digital domains is very useful. Digital communication has now largely taken over from analogue and, in the main, has distinct advantages, eg television and telephone systems. Via synthetic biology we are now beginning to enter the biological domain in ways that have hitherto not been possible.

The future of synthetic biology will now be described in terms of 5, 10 and 25 year visions.

3.5: Five year vision

3.5.1: Health

Over the next five years it is likely that the anti-malarial drug artemisinin will go into full production and have an impact on malaria worldwide. Artemisinin is based on an area of synthetic biology which really comes under the heading of metabolic engineering. It is, therefore, likely that other drugs will be developed using this approach particularly in relation to natural product based drugs and biopharmaceuticals. Many drugs which are currently available are based on the known therapeutic properties of various types of plants which are found throughout the world. It is likely that synthetic biology will be used to either produce synthetic versions of these natural substances in the form of new drugs or to optimise their properties, whilst reducing side effects. Another area of development is in relation to genetically engineered machines which are capable of detecting various types of infection. One example of this is the development of a detection device for urinary tract infection which uses green fluorescent protein as its display. This technology is now being extended to the detection of MRSA.

3.5.2: Energy

There is a considerable amount of activity in the area of the development of biologically based fuels. Current biofuels result from either the production of ethanol from sugars or biodiesel from vegetable oils, however, these have the disadvantage of not being particularly efficient processes that waste much of the organic matter or biomass. Much more efficient methods able to utilise more of the biomass are now being developed. Many of these techniques also use metabolic engineering to optimise the process, including the use of transgenic plants. At a slightly earlier stage, but showing significant promise, is the optimisation of similar chemical processes to produce ethanol from sugar - but with the input being various types of perennial crops such as grasses that have the advantage of growing all year round rather than a single crop per year. Finally, aviation fuels are now being developed on the basis of synthetic biology techniques.

3.5.3: Environment

There are a number of interesting developments relating to environmental applications which are likely to be successful in the relatively short term. Biosensors have been developed that detect arsenic in drinking water; a problem in many areas of the world. An adjunct to this technology is likely to be the coupling of advanced biosensors to purification processes in order to produce clean water on both small and large scales. Biologically based sensors are also being developed to detect explosives such as TNT and harmful chemicals.

3.5.4: Agriculture

There are a number of areas which are likely to be successful in the short term, many of which overlap with the environment and energy. The development of new gene-delivery technologies will enable the development of new seed products with multiple genetic traits. This will allow the development of new engineered and optimised crops that can feed biofuel applications and enable new optimised food production. For example, feedstock products from crops such as switchgrass, miscanthus, sorghum and sugarcane will have engineered genetic traits that will improve crop and sugar yields and allow digestion of cellulosic fibre.

3.5.5: Other

In the area of the early development of synthetic biology based biomaterials, a good example is a synthetic version of the silk produced by the golden orb spider. Populations in the South Pacific have long used the silk of the orb spider web to make fishing nets and traps - because of its strength and its very low weight. The synthetic version is in an advanced stage of development and should lead to the mass production of new, light-weight and strong materials for use in a wide range of applications. The development of multi-enzyme pathways for the *in vitro* production of complex fine chemicals such as unnatural monosaccharides for the pharmaceutical industry is also currently under way.

One of the major areas of activity in synthetic biology revolves around the concept of parts, devices and systems (described in more detail elsewhere in this report). Developments in this area over the next five years will involve designing and producing reliable and controllable devices such as biologically based oscillators, switches and logic gates (AND, OR, NAND etc). Considerable effort will go into the full characterisation of such parts, resulting in a totally reliable registry of professional parts. These will be used in devices such as advanced biosensors.

3.6: 10 year vision

3.6.1: Health

A major development in synthetic biology over the next 10 years is likely to be the realisation of personalised drugs. This will probably involve the incorporation of synthetic biology techniques into biotechnology processes. Part of this development may well involve the fine tuning of existing drugs to improve their therapeutic properties and to produce low or no side effects for the individual. A direct extension is likely to be the application of synthetic biology to the production of new drugs which are based on the known therapeutic properties of certain plants. This may well involve modifying the genome of the plant to enhance its therapeutic properties and to incorporate it into a synthetic chemical process. Another area is in the production of biopharmaceuticals as these processes are already biologically based. Synthetic biology will allow both the optimisation of existing production processes and the design of new process systems.

Another area which is likely to develop quite rapidly over the next 10 years is the coupling of synthetic biology to tissue engineering. Currently, tissue engineering relies very heavily on the development of scaffolds to which various kinds of cells attach themselves (one example being chondrocytes in relation to artificial cartilage). The problem with current techniques is that it is difficult to control the exact shape of the scaffold. New techniques are now being developed on the basis of synthetic biology, which allow the biofabrication of accurate 3D scaffolds. This has the potential to make engineered tissue of various kinds much easier to construct.

3.6.2: Energy

It is likely that over the next 10 years more advanced biofuels (typically biodiesel and bio-aviation fuels) will be developed. Associated with this is the likelihood that new synthetic biology based processes for fuel production in large quantities (equivalent to refining) will be developed and perfected. An important aim will be to use as much of the current supply chain as possible in order to minimise the disruption to the current facilities. In addition, new types of synthetic biofuels are likely to be developed from renewable resources using

branch-chain higher alcohols such as isobutanol, 1-butanol and 2-methyl-1-butanol. It is also possible that new types of *E. coli* and other laboratory based micro-organisms such as yeast will be developed which are butanol tolerant and capable of direct production of biofuels.

3.6.3: Environment

Emissions of CO_2 are the major contributor to global warming. A very promising area is the development of artificial leaf technology which is a synthetic version of the photosynthetic process. From a synthetic biology standpoint, this new technology for the conversion of CO_2 is likely to be based on modification of natural photosynthesis.

Under the five year time scale, bio-detectors were described for detecting arsenic in drinking water. Over the 10 year time scale, it is likely that synthetic biology based biosensors will be developed to detect a range of toxins and heavy metals. These could be coupled to genetically engineered bacteria which are capable of digesting and neutralising toxins and heavy metals.

3.6.4: Agriculture

One of the most likely developments in agriculture will be the production of new types of pesticides which are environmentally friendly. Synthetic biology techniques will be used to engineer these pesticides so that they are very specific and have a natural life in the ground which is consistent with carrying out their function. Also likely will be the routine optimisation of seed stocks to produce effective crops in difficult and complex environmental conditions, which is particularly relevant to climatic changes in developing and populous countries. The optimisation of such crops will also be necessary for providing the core ingredients for biofuel production as land mass and fuel production become rate-limiting.

