Emerging Policy Issues in Synthetic Biology

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BETTER POLICIES FOR BETTER LIVES

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Foreword

Synthetic biology is an emerging technology that shows promise for investigating some of the burning issues in biological research. It also has the potential to address some of the grand challenges facing society, such as climate change and energy security. Some argue that it has the potential to create a new manufacturing paradigm and has obvious roles in a future bioeconomy. With the creation of engineering standards, it is hoped that synthetic biology will enable mass manufacturing based on several decades of biotechnology research and development.

Applications are envisaged in important economic sectors, such as energy, chemicals, medicine, environment and agriculture. Policy development is as yet rather limited. Several countries, and especially the United States, have taken a lead in subsidising R&D, and the international Genetically Engineered Machine (iGEM) competition goes from strength to strength, bringing in large numbers of talented young entrants from many countries. Synthetic biology challenges higher education's ability to provide the required workforce, which will need a multidisciplinary education that covers both science and engineering. There are intellectual property issues, but the community does not consider them insurmountable. Synthetic biology benefits from the decades of regulation and governance that has been developed for genetically modified organisms, but it may be hindered in some parts of the world by over-regulation.

Roadmaps hold promise in the area of policy. Technology roadmaps are generally held to be useful for setting the development agenda for a new technology. For the semi-conductor industry they may even have been instrumental in the successful development of that industry. To date very few countries have a synthetic biology roadmap, but some are under development. If carefully formulated, a technology roadmap can be a policy roadmap, and it can contribute to public awareness and debate. While there is currently no international forum for addressing all of these issues, the OECD is well placed to take the lead.

The work described herein builds on a synthesis report published in conjunction with the Royal Society[1]; the report of the expert meeting on synthetic biology held in conjunction with the SynBio5.0 meeting in Palo Alto, California on 15-17 June 2011; and work on the challenge of intellectual property access and sharing in the field of synthetic biology. The expert meeting at Palo Alto helped highlight the three areas of greatest challenge: i) infrastructure; ii) IP access and sharing; and iii) standards and interoperability, and this current work was partly shaped by the conclusions of that meeting.

It also draws on discussions at the OECD International Summit on Delivering Economic Value from Synthetic Biology: Current Challenges and Opportunities (12 March 2012, Sydney, Australia) and the Forum on Synthetic Biology: Challenges and Opportunities for Australia (13 March 2012, Sydney, Australia). These events were held in conjunction with the Human Genome Meeting, HGM 2012, from 11-14 March 2012 in Sydney. We are particularly grateful to the outgoing Chairman of the OECD Working Party on Biotechnology (WPB), Dr Gerardo Jiménez-Sánchez, who was instrumental in establishing the partnership between the OECD and HUGO (the Human Genome Organisation).

The report was drafted primarily by Jim Philp with significant contributions from Mineko Mohri and Rachael Ritchie. Further contributions were made by Krishna Chandran and Nicola De Sanctis. Expert oversight of the projects was provided by the OECD WPB with further inputs from the OECD Task Force on Industrial Biotechnology (TFIB).

[1] See www.oecd.org/sti/biotechnology/synbio.

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Abbreviations and acronyms

APHIS	Animal and Plant Health Inspection Service
BBSRC	Biotechnology and Biological Sciences Research Council, United Kingdom
BIO	Biotechnology Industry Organization
BiOS	Biological Innovation for Open Society
CAD	Computer-aided design
CAGEN	Critical Assessment for Genetically Engineered Networks
CDIP	Committee on Development and Intellectual Property, WIPO
CellML	Cellular Markup Language
CNRS	Centre National de la Recherche Scientifique, France
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DNA	Deoxyribonucleic acid
EPA	Environmental Protection Agency, United States
EPO	European Patent Office
EPRSC	Engineering and Physical Sciences Research Council, United Kingdom
FTO	Freedom to operate
GCAT	Genome Consortium for Active Teaching
GHG	Greenhouse gas
GM	Genetic modification
GMO	Genetically modified organism
HHS	Department of Health and Human Services, United States
IASB	Industry Association Synthetic Biology
ICT	Information and communication technology
IDRIS	International distributed research infrastructure
iGEM	International Genetically Engineered Machine
INRA	Institut national de la recherche agronomique, France
INSA	Institut national des sciences appliquées, France
IP	Intellectual property
IPO	Initial public offering
IPR	Intellectual property rights
JPO	Japan Patent Office
KTN	knowledge transfer network
LIMS	Laboratory information management systems
MBA	Masters in business administration
MIT	Massachusetts Institute of Technology

MTA	Material transfer agreement
NHGRI	National Human Genome Research Institute, NIH
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
PCR	Polymerase chain reaction
PPP	Public-private partnership
R&D	Research and development
RBS	Ribosome binding site
RNA	Ribonucleic acid
SBGR	Systems Biology Graphical Notation
SBML	Systems Biology Markup Language
SME	Small and medium-sized enterprise
SynBio SIG	Synthetic Biology Special Interest Group, United Kingdom
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TSB	Technology Strategy Board, United Kingdom
UKIPO	UK Intellectual Property Office
USPTO	US Patent and Trademark Office
VC	Venture capital
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization
YIC	Young innovative company

Executive summary

The potential of synthetic biology

As a platform technology, synthetic biology addresses a wide range of industry sectors and types of applications. It has the potential to offer significant economic benefits and bring greater efficiency to manufacturing (e.g. low production volume, high-value medicines and high volume, relatively low-cost transport fuels). It may also help meet bioeconomy objectives: reduction of greenhouse gas (GHG) emissions, food and energy security.

The future of synthetic biology depends on reliable, low-error, accurate and inexpensive DNA synthesis. Since 2003, the cost of DNA sequencing has dropped a million-fold and is now negligible. For DNA synthesis, i.e. writing the genetic code, costs need to tumble by similar orders of magnitude.

Meeting the technical difficulties

The technical difficulties involved in reaching parity with sequencing (the "tipping point" of DNA synthesis cost) are considerable and create high financial risks for the typically small, high-technology companies working to develop synthetic biology. These companies are always vulnerable in their formative years.

Governments can support them through grant schemes, loan guarantees, R&D tax credits, advanced manufacturing tax credits and public procurement. Governments might also examine ways to overcome barriers to venture capital investment raised by the lengthy innovation cycle in the life sciences. Innovative tools for decreasing private investment risk could reap rewards, and public-private partnerships may help reduce risk for vulnerable small companies. Eventually, synthetic biology might reduce innovation cycle times.

Major hurdles must also be overcome in bioinformatics and software infrastructure. The relevant software will become accessible to a mass audience long before DNA synthesis. This can be good for synthetic biology (e.g. by creating interest among school pupils) but it increases the need for biosecurity vigilance, as sequence designs could be sent to other countries for manufacture without appropriate controls.

Developing the research infrastructure

Some countries are now actively developing infrastructure and creating roadmaps to advance these goals, with the United States, China and the United Kingdom in the lead. Europe has a growing number of research groups, and some countries have strategies for developing synthetic biology (e.g. the UK roadmap). The potential duplication and fragmentation of European efforts is an issue the EU is seeking to address, possibly through the development of an EU roadmap.

Synthetic biology is developing in strong research institutions and close to other important facilities, such as sequencing centres. To reach its fullest potential it will have to move into the mainstream, probably when the required lowering of costs has been achieved. Governments can set up centres of excellence based around key researchers and create dedicated calls for research proposals. They can also implement simple measures such as funding mechanisms for physical and virtual networking, e.g. knowledge transfer networks and international exchanges.

Education and skills

Education in synthetic biology is particularly challenging owing to its multidisciplinarity and the need for business and entrepreneurial skills, such as change management. The route from the laboratory to the market is complex and any country engaging in synthetic biology beyond the research stage will need a strong cadre of suitably trained individuals. Synthetic biology companies engaged in manufacture of advanced biofuels are finding the transition to full-scale production challenging. There has long been a shortage of biochemical engineers, and the role of the chemical engineer could be enhanced. Education and training policy will have to evolve to meet these challenges.

Intellectual property

Much has been learned over the last 30 years about patenting life science inventions. The challenges specifically raised by synthetic biology should be recognised but should not be insurmountable and are generally manageable within the current intellectual property system. Potential solutions include open innovation and patent clearinghouses. The biotechnology industry has always had technically complex patents, and intellectual property is a big draw for investors. Synthetic biology may also learn from the semiconductor industry. Indeed, synthetic biology patents may eventually resemble a semiconductor patent more than a typical life sciences patent.

Regulation

Most practitioners believe that regulation applicable to GMOs is sufficient for synthetic biology, except for DNA synthesis. DNA synthesis creates unique biosecurity issues, which the nascent research community and industry are addressing. Although synthesised DNA does not present a security risk as such, its translation into products may. Risk-based assessment could be used to deal with this.

If regulation is too heavy, countries/regions that undertake synthetic biology R&D may lose out, as commercial deployment and capacity building may take place elsewhere.

Public opinion and engagement

Use of synthetic biology to develop the bioeconomy can help address the grand challenges of our times. However, public resistance to GM technology can hinder the application of synthetic biology and inhibit bioeconomy capacity building. Stakeholders must engage with the public. Continuing discussion among scientists, policy makers and the public at large can help clarify misunderstandings. Governments can also support competitions (such as MIT's iGEM) to captivate young people's interest. They can encourage knowledge transfer networks and social media open to the public as well as the scientific community to facilitate exchange of ideas.

Key messages

Synthetic biology holds the promise of bringing biotechnology products to mass markets as a result of rational design. Many policy gaps and hurdles must be navigated. A long-term effort is required. It will require policy flexibility and recognition both of the potential societal benefits and the need for public acceptance for it to achieve its full capability. A high degree of international exchange and co-operation will be needed. The OECD can play a pivotal role in providing appropriate mechanisms for discussion and assisting countries to address the policy issues of synthetic biology in a constructive manner.

Chapter 1

Synthetic biology: A new and promising technology

Opinions on what synthetic biology actually is range from a natural extension of genetic modification and recombinant DNA technology to a new manufacturing paradigm. Synthetic biology attempts to bring engineering standardisation to biotechnology to enable many decades of biotechnology research to pay off in the form of mass-market applications. It has been championed and popularised through the international Genetically Engineered Machine (iGEM) competition, and now several governments are investing in developing national synthetic biology capabilities. However, it remains to some a controversial technology. Public policy issues range across R&D investment and commercialisation, education and training, biosafety and biosecurity, intellectual property issues, and public perception.

Introduction

Synthetic biology is at such an early stage of development that there is as yet no general agreement on what it is. To some, it is simply a natural extension of genetic engineering ("GM+"). To others, it is a route to mass manufacturing based on decades of biotechnology research and may lead to a new manufacturing paradigm. These views are apparent in the many proposed definitions of synthetic biology.

The critical technical differences between synthetic biology and genetic engineering and recombinant DNA technology are the much greater requirement for DNA synthesis and the concept of rational design, which brings the life sciences closer to engineering and thus the need for standardisation of procedures, parts and assembly (all essential to manufacturing). Concepts such as orthogonality, hierarchies of abstraction, separation of design from manufacture, standardisation and interoperability, all of which are central to engineering disciplines, have been largely absent from biotechnology. Instead, the research community has struggled to describe the overwhelming complexity of the life sciences and understanding it at the molecular level has been the work of many decades.

The broadest message regarding synthetic biology and associated policy needs is that, in many respects, there is no need for entirely new approaches. In its earliest applications, synthetic biology's basic tools and platforms are being created in industrial biotechnology, with the bio-based production of fuels, chemicals and materials. In many cases, this calls for the replacement of existing fossil-derived chemicals, usually with identical molecules, and the current regulatory systems appear adequate. New medicines are likely to require the extension of existing regulation, rather than a *de novo* approach. In specific instances synthetic biology appears to challenge details of the intellectual property (IP) system, but would not call for its overhaul. The most likely cause for concern is agricultural applications involving deliberate release to the environment and/or human consumption. However, experience with genetic modification (GM) regulation over several decades indicates modifications rather than massive changes that would hold up development.

