scottish science advisory council

Synthetic Biology: opportunities for Scotland

A Report by the Scottish Science Advisory Council

SCIENCE AND ENGINEERING DELIVERING THE FUTURE

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The terms of reference for the SSAC are to advise the Scottish Government's Chief Scientific Adviser on a broad range of scientific issues and science-related policies that will grow our economy and raise our quality of life and will further enhance Scotland as a science nation. To address the breadth of the remit of the SSAC the membership of the Council has been drawn from right across the science, business and academic communities and has a broad range of expertise and experience in science-related matters.

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Executive Summary

Synthetic Biology is a new and potentially disruptive technology that offers new opportunities for Scottish science and Scottish industry. Disruptive technology means a technology that displaces established methods and transforms industrial practice. In particular, Industrial Biotechnology is being transformed by the approaches that synthetic biology allows. It brings the principles of engineering to molecular biology and genetics, allowing rational design of the properties of organisms and the materials that they produce. Currently the near-application developments are mainly with microorganisms, although there are important research programmes on plants and animals.

At present synthetic biology is a significant incremental development on molecular biology and genetic approaches, made possible by advances in DNA sequencing, DNA synthesis and our understanding of biochemical processes. However, it has the potential in the long term to become a truly disruptive technology, allowing completely new approaches to industrial production, health and medicine, energy, agriculture and the environment.

Scotland has great strengths in synthetic biology. The collaborative research pools in our major universities are developing methods that will help create a platform technology that can be used in a variety of industries, and are training a new generation of researchers in these methods. The Industrial Biotechnology Innovation Centre has recently been created and has the potential to take forward the outputs of synthetic biology. It is important that the advances made by our research scientists have impact in the Scottish economy and are not taken to be developed elsewhere in the world. Several Scottish industries are developing expertise in synthetic biology to apply the methods to production of drugs and fine chemicals. The existing expertise in chemistry, fermentation and distilling, and pharmaceuticals will give Scotland an immediate advantage in commercialising our discoveries in synthetic biology.

The governance of synthetic biology research and development is covered by stringent regulations devised, in part, for GM technologies. It is anticipated that most applications of synthetic biology will be physically contained, using microorganisms that cannot survive outside the laboratory or industrial process. A key question for Scotland is how to translate its strengths in synthetic biology into economic impact and how the potential of synthetic biology and future applications can address the Scottish Government's purpose of supporting sustainable economic growth in areas such as food and drink (including agriculture), energy and life sciences.

Why is it important to consider Synthetic Biology now?

The UK's Synthetic Biology Roadmap[1] defines synthetic biology as: "*the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems.*" It further states that "*It has the potential to deliver important new applications and improve existing industrial processes – resulting in economic growth and job creation.*"

Simply put, this is the introduction of engineering design principles to the modification of biological systems, usually in order to develop new properties of such systems. To some it is seen as an extension of existing genetic tools, whereas to others it is a revolution in biological research and technology development, allowing greater precision in modification of the properties of living organisms and greater predictability of outcomes[1]. As such it has been the subject of scientific and public debate, with review documents produced by the Research Councils[2], The US Presidential Commission[3], NGOs[4,5] and other groups[6,7]. This year IAP, the global network of science academies, published their report on the opportunities and governance of synthetic biology[8] and the OECD has published a book outlining the emerging policy issues[9]. Synthetic biology is one of the Eight Great Technologies propounded by the UK Minister for Science[10], and has received considerable investment from the Research Councils[11] and within individual industries. Synthetic biology approaches are being used internationally both to understand fundamental biological processes, and to design new systems with novel properties.

Synthetic biology is a newly-emerging discipline that arises from recent advances in molecular biology and genetics. It is being used in the development of new vaccines, biofuels, chemical feedstocks and novel drugs, and it has the potential to reduce the costs of production of these. At present it may be viewed as an incremental step in molecular biology and precision genetic modification, but it has potential to be a future disruptive technology, creating novel scientific discoveries and developing new industries. The subject is developing rapidly and Scotland needs to continue to be at the forefront of the area if it is to reap the benefits of the potential applications. These are varied and some are described in the subsequent sections.

Scotland already has considerable academic expertise in synthetic biology at our major universities and the establishment of the Industrial Biotechnology Innovations Centre (http://www.ibioic.com) has the potential to transfer this academic expertise to commercial projects. Several industries have expressed their interest in developing this technology. Ingenza, a Scottish company with 37 employees, is currently producing speciality chemicals using a synthetic biology approach.

Scotland needs to develop the necessary framework for synthetic biology if it is to seize the opportunities that synthetic biology presents.

What is Synthetic Biology?

Synthetic biology is a relatively new technology, which has been made possible through developments in DNA sequencing, DNA synthesis and molecular cloning technologies. It has the potential to create new genetic variants of organisms. Alongside these biological advances, computer algorithms have been developed to model and predict the outcomes of these biological modifications. In addition, different functional segments of DNA (those encoding proteins, and those regulating the expression of these proteins) can be catalogued and their individual properties determined. This provides scientists with a toolkit to combine these different segments within a host cell in specific combinations to achieve a desired outcome, such as the production of a particular biomolecule, or a response to a defined stimulus.

Although methods of genetic modification are now much more precise and the outcomes more predictable than they were several years ago, as illustrated in the recent report to the UK Council for Science and Technology[12] and by the development of new techniques[13], these still mainly depend on pre-existing genes and gene products. Synthetic biology couples the ability to create completely novel biological systems with predictability of outcome. It is the promise of predictability in modifying biological processes, and the potential to create completely new processes, that underline the potential wide-ranging impact of synthetic biology.

Ultimately all biological information resides in nucleic acids, which encode the proteins that produce biological effects and the way they are expressed. In most cases the nucleic acid of interest is DNA. Our ability to sequence DNA rapidly and the computational power to analyse the function of different DNA sequences has provided us with knowledge of functions encoded within the genes of a wide variety of organisms. Combined with the ability to synthesise long stretches of DNA cheaply and quickly, this has allowed scientists to engineer biological systems capable of responding in a number of different ways (See Case Study 1[14]). A significant example in this area was the synthesis of the complete genome of *Mycoplasma genitalium (a simple bacterium),* its insertion into a bacterial cell from which the DNA had been removed, and subsequent confirmation of the viability of this constructed bacterium[15].

The process of expressing the genetic information encoded in DNA involves transcription into another nucleic acid, RNA, and translation of that RNA into protein, which may then be specifically delivered to its site of action in the cell. However, at each stage there are controls, not just of the on/off expression, but the rate and duration of protein production, and even the location of the expressed protein. In simple organisms, such as bacteria, regulation of the expression of genetic information is mostly at the transcription of DNA into RNA. In yeasts and higher organisms, control may be exerted at one or more stages in the expression of functional protein.

Synthetic biology is multidisciplinary, combining biological and physical sciences, information technologies and engineering. Importantly, it has the potential to underpin many different industries. The complexity of synthetic biology and its applications are summarised in the UK's Roadmap for Synthetic Biology (see Figure 1).