3.6.5: Other

Over the next 10 years we are likely to see the beginnings of the development of lightweight, very strong materials which would have direct application in the aircraft and automotive industries. An example has already been given of the use of the silk from the Golden Orb Spider; a synthetic version of this is likely to be produced in large quantities over a 10 year time scale. This synthetic form of thread could be woven into a whole range of different types of materials (both hard and soft). In addition, the properties of molluscs, in terms of their strength and lightness, have been studied extensively. The aim would be to produce synthetically engineered versions of mollusc DNA to produce a range of materials at a much larger physical scale; for example, for the construction industry.

Within a 10 year time scale it is likely that there will be major developments in the creation of minimal cells. Currently in synthetic biology, synthetic DNA is placed in a chassis, ie a host cell, typically *E. coli* or *B subtilis*. The problem with using a natural chassis is that it is often difficult to control and predict the reaction of the cell to the insertion of synthetic DNA circuits. Work is therefore under way to produce minimal versions of natural cells. This is mainly being carried out in prokaryotes. However, over a 10 year time scale it is likely that significant inroads will be made into predictable biological design in eukaryotes. One important example of this, in relation to human stem cells, is the significant potential for human medicinal applications. Another strand of the work relating to chassis is the development of large and small scale cell-free environments. The aim is that these environments will replace the need for cells in a range of applications – thus allowing much better control of chemical and biological processes. Cell-free environments are likely to include the

development of stable large vesicles which may or may not have a lipid bilayer. One natural end point of the work on minimal cells is likely to be the ability to produce so called cell factories where large numbers of cells work in parallel.

Over a 10 year time frame the parts which have been developed and placed in the professional register of parts (see the five year vision section) will be incorporated into devices such as various types of counters. In addition, it is likely that over this period of time it will be possible to produce biologically based memory (the direct equivalent to computer memory). Once this stage has been reached, then all of the components will be in place to produce biologically based microprocessors of different kinds. Like their electronic counterparts they will begin to perform control functions applicable to living systems.

Another major area of development within a 10 year time frame is in DNA synthesis. The costs and technologies that will allow the large scale synthesis and assembly of whole genomes will converge making it possible for researchers to design large genomes for synthesis. These developments will run in parallel with work on the minimal genome and it is likely that the first new genomes will be functioning in minimal chassis. Combining these two technology developments will underpin the 25 year vision discussed below.

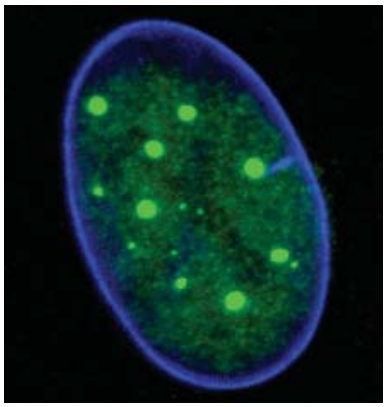
3.7: 25 Year Vision

History shows that a 25 year vision is difficult to predict with any accuracy. Areas where it is fairly certain that major progress will be made often turn out to have hidden problems. Other areas of development, which seem impossible, make major strides because of some unforeseen discovery or breakthrough. When predicting the future of synthetic biology, these caveats must always be borne in mind. Nevertheless, it is likely that one of the areas which will see significant progress is healthcare. Biosensors which permanently reside in the body to detect a particular type of abnormally; for example a type of cancer or arterial disease. The biosensor will be part of a genetically engineered machine which then manufactures a drug to kill off the cancer or destroy the arterial plaque. An extension to this is the concept of highly adaptive vaccines and antibiotics. One example would be a vaccine which rapidly adapts to kill a particular type of influenza – thus avoiding a new pandemic. One of the problems with current antibiotics is that the bacteria which they are designed to kill adapt to the antibiotic, which then becomes ineffective (this already true in the case of so called hospital superbugs, such as *C. difficile*). Synthetic biologically engineered antibiotics could be developed which monitor the adaptation of the bacteria they are designed to kill and modify their response accordingly. For example, the aim might be to develop a range of synthetically engineered T-cell components in order to develop a device which is capable of finding and killing cancerous cells. On the basis of this, or by other means, it should be possible to produce devices that will enhance the human immune system. These devices could then be applied to the treatment of HIV and AIDS. Other biologically engineered devices, such as retinal implants, which will be close in function and size to their natural counterparts, should also be possible over this time scale.

Over the next 25 years more and more advanced biofuels will be developed for different applications. These fuels may be mixed with more traditional fuels. One of the key problems relating to biofuels today is that a large percentage of the biomass, eg stalks and leaves, are discarded because, although they are a rich source of sugars, they are difficult to break down. This is a key reason why

today large areas of land are needed for crops for biofuels. Artificial enzymes are already used in the detergent industry. Synthetic biology will allow the development of enzymes which can break down a much wider range of biomass into useful forms. It should also be possible to develop plants whose whole biomass is readily convertible. It is also likely that many products which are currently derived from oil will be replaced by biologically engineered substitutes. One example is plastics. There would be major advantages in producing biologically based materials which have the same properties as plastics, but are environmentally friendly and biodegradable.

The development of biologically based parts and devices has been discussed in the previous two sections. The aim of this work is to develop biologically based devices and systems that have a wide range of applications. Twenty five years from now, the operation of minimal or artificial cells may be controlled by such devices. This would involve signalling and actuators which replace or modify their natural equivalents. Microprocessors and computers are key parts of control and communication systems and are used today in a wide range of applications. In a similar way their biologically engineered equivalents will perform a wide range of functions, but in the biological world. In addition, sophisticated interfaces are likely to be developed which link biology to electronic systems, eg for cellular and intracellular monitoring.



Chapter 4 : Implications

4.1: Ethics, security and safety

It is perhaps not surprising that the field of synthetic biology gives rise to concerns relating to ethics, security and safety, because one of its objectives is to produce novel living organisms. In addition, with the growth of the internet and the standardisation of many biotechnological procedures, the tools for doing synthetic biology are increasingly becoming more accessible.

The creation of synthesised organisms that are not found in nature leads to ethical questions about the role and responsibility of human beings in creating novel life forms. Statements to the effect that the next 50 years of DNA evolution will take place "not in nature but in the laboratory and clinic" [38] clearly challenge our understanding of the natural world and our place within it. With innovations such as cell-free approaches, synthetic biology raises difficult questions about where the line should be drawn between what is 'natural' and what is not, and whether it is helpful to attempt to draw such a line at all.

Since synthetic organisms could be created for malevolent purposes, developments in synthetic biology have given rise to concerns about biosecurity. In the US this is the most heavily debated social risk associated with synthetic biology. This has led to criticisms that the focus on biosecurity has marginalised other, equally pressing, issues. Biosecurity concerns were triggered by the synthesis of several pathogenic viruses, including the 1918 influenza virus[39] and an infectious poliovirus that was synthesised using only published DNA sequence information and mail-ordered raw materials[40]. Such developments have led to concerns that 'biohackers' could recreate known pathogens and perhaps even make them more virulent.