Synthetic biology is still in its infancy, and policy issues that are just arising will have to be addressed. They include the need to ensure: a critical mass of trained researchers and other professionals; support for research and innovation through public funding and technology transfer; investment-related subsidies; clarity on intellectual property issues; and governance in terms of the regulation of synthetic biology. Moreover, it is essential that the

various publics and stakeholders play an essential role in its development. This report seeks to clarify some of the policy issues and their implications.

Perhaps the most significant policy signal is the emergence of national roadmaps. A roadmap conceptual design appeared in a European Union project in 2009 and in July 2012 the United Kingdom Technology Strategy Board published a roadmap for synthetic biology reaching out to 2030 (see Chapter 7). Technology roadmaps focus on the challenges and opportunities related to the development of a technology, consider possible future developments in the technology and its environment and create a framework to help to plan and co-ordinate actions (e.g. research, development, finance, legislation, stakeholder engagement and wider communication) to meet short-, medium- and long-term goals. Roadmaps can also lead to the identification of barriers (e.g. technical, social, ethical) to the development and/or use of a technology.

Given that public opinion will be an important factor in the development of synthetic biology, roadmaps can have an extremely important function. If the applications of the technology are widely discussed with the public, the roadmap could include the applications that are most acceptable to the public, and this transparency may help reduce negative perceptions, such as those that have arisen in the past for biotechnology. In a limited UK survey of opinion, "conditional" support was given to synthetic biology applications that were perceived as beneficial.

The international Genetically Engineered Machine (iGEM) competition is considered instrumental in the birth of the discipline of synthetic biology. It was initiated at the Massachusetts Institute of Technology (MIT) in 2003 for undergraduate students, and has rapidly grown in popularity. It has played an essential role in making synthetic biology an international discipline. Its appeal to young minds has captured the attention of industry, academia and governments. Since those early days, synthetic biology research has expanded very rapidly. By around 2010, synthetic biology-based companies were reaching the stage of initial public offering (IPO), with successes especially pronounced in the United States. For a discipline that lacks engineering standards and therefore a means of mass production, this is an astonishing rate of progress.

What is synthetic biology?

There are many definitions of synthetic biology, of varying degrees of complexity, and several organisations are working on a definition. A simple definition that seems to crystallise the issue without resorting to the jargon of the life sciences or engineering comes from the Royal Academy of Engineering (2009):

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

The use of the terms "design", "engineer" and "devices" sets synthetic biology apart from systems biology. A theme that is implicit in synthetic biology is that of rational design. Biology has always been a very descriptive science that does not lend itself to standardisation, a necessity in manufacturing (see Box 1.1).

Box 1.1. Synthetic biology for a better understanding of biology

In many academic courses on synthetic biology, the emphasis is on the application of engineering principles to deliver a new means of production. However, another definition of synthetic biology contains the idea of using synthetic biology to advance basic biological theory: "Synthetic biology is the design and construction of biological systems guided by engineering principles, with the aim of understanding biology or producing useful biological technologies." (Bayer, 2010) In other words, while biotechnology focuses on the use of controlled biological circuits in the design and manufacture of new products, synthetic biology offers new opportunities in the opposite direction – the use of artificial biological circuits to understand fundamental biological problems.

Biological systems are, in essence, extraordinarily complex genetic systems that maintain, repair and build themselves in highly integrated environments. One of the most fundamental biological problems is our limited understanding of how these genetic systems work. Expressed in another way, we do not know the basic design principles of gene regulatory systems (Elowitz and Leibler, 2000).

Using an analogy with electronics and electronic circuits, one way of increasing our understanding is to use synthetic biology to construct simple biological components that can be linked to form very simple, elementary biological systems or "circuits" whose functions can be studied, followed by the progressive construction and study of systems or circuits of increasing complexity that mimic the behaviour of real genetic systems:

"The possibility of a minimal core network driving robust cellular behaviour has inspired the development of an alternative approach to the study of gene-regulatory networks: create the network, beginning with a one or two-component system and then rebuild the network from the bottom up. In this way, we can gradually assemble increasingly complex systems that mimic the native network, while maintaining at each stage the ability to model and test the network in a tractable experimental system." (Cookson et al., 2009)

The major contribution of synthetic biology to basic science is likely to be an increased understanding of gene regulation and expression, which has long been hypothesised to be the basis of the evolution of phenotype rather than changes in encoded proteins (Dickinson, 1988), all of which makes the potential contribution of synthetic biology to biological theory enormous.

Panke (2008), summarising a number of influential papers, identified five points that are crucial in engineering but are by and large absent from biotechnology.

1. *Comprehensiveness of available relevant knowledge*. In mechanics, electrical and chemical engineering, the mathematical formalities are well known. In biology, this is far from the case.
2. *Orthogonality* i.e. independence. This is absolutely essential in engineering. For example, a car must be able to accelerate independently of its wing mirrors, electric windows, alternator, steering, etc. In biology, changes in one metabolic pathway effect changes in another as they are often interlinked. A change in one often causes interference in, or from, others. In a bacterial cell, the cytoplasm hosts hundreds of different simultaneous chemical reactions, and orthogonality is largely missing.
3. *Hierarchy of abstraction*. If the overall system can be divided into meaningful subsystems that can again be divided into meaningful subsystems, and so on, the design task can be distributed over several levels of detail at the same time. The advantages are two-fold: parallel advances reduce development time and specialists can address specific levels of detail in the system. The description of biological systems, by contrast, usually focuses on the molecular level, and formalised, abstract or functionalised descriptions in the above sense are rare.
4. *Standardisation*. The lack of standards in biotechnology has far-reaching consequences: different lengths of promoters used in different plasmids, with different copy numbers, used in different *E. coli* strains, grown on different media at different, and often variable, temperatures show why it is extremely difficult to standardise data output. Mining the literature to discover all the different variables involved is very time-consuming.
5. *Separation of design and manufacturing*. This is a mantra of engineering. Going back to the car analogy, the design of a car is separate from its assembly at the assembly line, which requires comparatively little effort. The different groups of employees have different specialist training; this makes it feasible to design and manufacture a car. In biotechnology, the manufacturing of the system is still a major part of the research project and in many cases a research project on its own.

Synthetic biology differs from genomics. Genomics, or gene sequencing, can be viewed as the ability to read the genetic code, and the relevant technology has made huge strides in recent years. Since 2003, the cost of sequencing has dropped by at least one million fold. The acceleration of sequencing speeds in successive generations of equipment has exceeded even computer processing's Moore's Law (Moore, 1965).

Synthetic biology relies on the ability to make gene sequences routinely. The fundamental difference with genomics is that gene synthesis is the ability to write the genetic code, not read it (Goldberg, 2013). This has proven altogether more difficult than sequencing. The problems include the accuracy, reliability, cost and turn-around time of DNA synthesis. These capabilities currently lag far behind the ability to sequence DNA. Given the importance of DNA, this is a very serious impediment.

Technology roadmaps for synthetic biology

In considering how to bring technologies from the laboratory to commercialisation, a roadmap can help to clarify the challenges and opportunities related to the development of a technology, to consider possible future developments, and to create a framework to help to plan and co-ordinate actions (e.g. research, development, finance, legislation, stakeholder engagement and wider communication) to meet short-, medium- and long-term goals. Roadmaps can also lead to the identification of barriers (e.g. technical, social, ethical) to the development and/or use of a technology.

Roadmaps addressing these issues exist or are being developed for synthetic biology in various countries (e.g. the United Kingdom) and are under consideration elsewhere (e.g. the United States, the European Union). Relevant policy issues include education, skills and training; infrastructure for research; technology transfer and commercialisation; and issues relating to companies and public-private co-operation (see Chapter 7).

A major function of roadmaps is to identify problems that could become major roadblocks (Galvin, 2004). Policy discussions in these early days of synthetic biology therefore cannot be restricted to the near term. It is clear that synthetic biology can make major contributions to a bioeconomy but will also create challenges, so that, from the start, policy must also look to the long term.

Workshops that include as wide a range of stakeholders and experts as is practicable are needed to achieve an effective roadmap. Public engagement will be needed from the start to try to avoid the situation that has arisen with recombinant DNA technology. A monitoring strategy will also be needed to follow developments in the area. A co-ordinated international effort has the

potential to increase the efficiency of the development of synthetic biology by minimising overlaps and duplication of effort and resolving issues arising in terms of governance and regulation.

The need for education, skills and training in synthetic biology

As a multidisciplinary field, synthetic biology incorporates elements of biology, engineering, chemistry and, when it leaves the laboratory, environmental science. Its multidisciplinary nature challenges traditional scientific education, which separates disciplines such as microbiology, chemistry and computing. In particular, there is a fundamental difference between the education of scientists and engineers. Scientists need to be able to question, and freedom is important. Engineers need rigour and standards. Systems modelling and design are well established in engineering disciplines but until recently have been rare in biology. Synthetic biology is clearly a hybrid field that will require a barrier-breaking approach to education.

The education system has been responding to the needs of the growing synthetic biology community. Educational programmes are already available in some countries from school to postgraduate and postdoctoral levels. However, the institutions offering these programmes are still pioneers. A web-based resource[1] quotes over 100 different institutions offering graduate-level education in synthetic biology.

As a mainly postgraduate subject in higher education, synthetic biology lends itself to a research Master's degree that emphasises practice-led research combined with relatively few taught modules compared with other Master's degrees. This type of Master's degree is generally designed to prepare students for doctoral research, but is also useful for those considering a career in the commercial world where research is a key focus but a PhD is not required. As synthetic biology leaves the laboratory and more applications are commercialised, a research Master's degree of this type may become a popular route to entering the field.

There are concerns that the lack of a skilled cadre of workers could be a roadblock to the development of synthetic biology. One option would be to develop truly interdisciplinary education, leading to graduates with science, engineering and computing skills along with the business skills found in a typical MBA programme (change and risk management, venture capital skills, intellectual property management, entrepreneurship skills).

Different countries and organisations are responding to these educational needs in different ways. For example, the Danish Council for Strategic Research has prioritised synthetic biology and is encouraging scientists to work in international networks in order to pool competences and resources.

In addition to performing world-class research in synthetic biology, it is developing an education programme at the undergraduate, postgraduate and doctoral levels. In the United States, many of the best-known universities offer education in synthetic biology. MIT, for example, has a course, intended for the 12th grade, to demonstrate the complete process for cloning a gene. It is also developing integrated interdisciplinary graduate courses that are accessible to students from different backgrounds. An undergraduate programme at Princeton covers the core material of introductory physics, chemistry, biology (genetics and biochemistry), and computer science in an integrated manner, in that they are taught together, with examples drawn from biology.[2] It is argued that the continuing relationship between technology and discovery means that in the next 50 years cell biologists will have to be conversant with fundamental concepts from physics, chemistry and genetics and especially with the mathematical and computational ideas and methods that dominate technology development (Botstein, 2010).

Practitioners of synthetic biology must manage complexity rather than describe it as traditional biologists have generally done, and engineers must build using material under evolutionary pressures in the absence of fixed standards. Students who enter synthetic biology perceive the promise and limitations of the emerging discipline, but they are still required to define themselves as engineers or as scientists. Although the quantitative theoretical and computational component represents a fundamental departure from the tradition of the life sciences, Tadmor and Tidor (2005) stressed that modelling should not be construed as a replacement for experimentation. The major departure experimentally for students is that this is the experience of working with DNA by "making it" instead of recovering it from biological samples (Czar et al., 2009). This exposes the classic conundrum of multidisciplinary education: laboratory skills require depth but also breadth, and achieving the optimum balance of depth and breadth is difficult.

Education in synthetic biology must go beyond science and engineering. Given the history of the GM debate, public perceptions will also play a role. There is already evidence that political and economic pressures, as well as technical achievements, will guide the development of synthetic biology (Rai and Boyle, 2007). Kuldell (2007) argues that education must equip students to deal with these aspects of the emerging discipline. A recent textbook (Schmidt et al., 2010) purports to be the first comprehensive overview of societal issues relevant to synthetic biology, setting the scene for important discussions within the scientific community and with civil society.

Any discussion of education and training must inevitably consider high-school students. Capturing the interest of students at an early age can be critical to the development of synthetic biology and may have a positive effect on public opinion. If parents see that their children are interested in synthetic

biology, that it offers career prospects, and that they are enthusiastic and develop related social networks, they may be less inclined to develop the negative perceptions associated with GM technology.