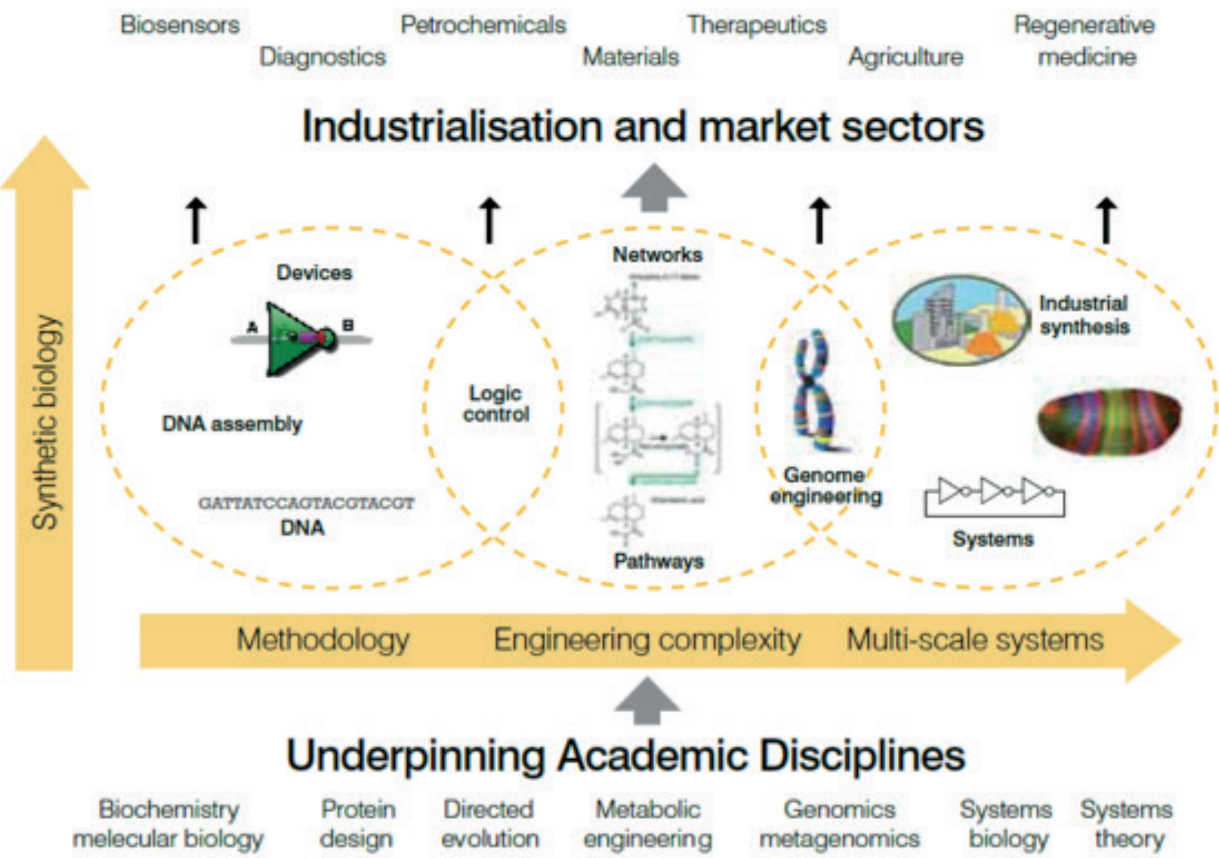


Figure 1. Taken from "A Synthetic Biology Roadmap for the UK". "*Synthetic biology is both a platform technology (building a systematic basis for design – combining biological, engineering and computational capabilities) and a translational technology (providing the link between a wide range of underpinning disciplines – ranging from biochemistry to systems theory – and practical applications in a wide range of different market sectors).*"

Applications of Synthetic Biology

Synthetic biology is a platform technology that supports product development across many different industries, such as chemicals, health and medicine, energy, and agriculture. Scottish scientists are actively involved in developing the technology.

As an enabling and disruptive technology, potentially displacing the way in which products are currently manufactured, there are three broad areas to be considered:

- *Fundamental and applied research.* This underpins the understanding of how different DNA sequences can be combined to achieve different end-results, and incorporates RNA, protein, carbohydrate, lipid, and systems biology research. One way of looking at this, quoted by one of the practitioners interviewed for this project, is 'learning by building'. To do so effectively also requires significant computational capabilities to understand and use biological data to simulate or model the interaction of components. One ultimate goal of such research will be a catalogue of standardised biological parts, an achievement where the function and interplay of components with each other will be understood, allowing transfer of designs between biological systems with the confidence that they will work as expected.
- *Economic and environmental impact.* There is broad consensus that synthetic biology will have significant economic impacts through its applications in industrial biotechnology (including the production of fine chemicals, pharmaceuticals, biosensors, and biofuels), in medicine and health (including pharmaceuticals and diagnostics) and in agriculture (including agrochemicals, sensors, new plant and microbial crop varieties, and improvements to livestock). Many of the perceived applications will be under conditions where the synthetic organisms are contained by both physical and biological barriers. The technology could lead to considerable environmental benefits through, for example, using the products of synthetic biology for sensing environmental chemicals (such as pollutants or agrochemicals), for replacing fossil fuels with biofuels or non-carbon fuels (such as hydrogen), and for treatment of toxic wastes before release of the detoxified material to the environment. Any potential environmental or other risks from synthetic organisms being released into the environment would require mitigating regulation based on substantial scientific investigation to develop the evidence base to inform policy decision and regulatory needs.
- *Societal aspects.* The potential for desirable impacts on human health and the environment, and the issues of equitable access to knowledge and products have driven significant academic research and commercial interest. There appears to be little

public interest or understanding of synthetic biology, although a number of NGOs have expressed views internationally. The stakeholders in the future of synthetic biology in Scotland include large multinational companies, SMEs, the public, Scottish NGOs, local and national governments and academic, government and industrial natural and social scientists.

When considering the impacts of synthetic biology, it must be appreciated that we are at an early stage in the realisation of its full potential. There is much more to be learned at a fundamental level; so the current opportunities are more about the development of the tools that will enable the development of future products rather than about the specific products themselves. Nevertheless, one market research company has published its estimates for the global value of the synthetic biology market as $1.6 billion in 2011 and projected to rise to $10.8 billion by 2016[16].

As an enabling technology, synthetic biology supports a large number of industrial sectors through the realisation of new methods for the manufacture of chemical precursors and final products. In some cases the final products may be the engineered organisms themselves, such as engineered microorganisms to catalyse specific reactions, or disease-resistant crops or livestock. It is also a disruptive technology that may displace existing ways of manufacturing through the use of different raw materials and new process technologies. Ultimately, it is hoped that it will improve efficiency, sustainability and the environmental impact of some manufacturing processes.

It is clear that we should not limit the application areas of synthetic biology to a few industrial sectors. It has potential that is perhaps better thought of as partially visualised, but in the short term (15 years) impacts can be predicted in the following areas: energy, medicine and health, agriculture, and the environment.

1. Fundamental Research

Synthetic biology has a significant role to play in understanding how living organisms work. We are still some way from full knowledge of the function of all genes in the best studied of all organisms, the laboratory bacterium *E. coli,* for which the functions of some 20% of its genes are still not known[17]. Other microorganisms which are pathogenic or may be industrially important and all higher organisms are even less-well understood.

The ability through synthetic biology to make highly specific modifications to the genetic make-up of a model organism and to study these in the laboratory provides a powerful tool to understanding of fundamental processes in microorganisms, plants and animals and in the study of disease.

As well as making a major contribution to the advancement of knowledge, such studies will underpin many areas of application. Allied with this work is the expansion of the biological repertoire available to scientists to construct new genetic pathways, proteins and cells to catalyse reactions that would not normally occur in nature. Researchers in Scottish universities are at the forefront of developing the techniques of synthetic biology in order to understand how organisms work, as well as to apply these techniques to create novel products.

The ambition of many academic researchers in the field is to create a database of standardised parts and shared tools for manipulating DNA. The BioBricks Foundation (http://biobricks.org/) is such an initiative. This provides open access to DNA sequences (through a parts registry), and protocols for cloning and expressing different nucleic acids and proteins. Information is also shared through an annual international conference and an annual international competition (iGEM) for student teams from across the globe to address real-world problems (e.g. pollution) through engineered biological solutions (see section on International Activities and Perspectives).

Despite the fact that there are already commercial products utilising synthetic biology (see sections below), there are still many unknowns. To synthesise the kinds of novel compounds within cells that are of most interest (such as precursors for biofuels, pharmaceuticals, and agrochemicals) may require the introduction of new steps within metabolic pathways, or even completely new pathways. Achieving this requires the identification and characterisation of all the steps within the relevant pathway(s) to synthesise the desired product[18].

2. Industrial Biotechnology

Industrial biotechnology underpins many relevant areas, and it is here that synthetic biology will have a most immediate impact in improving existing bioprocesses and introducing new biotechnology for the production of simple and complex chemicals. These include fine and speciality chemicals (the precursors of many pharmaceuticals and agrochemicals), biofuels and bioplastics. Such products are currently often sourced from petrochemicals, and synthetic biology may allow renewable biomass to replace fossil resources. Using a synthetic biology approach, the company Ingenza is developing replacement routes to petrochemical starting materials to make products for Lucite International, Invista and other global leaders in polymer manufacture.

Synthetic biology approaches may also help replace toxic or noxious materials, used in current processes, with biobased ones (e.g. reducing the need for heavy metal catalysts and organic solvents). It may also help reduce resource use (energy, water, feedstocks), improve production rates, reduce waste, and minimise contaminating residues in the final product. Thus, there are both environmental and quality benefits to be realised through a biotechnology approach.

Modifying existing biochemical pathways within microbial hosts will be critical to the success of such novel processes (see Case Study 2). In some cases this will require new or modified enzymes to be created which will catalyse new reactions[18]. This has been done using existing methods of genetic manipulation (such as the formation *in vivo* of novel hybrid antibiotics[19]), but synthetic biology allows more precise regulation of expression. Genetic regulatory sequences may allow switching between different metabolic pathways in industrially-relevant microbes. This could potentially allow fine-control of product output[20].

Microbial cells are central to the realisation of such synthetic pathways, as they grow rapidly and can produce significant quantities of biomass or metabolites. It is also easier to purify expressed products from microbial extracts. The production of simple chemicals or purified enzymes from modified microbial cells could happen within a year or two. There is interest in using synthetic biology methods to produce urgently-needed novel antibiotics[21].

In some cases the approach might be to engineer a microbial cell to express a suite of enzymes that perform multi-step processing, in order to simplify and/or increase the efficiency of existing industrial processes, such as in the manufacture of biofuels as discussed in the section on Energy. In others, a novel enzyme may be extracted and used alone, for example in the food and drink industries, in which the enzyme is a processing aid rather than an ingredient of the food or drink product.