Although there are currently much easier ways of obtaining pathogens than by synthesis, commentators predict that the relative ease of synthesis will change with time, since faster and cheaper DNA synthesis is one of the key objectives of synthetic biology. Furthermore, the availability of DNA sequence data and explanations of molecular biology techniques online, combined with the ease of getting a DNA sequence synthesised by a specialised company, means that these technologies are becoming available to an increasingly wide range of people. The iGEM competition is a demonstration of the accessibility of the technology to undergraduates across the world.

In response to these concerns, a range of different options for regulatory intervention have been suggested. These include the screening of customers by DNA synthesis companies; educating scientists about biosecurity issues; the formation of a professional society for synthetic biology; and a biosafety manual for synthetic biology laboratories[41].

Even if synthetic organisms are not purposely released into the environment, there is the risk of accidental release of such organisms which could have unintended detrimental effects on the environment or on human health. The flexibility of synthetic biology means that micro-organisms could be created which are radically different from those that we know today. Such micro-organisms might have unpredictable and emergent properties.

Synthetic biologists have pointed out that these problems are not imminent since it is currently much easier for a synthetic organism to survive in an artificial environment than in a natural environment. It has also been suggested that synthetic organisms could be made to be dependent on nutrients that are not found in nature, or that they could have built-in safety features such as

38. Benner, SA. Acc. Chem. Res. 37: 784-797 (2004)
39. Tumpey, TM et al. Science 310: 77-80 (2005)
40. Cello J et al. Science 297: 1016-1018 (2002)
41. Garfinkel, MS et al. Synthetic Genomics: Options for Governance. J Craig Venter Institute, Rockville, MD (2007)

'fail-fast' mechanisms. However, some commentators think that all uses of synthetic biology in the open environment should be banned "until a robust risk assessment can be conducted for each proposed application"[42] .

Others think that such a step would make research expensive and restrict synthetic biology to a few laboratories.

4.2: IPR issues

Since synthetic biology is a new field, the intellectual property issues are still in flux. Intellectual property (IP) law works on the basis of precedent, and attempts to draw parallels with already existing technologies. This is problematic in the case of synthetic biology, because it sits at the intersection of biotechnology, software and electronics[43] .

Some commentators have expressed the view that the main objective should be to develop some form of protection of intellectual property in synthetic biology "without stifling the openness that is so necessary to progress"[44] . But patents already exist that could inhibit the progress of research in the field. Some of these are very broad patents relating to foundational technologies - such as methods of producing synthetic DNA. Other patents are narrower, eg patents on the biological functions encoded by bioparts. Others relate to software and computer simulations.

Perhaps the most famous synthetic biology patent application is Craig Venter's application, filed in May 2007, for his *Mycoplasma laboratorium* genome, the smallest genome needed for a living organism. The patent also claims any method of hydrogen or ethanol production that uses the minimal genome as a chassis. It has received a great deal of media attention, because it can be interpreted as a patent on the 'essence of life' itself. However, analysts think it is unlikely to be granted on the grounds of lack of enablement. The company Scarab Genomics has a patent on a minimised *E coli* genome, which, some argue, may prove to be more important[45] .

One group of synthetic biologists, working on standard biological parts, have set up the BioBricks Foundation in an attempt to ensure that the parts they create are freely available in the public domain (see section 1.3.6). The economic rationale for this is that the products of synthetic biology are likely to require many different bioparts, and that some bioparts will be used in many different applications (such as logic gates). If such bioparts were patented, this could lead to 'patent thickets' or 'blocking patents'. The BioBricks Foundation are modelling their Registry on open source principles, meaning that anyone who takes a part from the Registry is free to modify and improve on it, although they must make the information about all BioBrick parts used in any product freely available. But are there other ways of organising intellectual property around bioparts, and is an open source analogy feasible and sustainable? There is currently a great deal of debate about these issues[46] .

Synthetic biology encompasses more than just bioparts. There has been discussion about whether there should be different ownership regimes for different levels of a synthetic entity, such as parts, devices and systems.

Some argue that since any systems and organisms produced by synthetic biology will be the result of a great deal of work, they should be subject to more stringent forms of intellectual property protection than bioparts. This approach raises the question of whether it is possible to separate different levels of synthetic entity.

42. Tucker JB & Zilinskas RA. New Atlantis 12: 25-45 (2006)
43. Rai A & Boyle J. PLoS Biol 5: e58 (2007)
44. NEST Synthetic Biology: Applying Engineering to Biology. European Communities (2005)
45. Nature Biotechnology, 25: 822 (2007)
46. Henkel J & Maurer SM Mol Syst Biol 3: 117 (2007); Kumar, S & Rai, AK Texas Law Review 85:1745-1768 (2007)

The intellectual property issues raised by synthetic biology are closely related to the ethical concerns elicited by the field. In Europe there are explicit connections between ethics and intellectual property in the morality clause in EU patent law. As a result, some commentators think that the patents in synthetic biology will be more stringently evaluated in Europe than in the US[47] . Another clear link between intellectual property and ethics in synthetic biology is the issue of 'owning life'. Much of synthetic biology involves the creation and the patenting of novel living organisms. The 'unnaturalness' of the creations in synthetic biology may actually make it easier to patent them, because they will clearly be human inventions rather than products of nature.

4.3: Sensitivity of the public debate and social issues

Although synthetic biology can be separated from genetic engineering by its sophistication and its genuine grounding in engineering principles, the fact that it involves the creation and manipulation of living organisms is likely to give rise to many of the same fears that were encountered with genetic engineering. Furthermore, while genetic engineering often involves small changes to existing organisms, synthetic biology has the potential for fundamental design and construction. The creation of synthetic living organisms according to rational and reductionist engineering principles is likely to invoke worries about scientists 'playing God', and some may object to synthetic biology at the outset for this reason.

Another sensitive issue which was central to the GM crops debate was the perceived monopoly on the technology by multinational corporations. In the context of synthetic biology, this suggests that how the intellectual property issues are negotiated is likely to be very important. If it is perceived that a small number of profit-driven companies have secured the rights to develop synthetic biology; this is likely to lead to negative public responses to the technology. A related issue is the potential for global inequalities to be exacerbated by synthetic biology if, for example, products currently made in developing countries were no longer required because of advances in synthetic biology[48] .

The synthetic biology community is aware that their research has the potential to be highly contentious. Consequently, many scientists regularly write about and publicly discuss the broader implications of their work. At the Second International Meeting on Synthetic Biology (SB2.0) in Berkeley in 2006 the participants put forward a declaration on the governance of the field, which focused on biosecurity issues and emphasised self-regulation. This call for self-regulation met with a negative response from civil society organisations and NGOs. A global coalition of thirty-eight international organizations including scientists, environmentalists, trade unionists, bio-warfare experts and social justice advocates wrote an open letter asking for the withdrawal of the declaration; saying "we believe that this potentially powerful technology is being developed without proper societal debate concerning socio-economic, security, health, environmental and human rights implications" [49]. The letter emphasised the necessity for broad and inclusive public debate on the development of the field.