The role of competitions

National and international competitions can drive innovation and drive down costs, encourage school leavers to want to become students, provide opportunities to spot talent, and increase awareness of synthetic biology. They may also serve a role in changing the negative perceptions of biotechnology. The educational experience gives the participants hands-on laboratory experience and vital skills that other students would find it hard to acquire. Generally they are an excellent means of allowing various stakeholders to network, potentially improving the job prospects of students and exposing industry to the best young talent.

iGEM BioBricks competition

Arguably, synthetic biology has been best championed and publicised by the influential international Genetically Engineered Machine competition, created at MIT in 2003. This annual interdisciplinary competition was originally designed for undergraduates. It has grown rapidly, with 32 teams in 2006, 84 in 2008 and 165 in 2011. It has proven so popular that the 2011 competition was expanded to include a high-school division, and again in 2012 to include an entrepreneurship division. In January 2012 the iGEM Foundation was spun out of MIT as an independent non-profit organisation located in Cambridge, Massachusetts. The iGEM Foundation[3] supports scientific research and education through the iGEM competition.

The goal of the competition is to design and assemble creative genetic systems by combining existing BioBrick parts[4] and creating new ones. The climax of the competition is the convergence of all teams in Cambridge for the iGEM Jamboree. If iGEM is a summer project for most teams, some universities are taking advantage of this event to create innovative educational programmes (e.g. the Genome Consortium for Active Teaching, GCAT[5]).

The iGEM competition has generated so much information over the years that a company has built a map interface[6] using the Creative Commons data available from iGEM.org. This tool can be used to search, navigate and sort through hundreds of projects and get access to videos, posters and presentations directly from the interface.

BIOMOD

Launched for the first time in 2011, BIOMOD[7] is a bio-molecular design competition that provides undergraduates with an opportunity to engineer the self-assembly of biological macromolecules into complex nanoscale machines for scientific and technological purposes.

Students form teams in the early spring, and then spend the summer to design, build and analyse their systems. All teams converge at the Wyss Institute for Biologically Inspired Engineering at Harvard in the autumn to present their work.

CAGEN

The Critical Assessment for Genetically Engineered Networks (CAGEN)[8] is designed to improve the robustness and performance of human-designed biological circuits and devices operating in cells. The competition aims to bring together leading research groups in biological circuit design to demonstrate their ability to design circuits that perform in a prescribed manner in a variety of cellular contexts.

Each year, a steering committee proposes a challenge involving the design of an increasingly complex set of biological functions in a range of environments. Teams must submit their sequences, plasmid DNA implementing their circuit and data characterising the performance of their system against a specified test suite. The three to five best performing designs are selected as finalists and results are reviewed and verified by the CAGEN steering committee, which selects the overall winner based on a set of quantitative metrics. The CAGEN competition is sponsored by the Keck Foundation, as part of the National Academies Keck Futures Initiative.

Gen9 G-Prize

Gen9 has developed a unique technology to synthesise DNA constructs and has used it to build a novel fabrication capability for next-generation gene synthesis. The inaugural G-Prize contest, conceived and sponsored by Gen9, was launched to foster creative and innovative approaches to using synthetic DNA libraries to advance industries such as pharmaceuticals, chemicals, biofuels and agriculture. The competition is open to academic and non-profit scientists. In 2012, the G-Prize judges identified five separate winners, and Gen9 awarded them 1 million base pairs of dsDNA. In 2013, in order to further catalyse innovation, Gen9 awarded the entire 1 million base pairs to one research group,[9] a group from Yale University that will utilise these made-to-order DNA constructs to decipher cellular signalling networks and to create the largest-ever data set of *in vivo* protein-protein interactions.

Competitions for industry

On 18 November 2013, the UK Technology Strategy Board (TSB), the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC) and the Welsh government opened a competition for business-led projects. An investment of GBP 3.8 million aims to develop innovative tools and services for the UK synthetic biology industry, and can include companies of any size, rather than just small and medium-sized enterprises (SMEs).

Policy makers should monitor these competitions, which help to reveal trends in the development of synthetic biology. In particular, the iGEM competition is now truly global. Several countries have stressed the need for international communication and exchanges, and iGEM has been a springboard for globalisation. Moreover, the iGEM community has a history of involving students and the public. Public engagement, from an early stage and as a continuous process, should be made a major goal in the development of the field.

The following chapters of this report draw attention to emerging policy-related areas that will be important for the future development of synthetic biology: current and potential applications, the required research infrastructure, investment, the intellectual policy issues and regulation. A final chapter describes various countries' development of technology roadmaps.

Chapter 2 sets the scene. It describes how synthetic biology arose in the United States, following a rapid rise in research grant funding due to the rise in interest in biofuels. The life sciences research community has embraced synthetic biology, and some applications are appearing, with many more being researched. Many early applications, and some of those that reached the market earliest, are related to bio-based production of fuels and chemicals. The platform tools of synthetic biology are emerging from these applications.

There are also many health-care applications, from new drug design to tissue engineering and diagnostics. In particular, synthetic biology promises to transform medicine and health care in developing and poor countries, which have health-care problems different from those in developed countries. Many recent projects of the Bill and Melinda Gates Foundation (see Annex A) reflect this. For example, malaria is very difficult to control in poor countries, while developed countries are barely touched by it. In developed countries, the re-emergence of many bacterial scourges in the form of multi-drug resistant strains, such as the multi-drug-resistant tuberculosis that appeared in New York City in the early 1990s, requires new approaches to antibiotic discovery and development.

Agriculture is another area of great promise. The strides made in agricultural productivity and efficiency in the developed countries are now slowing. Some of the greater effects of synthetic biology in this area are likely to be felt in developing countries. The more obvious relate to increasingly "efficient" plants that have, for example, a higher yield or produce less CO_2. Agriculture would be revolutionised if plants can be engineered to fix their own nitrogen; this would free agriculture from synthetic nitrogenous fertilizers and significantly decouple it from the fossil fuel industry. Disease resistance in crops has always been an issue, especially in industrialised monocultures where disease can destroy whole crops over very large territories. With an expected nine billion people on the planet by 2050, food security is one of the Grand Challenges. Inextricably linked to it is water security: humans are expected to appropriate 70-90% of the planet's fresh water by 2025, most of it for agriculture. Synthetic biology's potential to address the Grand Challenges of climate change, energy security, food and water security and health care means that it is likely to shape the research and political agendas of the life sciences in this century.

In terms of research infrastructure needs, Chapter 3 shows that many of the issues are those that apply to any emerging technology: research subsidies and international co-operation. At this point the most important technical barrier to synthetic biology is the speed, cost and accuracy of DNA synthesis of long sequences (i.e. writing the code). Rapid progress has been made, but there is still a large gap between the cost of synthesis and sequencing. There will be a landmark shift in the way many laboratories work when commercial gene synthesis is on par with synthesis of synthetic oligonucleotides, with similar costs and turn-around time. Much of the laborious work currently done to manipulate DNA will be phased out of routine use. Several companies appear to be poised to make significant breakthroughs in the high-throughput, automated production of DNA sequences at lower cost and higher accuracy than currently available, with a turn-around time in the range of 5-12 days.

Another important challenge arises from the success achieved in DNA sequencing, i.e. reading the code. So much sequence is being generated that the bottleneck has shifted from its creation to its storage. With the huge advances in DNA sequencing made from the mid-2000s, the capacity to store the information arises. With the number of new DNA sequencers entering service, the storage issue can only become more serious.

As public and private investments in synthetic biology increase (Chapter 4) and the first products appear, two policy areas are vitally concerned: intellectual property (Chapter 5) and governance (Chapter 6). The biotechnology industry has been characterised as one that files many technically complex patents. Evidence links the possession of IP in the biotechnology

industry to success in attracting investment. For synthetic biology, the most important IP issues that have arisen are:

- The tension between the need for openness, especially concerning DNA parts and the ability to communicate in the academic world, and the need for IP protection in order for companies to be able to appropriate the returns to their investment.
- Freedom to operate (FTO) and transaction costs, specifically the costs involved in guaranteeing FTO, and the costs associated with material transfer agreements (MTAs). In a device that might contain several hundred parts, the cost of appropriating FTO could be excessive.
- The complexity of the patent landscape and potential problems raised by broad, prophetic patents.
- The need for patent clearing houses, organised by a third party, to accept the registration of synthetic biology inventions, both sequence and functional claims, as a potential solution to some IP challenges.
- The likely expansion of the IP landscape to involve forms of IP such as trademarks, copyright and protection of databases.

However, communications from some national and international patent offices suggest that synthetic biology does not create fundamentally new challenges that would overwhelm the IP system. It would be a mistake to give the impression that these challenges are insurmountable.

In terms of regulation, several decades of regulating genetically modified organisms (GMOs) have positive and negative implications for synthetic biology. On the positive side, there is no need to start from scratch; a huge amount of experience has been gained. To date, synthetic biology regulation is covered by GMO regulation. Scientists in the field seem to think that there is no need for massive modification of the current system. The biosafety issues appear to be the same, except that the multidisciplinary nature of synthetic biology creates a need for greater awareness and training of stakeholders who are new to the field, such as engineers who are not familiar with biosafety procedures or the growing body of amateur scientists for whom the field may be a mystery.

DNA synthesis and biosecurity is a more serious concern. Two issues differ from GM biosecurity concerns:

- DNA can be readily designed in one location, constructed in a second and delivered to a third. The use of the finished material is therefore not under the control of its originators.
- Synthesis might provide an effective way to obtain specific pathogens for the purpose of causing harm, thereby circumnavigating national or international approaches to biosecurity. Currently, however, it would be much easier to modify an existing pathogen than to try to create a pathogen through synthetic biology.

Many agree on the need for a screening process for synthetic DNA manufacture and sale. The main aspects deserving consideration for control are: sequence screening for select agents to avoid synthesis of known pathogens or toxin-related DNA; customer screening to avoid shipment to dubious clients; and licensing of equipment and substances required for the synthesis of oligonucleotides.

One of the greatest challenges facing those who develop regulations will be to weigh the costs and benefits of rules and to develop an effective enforcement system. A government role at the international level will be necessary, and harmonisation among countries will be important. Otherwise, potential violators of biosecurity regulations may simply transfer their design and construction activities to a less regulated country. Chapter 6 summarises how regulatory interaction between governments, synthesis companies and customers might be achieved.

Regulation is intimately related to public opinion and acceptance. In the on-going debate about whether or not there is already enough regulation, it is worth re-emphasising that GM concerns have been much more of an issue in Europe than in other regions. It is not a significant issue in much of Asia, the Americas or some of the OECD partner economies. The negative reaction to GM technology is not gradually disappearing in Europe as was expected, although there are recent signs of a change in attitude in some countries. There is a possibility that Europe might undertake break-through research in synthetic biology but be unable to move to capacity building or wealth creation if its results cannot be deployed. The growing support in Europe for the idea of a future bioeconomy creates a quandary: many bioeconomy strategies and blueprints rely on synthetic biology as a platform technology but if public opinion rejects synthetic biology it will be difficult to achieve the desired bioeconomy. Public engagement must therefore start early and be maintained. GM has a sterling safety record, but that has not made it attractive to some publics. A new way of communicating the risks and benefits is needed. Aside from objections relating to release to the environment and biosecurity, other societal concerns include the distribution of benefits, and ethical and religious concerns.

The extreme youth of synthetic biology means that there is not a great deal of policy specifically directed to it. Chapter 7 looks at some of the roadmaps and policies that are being developed in a few countries. There are no real surprises: issues of early technology development such as education, R&D infrastructure, research funding and public engagement all feature. Some countries are more proactive than others. China is positioning itself to be a leader in the field and is developing policy on several fronts. The main point for governments is that the potential benefits of synthetic biology are greatest once it moves out of the laboratory. If its aspirations to bring engineering to the life sciences and enable a new future for manufacturing are to be realised, this can only be achieved in a globalised economy through international agreement and harmonisation. This is not a task for the private sector but for governments. The OECD, through its members and global outreach, would be well placed to act as the forum for co-ordination.