The recent funding of the Industrial Biotechnology Innovation Centre by Scottish Funding Council and Scottish Enterprise will provide a focus for commercialisation of Scottish science in industrial biotechnology. The National Plan for Industrial Biotechnology[22] notes that industrial biotechnology offers the opportunity for future sustainable growth. To achieve maximum economic benefit, synthetic biology must be part of industrial biotechnology in Scotland.

3 Medicine and Health

The application of synthetic biology in medicine and health includes the rational design of new active therapeutics for the treatment or prevention of a wide variety of diseases, the manipulation of existing disease vectors to reduce or eliminate the spread of disease, and theranostics (combined detection and treatment of disease).

The active components of approximately 20% of pharmaceuticals are biomolecules (e.g. insulin), and this has increased from approximately 10% in 2002 as our understanding of bioactive compounds increases and as industrial biotechnology processes can manufacture these at high purity. Synthetic biology is expected to further increase this share by simplifying production processes, reducing the cost of manufacture, and increasing the availability of variants on natural products. Synthetic biology may also go some way to reducing side-effects through limiting the presence of co-purifying biomolecules in the final preparation.

A number of potentially beneficial drugs are not brought to market because the costs of production are higher than the market will bear. Synthetic biology may provide a cheaper alternative to production that will bring such pharmaceuticals into clinical use.

The anti-malarial drug, artemisinin is normally made by extraction with organic solvent from the sweet wormwood plant, *Artemisia annua.* However, artemisinin levels in the plant are low, and highly dependent on growth conditions. In 2006, artemisinic acid (the precursor for artemisinin) was successfully produced in yeast[23]. This was the first time a complete multi-step pathway had been constructed in the laboratory and introduced into a host cell. It was subsequently commercialised by Amyris Inc (a US-based company) with the support of a $42.6m grant from the Bill and Melinda Gates Foundation, and is now being manufactured in sufficient quantities by Sanofi for global distribution.

Theranostics, the combination of a diagnostic element with a therapeutic response, has raised public concerns[24] due to the automatic dosing and removal of human control. Nevertheless, it offers a potential solution to chronic and lifestyle illnesses. Through systems biology knowledge, it is possible to design complex gene expression systems for components that detect the presence (or an increase in the level) of a specific target, produce a response to decrease that level, and switch off this response when the target concentration returns to normal levels. A good example of this is for type 1 diabetes, where systems can be engineered to monitor blood glucose level and release insulin in response to an increase, switching off insulin production when glucose levels return to normal. Such engineered networks can be housed within human cell types (from the patient or a donor, in which case they can be contained within a protective mesh to prevent rejection by the patient's immune system) or in bacteria (as described above).

4. Energy

Synthetic biology may contribute in several different ways to the sustainable energy agenda. The generation of fuels from biological materials as a direct replacement for petroleum-based fuels can be carbon-neutral. Other fuel products, such as hydrogen, might be generated from waste materials or from sunlight; microbial generation of electricity from hydrogen is a possibility. The drivers are sustainability, e.g. reducing dependence on non-renewable fossil fuels, and potentially decreasing greenhouse gas emissions, e.g. for compatibility with existing energy supplies.

A number of useful fuel components have been produced from plant materials, either the structural components of plants, such as cellulose and lignin in wood, or from the sugar and starch products. Some of these chemicals, such as alcohols, can be added directly to petroleum fuels, while other, more complex long-chain hydrocarbon compounds can be converted into diesel-like fuels. There has been concern raised about competition between fuel production and food production, both in terms of the use of cereals, but also in the use of land. Use of the non-food components of food crops (leaves, stalks, etc.) or specific fuel crops, such as energy beet, and the use of marginal land that is not appropriate for growing food, is minimising the competition for food crop resources. Synthetic biology may help in several ways – as a technique for assisting rapid breeding of plants (see section on Agriculture below) which are capable of withstanding climatic changes, such as drought, and in the creation of microorganisms that can catalyse bioconversions of plant materials to desirable products.

The conversion of biomass into useful feedstocks or end products has been a challenge for conventional industrial technologies, with low throughput and low yields commonplace as a result of the inefficiency of metabolic pathways, and toxicity of products to the host cells. Synthetic biology, combining multiple enzymatic steps within a single host cell, and at the same time optimising output towards the compound of interest, could address this.

Photosynthetic algae have the potential to produce hydrogen, ethanol, and precursors for diesel production [25]. The main attraction is that they can produce more than 50 tons of biomass per acre per year, and only require light, water and simple nutrients. Although there are still knowledge gaps, algal genomes can now be effectively manipulated, and there is a greater understanding of the different metabolic pathways involved in the synthesis of more complex carbon-containing molecules (such as lipids), and the factors which control them, allowing efficient production of a desired product and minimal production of contaminants.

Bacteria, grown as films on the surface of electrode materials, show great promise for the production of hydrogen from a variety of feedstocks in response to an electrical circuit (which can be produced from simple salt concentration gradients) and are more efficient at producing hydrogen than solar hydrolysis of water or fermentation[26]. Essentially these are operating as microbial fuel cells, and have great potential in managing wastewater streams[27].

There is a number of commercial players in this area. Amyris (http://www.amyris.com/) is probably the best known, and has engineered yeast to manufacture 'Biofene' the brand name for farnesene (a terpenoid) produced from sugarcane. Biofene can be further processed to supplement or replace diesel and aviation fuel[28]. Sugarcane is the world's largest crop, so there is considerable potential for its diversion to biofuel production, to either generate long chain hydrocarbons such as farnesene or simple alcohols such as ethanol. Amyris and other companies such as Mascoma (http://www.mascoma.com) and Coskata (http://www.coskata.com) are also using synthetic yeast and bacteria to produce biofuels from a number of more complex cellulose-based sources. Such microbes have additional enzymatic pathways that allow them to break down complex carbohydrates and make use of their different component sugars.

5. Agriculture

One of the main agricultural applications of synthetic biology is the synthesis of useful compounds from crop and agricultural wastes[29]. However, there is also growing interest in the use of synthetic biology tools to support crop and animal breeding[30] through directing traditional breeding programmes to realise desired outputs in a shorter space of time. Synthetic biology creates an opportunity for better understanding of genetic traits responsible for desired characteristics and to improve disease resistance, nutritional value, and the expression of desired compounds.

Traditional methods of plant breeding can take up to ten years to produce new varieties and involve crossing existing varieties that exhibit different desired traits (e.g. drought, wet or cold resistance, grain productivity, disease resistance). This process may well take several plant generations to yield results. A method known as marker-assisted breeding can shorten this process considerably by cloning relevant genes and using these to analyse the progeny of a cross between varieties. Such methods are already used in Scotland[31]. Synthetic biology may simplify the analysis of the complex genetic differences between the varieties, to monitor and direct the approach of breeding programmes. Unlike GM technologies, these approaches do not directly modify the parental lines but analyse their traditionally-bred progeny. It also enables the breeder rapidly to check that other desirable properties are maintained, whereas they may be inadvertently lost in traditional breeding methods which focus on a single genetic property.

Synthetic biology can also be used to support marker-assisted breeding of domesticated animals (for example, cattle and salmon). There are currently insufficient data to model outcomes of large scale breeding successfully. However, advances in DNA sequencing, leading to a greater availability of animal genomes and the characterisation of genetic traits, are allowing design of breeding programmes[32]. Such approaches, rather than selecting sires for artificial insemination on the performance of their offspring, could immediately allow selection for better disease resistance, improved meat or milk production or quality, or improved utilisation of feed[33,34]. Other research of relevance to Scotland is focused on understanding the pathogenicity of microbes that exist in livestock and can affect quality and output. There are particular strengths in these areas at Scotland's Rural College, The Roslin Institute and The Moredun Research Institute.

There is also the potential to modify plants to contain novel synthetic pathways that allow the enhanced (or novel) production of valuable materials, such as nutritional proteins, oils, vitamins, and precursors of fine and speciality chemicals. Examples include production of omega-3 and omega-6 oils expressed in soya, canola, and linseed[35]. This research has also underlined the complex interaction of the proteins encoded by the introduced genes (several of algal origin) with that of the host enzymatic pathways, with some hosts performing poorly or not all. Thus, ongoing research to understand and model such biochemical pathways and the interplay of component enzymes is required.

Other advances that could have an impact on the agricultural industry include biosensing using whole microbial cells for the measurement of agrochemicals and pollutants in soil and groundwater, or the presence of specific biochemicals in crops or livestock. These could replace crude measurement technologies currently in use on the farm or the more expensive and time-constraining off-site laboratory analyses using specialist analytical equipment. Such systems could be used for the real-time monitoring of growing conditions of crops or the health and welfare of livestock. The sensor system may exploit the normal microbial pathways to detect and respond to the presence of the target and link this with an electrical or optical readout (e.g. fluorescence or colour change)[36]. Such systems also have applications in human health to monitor blood metabolites and in *in situ* environmental monitoring.