4.4: Enabling public engagement

IIn addition to an academic exploration of the issues by social scientists, ethicists and philosophers, it is equally important to gain an understanding of the hopes, expectations and concerns of wider society. An embedded programme of public engagement (see box 1) should, in principle, lead to the development of synthetic biology applications and associated policies

47. De Vriend, H Constructing Life. The Hague: Rathenau Institute, (2006)
48. Balmer, A & Martin, P Synthetic Biology: Social and Ethical Challenges, BBSRC, Swindon (2008)
49. http://www.etcgroup.org/en/materials/publications.html?pub_id=8

emerging and being influenced by wider cultural and ethical issues, and by the hopes, desired future outcomes and concerns of a plural society. For this to happen there is a need for the research community to consciously and proactively raise debate with the public - and, most importantly, listen to the findings.

One of the major criticisms of the nationwide public engagement programme 'GM nation?' [50], which took place in 2003, was that it happened at a very late stage, once positions were polarised, the debate framework had been set, and there was little opportunity for public views to feed into higher level debates, policy formation, regulation, research direction or application. It is therefore vital that engagement with wider society is conducted at an early enough stage to observe how the public frame[51] and interpret the issues from the beginning. Public dialogue must begin 'upstream' before the parameters for debate have been narrowed down and decided upon. As mentioned previously, public debate on GM revealed anxieties over the monopolisation of this technology by large corporate organisations. This was a largely unforeseen concern until the public engagement activities had started in earnest - by which time it was too late to attempt to address these and other concerns.

Furthermore, there can be a tendency for societal implications of future technological applications to be framed in terms of safety and regulation only. However, as with other emerging areas of science and engineering, synthetic biology brings with it a wide variety of significant societal, ethical, cultural and economic implications which are likely to be raised during public debates, and are worthy of wider consideration. These include the more philosophical issues surrounding what is 'natural' and the creation of 'new life'.

Therefore, early public dialogue activities need to open-up the debate and be as non-prescriptive as possible. This allows people to decide for themselves what the most pressing issues are and to explore their own desired future outcomes, which are often not viewed in the same way as by the research community or policy makers.

Public engagement needs to be embraced as a long-term and integral activity that is embedded into the development of the field of synthetic biology, and not a one-off hurdle to overcome. As described in chapter 3, the field of synthetic biology is expected to require at least a 25 year period for its full potential to be realised. The purpose of the anticipated dialogue activities will vary over time (as will the participants required, and the methodology to be used) as the technology develops. While initial public engagement activity should be exploratory, as the technology matures the types of public dialogue activities that take place can similarly become more focused and deliberative (socio-analytical processes and more in-depth activities such as consensus conferences and citizens juries that aim to arrive at a judgement regarding future courses of action) and more widespread in order to reach out to people from different socio-economic groupings, ethnicity, ages and regions.

Engagement activities do not result in a set of neat recommendations that, if followed, will guarantee wider and automatic public acceptance of the technology. The outcomes of public dialogues reveal a variety of points of view from different perspectives, and any recommendations produced are often conditional. Nevertheless, these views can be invaluable in opening up the debate and informing, rather than dictating, research development direction and policy making, alongside the consideration of other forms of evidence, knowledge and the recommendations of other stakeholders.

50. http://www.aebc.gov.uk/reports/gm_nation_report_final.pdf

51. For further discussion on 'framing' see Scheufele DA, Messages and heuristics: how audiences form attitudes about emerging technologies. pp. 20 – 25. Engaging Science – thoughts, deeds, analysis and actions (Ed: Turney J; Published: The Wellcome Trust).

Box 1: Public Engagement

In the scientific and engineering community, 'public engagement' is a widely used term to describe a range of activities with a variety of objectives. These include providing careers information to recruit the next generation of scientists and engineers; organising events and exhibitions to inspire and inform both young people and adults; performing public consultations and setting up forums that enable citizens to engage in the policy making process.

For the purposes of this report, we refer to public engagement as that which aims to raise awareness and encourage informed dialogue, debate and reflection on the impact of science and engineering (in this case synthetic biology) on society. The goal is to enable the voice of different sectors of society, typically non-specialists in synthetic biology, to inform and influence the development and application of this emerging technology, by contributing to 'higher level' debates and influencing decision making.

Public engagement with synthetic biology should be perceived as an asset that can assist in the generation of well-developed, robustly debated and considered policy - rather than as a 'box to tick' or a public relations exercise to convince people to accept a new technology. However, the value and effectiveness of such public involvement in the development of a new technology, ie on its direction, application, regulation, associated policy and social acceptability, has yet to be clearly demonstrated. Therefore, in addition to the development of an extensive programme of public engagement, an evaluation strategy should also be put in place to measure the outcomes and any impact on the development of synthetic biology and its associated policy and regulatory frameworks.

4.5 Embedding public engagement

Gathering public and stakeholder views on the future direction of science and engineering is taking place with more frequency in the UK. This increase in the volume of activity has been enabled by the strengthening of the UK's public engagement infrastructure over a number of years. Many science and engineering institutions and other organisations have strategies, programmes and committees in place to specifically consider societal issues, eg the Royal Academy of Engineering, the Royal Society and the Research Councils. The growth of public engagement has also been enabled by the provision of funding, support and resources from other initiatives such as *sciencewise*[52] , which was set up by DIUS to enable government departments to commission and use public dialogue to inform policy decisions on emerging areas of science and engineering.

It is important to ensure that public engagement is either led by, or at least takes place in partnership with, the synthetic biology research community and other stakeholders. It would be disappointing for an exploration of the wider issues in synthetic biology to be led by public engagement practitioners alone, or to develop as a small social science field in its own right, without ownership and involvement from the scientists, engineers and policy makers involved.

Indeed the value of any public engagement activity is founded on enabling a space or platform for an exchange and exploration of ideas, values and knowledge between the citizens, government, scientists and other stakeholders, such as civil society groups and non-governmental organisations.

The DIUS "A Vision for Science and Society" consultation[53], published in 2008, states the need for a more mature relationship between scientists and engineers, policy makers and the public. Research has demonstrated that the public themselves want to know more about scientific developments at an early stage and recognise the need to become more involved in decisions relating to science and technology[54]. However, recognition of the potential value of involving the public in debates about the future direction of developing technologies, in addition to an understanding of the practices involved and the underlying strategy, is still fairly low within much of the policy making and research community. Research commissioned by the Royal Society[55] revealed that scientists and engineers typically view public engagement as a means to educate rather than to debate the issues and take part in a genuine dialogue.