Notes

1. http://syntheticbiology.org/Graduate.html.
2. www.princeton.edu/integratedscience/curriculum.
3. http://igem.org/Main_Page.
4. BioBrick standard biological parts are DNA sequences of defined structure and function that share a common interface and are designed to be composed and incorporated into living cells such as *E. coli* to construct new biological systems.
5. www.bio.davidson.edu/GCAT.
6. http://synbioconsulting.com/igem-synthetic-biology-map/.
7. http://biomod.net/about-biomod.
8. http://openwetware.org/wiki/CAGEN.
9. http://gen9bio.com/g-prize/.

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Chapter 2

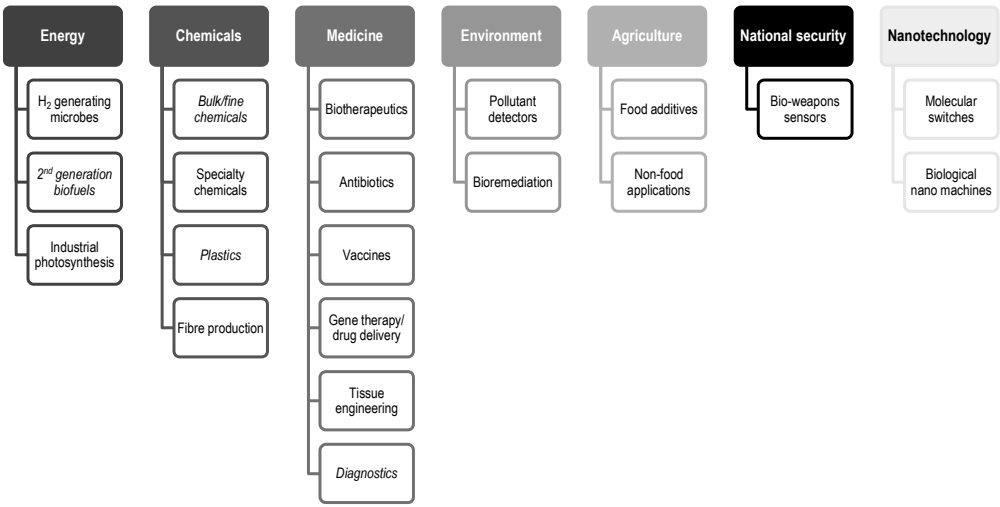
The applications and potential benefits of synthetic biology

Synthetic biology can be regarded as a platform technology that cuts across several key market sectors, such as energy, chemicals, medicine, environment and agriculture. Its formative years have been spent in developing the basic tools for applications in biofuels and other bio-based products, where the earliest products have been seen. It holds out very high expectations and potential for applications to human and animal health, with the potential for greatest benefits in the developing and poor nations. With a growing global population and threats to water and soil quality, agricultural applications are envisaged that could have far-reaching consequences for productivity and efficiency, but in many parts of the world such agricultural applications are controversial.

Introduction

One of the reasons synthetic biology attracts such a high level of interest is that it can be seen as a platform technology that cuts across business sectors. Figure 2.1 identifies some of these sectors and some specific applications of synthetic biology in each. The earliest interest concerned energy applications: several start-ups have been formed in the United States for these applications. Applications in medicine and health care are much more diverse, but it takes a great deal of time to bring the products to the market. The chemicals sector also has a large body of research on the application of synthetic biology to the production of bio-based plastics, for example (e.g. Jung and Lee, 2011).

Figure 2.1. Applications of synthetic biology across sectors



Note: Italics denote the earliest industrial applications.

Source: Adapted from Collins (2012), "Win-win investments: synthetic biology for growth and innovation", paper presented at the Science and Technology Options Assessment (STOA) workshop "Synthetic biology – enabling sustainable solutions for food, feed, bio-fuel and health: New potentials for the European bio-economy", European Parliament, Brussels, 6 June 2012, www.europarl.europa.eu/stoa/cms/home/events/workshops/synthetic_biology.

Industrial biotechnology and synthetic biology

As a large-scale commercial activity, industrial biotechnology foundered after the failure of single cell protein (Bud, 1993). It has since rebounded strongly in the form of liquid biofuels, ushering in a new wave of growth following the success of bioethanol in Brazil (Goldemberg, 2008). Between 2005 and 2010, fuel ethanol production worldwide more than doubled (FO Licht, 2010a), and biodiesel production more than quadrupled (FO Licht, 2010b).

Industrial biotechnology has matured rapidly and has produced a large number of bio-based chemicals and bioplastics (OECD, 2011a). Bio-based production can also partially replace petrochemical production in order to mitigate climate change. As biomass is the feedstock for industrial biotechnology, significant savings in greenhouse gas (GHG) emissions are possible compared to production from oil (OECD, 2011b).

For the vast majority of its applications, industrial biotechnology faces a difficulty: the best biocatalyst for a particular conversion or synthesis rarely occurs in the best organism for industrial exploitation. Production microorganisms have to be engineered, both to maximise yield (e.g. prevention of the loss of plasmids during fermentation) and to tolerate the artificial, and sometimes extreme, conditions of the fermentation process (Murakami et al., 2008). This is an area in which synthetic biology holds great promise.

Synthetic biology has already made significant contributions to industrial biotechnology and is poised to make more. Recent market research (Bergin, 2009) predicted that the world market for synthetic biology products could expand to USD 2.4 billion by 2013, largely in the chemicals and energy sectors. Between 2008 and 2013 this would mean a compound annual growth rate of 59.8%. Although the focus of the synthetic biology biofuel community has been on the production of diesel, jet fuel, automotive fuels and other industrial oils, the biofuels campaign will enable the development of generic synthetic biology technologies and platforms, including the creation of a technical metabolic engineering knowledge base, the training of a cohort of practitioners skilled in the discovery of practical solutions to important problems in metabolic engineering and their dissemination as general principles.

Some examples of metabolic engineering/synthetic biology for the production of industrial materials are given below and indicate the extent to which synthetic biology already contributes to industrial biotechnology. BIO, the Biotechnology Industry Organization, maintains a resource centre on its website and publishes overviews of member companies' development of commercial applications of synthetic biology, such as OPX Biotechnolo-

gies (bioacrylic), Goodyear/Danisco-Genencor (rubber for tires), Modular Genetics (converting agricultural waste into surfactants), and DSM (synthetic antibiotics and vitamins). Other companies investing in synthetic biology include Codexis (enzymes and catalysts), DuPont (polymers), and BP (butanol). Dozens of biofuel or related start-ups have emerged since 2005, including LS9, Solazyme, Gevo, Synthetic Genomics and Joule Unlimited (Dress et al., 2011).

Bio-isoprene

Isoprene is an important commodity chemical with a range of applications. Before the efforts of the Goodyear Tyre and Rubber Company and Genencor, there was no obvious biological route to this compound. There is an increasing need for isoprene and a simultaneous environmental imperative to reduce GHGs, but neither natural rubber nor synthetic rubber compounds can be sourced in sufficient quantities to meet anticipated future demands. Before the recent economic recession, more than 70 million motor vehicles were sold every year around the world, bringing the total number on the road to over 800 million recently. By 2030, this figure could reach 1.3 billion, increasing the demand for rubber in parallel.

The development of bio-isoprene represents a major achievement for industrial biotechnology and synthetic biology because it has the potential to enable production of isoprene from renewable raw materials and represents a key bio-based intermediate that can be converted to a drop-in transport fuel additive (using chemical catalysis) to C_{10} and C_{15} bio-based hydrocarbon fuels for performance gasoline, jet fuel and biodiesel markets. Current state-of-the-art technology has resulted in production, recovery, polymerisation and manufacture of tyres with the isoprene component produced via fermentation.[1]

1,3-propanediol (1,3-PDO)

The appealing properties of 1,3-propanediol for many synthetic reactions, such as polycondensation, and for uses in solvents, adhesives, resins, detergents and cosmetics (Zeng and Sabra, 2011) make it a classic platform chemical. It has long been known that it is produced by microorganisms but none of these would be treated seriously as an industrial biocatalyst.

Nakamura and Whited (2003) described the strategy and progress of an effort by DuPont and Genencor International, Inc. to design and build a single organism catalyst for the direct conversion of D-glucose to 1,3-PDO as a textbook example of metabolic engineering. The strain is based on an *E. coli* K12 strain, which is eligible for favourable regulatory status in the United States, and is also in Risk Group 1 (the lowest risk under NIH guidelines).[2]

In contrast to processes that use naturally available organisms, the DuPont/ Genencor process is aerobic and inherently more efficient. By introducing a four-step pathway consisting of genes from PDO-synthesising bacterial species, together with targeted changes to the host central metabolism, researchers were able to achieve PDO production with high rate and titre. This led to a commercial process.

It is worth mentioning the need to shorten the innovation cycle in bio-based production, as its lengthy duration often dissuades potential investors, especially venture capitalists. It took DuPont and Genencor approximately 15 years and 575 person years to develop and produce 1,3-PDO (Hodgman and Jewett, 2012). One of the great hopes for the integration of software and wetware development in synthetic biology is to shorten the innovation cycle for making new bio-based products drastically.

Marine biotechnology: a potentially disruptive technology

Production of algal biofuels has the potential to be disruptive owing to the very high potential yields (Table 2.1), as oil crops cannot significantly replace petroleum-derived liquid fuels in the foreseeable future.

Table 2.1. Comparison of some sources of biodiesel

Crop	Oil yield ($l\ ha^{-1}$)	Land area needed [a] (M ha)	% of existing US cropping area
Corn	172	1 540	846
Soybean	446	594	326
Canola	1 190	223	122
Jatropha	1 892	140	77
Coconut	2 689	99	54
Oil palm	5 950	45	24
Microalgae[b]	136 900	2	1.1
Microalgae[c]	58 700	4.5	2.5

Notes:

a. For meeting 50% of all transport fuels needs in the United States.

b. 70 % oil (by weight) in biomass.

c. 30 % oil (by weight) in biomass.

Source: Tan, T., J. Yu and F. Shang (2011), "2.58 – Biorefinery Engineering", in *Comprehensive Biotechnology* (2nd edition), Vol. 2, pp. 815-828.

The magnitude of the difference in oil yield from microalgae and the relatively low land area requirements have meant that algal biofuels technology is being intensely researched. Many of the major oil companies are investing heavily. But technical hurdles, particularly in production and harvesting, mean that algal biofuels will be among the last of the biofuels to be commercialised.

As an example of the potential of synthetic biology, Joule Unlimited Inc. of the United States is working on a direct algal process that combines an engineered cyanobacterial organism supplemented with a product pathway and secretion system to produce and secrete an alkane diesel product continuously. The process is closed and uses industrial waste CO_2 at concentrations 50-100 times higher than in the atmosphere (Robertson et al., 2011). If successful, this technology has the potential to change the dynamics of biofuel production as it does not require the extraction of fuels from large amounts of biomass. The company now has a commercial arm, Joule Fuels.[3]

How much of the oil barrel can be replaced?

Many governments are sceptical about the potential of bio-based production to have a real impact on energy security and reduction of GHG emissions. To do so, industrial biotechnology products cannot be limited to a few specialty and platform chemicals. However, Jay Keasling, a leader in the field, has stated[4] that he believes that "through synthetic biology all petroleum-based products can be produced from sugar-based microbes resulting in cleaner processes and slowing global warming". There is mounting evidence, especially from efforts in metabolic engineering and synthetic biology, that even completely unnatural compounds can be manufactured using microbial cells.

For example, 1,4-butanediol is non-natural and highly reduced and very difficult to biosynthesise from carbohydrates. However, its biosynthesis as a combination of software design and metabolic engineering (Yim et al., 2011) has shown that, at laboratory scale, such improbable syntheses can be achieved. On 18 October 2013 it was announced that a joint venture (Mater-Bi) between Novamont and Genomatica will start commercial production of butanediol in 2014 in Italy.

The short-chain olefins are the building block chemicals for making many other petrochemicals and polymers, and thus are at the heart of the petrochemicals industry. Global Bioenergies[5] plans to make short-chain olefins through microbial fermentation rather than from fossil resources. Late in 2013, Choi and Lee (2013) reported on metabolic engineering of *E. coli* to produce short chain alkanes. This opens up the possibility of bio-based petrol as well as short-chain chemicals derived from fatty acid.