We anticipate that with increasing pressure for sustainable intensification to feed the increasing human population, the food industry will use the products of synthetic biology to process foodstuffs even if the products are not a significant component of the food itself. This is being seen with GM as it becomes a more widely-used technology outside Europe. We anticipate that agricultural products created by synthetic biology will be part of international trade within the next decade. The expertise in land-based studies in Scottish research institutes will be important in understanding the impacts of synthetic biology in agriculture and in the environment.

6. Environment

Synthetic biology could have wide-reaching environmental benefits including:

- Monitoring the levels of agrochemicals in crops (to target sprays and reduce accumulation in the environment).
- Remediating contaminated land and ground water (through sequestration of toxins, or conversion into benign products).
- Concentrating valuable and rare minerals (such as precious metals).
- Minimising crop losses and the use of agrochemicals through supporting the breeding of crops that are more resistant to diseases or to environmental stresses, such as drought.

Microbes, and in particular bacteria, are known to be capable of degrading or transforming industrial waste into a source of energy and food[37]. The University of Minnesota database (http://umbbd.ethz.ch/index.html) lists over 200 relevant microbial biocatalytic and biodegradation pathways from 540 different microorganisms. Even remediation of contaminated land and concentrating valuable and rare minerals can be part of a contained industrial process, such as those already used for end-of-pipe remediation of wastes[38]. Work at the University of Edinburgh (and other UK institutions) uses bacteria modified with synthetic pathways to isolate and identify pollutants from the environment (see Case Study 3). This may have a major impact on industries such as the whisky industry, which releases copper from the distillation process into the environment and is looking for an economical method to reduce this to zero by 2020.

Chlorophenols are an important group of pollutants, used in the production of a number of pesticides and released into the environment as a by-product of industrial processes. Although several different bacterial enzyme pathways have been identified that can catalyse the breakdown of chlorophenols[39], research has revealed that the presence of such biocatalytic pathways does not always translate into activity, and in some cases only part of the pathway may be active. It is therefore likely that in natural environments multiple microbial species interact synergistically to degrade pollutants. One future approach will be to use synthetic biology to engineer ‘consortia’ of microorganisms, each performing a specific function, which combine to fully degrade pollutants in a contained system[37]. Such research will be supported by extensive biopart databases, greater understanding of microbial synergy, and modelling tools to predict outcomes.

Case studies

Case study 1:

Constructing Artificial Yeast Chromosomes (University of Edinburgh)

The University of Edinburgh is a partner in the international project to build complete synthetic yeast chromosomes. Such research will allow scientists to study and understand the interplay between different genes and genetic regulatory sequences in this important commercial and model organism. The first results of this work were published earlier this year[40].

http://www.synthsys.ed.ac.uk/news/synthsys-pi-world-first

Case Study 2:

Genome Segment Assembly (Ingenza, Roslin Biocentre)

inABLE® is a proprietary technology that allows many different combinations of DNA sequences to be designed and tested in parallel (all are expressed in bacteria). The approach might be to take a bacterial gene encoding a desired protein (e.g. one that synthesises an industrially relevant chemical) and look for similar genes (homologues) in species that are adapted to environments that might be expected to improve the original protein's function (e.g. thermophiles, allowing the protein to work at higher temperatures). Parts of the original gene are substituted for those in the homologue to create many different combinations, which are screened to identify constructs showing the desired improvement on the original. This approach massively increases throughput and therefore decreases development time.

http://www.ingenza.com/technology-overview.php

Case Study 3:

Cleaning Land for Wealth (University of Edinburgh)

This project aims to generate useful products from contaminated land. In the first stage plants (such as ferns and sunflowers) accumulate heavy metals from contaminated soils (a process plants do naturally, different species accumulating different metals). In the second stage the plants are macerated and digested in a contained bioreactor using bacteria (containing synthetic pathways) to extract the metals and deposit them as nanoparticles. These have many applications such as industrial catalysts or for medical treatments. Additionally lignocellulose from the plant material can be processed into useful chemicals.

http://horsfall.bio.ed.ac.uk/page2/page2.html

Case Study 4:

Solar energy to produce fuels (University of Glasgow)

A project at the University of Glasgow aims to use 'artificial photosynthesis' to generate hydrogen from water and to combine the hydrogen with carbon dioxide to produce methanol and other potential liquid fuels. It combines biological systems and inorganic chemistry to generate catalysts for these reactions. The intention is to use the power of sunlight to produce fuel on a large scale. This had advantages over just using solar panels to convert solar power into electricity as on a large scale fuels are easier to store than electricity[41].

http://www.glasgowsolarfuels.com/proj.bio-insp.html

Societal views

The BBSRC and EPSRC undertook a large public consultation in 2009-10 involving 160 members of the UK public in three workshops, preceded by 41 stakeholder interviews (with scientists, engineers, social scientists, religious groups, NGOs, consumer groups, industry, funding agencies, and government) to understand the perspectives of key groups (http://www.bbsrc.ac.uk/syntheticbiologydialogue). This study found that once introduced to the concept of synthetic biology, the wider public recognised and was enthusiastic about its potential benefits, however this was conditional, as they also recognised the uncertainties and potential risks, summarised as:

- Progressing too quickly to be certain of understanding all the potential risks (e.g. the (un)intentional release of novel organisms into the environment raised significant concerns, the ultimate effects of which would be unknown due to the many variables that have not yet been studied);
- A lack of common international regulation and legislation, and adequacy of existing systems, a strong sentiment that self-regulation by scientists was insufficient, and that DIY synthetic biology was a real concern in this respect;
- The role of scientists, who are perceived to be concerned primarily with their own research area, and not the larger potential impacts that will come about through the totality of synthetic biology research;
- Reducing nature to a catalogue of parts, which fails to take account of its vast complexity, and thus introduces uncertainty in the outcomes of a designed system.

In terms of the perceived balance between benefits and risks, there was greatest support for medical technologies (80%), followed by energy topics (78%), as long as these did not lead to a greater burden on arable land and water. In contrast, perception about risks versus benefits for environmental remediation and agriculture were more equally divided.

In this respect, informed public opinion on synthetic biology is similar to other emerging technologies, such as nanotechnology. It is acknowledged that such technologies can address the key societal challenges of health, energy, food, water, and sustainability, and also a recognition that there will be uncertainties associated with any technological development. So it is imperative that scientists and industry are open about the potential risks and engage with regulators and the wider public at the earliest stages. Furthermore, there is a strong sentiment that addressing societal needs should be at the heart of new developments. In this regard, scientific leadership was seen to be important in framing the direction of research and embedding societal values from the beginning.

Although the majority of the public is not aware of the nature of synthetic biology, most of those that become aware realise that it has the potential to address many societal grand challenges. At the same time many also believe that it has the potential to do harm if not regulated properly[7]. A recent Ipso MORI poll ("Public Attitudes to Science 2014"[42]) revealed that many more people believe that the benefits from synthetic biology outweigh the risks than the other way round (42% to 9%). Whereas, in the same poll 36% believed the benefits of GM outweighed the risks compared with 28% who believed the opposite, although the respondents felt better informed about GM than about synthetic biology.

Public opinion and understanding of the nature and purpose of synthetic biology developments will be critical to its potential success. Transparency in this engagement is essential, unknowns and potential risks must be discussed to address them and maintain trust. In this respect, it was also pointed out that there was a fundamental difference between GM and synthetic biology. GM has been essentially viewed as industry-driven, whereas synthetic biology is being driven forward in a collaborative manner, principally by scientists and other interested stakeholders, such as small industrial biotechnology companies. Moreover, GM products have been used for a number of years and have become more acceptable in many parts of the world, with a growing evidence base that suggests that they are safe for human health. With the greater precision available to synthetic biology, it may be a technology that the public finds easier to accept.

Appropriate governance will be critical to the success of synthetic biology. As advocated by a number of researchers and policy organisations, this will need to adapt to the changing knowledge regarding the interaction of bioparts with each other inside a synthetic organism, and the interaction that organism has within its contained environment[3,43,54].

Several international NGOs have expressed strong negative views about synthetic biology[4,44,45] and have called for a societal debate about issues including risk, transparency, environmental protection, governance and intellectual property rights.

UK environmental NGOs are reviewing and responding to developments in synthetic biology including Friends of the Earth (http://www.foe.co.uk), Genewatch (http://www.genewatch.org) and EcoNexus (http://www.econexus.info/,). The Soil Association (http://www.soilassociation.org) is currently developing its position on synthetic biology.

We were unable to consult with many Scottish NGOs or Scottish branches of UK NGOs as they had apparently not yet developed their thinking on synthetic biology. However, we were able to engage with a number of other stakeholders including academics, industrialists, patient groups, medical and health professions, and agricultural professions. These were broadly supportive. The Church of Scotland has published a report on synthetic biology, which recognises the potential benefits to be derived from synthetic biology, but is also concerned about deconstructing life, risks and equitable access (http://www.churchofscotland.org.uk/speak_out/science_and_technology/articles/synthetic_biology). The consumer organisation Which? has not assessed synthetic biology to a large extent but is monitoring developments and considers aspects relevant to other new technologies as equally important here. This includes ensuring public engagement from an early stage (to understand public concerns and what is/is not acceptable), and adopting an approach to regulation and funding that ensures safe and responsible innovation. In this, we must anticipate that there will be many different views expressed and no single voice should necessarily predominate. While ensuring engagement with many disparate views present challenges, there is considerable experience in this area and Scotland is world-leading in this regard. Work on societal views of synthetic biology must be linked with work on its governance.