Learning about wider societal issues and public engagement theory and practice should form a core part of the training for any undergraduate and postgraduate degree courses in synthetic biology.

52. http://www.sciencewise-erc.org.uk/
53. http://interactive.dius.gov.uk/scienceandsociety/site/
54. Public attitudes to science (March 2008). A report prepared for Research Councils UK and the Department for Innovation, Universities and Skills by People Science & Policy/TNS.
55. The Royal Society (2006). Survey of factors affecting science communication by scientists and engineers.

Provision should also be made for more senior researchers and policy makers involved in synthetic biology to undertake professional development in this area.

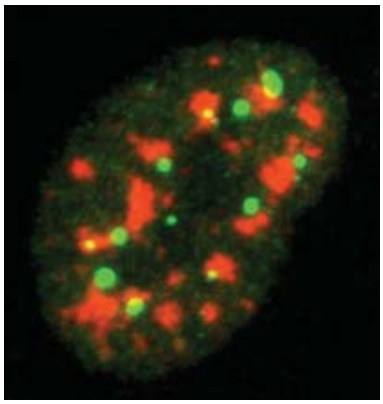
4.6: Regulatory framework

Regulation will play an important role in the development of synthetic biology, particularly in terms of public attitudes towards the emerging applications. In the UK, the main organisations with responsibility in this area are Defra (particularly ACRE - Advisory Committee on Releases to the Environment) and the Health and Safety Executive (particularly SACGM - Scientific Advisory Committee on Genetically Modified Organisms).

At present the official view in the UK is that the majority of synthetic biology research will be covered by current GMO regulations and that there is no need for any new regulations relating specifically to synthetic biology at present. However, this may not be the case in the future. What is most important is that an open dialogue between the regulators and researchers (both academic and industrial) is maintained. A good example of such a dialogue was the Synthetic Biology Regulators Meeting held by BBSRC in autumn 2008 on behalf of Research Councils UK[56] . This brought together practising scientists, research funders, policymakers, regulators and advisers to consider the adequacy of the UK's regulatory framework for products that might arise from synthetic biology. It is also important that the regulators are actively involved in the public engagement process so that the public is well informed on all aspects the process.

Overall, the existing regulatory framework is working well. However, the Government should ensure that the regulators are given adequate support to maintain continued dialogue between them and researchers in order that advances and innovations are covered by the regulations and also that the public are kept informed.

56 .http://www.bbsrc.ac.uk/society/dialogue/activities/synthetic_biology_public_statements.pdf



Chapter 5 : Education and Training

5.1: Education and training

If the UK is to be competitive in synthetic biology and able to take advantage of new opportunities for wealth creation, an essential first step will comprise training a cadre of researchers able to deliver effectively the necessary capability to undertake research in synthetic biology.

At present university teaching in the biological sciences and the more numerate subjects is generally arranged into separate areas with little exchange between them. But research in synthetic and systems biology requires engineers, mathematicians and physical scientists to have a thorough understanding of biology; they need both the expertise and the environment necessary to think about fundamental biological problems and simply adding a little biological knowledge to their background will not be sufficient. It is of paramount importance that students who embark on synthetic biology courses undergo rigorous training. For this reason teaching, at any level, should be delivered by the research active staff in the areas being taught.

Inevitably, training in synthetic biology will be lengthy and expensive. A key question to consider is the amount of expertise that future synthetic biologists will require in a core discipline before moving into interdisciplinary research. Most academics need to feel rooted within a parent discipline because from it they derive their primary peer support and recognition. Discipline-hopping awards can help researchers to begin exploring a new subject. But, in their present form, these schemes aim more at familiarising the awardees with the working culture of another discipline – rather than allowing the researchers to acquire new skills.

It can therefore be argued that future synthetic biology researchers should initially be trained in a parent discipline, eg engineering, at an undergraduate level before moving on to more explicit postgraduate courses. Nonetheless, their undergraduate courses should also include exposure to problems and interaction with peers from other disciplines. For instance, final year undergraduate programmes in engineering and physical science could include discipline-hopping modules in the life sciences. Indeed, some universities have, or will be introducing, Masters or PhDs in synthetic biology. The tendency to establish postgraduate courses reflects the importance of mastering a parent discipline before moving on to a more wide-ranging training.

5.2: Interdisciplinary skills

The main challenge to providing training in synthetic biology is that its interdisciplinary nature does not fit naturally into the traditional university structure or the standard funding mechanisms. Greater coordination is needed between the various disciplines (and their associated departments) which comprise synthetic biology in order to produce graduates with the necessary skills and new methods of working. Interdisciplinary training is particularly important in synthetic biology because students not only require a detailed knowledge of their primary discipline and how it pertains to the field, but, also, a thorough grounding in the other scientific disciplines involved. In addition, they need to be fully conversant with the ethical and societal issues which are germane to synthetic biology.

The UK is only now beginning to develop provision for training in systems biology. The substantial investment in Doctoral Training Centres that EPSRC and BBSRC are leading comprises a 4 year model. A similar model needs to be introduced for synthetic biology. The upbringing of researchers with sufficient theoretical background to apply and develop modelling techniques and, at the

same time, with an adequate knowledge of experimental biology to engage with the functionality of the data, will require cross-disciplinary training. Students may benefit from having supervisors in two of the disciplines that underpin synthetic biology, for example an engineer and a biologist.

5.3: Education and training model

Training in synthetic biology can begin with an introductory module during a degree in either engineering or the life sciences. At the postgraduate level it should comprise a Masters Degree followed by a PhD. New postgraduate courses and the expansion of post-doctoral opportunities should be created.

Examples of each of these approaches can be found at Imperial College, the first European university to introduce courses in synthetic biology. The strategy for the new courses and their implementation is seen as a possible template for how such courses might be introduced more widely in the UK. It should be noted that at the recent SB4.0 international conference on synthetic biology[57] these courses were cited as a possible template for the EU.

There are currently three possible routes for students to take into synthetic biology at Imperial College:

- **Final year option in Synthetic Biology:** This is a 12 week module that students can choose during the final year of their undergraduate course. The module comprises lectures and laboratory work. The course is divided in two halves. During the first half of the course, the students follow parallel streams: the bioengineers receive lectures on particular topics in biochemistry and some of the enabling technologies, and carry out wet lab practicals in DNA manipulation while the biology and biochemistry students receive lectures on engineering principles and modelling and carry out computer practicals on modelling of biosystems.

  The students from both disciplines then combine for the second half of the joint programme. This common section of the course introduces specific topics in synthetic biology via lectures, case studies and further practicals – including a mini iGEM competition.