In 2013 the scope of bio-based production of fuels and chemicals has significantly increased. Such developments, if commercially viable, may open the door to greater replacement of the oil barrel. Demonstrating this to governments may reduce scepticism and improve the prospects for a supportive policy environment.

Environmental applications and biosensors

The European Environment Agency estimates that, in Europe, potentially polluting activities have occurred at about three million sites, of which more than 8% (nearly 250 000) are highly contaminated and require remediation. The total number of contaminated sites requiring remediation may increase by more than 50% by 2025 (European Environment Agency, 2007). In fact, the scale of the problem has not yet been properly identified. Although it is seldom acknowledged in discussions of agricultural genetic resources, soils are the critical life-support surface on which all terrestrial biodiversity depends. Meanwhile, the world's soil is being lost 13-80 times faster than it is being formed. It takes some 500 years to form 25 mm of soil under agricultural conditions, and about 1 000 years to form the same amount in forest habitats.[6] In the face of soil destruction, more crops will have to be grown more efficiently, and methods will have to be sought to halt or limit soil destruction. Bioremediation can be applied to contaminated soil to bring it back into productive use.

Bioremediation is used for site clean-up in approximately 10% of applications (Roelofsen et al., 2011). This is a surprisingly low figure, given that it may improve soil quality and appears more sustainable than other remedial technologies (e.g. treatment of contaminated soil by incineration offers greater certainty but completely destroys the soil). This is principally because of a still widespread perception that bioremediation is less reliable than other means, difficult to predict in terms of the rate and extent of remediation (in particular whether specified endpoints will be reached), and requires more extensive, intrusive and expensive site assessment. The result is a lack of confidence among stakeholders, especially land developers and regulators.

Laboratory research can address these problems in broadly two ways. The utility of bioremediation in the field, and confidence in its use, could be enhanced by research directed at understanding and improving predictability. A plethora of "-omics" technologies, biosensors and community profiling techniques could act as enabling technologies (so-called "ecogenomics") to achieve these ends. Ecogenomics approaches might be used to characterise contaminated sites and monitor the bioremediation process (Stenuit et al., 2008), especially for sites with many recalcitrant pollutants. Eventually,

these ecogenomics techniques could be combined with software tools in order to translate knowledge about biodegradation into the ability to predict the power of bioremediation. This will take time, since the technology will have to be proved and then approved by the regulators of contaminated land, who are comfortable with the certainties afforded by chemical analysis and characterisation. It would free bioremediation contractors from uncertainties about the applicability of bioremediation and would in turn improve the confidence of other stakeholders.

Synthetic biology has a role in environmental sensing. Microbial resistance to heavy metals and hydrocarbon biodegradation is often encoded on genes and operons. These genes can be combined with a convenient reporter function to determine the concentrations of metals or hydrocarbons in soil and water. Whole cell biosensors that detect arsenic have been developed. Arsenic in groundwater used for potable water is a serious health problem in some parts of the world. The current recommended World Health Organization (WHO) limit for drinking water is 10 parts per billion (ppb) arsenic. Bangladesh and some other countries maintain an earlier limit of 50 ppb, but many groundwater wells in Bangladesh exceed this by a large margin. Chronic consumption of water with high arsenic concentrations leads to arsenicosis, which results in the skin lesions and various cancers that affect 0.8% of the population in Bangladesh (Bryce and Philp, 2005). French et al. (2011) have shown that an arsenic detection system linked to a simple pH change using synthetic biology techniques gives robust and reliable responses to arsenic concentrations as low as 2.5 ppb.

Medical applications

According to Donald Johnston, former Secretary General of the OECD, good health for all is a vital pillar of sustainability, and it is for OECD countries to shoulder much of the responsibility for delivering it (OECD, 2003). Synthetic biology holds the promise of solutions to a range of medical conditions, from microbial infections to cancer therapies (Xiang et al., 2006), from diabetes (Ye et al., 2011) to artificial insemination (Kemmer et al., 2011). Perhaps the most progress to date has been made in drug discovery and synthesis, but many fronts in biomedical research are being investigated using synthetic biology approaches.

Drug discovery

Many of the scourges that were thought to have been defeated during the golden age of antibiotics have come back, more lethal than ever owing to acquired drug resistance. With globalisation, these and other infectious agents can spread rapidly across the world, bringing new challenges.

Some infections are now resistant to all current anti-bacterials, and bacteria are becoming resistant to antibiotics faster than effective replacements are developed (Dwyer, 2009). While some drug candidates currently in preclinical development have generated optimism, there is nevertheless an urgent need for new agents to combat these resistant organisms. There is no evidence that this need will be met in the foreseeable future (Boucher et al., 2009). In the European Union alone, some 25 000 deaths a year are due to multi-drug resistant bacteria (European Centre for Disease Prevention and Control and the European Medicines Agency, 2009).

Combinatorial chemistry has failed to deliver the anticipated wealth of new drug candidates (Weissman, 2004). Natural products, derived from the secondary metabolism of bacteria, fungi and plants, have long been a reliable source of new therapeutic leads. However, large collections of pure natural products are rare because they are hard to build through classical fermentation methods, and in recent years this source has fallen into disfavour. The convergence of next-generation sequencing and synthetic biology opens the door to the creation of large, reliable libraries of pure natural products for drug discovery (Mitchell, 2011). Lee et al. (2009) cite over 30 drugs and drug precursors being produced by metabolically engineering microorganisms; they include a range of antibiotics, anti-cancers, anti-oxidants, anti-parasitics, anti-tumours, anti-virals, hormones, cholesterol-controlling drugs, human gamma-interferon, human interleukin-3 and IgG antibodies.

The marine environment is seen as a particularly important source of future drugs. The wealth of the marine pharmaceuticals pipeline is evidenced by at least three compounds in Phase III trials, seven compounds in Phase II trials, three compounds in Phase I trials. Numerous marine natural products representing potential clinical candidates are also being investigated (Mayer et al., 2010). Moreover, the impact of genomics and proteomics on the biotechnological exploitation of marine organisms has hardly been felt. Given the overall importance of the marine environment, it is inevitable that a large number of marine organisms (and microorganisms) will be brought into genome programmes (Borresen et al., 2010).

Artemisinin is an often-cited example of the potential of synthetic biology for drug design and development. Artemisinin is a botanical anti-malarial isolated from *Artemesia annua*, a wormwood related to *Artemesia absinthium*. Like other natural products, artemisinin is biosynthesised in multiple, sequential steps by a suite of functionally related enzymes, which in bacteria are coded on an operon. By transferring plant genes for the artemisinin pathway into a fermentable chassis organism and forcing production of the artemisinin precursors, the cost of artemisinin was cut in half, opening access to artemisinin combination therapy for low-income malaria victims in developing countries (Hale et al., 2007). It should be noted, however, that

programming microbes for expression of artemisinin is still laborious; it has taken 150 person years of work (Kwok, 2010).

Another example is taxol, a diterpenoid derived from the Pacific yew tree (*Taxus brevifolia* Nutt.) with a high chemotherapeutic value in lung, ovarian and breast cancer (Chang and Keasling, 2006). Taxol precursors are currently produced from plant cell culture and transformed into taxol by chemical synthesis. This is a costly process, given the low yields from plant cell culture. Synthetic biology offers a cheaper, more efficient route to production by assembling complete biosynthesis pathways in *E. coli* and *Saccharomyces cerevisiae* (Weber and Fussenegger, 2009).

Disease prevention

Synthetic biology principles are providing new opportunities for the design of attenuated pathogens for use as vaccines. Wimmer and Paul (2011) described the first synthesis of a virus (poliovirus) in 2002 accomplished outside living cells. They commented on the reaction of lay people and scientists to the work, which shaped the response to *de novo* syntheses of other viruses. In pioneering a safe live vaccine Coleman et al. (2008) synthesised *de novo* large DNA molecules for the rational design of live attenuated poliovirus vaccine candidates. They postulated that this strategy could be used to attenuate many kinds of viruses.

Similarly, the synthetic attenuated virus engineering approach was applied to influenza virus strain A/PR/8/34 for the rational design of live attenuated influenza virus vaccine candidates. Mueller et al. (2010) state that the approach can be applied rapidly to any emerging influenza virus in its entirety, an advantage that is especially relevant for seasonal epidemics and pandemic threats, such as H5N1 or the 2009 H1N1 influenza. During the latter pandemic, vaccines for the virus became available in large quantities only after human infections peaked. To accelerate vaccine availability for future pandemics, a synthetic approach that rapidly generates vaccine viruses from sequence data has been developed (Dormitzer et al., 2013).

The mosquito-borne viral disease dengue fever, including dengue haemorrhagic fever and dengue shock syndrome, is an increasing public health problem, with an estimated 50–100 million new infections each year. Suppression of insect vectors using transgenic insects containing a synthetic gene network could provide pest control by disseminating a conditional flightless female phenotype (a female-specific indirect flight muscle promoter) among natural insect populations (Fu et al., 2010). In future this strategy may control the transmission of malaria parasites and could eventually control the spread of untreatable diseases (Weber and Fussenegger, 2012).

Cancer therapies

With a global mortality rate of 12%, malignant tumours are among the most severe of human pathologies. Surgery remains a common cancer treatment, and when radiation and chemotherapy work, off-target effects on patients can result in considerable damage to healthy tissue. New therapies that exclusively target diseased tissue while leaving normal tissue intact would make landmark changes in cancer treatment. This has been the goal of some synthetic biologists.

Naturally occurring bacteria that self-propel towards tumours have been engineered to invade and proliferate selectively in tumour tissues, produce cytotoxic compounds to kill tumour cells, and contain reporter proteins for non-invasive follow-up on tumour regression (Forbes, 2010). Forbes proposed that synthetic biology techniques can be used to solve many of the key challenges associated with bacterial therapies, such as toxicity, stability and efficiency, and can be used to tune their beneficial features, allowing the engineering of "perfect" cancer therapies. Synthetic virus particles have also been designed that exclusively package therapeutic proteins and can be released in a dose-dependent manner. This approach has been shown to eliminate tumour cells both *in vitro* and *in vivo* (Link et al., 2006).

Pharmacogenomics and personalised medicine

The inability to predict the pharmacology and toxicology of drug candidates in preclinical studies has led to a decline in the number of new drugs that make it to market and to the rise in cost associated with drug development (Gresham and McLeod, 2009). Generally speaking, the challenge is to find the balance between patient benefit, economic value and clinical merit for biomarker-based diagnostics (Jakka and Rossbach, 2013). Today, a majority of drugs in the developmental pipeline have associated biomarker programmes, and the number is likely to increase.

In oncology, genome-based diagnostics are rapidly evolving as many pharmaceutical companies focus on the development of targeted therapies and consider the benefits of a diagnostic test that pairs with a specific treatment. Such tests are showing potential in reducing the costs of clinical trials tremendously (around 60% of clinical trial costs in some cases). A recent report estimates over USD 130 million in savings per approved compound for pharmaceutical companies. Diagnostic tests are likely to be the first synthetic biology health-care products on the market.

Recent synthetic biology health-related projects

Grand Challenges Explorations, an initiative funded by the Bill and Melinda Gates Foundation, supports "creative projects that show great promise to improve the health of people in the developing world". The grants (see Annex A) awarded in May 2012 were on the topic "Apply Synthetic Biology to Global Health Challenges". They exemplify the range of applications of synthetic biology to medical challenges.

There is much work to do before synthetic biology-based health-care solutions find clinical application. Progress on strategies for classical biomedical applications has advanced substantially and may ultimately lead to shorter drug discovery and development timelines, increased precision of drug delivery, and the production of new and more affordable medicines as the human population expands towards nine billion.

In the near term there will be an increasing need to move towards mammalian systems. Most constructs so far have been made in microbes, but moving towards clinical practice will require more complex, clinically applicable circuits, the identification of new mammalian modules and components, and synthesis and characterisation of diverse component libraries (Ruder et al., 2011). The clinical use of these devices and therapeutic scenarios will face the same legal, ethical, regulatory and governance issues as any gene- and cell-based therapy (Weber and Fussenegger, 2012).

Agricultural applications

Bioeconomy strategies envisage the expansion of agriculture both to feed the world's population and to provide the raw materials for bio-based industries, including biomass for fuels. One of the primary drivers of bio-based production is rural regeneration. This expansion will however mean an increasing use of land to produce crops not intended for food or feed and will have to take place against a backdrop of rapid destruction of soil, a trend that urgently needs to be reversed.