Governance

Minimising risk is of paramount importance to any new technological development. Risk, defined as the combination of hazard and exposure, cannot be completely eliminated but can be minimised. The initial concerns regarding the unpredictability of outcome in the development of genetically modified organisms (GMOs), and in particular of GM crops, do not apply directly to synthetic biology. Although both technologies involve genetic modification of organisms, the fundamental tenet of synthetic biology is that the modifications are modelled and the properties of the organism are predicted. The use of the modified organism under containment will minimise the environmental risk.

The regulation of synthetic biology has been the subject of considerable debate. In 2010 the US Presidential Commission published a report on the *Ethics of Synthetic Biology and Emerging Technologies*[3] in which the mechanisms of management of risk and the necessity for international coordination and dialogue were proposed. In Europe there has been a number of publications in the scientific literature(e.g. [46,47,48]) and from the EU[49].

The principles of synthetic biology should be based on safety by design. Microbes that have been developed using synthetic biology techniques, whether for lab research or industrial production, can be contained both physically (in closed fermenters) and biologically (require defined nutrient and growth conditions not found in the outside environment). This has been standard practice in the biotechnology industry for the past 30 years or more and there are robust regulations in place. The products of synthetic biology, whether they are living organisms or chemical products, will be subject to existing regulatory systems that are very stringent, although these may need to adapt as the technology develops. The primary international agreement is the Convention on Biological Diversity (https://www.cbd.int/) and its Cartagena and Nagoya protocols.

Further research looks to build upon this through engineering multiple built-in safety mechanisms to limit or prevent growth outside of their intended environment, and prevent the transfer of novel genes to other microorganisms[50]. Such 'biological containment' includes genetically altering microbes to require a supplement (not found in nature) for their survival, such as inactivating an enzyme responsible for the production of an essential metabolite, or expressing inhibitors of essential proteins within the microbial cell. Other more radical options make use of synthetic DNA or amino acids (the building blocks of proteins), plus the cellular machinery that controls gene expression and protein translation, to confer both dependence on synthetic growth media (thus preventing growth outside of laboratory conditions), and prevent any expression of genetic material in case of transfer to a natural microbial cell[51]. Such biological containment associated with physical containment systems means that release and survival of such synthetic organisms in the environment is of minimal risk.

International Activities and Perspectives

Synthetic biology research and development is taking place in most nations with a strong technological research focus, although it does not rank prominently in many government strategies. A brief review of the strategies in selected countries and the EU is given in Annex 1.

There are several international activities supporting and monitoring the development of synthetic biology. One of the main collaborative networks is the BioBricks Foundation (http://www.biobricks.org) which was set up in 2006 by researchers at MIT. Its mission is to '*ensure that the engineering of biology is conducted in an open and ethical manner to benefit all people and the planet.'* To achieve this it hosts a variety of online tools and opportunities for individual researchers to connect and collaborate:

- An online catalogue (http://openwetware.org/wiki/Labs) of synthetic biology protocols and training courses, and a directory of labs performing synthetic biology research;
- An open source repository of DNA sequences that are known as BioBricks;
- An annual international conference that brings together researchers and other interested individuals to discuss developments in synthetic biology.

Associated with the BioBricks, is the iGEM Foundation (http://igem.org/). This holds an annual competition for the design of synthetic biology solutions to real-world problems. Known as the International Genetically Engineered Machine competition (iGEM), it is open to teams of undergraduate and postgraduate students from research institutions across the globe. These students make use of standard parts (either those catalogued by the BioBricks Foundation, or generated through iGEM) or develop their own new parts to address a specific issue. Examples of previous competition entries include a bacterial biosensor to detect arsenic in groundwater, a red blood cell substitute using adapted bacterial cells, and an engineered bacterium that produces a spectrum of different colours in response to the presence and amount of a specific target molecule. The first iGEM competition took place in 2005, and 133 teams from around the world took part in the 2013 competition. Teams are multi-disciplinary, involving biologists, engineers, chemists, physicists, and information technologists. It is seen as a valuable learning experience by those participating, allowing individuals to collaborate on solution inspired projects at a stage in their careers when they are not yet pre-conditioned to think what is possible or not. There is a large network of synthetic biologists who make use of shared resources and access to relatively inexpensive equipment for the synthesis of DNA and growth of microbial cultures.

Scottish universities have shown great success in the iGEM competition. Examples can be found at http://igem.org/Team_List?year=2013 (=2012, =2011, etc.) and include over the last five years:

- University of Dundee:
  - TOXiMOP – using synthetic biology to monitor and remove toxins from algal blooms in freshwater bodies (2013). This won a prize in the international competition.
  - Sphereactor – synthetic vessel containing different enzyme cocktails (and no genetic material) to perform specific tasks dependent on the enzymes included, such as the degradation of toxins (2011).
- University of Edinburgh:
  - WastED – remediation and valorisation of industrial waste streams, with a particular focus on Scottish leather, textile, and whisky industry waste waters (2013).
  - EdiGEM – connecting biological and electronic systems in a standardised, inducible and quantifiable way (2012).
  - Synergy – manipulating E. coli to improve conversion of biomass (2011).
- University of Glasgow:
  - DISColi – bio-photolithography in device engineering using different wavelengths of light (2011).
- University of St Andrews:
  - Omega-3 fatty acid synthesis in E. coli with genes introduced from cyanobacteria and trypanosomes (2012).
- University of Aberdeen:
  - ayeSwitch – a genetic toggle switch in yeast for bistable expression of proteins (2010).

Aberdeen, Dundee, Edinburgh and Glasgow universities are entering teams into the 2014 iGEM competition. This will provide another cohort of undergraduates and graduate students trained in synthetic biology techniques.

The main international legislation that would govern synthetic biology is the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. This is an international agreement to which 166 nations, including the UK, have signed up and which *"aims to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking* *also into account risks to human health."* The Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) of the United Nations Convention on Biological Diversity considered synthetic biology's potential implications in 2012. In their report[52] the committee recommended a number of options regarding the potential impact of synthetic biology on conservation and sustainable use of biodiversity, namely that all relevant organisations should consider the impacts of synthetic biology techniques, organisms and products, and submit relevant information to the committee, and that neither synthetic genetic parts or LMOs are released into the environment without proper scientific justification and consideration of associated risks.

The Organisation for Economic Co-operation and Development (OECD) views genomics, biotechnology, and sustainable production of biomass as priority development areas for the next 30 years. According to Gerardo Jiménez-Sanchez (Chairman, Working Party on Biotechnology), half of the OECD member countries are conducting research in synthetic biology. The OECD has undertaken joint initiatives with a number of other organisations including the Royal Society and the BioBricks Foundation, and as a result identified three areas where it might focus its attention: 1) needed infrastructure; 2) approaches for intellectual property (IP) access and sharing; and 3) standards and interoperability.

The World Health Organisation (WHO) published a guidance document in 2010 for responsible life sciences research relating to global health security. In this report the opportunities in health care to be derived from synthetic biology are clearly stated, as are the potential for misuse and ethical, legal and societal aspects, including IP issues and responsibility for oversight[53].

The Bill & Melinda Gates Foundation (http://www.gatesfoundation.org/) has also supported synthetic biology to address global health challenges, with a specific call for proposals in 2011. Funded projects include the development of microbial systems to discover, develop and produce new drugs based on natural products, and the reconstruction of bacterial pathways to screen for novel multi-drug resistant *M. tuberculosis.*

In 2010 and 2011, the national academies for science and for engineering in the US and China partnered with the UK's Royal Academy of Engineering (RAE) and Royal Society (RS) to hold a series of symposia to discuss and deliberate the potential applications of synthetic biology, in terms of its potential to address key issues of climate change, food security, and global health; and also consider the potential risks and obstacles. Participants came from a wide variety of backgrounds including academia, industry, government and NGOs.

Opportunities and Threats

Discussions with practitioners and stakeholders in Scotland indicate the broad belief that synthetic biology is still relatively young with far more potential ahead of it than has been currently realised. As such it would be narrow-sighted to place too much emphasis on specific product development.

It also became clear that knowledge and the ability to put this to practical use were highly valuable in the context of synthetic biology, rather than developing specific products. A number of successful companies are essentially "design houses". These businesses combine their knowledge and understanding of genetic circuits with that of a client to address the client's specific needs (e.g. production of a biomolecule, or adaptation of a microbe to a certain environment) – see for example Case Study 2.

In this context there are parallels with the computing industry – future developments will be ever more sophisticated, requiring considerable know-how to design, implement and control (in the same way that computers evolved from valves to silicon semiconductors, with co-development of complex software and the new discipline of software engineering). This will require strong collaboration and provides opportunities for small businesses to develop niche markets.