- **MRes in Systems and Synthetic Biology:** The aim of the MRes is to provide graduate students from the life sciences, engineering and physical sciences with a platform to overcome traditional barriers and to work collaboratively on problems and applications in systems and synthetic biology. The MRes students gain intensive hands-on experience in a combination of experimental biology and modelling to understand, predict, and redesign biological pathways. In addition to a minimum set of conventional lectures, these objectives are achieved through active engagement by the students in the programme, ie through practicals, bench work, case studies, journal clubs, and an 8-month long interdisciplinary research project. For further enrichment of the programme, connections to industry and medicine are provided through research projects being undertaken by members of the Institute of Systems and Synthetic Biology, as well as additional courses and workshops.

- **MSc in Bioinformatics and Theoretical Systems Biology:** This is a multidisciplinary research-based MSc course, designed for applicants with a biomedical, computational or mathematical background. It equips students with the necessary skills to produce effective research in computational genetics and bioinformatics. The course has been designed and is taught by staff from the Faculties of Natural Sciences (Chemistry, Mathematics), Engineering (Computing) and Medicine. Teaching is by experts in relevant

57. The SB conferences (SB1.0 –SB4.0) are a series of annual international meetings which are organised by the international community in synthetic biology. Each year, one university has taken responsibility for organising the conference. To date, because of the relatively small size of the field, all the key players have attended. See http://sb4.biobricks.org/ for further details.

fields within the College but also makes use of collaborations with other researchers.

In the first term, students are provided with information not covered by their first degree courses, in addition to the following compulsory elements: bioinformatics, computing, mathematics and statistical inference.

In the second term, areas in computational biology are addressed through a core module in bioinformatics. The remainder of the year is devoted to two 12-week full-time research projects, undertaken under the supervision of researchers at Imperial College (this may also involve collaboration with other academic centres or industry).

In addition to the courses at Imperial College detailed above, courses in synthetic biology are also planned or offered by a number of other UK universities. Examples are:

- **University of Edinburgh**
  MSc in Bioinformatics plus Synthetic Biology starting September 2009
  MSc in Synthetic Biology starting in October 2009
- Post Graduate Summer School on Computational Methods in Synthetic Biology, in conjunction with Heriot-Watt University
- **University of Cambridge**
  Fourth Year Course in Systems and Synthetic Biology plus plants. Summer School – duration 2-3 weeks.

Beyond the UK, the United States are most active with MIT, Princeton, Stanford, UC – Berkeley and Harvard all offering, or planning to offer, courses in synthetic biology. In Europe, Genopole in France are planning to start a 2 year Masters in Systems and Synthetic Biology in autumn 2009.

Until recently the US, UK and EU were, essentially, the only geographical areas where there was activity in synthetic biology research. This situation is now changing, in terms of research, as illustrated at SB4.0 and new courses are bound to follow in the other universities which are active in the field.

5.4: iGEM

A key driver in the development of synthetic biology is the International Genetically Engineered Machine competition (iGEM)[58] , organised by Randy Rettberg at MIT. This competition has very effectively raised the profile of parts-based synthetic biology, expanded the BioBrick resource and educated future synthetic biology researchers in the BioBrick approach. It is an annual event where undergraduate teams from around the world endeavour to design and build a functional biological device. This event has run in its current form since 2006 and in that time the students have developed many weird and wonderful devices such as photographic film from lawns of bacteria and bactoblood – see appendix 2 for a summary of recent iGEM projects. Whilst some of these devices are little more than toys, they provide vital proof-of-concept for a wealth of potential applications of synthetic biology.

iGEM takes place in two discrete phases; a design and build period over 10 weeks of the summer vacation and a two-day jamboree where the participating teams meet to vie for the coveted 'BioBrick' trophy. The competition is organized and hosted by MIT in Boston. At the jamboree the teams share their projects and experiences. Teams are expected to be self-motivating, ideas driven and goal oriented.

iGEM has experienced rapid growth and in the 2008 competition 84 teams from across the globe were involved with six from the UK. In 2007, 54 teams from 19 countries took part and appendix 2 lists some of the key projects

58. http://2009.igem.org/Main_Page

which have been part of the iGEM competition over the last two years. The competition serves as a wonderful vehicle for promoting parts-based synthetic biology and engaging new research students into the field. In addition, the small army of diligent workers create numerous new parts each year to populate the Registry.

The Academy notes the crucial role that vacation bursaries can play in enabling undergraduate participation in iGEM and the development of synthetic biology. The continued participation of UK students is important.

Any success by UK students should also be widely publicised to increase the exposure of synthetic biology to the public, highlight potential applications and showcase UK talent. The Academy can play an important role to support these promotional activities along with the Research Councils and the participating universities.

Appendix 1: Working group and terms of reference

Contributions by the working group were made purely in an advisory capacity. The members of the working group participated in an individual capacity and not as representatives of, or on behalf of their organisations

Chair of the working group

Professor Richard Kitney OBE FREng
Professor of BioMedical Systems Engineering
Imperial College London

The following academics were included to cover all relevant aspects of synthetic biology: engineering, biology, physical sciences and social sciences.

Dr Jane Calvert
RCUK Academic Fellow
University of Edinburgh

Professor Richard Challis FREng
Professor of Ultrasonic Engineering
University of Nottingham

Professor Jon Cooper FREng FRSE
Chair in Bioelectronics
University of Glasgow

Dr Alistair Elfick
Reader and Director of Centre for Biomedical Engineering
University of Edinburgh

Professor Paul Freemont
Head of Molecular Biosciences
Imperial College London

Dr Jim Haseloff
Sainsbury Research Fellow & Lecturer
University of Cambridge

Professor Mike Kelly FREng FRS
Professor of Technology
University of Cambridge

Dr Lesley Paterson
Head of Public Engagement
The Royal Academy of Engineering

In addition to the academic members of the working group listed above, the following representatives of Research Councils and research charities were also involved, providing particular advice on the current funding of synthetic biology.

Biotechnology and Biological Sciences Research Council (BBSRC)
Dr Amanda Collis: Head of Tools and Resources

Engineering and Physical Sciences Research Council (EPSRC)
Dr Annette Bramley: Head Engineering Programme and Complexity Science Programme
(Dr Bramley has since left EPSRC and been replaced by Dr Mark Claydon-Smith)
Dr Katie Finch: Engineering/Economy, Environment and Crime Portfolio

Wellcome Trust
Dr Deborah Colson: Science Programme Manager
(Dr Colson has since left the Trust, her role concerning synthetic biology has now been taken over by Dr Ruth Jamieson, Science Portfolio Adviser)

Secretariat

Dr Alan Walker
Policy Advisor
The Royal Academy of Engineering

Terms of reference

The study was carried out with the following objectives:

1. To define what is meant by the term synthetic biology.
2. To consider current and potential future developments in synthetic biology and its likely impact, including the role of industry and business.
3. To consider the impact of synthetic biology on education and the benefits that could be derived.
4. To assess the potential ethical and societal impacts of synthetic biology, both in the UK and internationally.
5. To carry out a review of the existing activity and capacity within the UK.
6. To consider the interface between engineering and other disciplines and how they should be developed to maximise opportunities.
7. To identify key policy issues relating to synthetic biology and potential opportunities for synthetic biology to contribute to the wealth of the nation.
8. To advise The Royal Academy of Engineering, Government, industry, academia and other stakeholders of the findings of the report and, where appropriate, recommend action.