Discussions of agriculture and synthetic biology revolve around increasing efficiency to feed more people and accommodate other demands on agriculture. Over the past decades, agricultural efficiencies have increased, and global agriculture has been characterised by policy-induced production surpluses in industrialised countries and stagnating growth in developing countries (OECD/FAO, 2013).

Synthetic biology can play a role, for example in producing crops with higher yields per acre through increased resistance to disease to reduce crop losses. It is important to clarify that there are no synthetic biology applica-

tions in agriculture at present. However, an increasing number of applications of genetic engineering have resulted in safe genetically modified (GM) products in modern agriculture. Table 2.2 shows the top 18 countries (by acreage) of GM crop production in 2012. An excellent searchable approval database on genetically modified organisms (GMOs) is available.[7]

By 2008 GM crops were grown on almost 300 million acres in 25 countries, of which 15 were developing countries (James, 2009). Acceptance and planting of GM crops has continued to increase, but bottlenecks continue to exist in Europe. At present the poorer countries of the world would benefit most from synthetic biology or GM technology. For example, 40 grams of GM Golden Rice a day (modified for the production of vitamin A) are sufficient to prevent the severe health consequences of vitamin A deficiency in rice-dependent poor populations (Potrykus, 2013).

Table 2.2. Land used for GM crops, countries growing 50 000 hectares or more

Country	Million hectares	Crops
Americas		
United States	69.5	Maize, soybean, cotton, canola, sugar beet, alfalfa, papaya, squash
Canada	11.6	Canola, maize, soybean, sugar beet
Mexico	0.2	Cotton, soybean
Brazil	36.6	Soybean, maize, cotton
Argentina	23.9	Soybean, maize, cotton
Paraguay	3.4	Soybean, maize, cotton
Uruguay	1.4	Soybean, maize
Bolivia	1.0	Soybean
Chile	<0.1	Maize, soybean, cotton
Colombia	<0.05	Cotton
Honduras	<0.05	Maize
Cuba	<0.05	Maize
Costa Rica	<0.05	Cotton, soybean
Europe		
Spain	0.1	Maize
Portugal	<0.05	Maize
Czech Rep.	<0.05	Maize
Romania	<0.05	Maize
Slovak Rep.	<0.05	Maize

.../...

Table 2.2. Land used for GM crops, countries growing 50 000 hectares or more *(continued)*

Country	Million hectares	Crops
Africa		
South Africa	2.9	Maize, soybean, cotton
Burkina Faso	0.3	Cotton
Sudan	<0.05	Cotton
Egypt	<0.05	Maize
Asia		
India	10.8	Cotton
China	4.0	Cotton, papaya, poplar, tomato, sweet pepper
Pakistan	2.8	Cotton
Philippines	0.8	Maize
Myanmar	0.3	Cotton
Australia	0.7	Cotton, canola

Source: International Service for the Acquisition of Agri-Biotech Applications (2012), www.isaaa.org.

So far there is little literature on synthetic biology applications in agriculture. Some obvious areas of interest for agriculture are: reduced water use (crops that use less water); more efficient nitrogen use (less fertiliser); greater disease resistance; more "efficient" plants (increased yield, less production of CO_2). Other, less strategic, applications could include: better quality products (flavour, aroma, colour, anti-oxidant content, altered oil content, improved fibre quality); and improved processing characteristics (high solids tomatoes, high cellulose cotton).

Resistance to drought and other abiotic stresses

Water is the primary limiting factor in global agriculture, yet water availability and quality for crops diminish as cities grow and as irrigation and land-clearing salinise soil and underlying water tables. Humans are expected to appropriate from 70% to 90% of all accessible freshwater by 2025. As agriculture accounts for almost 70% of all human use of water (Sophocleous, 2004), measures to conserve water in agricultural use are of the utmost importance.

Water deficit, salt and other abiotic stresses are exacerbated by global warming and climate change (Fedoroff et al., 2010). Yields of the most important food, feed and fibre crops decline precipitously at temperatures much above 30°C (Schlenker and Roberts, 2009), and water shortages amplify the problem. The 1988 drought in the mid-western United States re-

sulted in a 30% reduction in US corn production and cost about USD 39 billion (Mishra and Cherkauer, 2010). The United States has also just experienced its most widespread drought in more than half a century (Reardon and Hodson, 2013).

A looming gap between water supply and demand calls for major advances in adapting crops to drought and salt stresses through more efficient use of water and increased tolerance to saline soil. Increasing evidence suggests that plants' adaptation to shortage of water and other abiotic stresses is under genetic control and epigenetic regulation, so that the rational design approach of synthetic biology may lend itself to crop modification.

Excess water can also be a problem. Rice is a crop well adapted to wet, monsoon climates and allows farmers to produce food in flooded landscapes. Of the lowland rain-fed rice farms worldwide, over 22 million hectares, representing 18% of the global supply of rice, are vulnerable to flash flooding. Most rice varieties can tolerate only a few days of submergence and die after about a week. Success in fine mapping of SUBMERGENCE 1 (SUB1), a robust quantitative trait locus from the submergence-tolerant FR13A landrace, has enabled marker-assisted breeding of high-yielding rice capable of enduring transient complete submergence (Bailey-Serres et al., 2010).

Reducing fertiliser and pesticide use

Nitrogenous compounds in fertilisers are major contributors to waterway eutrophication and GHG emissions, and the Haber-Bosch process for making fertilisers is very energy-intensive. When the price of Brent crude oil rose from around USD 50 per barrel to about USD 110 by January 2013, the prices for ammonia in western Europe and the mid-western corn belt in the United States roughly tripled.[8] An important goal of synthetic biology research could therefore be more efficient uptake and use of nitrogen in crops.

Although there is plenty of nitrogen in the atmosphere, atmospheric nitrogen is not in a form plants can use. Atmospheric nitrogen must be "fixed" or converted into compounds that make the nitrogen available to plants. Synthetic biologists at Washington University have taken the first proof-of-principle steps towards inserting the genes needed to fix nitrogen (otherwise found only in bacteria and the bacteria-like Archaea) into the cells of crop plants.[9] This opens up the possibility of creating plants that make their own fertilisers. This could revolutionise agriculture and would significantly decouple agriculture from the oil industry.

The first few GM crops that have been widely grown, including insect-resistant and herbicide-tolerant corn, cotton, canola and soybeans, are reported to have increased agricultural productivity and farmers' incomes

(Federoff et al., 2010). They have also had environmental and health benefits, such as decreased use of pesticides and herbicides and increased use of no-till farming (Brookes and Barfoot, 2010). No-till farming of GM crops reduced GHG emissions in 2008 by the equivalent of removing 6.9 million cars from the roads.

Resistance to disease

Sugar cane is a good example of a crop much in demand for different uses, especially its increasing non-food use for biofuels production. Sugar cane is attacked by over 1 500 insect species and over 80 diseases from bacteria, fungi and viruses. *Telchin licus* Drury (the giant cane borer) was recorded for the first time in 2008 in the São Paulo region, the main sugar-growing region of Brazil (Goebel and Sallam, 2011). The larva causes severe damage to sugar cane and significantly reduces biomass and sugar yields, thereby lowering both sugar and ethanol production. The struggle with plant disease is constant and is more difficult for large areas of monoculture. This is an area in which early success with synthetic biology could enhance its reputation and perhaps diffuse some of the political angst associated with genetic modification (Philp et al., 2013).

Furthermore, climate change and global warming are likely to result in changes in the microbial and insect disease patterns in crops (Gregory et al., 2009). Synthetic biology may be able to develop understanding of disease mechanisms and resistance to disease faster than is possible through GM technology. This would improve responsiveness to changing patterns of plant disease under stresses of global warming.

Molecular farming

The use of transgenic plants as bioreactors is relatively new in the biosciences but is gaining some momentum. It involves the genetic modification of the host plant through the insertion and expression of new genes. It can be argued that this approach is in the grey area between genetic modification and synthetic biology but, with the passage of time, projects will arise that appear to be closer to synthetic biology. Products currently being researched for production in plant bioreactors include bioactive peptides, vaccine antigens, antibodies, diagnostic proteins, nutritional supplements, enzymes and biodegradable plastics (Sharma and Sharma, 2009). The other links to the bioeconomy are the potential GHG emissions savings and creation of rural jobs.

For example, Somleva et al. (2008) demonstrated that polyhydroxybutyrate, a biodegradable plastic, can be produced at less cost from switchgrass. This non-food crop has proven amenable to the complex meta-

bolic engineering necessary to produce high-value biomaterials with lignocellulose-derived biofuels as a co-product.

Astaxanthin is a carotenoid found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish, crustaceans and the feathers of some birds. It provides the red colour of salmon meat and the red colour of cooked shellfish. It is employed widely as a component of the feed used by fisheries and poultry farms (Aflalo et al., 2007), but it adds significantly to costs, as synthetic astaxanthin costs some USD 2 000 a kilogramme (Guerin et al., 2003). Non-synthetic sources are limited and extremely expensive.

Recently, Huang et al. (2013) described the engineering of tomato for high-yield production of astaxanthin by expressing a specific pair of algal genes that were identified as the best combination for astaxanthin production from β-carotene. Compared to the microalga *Haematococcus pluvialis,* which needs a well-controlled environment (e.g. growth in an enclosed photobioreactor) for pure culture, tomato is a food crop cultivated cost-efficiently worldwide with very high yields. Therefore, astaxanthin production in tomatoes might be an effective commercial production route for the natural compound.

Conclusion

This chapter should demonstrate why synthetic biology has created the excitement that it has. It has potential applications in a broad range of economic sectors. Moreover, it can be used to address some of the grand challenges facing society: climate change mitigation, energy security, applications in agriculture to address water, soil and food security, improving the health of the world's poor and of ageing populations, and environmental protection. The earliest products of synthetic biology, bio-based chemicals, are now arriving in the market place. The large scale associated with transport fuels is a problem still being addressed. The first synthetic biology food ingredient is due to be released in 2014. Medical applications are clearly going to be in the next generation of synthetic biology achievements. Meanwhile, fuel and chemical applications are also producing the required platform tools and technologies.

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Chapter 3

Research infrastructure challenges for synthetic biology

While many of the fundamental laboratory techniques of biology and biotechnology are also applicable to synthetic biology, the major departure from the biological sciences tradition is in the development of technologies for the synthesis of large DNA sequences (of the gene and operon scale and above). Currently the cost of DNA synthesis lags a considerable way behind the spectacular advances in lowering the cost of DNA sequencing, although progress is being steadily made. In line with the aspirations to bring engineering standardisation to synthetic biology, there is a pressing need for new software developments, especially in design and manufacture. Chassis organisms, usually microorganisms engineered to be "minimal" life forms, are being developed as hosts for synthetic biology applications to reduce the noise and interference that is typical in biology. The bottleneck in synthetic biology is now shifting from DNA synthesis to dealing with the massive amounts of genetic and digital data being produced. If there is any role for co-ordinated international research infrastructure, it is to deal with this issue.

Introduction

The synthetic biology laboratory contains many of the same materials and equipment as a general molecular biology laboratory. However, technical barriers currently inhibit the widespread implementation of synthetic biology. To understand these barriers it is useful to recall the three core technology areas of synthetic biology: DNA synthesis and assembly, sequencing, and modelling.

A major goal in synthetic biology is to design and construct new metabolic pathways within a producer cell. This requires addressing three important obstacles (Notka et al., 2011):

1. For a stable and efficient series of reactions, the enzymes involved must be expressed in a highly concerted manner. As for other engineering technologies, this requires the availability of standardised regulatory parts and elements, e.g. promoters, ribosome binding sites, terminators, DNA-binding proteins (see Annex3.A1).
2. Fast and efficient formation of new gene clusters or operons requires the simultaneous assembly of such parts in a robust, yet flexible way.
3. Establishing an extrinsic biochemical pathway within a living cell must always be perceived in the context of its entire metabolism. For an industrial production organism, its metabolism should be limited to prevent interference from other pathways.