Specific opportunities and threats will be described in tables below. However, in broad terms, regulation, intellectual property rights, and standardisation all provide opportunities and threats to the development of synthetic biology in Scotland.

The official position of the EU and many other national governments is that current regulatory guidelines for GMOs are sufficient, but may need to be adapted as knowledge grows regarding synthetic biology. In essence this means proceed with caution and engage in horizon scanning for future issues. One of the key issues, raised by scientists and NGOs, is the issue of containment, and in particular the growth of synthetic algae in open ponds. At present this is not relevant to Scotland, partly because of current climate constraints, but mainly because all discussions with practitioners indicate that current and immediate future uses of synthetic biology under current policy and regulation in Scotland will be in contained systems, either for industrial production, or as laboratory-based tools to support research and development.

This also presents an opportunity for policy-makers in Scotland to play an active part in the shaping of new regulations (or refining existing regulations) to maintain public and environmental safety, but allow greater freedom to innovate. Scotland's expertise in land-based studies in its research institutes and universities enable it to lead the world in developing an evidence-based framework for governance of potential environmental and agricultural uses of synthetic biology. Those responsible for shaping regulations have the opportunity to set the framework in which businesses must operate.

Intellectual Property (IP) presents both opportunities and threats. Opportunities, because many of the technologies developed will have broad applications, allowing businesses to operate across a spectrum, reducing dependencies on one single industrial sector, and additionally (or alternatively) licensing technologies to multiple end-users. On the other hand initiatives such as BioBricks and iGEM offer open source access to material for research and technology development (RTD), which could limit the commercial opportunities to be derived from these (and thus the necessary investment to develop products). Regardless of the way in which IP is managed, there are concerns amongst different stakeholder groups about the equitable access to biological information, and what can and should be patented. Some estimates are that around 60,000 patents have been issued world-wide for DNA-related innovations. If these rights are too broad then this may also limit the development of new innovations. Discussions with practitioners in this project suggest there is a real need for structured IP support around synthetic biology in Scotland, to ensure that there is fair assessment of value, and improved conditions for licensing or transfer of rights from academia to industry to support commercial exploitation.

Standardisation also presents significant opportunities. Adopting a leading role in international standardisation processes enables compatibility and acceptance of industrial products, and supports national industries to be market leaders, or at the least early adopters of new technologies. As with regulation, standards set the framework in which businesses must operate.

The following tables provide summary SWOT analyses for different aspects of synthetic biology for Scotland (in terms of broad platform applications, and related to medicine and health, energy, agriculture, and environment).

Synthetic Biology as a Platform Technology			
Strengths	• Systems biology – supports the development of advanced modelling software necessary for future synthetic biology development. Edinburgh, Glasgow, Dundee and Aberdeen all have strong capabilities. • Cloning capabilities (e.g. Edinburgh is one of only two UK centres capable of constructing a complete synthetic yeast chromosome). • Animal biotechnology (e.g. germ cell technology, vaccinology, animal security and health) is essential to future livestock development. Moredun and Roslin are key players. • Disproportionately larger community in Scotland than the rest of the UK (highest density outside of London). • Small but vibrant industrial community actively engaged in this space (e.g. Ingenza, GSK, Selex). • SULSA (Scottish Universities' Life Science Alliance) – championed synthetic biology and systems biology for many years. • Scotland (and UK as a whole) has expertise in the design of containment facilities.	Opportunities	• The biotechnology industry believes synthetic biology is critical for future product development (alternative feedstocks), cheaper production, and new products. • The agri-food industries believe such tools will be necessary to develop new crop varieties and animal breeds. • Reduces the risk of investing in the development of a specific product that might fail (because there is a longer pipe-line to commercial reality, potentially more investment required, and someone else might get there first). • Developing platform technologies positions those with the know-how as key service providers in the development of new products across many different industrial sectors. • Allows those nations leading such developments to drive forward new standards and regulations that set the framework in which businesses must operate. • Licensing opportunities to multiple end-users in different application and industrial sectors.
Weaknesses	• Suitable pilot scale facilities for scale up of microbial production from lab to industrial levels (although this should be provided through IBioIC). • Limited multidisciplinary training (biological, physical and mathematical sciences, engineering, IT) at Masters level (which is what industry needs) and providing future leaders through dedicated PhD programmes (e.g. Doctoral Training Centre). • Support for businesses in terms of accessing funding (particularly for first-mover), academic research expertise, technology translators, protecting IP, training and supporting entrepreneurs. • Private investment landscape – very little venture capital. • Lack of constructive networking (generating ideas and providing financial support for the best of these).	Threats	• Synthetic biology will be developed somewhere (if not Scotland), and many countries are investing heavily. • Industry will deploy where synthetic biology is supported, potentially resulting in the loss of manufacturing jobs and technology leadership (thus socioeconomic benefits). • Scottish academic output could be commercially exploited elsewhere (as seen for electronics). • Joint funding calls between other countries, that Scotland is not party to – lack of visibility of Scottish capabilities on the global stage. • Regulatory framework – unclear how this will develop in EU. • Misinformation to the wider public. • Training programmes in other countries, e.g. US has strong bioengineering departments containing both engineers and biologists and strengthening capabilities of next generation of graduates.

Synthetic Biology in Medicine and Health			
Strengths	• Can rapidly decrease the time-lines for new product developments (thus reducing costs). • Supports stratified medicine. • All pharmaceutical production facilities utilise established and regulated closed systems. • Stratified medicine initiative – linking academia with industry and NHS.	Opportunities	• Pharmaceutical companies believe that economics of drug development must change over the coming decades, becoming cheaper to accommodate personalised medicines and growing demand in developing countries. • NGOs representing patient groups and public engagement activities report that the wider public is generally supportive of new technologies that improve medical choice and efficacy. • Development of diagnostic tools (for healthcare and research) – presence of companies such as Life Technologies in Scotland. • Stem cells – understanding the mechanisms by which DNA is packaged and expressed through manipulating genomes. • Cancer – understanding the purpose and interaction between different cancer genes in cells.
Weaknesses	• Similar to those described under Platform Technologies.	Threats	• Technology will be developed elsewhere if the environment in Scotland is not conducive to supporting companies.

Synthetic Biology in Energy			
Strengths	• Makes use of waste from a variety of sources. • Can be designed within closed systems; so no environmental release. • Number of key academic groups researching biofuels and microbial fuel cells.	Opportunities	• Efficiently extract biofuel precursors from abundant plant organic materials (e.g. plant, algae, and waste materials). • Generate other forms of energy (electricity, hydrogen) directly from a variety of sources (sunlight, organic materials) – contributing to sustainable energy production. • Produce other useful chemicals and chemical precursors from these processes.
Weaknesses	• Scotland lacks centralised sites to handle waste materials on the scale that would be economically favourable to create biofuels.	Threats	• Massive funding in the US (several billions of dollars to three centres) to support lignocellulose RTD for the biofuel industry. • EU has decreased the percentage requirement for biofuels. • Fracking (shale gas) – massively reduced chemical manufacturing and energy costs in US.

Synthetic Biology in Agriculture			
Strengths	• Plant breeding expertise at the James Hutton Institute. • Animal biotechnology (e.g. germ cell technology, vaccinology, animal security and health) is essential to future livestock development. Moredun and Roslin are key players. • Scotland has strength in land-based studies required to analyse the potential effects of synthetic biology applications. • Other academic groups and companies positioned to support new developments.	Opportunities	• Improving variety development times for barley, and improving the performance of barley in the distilling industry. • Developing ruminant genomic tools to address various issues (e.g. decreasing methane production and improving biomass conversion).
Weaknesses	• Lack of high-level containment and surgical facilities for animal biotechnology (Category 4 containment is only available at Pirbright and Porton in the UK).	Threats	• Regulatory framework – unclear how this will develop in EU. • Direct action from lobbying groups. • Technology developed elsewhere, and imported to Scotland.

Synthetic Biology in Environmental Applications			
Strengths	• Existing partnerships between academic groups and SMEs to address environmental pollution through synthetic biology. • Scotland has strength in land-based studies required to analyse the potential effects of synthetic biology applications. • Can be designed as multi-stage processes comprising closed systems; so no environmental release.	Opportunities	• End-of-pipe remediation (such as removing copper from waste stream in the whisky industry). • Cleaning up contaminated sites (as a two stage process – plants, then fermentation with bacteria with synthetic pathways in a closed system – see Case Study 3).
Weaknesses	• Similar to those described under Platform Technologies.	Threats	• Regulatory framework – unclear how this will develop in EU. • Opposition from lobbying groups

Impact/Opportunity	Likelihood: Low	Likelihood: Medium	Likelihood: High
High	New animal breeds Bioelectricity	Disease-resistance livestock BioKerosene (aviation fuel) New diagnostic tools	Speciality chemicals Engineered vaccines BioDiesel
Medium		New crop varieties Cheaper drug production Modified ruminant nutrition	Chemical feedstocks BioPetrol Waste remediation
Low			New experimental model systems

Estimate of likelihood of particular advances in the next 5-10 years against the likely impact or opportunity these provide.