Appendix 2: iGEM projects from the last 3 years

Below is a sample of the teams that competed at the 2007 and 2008 iGEM competition along with a summary of the projects they worked on. See section 5.4 for more details of the iGEM competition.

Biofuels

Alberta (2007)	A genetically modified *E.coli* that produces butanol.
Duke (2008)	A biological system that is capable of converting the common component of plastics, polyethylene, into fatty acids. These fatty acids can then be converted into a hydrocarbon chain and used as a biofuel.
Edinburgh (2008)	A biological system capable of converting cellulose into starch and producing the vitamin A precursor, beta-caroten. The potential is to synthesise a food source rich in certain vitamins.
Mississippi (2008)	A biological system that converts the biopolymer lignin into a potential biofuel.
Virginia (2007)	A bacterial system that is capable of taking the inputs of cellulose and light to synthesis butanol for use as a biofuel.
Wisconsin (2008)	A biological system that produces ethanol.

Health

Berkeley UC (2007)	A biological system that is capable of acting as synthetic blood cells.
Caltech (2007)	Viruses engineered to attack sub-populations of cells (such as cancer cells) based on RNA and protein expression profiles.
Columbia (2007)	A biological system that is capable of detecting harmful levels of iron and producing a visual output.
Guelph (2008)	A biological system that is designed to complement and supplement the vitamins from the intestinal flora.
Heidelberg (2008)	A multi-cellular system that senses and kills harmful pathogens such as those within biofilms.
Imperial (2007)	A biological system that is capable of detecting pathogenic biofilms by detecting signalling molecules used by the pathogen.
Leuven (2008)	An intelligent drug delivery device in which drugs are delivered only when needed.
Princeton (2007)	Using RNAi enhanced logic circuits for cancer specific detection and destruction. The use of logic gates is to allow a reliable response that is only directed to the target cells, in this case breast cancer cells.

MIT (2008)	A biological system that produces a short peptide, p1025, that is capable of inhibiting the binding of bacterium capable of causing tooth decay.

Agriculture

Edinburgh 2007	A biological system that is capable of producing 'self flavouring yogurt'.
Istanbul 2008	A biological system that synthesises high levels of starch.
Naples 2007	Extra virgin olive oil detector based upon detection of a particular compound, oleic acid, found in extra virgin olive oil.

Environment

Beijing (2008)	A biological system that is able to detect and destroy the pollutant Polychlorinated biphenyls (PCBs).
Brown (2008)	A biological system that is capable of detecting harmful levels of arsenic and producing a visual output.
Glasgow (2007)	Development of a biological biosensor capable of giving an electrochemical output. The potential of this is to use this electrical current to make a microbial fuel cell.
Lethbridge (2008)	A biological system capable of detecting toxic aromatic pollutants that are created during oil refinery and mining processes
MIT (2007)	A biological device capable of the bioremediation of lead, involving both the detection and the removal of lead.
Penn State (2008)	A biological biosensors, that is capable of screening water for the harmful substances Phthalate and Bisphenol A.
Prairie (2007)	A biological system capable of simultaneously detecting the toxic metals nickel, vanadium and iron.
Munchen (2008)	A biological system capable of bioremediation of metal ions, involving both the detection and the removal of lead.
Sheffield (2008)	A biological system capable of detecting the pathogen Vibrio cholerae in water sources.
Southern Utah (2007)	A biological system that is capable of detecting harmful levels of cyanide and producing a visual output.

Other

Imperial (2008)	A biological system that is capable of manufacturing biomaterials with high level of control of micro and macroscopic properties of the biomaterial.
Paris (2007)	A synthetic multi-cellular network of cells.
Paris (2008)	A biological oscillator capable of acting as a biological clock.

Appendix 3: Examples of companies engaged in synthetic biology

Below is a sample of companies from around the world that are currently active in the field of synthetic biology. The companies are grouped geographically, highlighting the predominance of the east and west coasts of the US that exists at the present time.

California

Amyris Biotechnologie Drug Development and Biofuels

Amyris Biotechnologies is a spinout of UC Berkeley. Its primary role is to exploit the work of Professor Jay Keasling's laboratory in the development of a synthetic anti-malarial drug called artemisinin. The company is also developing a number of biofuels, including a biologically based aviation fuel.

LS9 Biofuels

LS9 are developing a range of biofuels produced by specially engineered microbes created via industrial synthetic biology. It is intended that these DesignerBiofuels™ will be cost-competitive with traditional petroleum products and be commercially available within a few years.

Synthetic Genomics Energy and environment

Synthetic Genomics are seeking novel genomic-driven strategies to address global energy and environmental challenges. They are using recent advances in the field of synthetic genomics to develop applications for the production of energy, chemicals and pharmaceuticals and to enable carbon sequestration and environmental remediation.

DNA2.0 Gene synthesis

DNA2.0 is a synthetic genomics company and one of the largest US providers of synthetic genes. They offer a number of services including gene synthesis, bioinformatics software, codon and amino acid reference tools, and a literature database.

Massachusetts

Greenfuel Technologies Corporation Biofuels

GreenFuel's high yield algae farms recycle carbon dioxide from flue gases to produce biofuels and feed, reducing net carbon dioxide production as waste becomes profit. Harvesting algae for biofuels enhances domestic fuel production while mitigating CO_2.

Mascoma Corporation Agriculture and energy

Mascoma's R&D team is focused on developing biofuels from non-food biomass wood, straws, fuel energy crops, paper pulp and other agricultural waste products. Their research laboratories are now developing a new generation of microbes and processes for economical conversion of cellulosic feedstocks into ethanol.

New England BioLabs Production and supply of reagents for the life science

Established in the mid-1970s as a cooperative laboratory of experienced scientists, New England Biolabs focus on the production and supply of reagents for the life science industry. They now offer one of the largest selections of recombinant and native enzymes for genomic research and are expanding their products into areas related to proteomics and drug discovery

The rest of the United States

Blue Heron (Washington) Gene synthesis

Blue Heron is a leader in gene synthesis. Their GeneMaker® technology can produce DNA sequences from 60 base pairs to well over 20,000 base pairs in length including the first synthetic DNA fragment over 50,000 base pairs. Their Expression Optimization and Codon Optimization services also offer the flexibility to design DNA sequences for various expression systems or future subcloning manipulations.