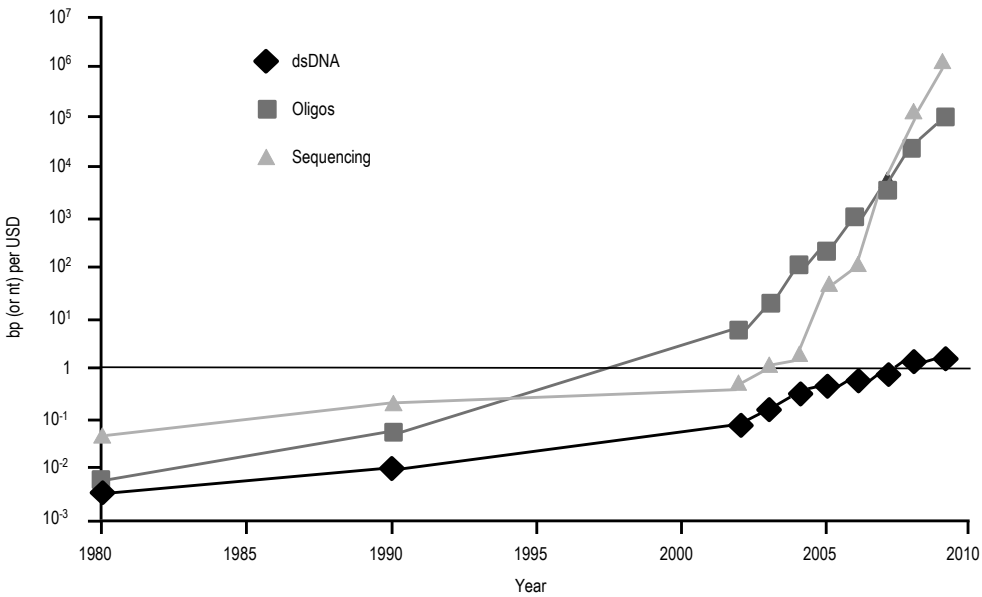
The most important technical barrier to progress in synthetic biology today is the cost and speed of fabrication of synthetic sequences. The need for routine large-scale synthesis of DNA hinders the ability to construct ever larger genetic devices and systems. By contrast, modelling does not require the development of entirely new technologies. This is the province of software design and construction and the field is progressing rapidly. DNA sequencing technologies have also moved rapidly in the last ten years, and are technically less demanding than large-scale synthesis.

Gene synthesis, the financial bottleneck

Maximising the potential of synthetic biology will require the development of cost-effective, high-throughput, high-fidelity methods of synthesising *de novo* DNA sequences of ever-increasing length and complexity. While the cost of sequencing has tumbled, the cost of gene synthesis had levelled out around USD 0.50 per base pair (bp) in 2010 (Jewett and Forster, 2010), of which USD 0.10 per bp for oligonucleotide synthesis (Cheong et al., 2010). This is prohibitive for most researchers at the genome level.

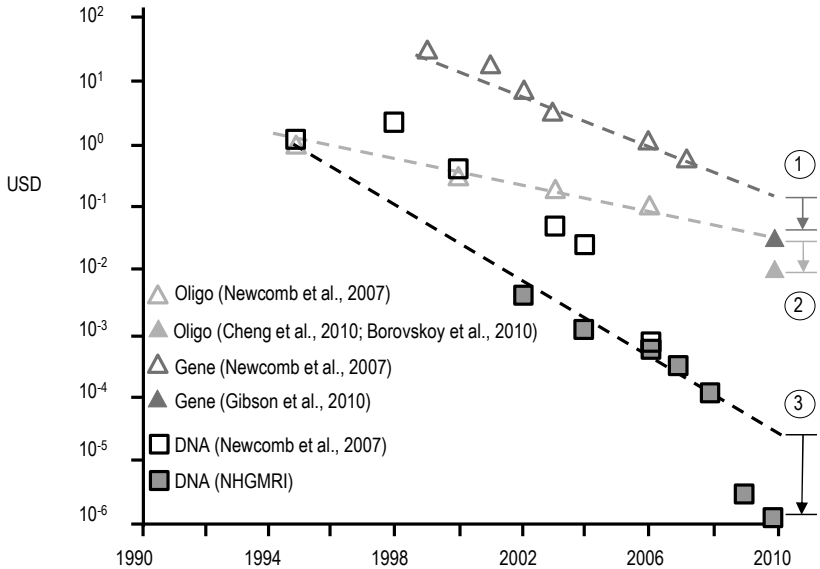
Figure 3.1 shows that gene synthesis (dsDNA), while improving rapidly, lags both oligonucleotide synthesis and sequencing. Figure 3.2 shows the decline in prices. Carlson gives data showing costs and productivity up to October 2012,[1] at which point the costs of synthesis were some four times the costs of sequencing. By February 2014, there was an apparent slowdown in the tumbling of prices, indicating that there may now be a phase in which prices will plateau.

Figure 3.1. Efficiency trends in synthesis and sequencing over the past 30 years (base pairs per dollar)



Source: Carr, P.A. and G.M. Church (2009), "Genome engineering", *Nature Biotechnology*, Vol. 27, pp. 1151-1162.

Figure 3.2. Declining cost trends for oligonucleotide synthesis, gene synthesis and DNA sequencing



Notes: Data sources shown on the graph. The recent declines are marked by downward pointing arrows drawn from the projected trend lines (based on about a decade of data) to the 2010 data points.

Source: Mitchell, W. (2011), "Natural products from synthetic biology", *Current Opinion in Chemical Biology*, Vol. 15, pp. 1-11.

Oligonucleotide synthesis

All gene synthesis technologies rely on the chemical synthesis of oligonucleotides to supply the building blocks for enzymatic assembly (Hughes et al., 2011). The most commonly used method is the cyclical, four-step phosphoramidite synthesis method developed in the 1980s. During the synthesis process, side reactions limit the quality and yields of oligonucleotides above 100 nucleotides (Hall et al., 2009). But the most crucial factor in DNA synthesis protocols today is the high error rate of oligonucleotide synthesis (Czar et al., 2009). Even an error rate as low as 1 in 10 000 bp can be a major concern if the product of interest is of that scale (10^4) or larger.

The robustness of solid phase phosphoramidite synthesis makes it easily amenable to automation, and this method is now used in almost all commercially available DNA synthesisers. However, for the assembly of long genes or even whole genomic sequences, the cost of the starting oligonucleotides alone can be prohibitive (for large-scale synthesis projects, of the order of hundreds of thousands of US dollars). Smaller-scale synthesis strategies are

needed to bring down the cost of starting oligonucleotides before *de novo* gene synthesis will be widely adopted.

DNA microarrays went part of the way to solving the problem. Depending on the chip platform used, several thousand to several hundred thousand distinct oligonucleotides can be synthesised on a single chip. In principle, these massively parallel microarrays can reduce the cost of oligonucleotides by orders of magnitude. However, microarrays produce very small amounts of oligonucleotides, and there are problems with purity and quality. Lee et al. (2010) reported the development of a microfluidic synthesis platform capable of generating a number of oligonucleotides in parallel for gene assembly. This system addresses many of the limitations associated with microarray technology. It is claimed that it can greatly reduce the cost of gene synthesis by reducing reagent consumption (by 100-fold) on a scale that removes the need for amplification before assembly.

Gene assembly

The yield of chemically synthesised oligonucleotides becomes exceedingly poor and the synthesis error rate increases with oligonucleotide length. To circumvent these limitations, methods have been developed to assemble relatively short synthetic oligonucleotides into longer gene sequences. They can be roughly grouped into ligation-mediated assembly and PCR-mediated assembly methods.

Ligation-mediated assembly has an inherently low mutagenesis rate (no errors due to DNA polymerase) and is relatively easy to use. For example, Blue Heron[2] uses a solid-support-based, ligation-mediated oligonucleotide assembly process to synthesise customer-supplied DNA sequences. The technology assembles a DNA duplex sequence on a solid support by iterative annealing and ligation of oligonucleotide pairs. This process is repeated until the entire gene sequence is sequentially assembled. As the technology has been fully automated, it allows for efficient, high-throughput synthesis of DNA sequences at commercial scale.

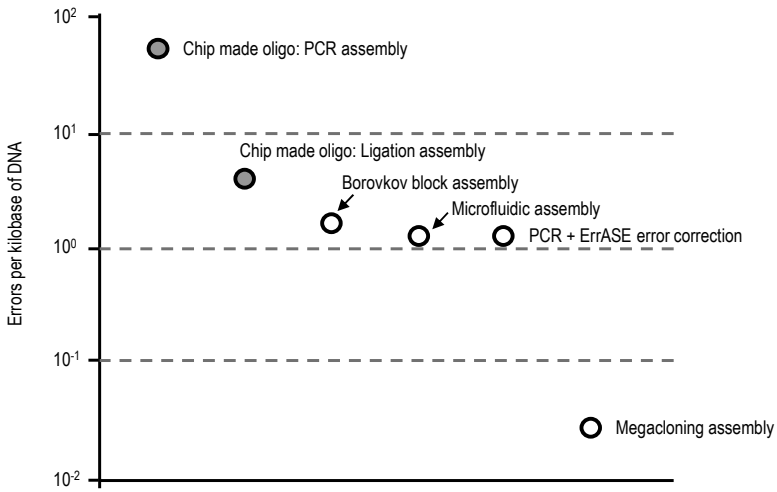
The most commonly used gene synthesis techniques currently rely on the polymerase chain reaction (PCR) to mediate assembly of a desired DNA sequence from short oligonucleotides. The desired gene product is assembled (often as a mixture of PCR products of varying lengths) in a single enzymatic reaction or as multiple-step assemblies that first divide the gene into separate sub-assembly reactions. In these methods, the various sub-assemblies are then mixed and joined in a series of thermal cycling reactions to yield the fully assembled gene products.

High error rates are a problem for many PCR-based gene synthesis techniques (Xiong et al., 2008). Errors are the result of mutations introduced during DNA polymerase-mediated synthesis and oligonucleotide synthesis procedures. At present, several methods of error correction of synthesised DNA exist, but they add complexity and cost to the process. A detailed discussion of these methods is beyond the scope of this paper, but some examples of research in the area are presented.

Improvements to PCR-based gene synthesis are published regularly. Mao et al. (2011) described a process they call Quikgene, a method that can assemble several hundreds of base pairs of genes. It can create complete *de novo* genes or extend or modify existing genes. The final genes are directly synthesised on desired vectors without any ligation or sub-cloning steps. Cheong et al. (2010) presented a simple, highly efficient, universal automatic kinetics switch gene synthesis method that enables synthesis of DNA up to 1.6 kbp (thousand base pairs) from 1 nano Mole oligonucleotide with just one PCR process.

A proof-of-concept experiment has demonstrated that the so-called "megacloning" method can reduce error rates by a factor of 500 (Figure 3.3) compared to the starting oligonucleotide pool generated by microarray (Matzas et al., 2010). In principle, with future development of platform automation, millions of oligos can be sequenced and sorted in a single megacloner run. This is paving the way to gene construction up to megabases in length (Ma et al., 2012).

Figure 3.3. Technology changes and reduction in error rates during DNA assembly



Source: Mitchell, W. (2011), "Natural products from synthetic biology", *Current Opinion in Chemical Biology*, Vol. 15, pp. 1-11.

A gene synthesis tipping point

Carr and Church (2009) describe a gene synthesis tipping point: the point at which commercial gene synthesis would be on par with synthesis of synthetic oligos, with similar costs and turn-around time, typically same-day shipping. When this occurs, there will be a landmark shift in the way many laboratories work. Much of the laborious work currently done to manipulate DNA will be phased out. Instead of cloning into vectors stored in laboratories, custom or standard vectors would simply be re-synthesised on demand. This will free up space and money: a lot of resources dedicated to deep-freezing of these materials will no longer be needed. Moreover, a much larger number of laboratories could undertake relatively large synthesis projects. In particular, small and spin-out companies would be relieved of this infrastructural expenditure and a new wave of synthetic biology companies may appear. The shift will also open the field to designers who need not be experts in traditional DNA manipulation techniques. It has been postulated that DNA fabrication will even lead to abiotic applications used in computing, detection or smart materials that will have very little in common with traditional biotechnology products (Czar et al., 2009).