Summary of key findings

1. Scotland has strength and depth in the technologies of synthetic biology. Scientists and engineers in Scottish universities and institutes are developing these techniques further as a platform technology. We should continue to invest in such research as an underpinning component of curiosity-driven research in the life sciences.

2. Through this strength in academic research and the presence of relevant biotechnology industry, coupled with the potential to make an impact in a number of industries in future, Scotland has an opportunity to capitalise fully on the technology.

3. Scotland needs to decide how best to lever economic impact from this emerging technology to reap the full benefits of developments in synthetic biology. This report has focused on the benefits of contained use. Some of the possible applications of synthetic biology outlined in this report have the potential to make a positive impact in key economic growth sectors for Scotland such as food and drink (including agriculture), energy and life sciences.

4. The potential cost of not fully engaging is that other countries, which are aggressively pursuing the applications of synthetic biology, could gain advantage in areas where Scotland currently has trade advantages. For example, these include seed potatoes, soft fruit, chicken breeding, whisky production, stratified medicine and renewable energy.

5. It is necessary to determine the Scottish publics' views of synthetic biology through an impartial and evidence-based national dialogue. Such dialogue is more effective when considering issues close to development, so a dialogue on industrial biotechnology is recommended as a useful starting point.

6. Current work in synthetic biology is restricted to contained systems with physical and biological controls to prevent environmental release.

7. The issue of environmental release of synthetic organisms in future and the governance of such work should be the subject of ongoing discussions between scientists, the public, industry and the Scottish Government, taking due note of parallel international discussions. Scotland is well-placed to lead internationally on such discussions because of the strength of its land-based science.

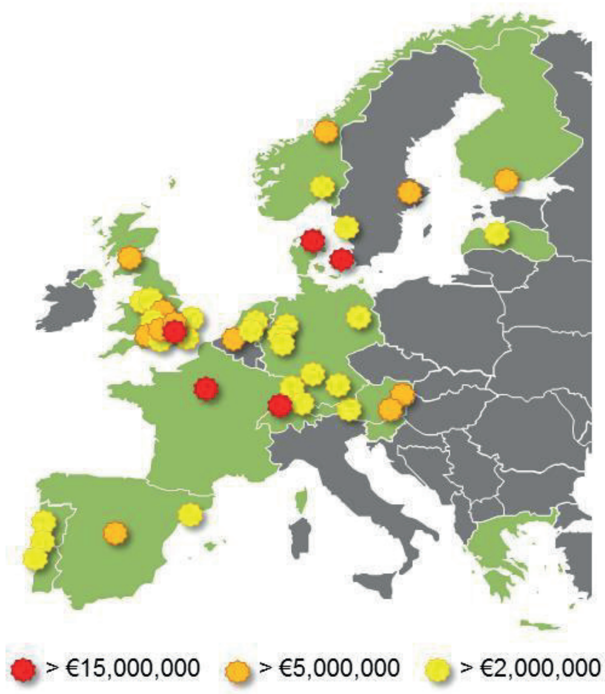
Annex 1 – National strategies on Synthetic Biology

EU

In 2005, the European Commission (EC) established a high-level expert group to debate the potential impacts of synthetic biology. This recommended a European strategy and roadmap for synthetic biology, consideration of training needs and skills to support its exploitation (combining engineering and biology), improved and coordinated funding through the Member States and the hosting of a major international conference. The EU has funded synthetic biology activities since the sixth Framework programme, with 16 projects funded through the New and Emerging Sciences and Technologies (NEST) initiative (more than €32m in total), including SynBioSafe which specifically investigated ethical and societal issues (http://synbiosafe.eu/).

In 2013, the SynBio ERA NET was launched (ERASynBIO; http://www.erasynbio.eu). This is a partnership between research funding agencies in 16 Member and Associated States (Austria, Denmark, Finland, France, Germany, Greece, Latvia, Spain, Netherlands, Norway, Portugal, Slovenia, Switzerland, and UK). In addition, the US NSF and the EPSRC act as observers (and may support specific, future funding calls). It will support research grants and also training and mobility between different European institutions. Importantly it coordinates national activities on synthetic biology at a European level.

ERASynBIO has compiled data on European synthetic biology funding which identifies the UK, Switzerland and Denmark as being major players (see Figure 2).



Total recorded public funding of €310 million

- **€204 million national**

- **€106 million transnational**
    - **European Commission**
    - **European Science foundation**
    - **Bilateral calls**

Total European funding is likely to be €450 million

Figure 2. European funding for synthetic biology, as determined by the ERASynBIO[1].

In 2009, the European Commission requested an opinion on synthetic biology by the European Expert Group on Ethics. This group provided 25 recommendations, encompassing safety, a code of conduct for research, research into potential environmental impacts, oversight by competent authorities, publicly available databases on developments, ethical and societal considerations for any research and technology development (RTD), including placing consumer rights at the heart of any developments[55].

The EU does not have specific regulations on synthetic biology, but does have several related to GMOs specifying how they are classified, and must be handled and contained for research and industrial purposes, that would be applicable to synthetic organisms[56].

1 Figure courtesy of Dr Rowan McKibbon, BBSRC (a member organisation of ERASynBIO).

UK

The UK reviewed its approach to synthetic biology in 2011 through BIS leadership, and published its roadmap in 2012. The main thrust of the UK strategy is to integrate the academic research community more effectively with industry, in order to realise commercial and societal benefits. Guiding this strategy is the Synthetic Biology Leadership Council (SBLC), co-chaired by UK Minister for Science and Lionel Clarke (Shell). The SBLC involves key government departments, industry, academia and funding agencies, and aims to:

- Provide a visible point for strategic co-ordination between the funding agencies, the research community, industry and other stakeholder including societal and ethical representatives;
- Create the conditions that allow the UK to become a world leading industrial hub in Synthetic Biology;
- Influence the development of policy and regulations to anticipate the developmental requirements of this emerging technology;
- Be open and transparent, with one 'open' meeting held each year and all agendas and records of decisions taken to be made public.

Other initiatives that support synthetic biology in the UK and work in concert with each other and through the SBLC are the Synthetic Biology Special Interest Group (SynBio SIG) with over 770 members and chaired by the Biosciences Knowledge Transfer Network (KTN), and the Innovation and Knowledge Centre in Synthetic Biology, which is led by Imperial College, includes the major academic and industrial players in the UK, and is business and industry facing.

In July 2013, BIS announced over £60 million of funding to support UK synthetic biology:

- £1 million from the Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC) for UK scientists to join an international consortium attempting to build a synthetic version of the yeast genome by 2017;
- £10 million from BBSRC, EPSRC and the Technology Strategy Board (TSB) to establish a multi-partner Innovation and Knowledge Centre (IKC) in synthetic biology based at Imperial College London;
- £20 million to fund a new set of multidisciplinary research centres, supported by additional investment from BBSRC and EPSRC;

- £10 million for a synthetic biology seed fund managed by BBSRC for companies to commercialise research;
- £18 million from the research councils for DNA synthesis;
- £2 million to support training in synthetic biology.

The BBSRC leads on the UK's research on synthetic biology and is the UK's partner in the pan-European SynBio ERA NET. In terms of innovation support, the TSB sees synthetic biology as an enabling technology and therefore supports applications to its Small Business Research Initiative (SBRI), although it does not have a specific funding scheme for synthetic biology.

Other recent investment in infrastructure will support the development of synthetic biology, in particular the advanced manufacturing catapult, and the recently announced Industrial Biotechnology Innovation Centre (IBioIC) headquartered at the University of Strathclyde and supported through the Scottish Funding Council.

The UK has considered the wider societal and regulatory aspects carefully, with the BBSRC and EPSRC holding joint public workshops and interviews with stakeholders in 2009-10 to discuss the implications of synthetic biology developments (see http://www.bbsrc.ac.uk/syntheticbiologydialogue). The UK government perceives current contained use and environmental release legislation to be appropriate for synthetic biology. However, environmental policy in Scotland is a devolved issue.

The UK has pursued bilateral opportunities through the BBSRC and EPSRC with the US's NSF – leading to a number of funded projects. At present the UK funds synthetic biology at a much higher level, and considers it a greater priority, than other EU Member States.

Germany

In 2009 the German Research Foundation (DFG) along with the German Academy of Science and Engineering, and the German Academy of Scientists Leopoldina presented a position paper on synthetic biology aimed at politicians and the wider interested public. It set out key aspects necessary for Germany to develop and exploit synthetic biology:

- The strengthening of basic research;
- The bundling of relevant disciplines in research and education;
- The development of patenting processes;
- The elimination of threats and the prevention of misuse;
- The monitoring of this new research field using technology assessment methods.

It concluded that the immediate focus of synthetic biology would lie in basic research.