Genscript (New Jersey) Pharmaceuticals and biotechnology

GenScript is a biology Clinical Research Organization that focuses on early drug discovery and development services. Built on their assembly-line mode solution, GenScript provide a range of services that include Bio-Reagent, Bio-Assay, Lead Optimization, and Antibody Drug Development

Scarab Genomics (Wisconsin) Clean genome *E. coli*

Scarab Genomics has bioengineered the Clean Genome® E. coli by deleting over 15% of the genome. Genome reduction optimizes the E. coli as a biological factory and makes the Clean Genome® E. coli a popular strain for a wide spectrum of applications ranging from routine cloning to production of biopharmaceuticals.

Gevo (Colorado) Biofuels

Gevo are developing next generation biofuels such as butanol by engineering suitable host organisms that utilize carbon and energy efficiently for fuel production. They have also developed a proprietary process to convert agricultural waste products into different types of renewable, alcohol-based, liquid fuels.

Chromatin Inc (Illinois) Agriculture

Chromatin Inc has patented mini-chromosome technologies that enable the development of new seed products and the delivery of multiple genetic traits in plant systems. The application of this technology will allow agriculture companies to develop new seed products with applications, primarily in biofuel feedstocks and optimised food production.

Europe and the rest of the world

ProtoLife (Italy) Modelling technology

As the amount of data generated using high-throughput experiments in synthetic biology increases, analysis becomes ever more difficult. In order to address this issue, ProtoLife have developed Predictive Design Technology™ (PDT), an automated, intelligent predictive modelling tool that finds optimal targets in huge, complex experimental spaces without exhaustive screening.

BP (Global) Biofuels

An important component of BP's activity in synthetic biology comprises partnering with Synthetic Genomics. The initial phase of the BP/Synthetic Genomics project will focus on identifying and describing the naturally occurring organisms and their natural biological functions that thrive in subsurface hydrocarbon formations. The main goal is to explore and understand subsurface microbial processes. Such an understanding would enable hydrocarbon quality enhancement or increased production. BP and Synthetic Genomics will seek to jointly commercialize the bioconversion of subsurface hydrocarbons into cleaner energy products. The second phase of the BP/Synthetic Genomics program will be a series of field pilot studies of the most promising bio-conversion approaches.

GENEART (Germany) Gene synthesis

GENEART is a company which specialises in synthetic biology. They supply a wide range of businesses such as pharmaceutical & biotechnology companies and the chemical industry as well as academia. Their services include the production of synthetic genes, the generation of gene variants, gene libraries in combinatorial biology and the production of plasmid DNA

DSM (The Netherlands) General

DSM is active in the field of synthetic biology across a wide range of products and services including nutritional and pharmaceutical ingredients, performance materials and industrial chemicals.

Genencor (Denmark) Agriculture and food

Genencor is a Division of Danisco, a multinational food ingredients, enzymes and bio-solutions company based in Copenhagen. Genencor's headquarters and R&D centres are located in the US. They are involved in gene expression, protein chemistry, protein engineering, expression and secretion, and immunology.

Bioneer (South Korea) DNA Purification

Bioneer is a privately held biotechnology company based in South Korea. Its core business is to provide total genomic research solutions ranging from reagents to state-of-the-art instruments used in molecular biology.

Appendix 4 – Call for evidence

Letters from the Chair of the working group were sent to a wide variety of organisations including Government Departments, funding bodies, universities, scientific societies, industries and individuals requesting any information on existing commitments and plans relating to synthetic biology.

Responses were received from the following organisations:

Government and Regional Development Agencies

- Ministry of Defence
- Department for Business, Enterprise & Regulatory Reform
- Department for Innovation, Universities and Skills
- Department for Environment, Food and Rural Affairs
- Technology Strategy Board
- Health & Safety Executive
- Department of Health
- Yorkshire Forward
- Advantage West Midlands
- East Midlands Development Agency
- East of England Development Agency
- London Development Agency

Industry

- Johnson and Johnson
- F. Hoffmann-La Roche Ltd
- Association of British Healthcare Industries
- The Association of the British Pharmaceutical Industry
- Hitachi- Europe
- Amyris BioTechnologies Inc
- Microsoft Research
- AstraZeneca

Research and Funding Councils

- Biotechnology and Biological Sciences Research Council
- Engineering and Physical Sciences Research Council
- Economic and Social Research Council
- Medical Research Council
- Natural Environment Research Council
- Scottish Further and Higher Education Funding Council

Research charities

- Wellcome Trust
- Leverhume Trust
- Cancer Research UK
- King's Fund

Scientific societies

- Royal Society
- Royal Society of Edinburgh
- Academy of Social Sciences
- Institute of Biology
- British Computer Society
- Scottish Crop Research Institute

Universities

- London School of Economics and Political Science
- University College London
- The University of Bristol
- The University of Cambridge
- The University of Oxford
- The University of Glasgow
- The University of Leeds
- The University of Liverpool
- Newcastle University
- The University of Sheffield
- The University of Strathclyde
- The University of Edinburgh
- University of Nottingham
- Lancaster University
- ETH Zurich

Other

- Dr Fillipa Lentzos
- Professor Paul Rabinow
- Professor Luis Campos
- Professor Sven Panke
- Dr Frank Breitling
- Dr Sibylle Gaisser
- Professor Jamie Davis
- Professor Andrew Millar
- Marcus Schmidt

The Royal Academy of Engineering

As Britain's national academy for engineering, we bring together the country's most eminent engineers from all disciplines to promote excellence in the science, art and practice of engineering. Our strategic priorities are to enhance the UK's engineering capabilities, to celebrate excellence and inspire the next generation, and to lead debate by guiding informed thinking and influencing public policy.

The Academy's work programmes are driven by three strategic priorities, each of which provides a key contribution to a strong and vibrant engineering sector and to the health and wealth of society.

Enhancing national capabilities

As a priority, we encourage, support and facilitate links between academia and industry. Through targeted national and international programmes, we enhance – and reflect abroad – the UK's performance in the application of science, technology transfer, and the promotion and exploitation of innovation. We support high quality engineering research, encourage an interdisciplinary ethos, facilitate international exchange and provide a means of determining and disseminating best practice. In particular, our activities focus on complex and multidisciplinary areas of rapid development.

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Excellence breeds excellence. We celebrate engineering excellence and use it to inspire, support and challenge tomorrow's engineering leaders. We focus our initiatives to develop excellence and, through creative and collaborative activity, we demonstrate to the young, and those who influence them, the relevance of engineering to society.

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Using the leadership and expertise of our Fellowship, we guide informed thinking, influence public policy making, provide a forum for the mutual exchange of ideas, and pursue effective engagement with society on matters within our competence. The Academy advocates progressive, forward-looking solutions based on impartial advice and quality foundations, and works to enhance appreciation of the positive role of engineering and its contribution to the economic strength of the nation.

The Royal Academy of Engineering promotes excellence in the science, art and practice of engineering.

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