DFG supports one of the main centres for synthetic biology in Germany, the Centre for Biological Signalling Studies (BIOSS) at the University of Freiburg (initial funding was €32.5 million between 2007 and 2012). In addition to this, €21 million has been provided by the Hessen regional government for a synthetic microbiology research cluster "SYNMIKRO".

The Helmholtz Association (http://www.helmholtz.de/en/about_us/) has supported synthetic biology since 2012 and launched Germany's first national network in synthetic biology which involves researchers in Heidelberg, Karlsruhe, Jülich, Munich and Braunschweig, and the universities of Heidelberg and Freiberg.

Industry has taken an active interest in synthetic biology, with a group of German biotechnology companies establishing the International Association Synthetic Biology (IASB) in Heidelberg (http://www.ia-sb.eu/go/synthetic-biology/). Although this remains fairly small (9 members) it has contributed to EU strategy (taking part in the 2010 EC sponsored workshop on synthetic biology).

There are no proposals for specific synthetic biology legislation in Germany.

France

France has been slower to develop a synthetic biology strategy, possibly because of the ethical and societal issues that synthetic biology research raises, and concerns over public sentiment (as has been seen for other emerging technologies). Interviews with the main French funding agencies (ANR and CNRS) in 2009, revealed no specific funding schemes, although there was an active research community[57] supported through non-specific funding and EU programmes. France did not participate in early European programmes on synthetic biology, such as the European Science Foundation EUROSYNBIO call, but is an active partner in the current ERA NET on synthetic biology.

France has long supported biotechnology, and established Genopole (http://www.genopole.fr) in 1998 as its first science park dedicated to genomics, genetics and biotechnology. This combines 21 academic labs, 71 biotech companies and 21 shared-use facilities, and includes the Institute for Systems and Synthetic Biology (formed in 2009). This currently has five research groups, a number of dedicated research facilities, and is involved in 21 contracts including 9 funded by the EU. One of its key partners, the University of Évry-Val-d'Essonne has established a Masters course in Systems and Synthetic Biology (according to the university, the first in Europe).

As a balance to research and technology development, the French government has established an observatory on synthetic biology (Observatoire de la biologie de synthèse; http://biologie-synthese.cnam.fr/), which is tasked with monitoring the development of synthetic biology from an ethical and societal perspective, and encouraging public debate.

It is interesting to consider France's approach to another enabling technology, nanotechnology. It has taken a unilateral decision within the EU to impose legal notification requirements for any company manufacturing, importing or using nanomaterials in France (http://www.developpement-durable.gouv.fr/spip.php?page=article&id_article=30578). One of the drivers for this decision was extensive public consultation. Given the similar sentiments expressed by NGOs and other civil society groups to synthetic biology, it seems likely that France will also consider the need for specific legislation.

Denmark

Denmark has invested significantly in synthetic biology and views it as a strategic area of future importance (primarily through the Danish Council for Strategic Research). Research funding began in 2005, and in 2008 120 million DKK (£13.2 million) was invested in the Centre for Synthetic Biology at the University of Copenhagen, which currently operates across four faculties and performs research in a wide variety of areas including light-driven biosynthesis (of industrially relevant compounds) and bionanoelectronics. Ethical and societal aspects are considered as core components of projects.

Further significant Danish funding includes €100 million from the Novo Nordisk Foundation in 2010 to establish the "Novo Nordisk Foundation Centre for Biosustainability". At present most Danish universities and a number of companies (such as Novozymes) are engaged in synthetic biology research and development.

Switzerland

Most synthetic biology projects are funded by the Swiss National Science Foundation (SNSF), which in 2007 established SystemsX.ch (http://www.systemsx.ch) to drive forward systems and synthetic biology. At £69.4 million, this is the largest ever public research initiative in Switzerland and brings together 12 partners with approximately 300 research groups, and more than 1000 scientists. In total, over 100 projects have been funded with the aim of supporting basic and applied research (including partnerships with industry), training the next generation of scientists, and participating in international programmes.

Switzerland has not adopted specific legislation on synthetic biology, but in common with the EU has legislation regarding the safe handling and use of GMOs. Switzerland funds some research into the ethical and societal aspects of synthetic biology, primarily through the Centre for Technology Assessment (http://www.ta-swiss.ch/en/projects/biotechnology-medicine/synthetic-biology/).

USA

The US government invests around $140 million (approximately £86.7 million) p.a. in synthetic biology research. However, there is no overarching Federal government plan for funding or governance (although it is mentioned in the National BioEconomy Blueprint).

Most funding is through the National Institutes of Health (NIH) and the National Science Foundation (NSF), however the Departments of Energy and Defense also fund research in SynBio. NSF has provided $16 million (approximately £9.9 million) in support for the Synthetic Biology Engineering Research Center (SynBERC), which is a multi-centre collaboration that aims to explore and develop 'foundational principles and technologies' in synthetic biology.

The Department of Defense is focused more on building production capacity and manufacturing capabilities in synthetic biology through its Defense Advanced Research Project Agency (DARPA), while the Department of Energy has a number of initiatives supporting biofuel production.

In response to the production of the first so-called synthetic cell by the Venture Institute, the US President directed the Presidential Commission for the Study of Bioethical Issues to review the field of synthetic biology and develop ethical guidelines[4]. This Commission did not find a need for new regulations at that time, but did provide 18 recommendations based on five ethical principles: 1) public beneficence; 2) responsible stewardship; 3) intellectual freedom and responsibility; 4) democratic deliberation; and 5) justice and fairness. As a result of this the NIH has revised its guidelines on recombinant DNA, considering the potential dual use of synthetic biology.

In contrast to European countries, the USA attracts significant private investment in synthetic biology, notably:

- $42 million from the Gates Foundation to Amyris Biotechnologies and UC Berkeley to develop synthetic artemisinin;
- $47 million from venture capital (VC) sources to Amyris to develop biofuels;
- $300 million (or more) from ExxonMobil to Craig Venter's Synthetic Genomics Inc to develop biofuels from photosynthetic algae.

This suggests that there is, at present, a closer connection between industry and academia, and a greater focus on applications in the USA than in Europe.

The US regards biosecurity as a bigger issue than the EU, in other words the potential use of synthetic organisms as weapons[58].

Japan

The Japanese government does not appear to have a distinct strategy for synthetic biology. However, it does support initiatives that are within the synthetic biology arena, mainly through biotechnology programmes. Examples include:

- The Japan Science and Technology Agency funded Institute for Bio-informatics Research and Development (http://www.jst.go.jp/nbdc/bird/index_e.html) which is developing and standardising a number of biomolecular databases that support systems biology and ultimately synthetic biology.
- The Ministry of Education, Culture, Sports, Science and Technology (MEXT) programmes that exploit genomic technologies for developments such as new systems for plant and animal breeding, production of artificial cells for regenerative medicine, better use of bioresources (including novel technologies for sugar synthesis), and biomass energy technology development.
- A leading facility for Systems Biology (http://www.cdb.riken.jp/lsb/index.html).

Japan had some International Cooperative Research Projects looking at synthetic biology (http://www.jst.go.jp/icorp/english/past_proj/index.html), however these are now concluded.

China

China is seeking to position itself as a global leader in synthetic biology, in order to address public health, nutrition, and resource needs, and its national strategy to promote progress in science and technology. China now produces about 10% of the annual papers published on synthetic biology (approximately 400 papers). China invests about 260 million Yuan p.a. on synthetic biology (approximately £12.2 million) equating to 3.25% of its annual research budget (which is 1.8% GDP). China has a strategic 20 year plan for synthetic biology which aims to achieve the following:

5 years:

- Database of standardised parts and computational competency for designing parts and devices;
- Module design and production of chemicals and biomaterials;
- Validated design of devices to increase plant tolerance of drought and salinity.

10 years:

- Expanded database of standardised parts and devices and computational competency for design of bio-systems;
- Commercial production of selected chemicals and biomaterials;
- Validated design of synthetic devices for nitrogen fixation.

20 years:

- Integrated platforms for design, modelling, and validation of bio-systems;
- Commercial production of a range of natural compounds, drugs, chemicals, and biofuels;
- Clinical application of devices and bio-systems for detecting, controlling, or treating major diseases;
- Creation of artificial microbial life.

The Chinese government is also considering the issues of health and safety, ethical and societal aspects (including equitable access), and intellectual property very carefully.

Annex 2 – Working Group

The following members of the SSAC were members of the Working Group

Professor Nigel Brown (Chair)
Professor Ian Boyd
Dr John Brown
Professor Muffy Calder
Professor Sir Ian Diamond
Professor Louise Heathwaite
Professor George Salmond

With assistance from Professor Joyce Tait (University of Edinburgh) and Dr Stuart Wainwright (Defra).

Dr Mark Morrison (Institute of Nanotechnology, Strathclyde) provided project support to the Working Group.

A number of groups and individuals was consulted during the development of the report. These included companies, trade associations, NGOs, Research Councils, natural scientists, engineers and social scientists. Some of these were attendees at workshops organised by SSAC in November 2013 and February 2014, and others were consulted on an individual basis.

The Working Group is grateful to those we consulted for their time and their input to our deliberations.

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