Examination of the literature and research trends suggest that the tipping point will be reached in the near future. It seems that key developments and advances will come from exploitation of the advantages of miniaturisation that microfluidics offers, increased levels of automation, and high-quality error-correction methods.

The savings in expensive reagents is the most obvious advantage of microfluidics. Microfluidic systems that cover all the necessary unit operations for cellular assembly and analysis from oligonucleotide synthesis through to -omics analyses have now been designed (Szita et al., 2010). Other advantages include shorter analysis times and higher sensitivities. Moving forward, there should be a drive to integrate more steps into a single system and towards automation and parallelisation to increase experimental throughput.

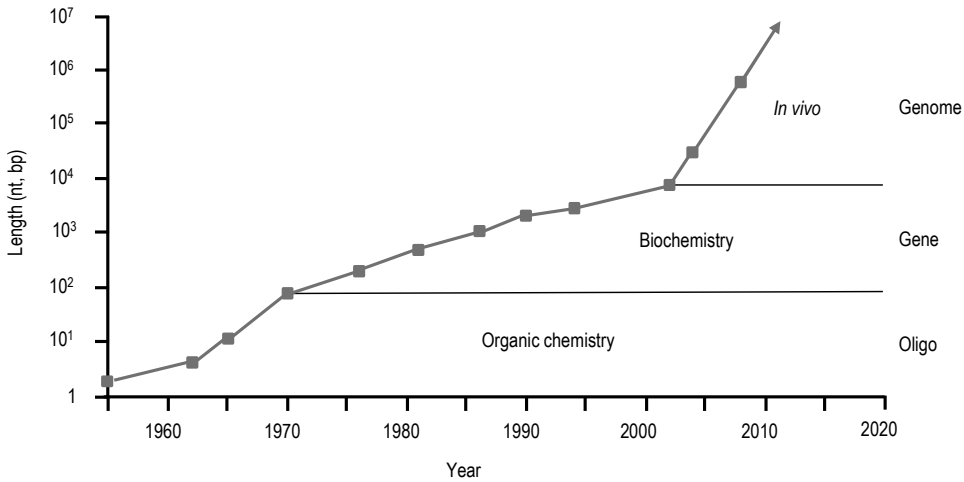
At the industrial scale, an increasing degree of automation of gene synthesis is mandatory to cut labour costs. Some steps are also simply no longer manageable by humans, such as the move from 96- to 384-well plates or the decrease of reaction volumes below 1μl. There is flawless interaction between automated pipetting and laboratory information management systems (LIMS). Notka et al. (2011) argue that the interplay between automation, LIMS and miniaturisation is the way to proceed to gene synthesis at industrial scale. Automation at least is not very technically demanding; current technology for robotics and automation should suffice.

Several companies (e.g. Gen9[3] and DNA2.0[4]) appear poised to make significant breakthroughs in high-throughput, automated production of DNA sequences at lower cost and higher accuracy than currently available. DNA2.0 now offers a rush service for DNA synthesis of <1 kilobase in five days, advertised as the fastest turnaround time in the industry, but still a way from overnight shipping for oligonucleotide synthesis.

Debugging of constructs

While testing, debugging and maintenance may appear of lesser importance than the actual synthesis operations described, they reportedly account for 80% of all software development costs. The Amyris five-year, USD 20 million artemisinin experiment reportedly spent 95% of its time trying to find and fix unintended interactions between parts (Henckel and Maurer, 2007).

Figure 3.4. Milestones in the sizes of *de novo* synthesized DNA



Note: Length is nucleotides (nt) for oligos before 1970, base pairs (bp) for double-stranded DNA from 1970 on. *In vitro* biochemical processing steps enabled the leap from oligos to genes, and *in vivo* processing steps (multiple cycles of cloning, sequencing and assembly) made possible the leap from genes to genomes.

Source: Carr, P.A. and G.M. Church (2009), "Genome engineering", *Nature Biotechnology*, Vol. 27, pp. 1151-1162.

Unfortunately, debugging a biological machine does not so far follow an apparent logical formula. Vast amounts of a genome can be completely deleted without apparent harm to the organism and even yield improved performance (this is, of course, an objective of minimal genome and cell research). At the same time, very modest changes can reduce performance,

and single-point mutations can easily be fatal. Biological complexity is the issue. Carr and Church (2009) describe two hierarchies of debugging:

1. All the separate genetic parts of a designed system should be tested singly in parallel, or in as simple a representation as possible. Where possible, combinations of simple parts into larger units should be performed along lines of linked function, so that these combinations can also be tested en route to final assembly. This is not unlike testing and debugging in other forms of manufacturing.
2. The ultimate testing environment is necessarily *in vivo* owing to biological complexity (Figure 3.4). Problems encountered at the drawing board or *in vitro* stages are likely to indicate real concerns for the *in vivo* context.

The chassis, or the minimal genome and cell concept

Although metabolic engineering has traditionally involved the manipulation of pre-existing cellular genomes, there is another way to think about the construction of industrial microbes. It involves the concept of a minimal genome: the minimum number of genes required to support basic life (Mushegian, 1999). The only minimal genome used as a starting point to date is the organism with the smallest known genome that can be cultivated under laboratory conditions, the bacterium *Mycoplasma genitalium* (Gibson et al., 2008; Glass et al., 2006). Precisely 100 of the 482 *M. genitalium* genes were deemed non-essential by genome-wide transposon mutagenesis. Deletion of these genes resulted in a strain with improved growth rates, as less energy is expended on non-vital cellular processes. The objective is to minimise the metabolic burden on the cell, so the remaining cellular energy can be directed towards the production of a desired industrial product, such as an industrial chemical or pharmaceutical drug (Pyne et al., 2011). Minimising the number of components required to support biological synthesis from synthetic DNA circuits or genomes enables adequate control of its function. The approach may also yield insights into the function of early cells, which were conceivably much simpler than modern cells (Stano et al., 2011). Insofar as the cell is the minimal form of the bioreactor, simpler, even artificial, cells make for more reliable bioreactors (Pohorille and Deamer, 2002). A further spin-off technology could be *in vitro* genome replication to replicate very large segments of DNA with high fidelity (Forster and Church, 2006).

For biotechnology applications, reducing the genomes of *E. coli* and other biotechnology workhorses is more useful than reduced-genome *M. genitalium* owing to the fragility and much slower growth rate of the latter (Jewett and Forster, 2010). Future work on *E. coli* and others will replace most current commercial bacterial strains, because in an industrial ferment-

er, an aerobic environment is usually desired and maintained, the nutrient concentrations are maintained within narrow ranges, and attachment to the vessel is not desirable. *E coli* is normally found in the (anaerobic) gut of mammals, although the genes required for survival in the gut may not be the same as those required for optimum industrial application (Sharma et al., 2007). Therefore many projects have aimed to reduce the size of the *E. coli* genome. For example, in 2006 targeted deletions removing 15% of the *E. coli* genome were not only viable, but also improved its properties for applications in molecular biology (Posfai et al., 2006). Synthetic genomics will be particularly helpful for redesigning microbes that possess potential biotechnology applications but have poor native genetic tools available.

Other chassis organisms

E. coli is the most commonly described chassis organism. However, despite its flexibility and its very low risk level, it is not always possible to ensure efficient transcription/translation of a heterologous gene in *E. coli*, and post-translational protein modification does not occur in prokaryotic[5] production systems, hence the development of specialised eukaryotic production hosts such as yeast. Such organisms have characteristics that lend themselves to use as a chassis organism.

The genus *Bacillus* has a long history in the biotechnology sector and various species have been used over the years to produce industrial enzymes such as amylases and proteases. About 60% of commercially available enzymes are produced by *Bacillus* species (Westers et al., 2004). Several species are non-pathogenic and have long been approved as safe to use as production hosts. A particular advantage is that they naturally secrete significant quantities of protein from the cell into the environment (Schallmay et al., 2004). They are easy to grow, and the genetics are well researched; the prototype species *B. subtilis* is second only to *E. coli* in terms of understanding both of its genetics and physiology. There are problems, however, of plasmid stability and there is no post-translational modification.

The use of yeast expression systems combines many advantages of complex mammalian hosts and prokaryotic hosts. Expression hosts such as *Saccharomyces cerevisiae* (the wine, beer and baker's yeast) are efficient at post-translational modification of other eukaryotic proteins, while, like *Bacillus*, they are non-pathogenic and can be grown in large volumes on simple growth media and can secrete proteins. In fact, yeasts are the most exploited group of industrial microorganisms (Fell and Phaff, 2003). In-depth knowledge of *Saccharomyces cerevisiae* genetics, genetic engineering, physiology and biochemistry has been accumulated, and industrial-scale fermentation technologies are readily available (for a review, see Nevoigt, 2008).

DNA sequencing: A challenge overcome?

Fortunately, sequencing technology is no longer the barrier to the development of synthetic biology that it once was, especially when compared to the difficulties of gene synthesis and assembly.

In 2004, the National Human Genome Research Institute of the National Institutes of Health (NIH – NHGRI) announced a total of USD 70 million in grant awards for the development of DNA sequencing technologies that would reduce the cost of sequencing the human genome from USD 3 billion, the amount spent on the public Human Genome Project, to USD 1 000 by 2014.[6] Already by 2008 massively parallel DNA sequencing platforms had become widely available, reducing the cost of DNA sequencing by over two orders of magnitude and bringing it within the grasp of individual investigators, not just genomics centres (Shendure and Ji, 2008).

As of December 2013 the routine cost of a human genome sequence had dropped to around USD 5 000, with the possibility of reaching USD 1 000 sometime in 2014. At least one company claims to have a technology that should soon become available that would bring the cost of the sequence of a human genome to USD 100.

Next-generation sequencing has shifted the bottleneck from sequencing to the best way to extract biologically meaningful or clinically useful insights from very large amounts of data (Shendure and Ji, 2008). The Short Read Archive at the US National Centre for Biological Information is soon expected to exceed a petabyte (National Academy of Sciences, 2013). As more and more high-throughput sequencers are deployed, not just in research but also in hospitals and biotechnology facilities and companies, growth of data on genomic information will be even faster.

Software infrastructure

Software infrastructure, the "unseen" infrastructure in the synthetic biology laboratory, deserves special attention for an essential reason. The "wet" technologies of synthetic biology described above will, at least in the medium term, be limited to research institutions and companies where oversight and regulation will be possible. However, as synthetic biology gains momentum specific types of software are likely to be increasingly accessible to non-experts working from a home computer who may start to use software to design parts. While in itself this does not represent a danger, subsequent construction of the designed part may. Therefore software use by non-experts (and experts, for that matter) represents a regulatory concern and may be far more difficult to monitor than the wet technologies of synthetic biology.

Technological advances have shown the utility and importance of using software tools that facilitate various engineering processes, such as computer-aided design (CAD). The application of computational tools in synthetic biology has not reached the stage at which the design and construction of biological parts has become routine, and some argue that there is a need for an integrated design environment for the synthetic biologist that is similar to CAD systems (Marchisio and Stelling, 2009). In recent years, many computational standards and tools have been developed, especially in the field of systems biology (Wierling et al., 2007), and most of these tools could be used in synthetic biology applications. While laboratory procedures are now borrowed from genetic engineering, concepts such as abstraction and interchangeable parts come from computer science and electrical engineering (Endy, 2005).

Since synthetic biology is its initial stages of development, best practices for the design, use and reuse of existing parts have not been widely established. The software infrastructure for synthetic biology at present raises several challenges, which have to be addressed in an efficient way to attain rapid growth and promote knowledge among young professionals wanting to enter this field.

Overview of existing tools and challenges

Computational tools that allow design and construction of model organisms *in silico* using scripts or visual interfaces have been developed in recent years (Table 3.1). A comprehensive list can be found at: www.sbml.org.

Biological computation and integration

Challenges such as programming life, with applications in DNA computing and synthetic biology, are already being addressed and represent a frontier for the convergence of computing with biology. For example, the Biological Computation Group at Microsoft Research[7] is working on projects that include designing molecular circuits made of DNA and programming synthetic biological devices to perform complex functions over time and space. The tools being developed are being integrated into a common software environment, which supports simulation and analysis on multiple scales and across many domains. This environment may in time serve as the foundation for a common language runtime for biological computation.

Table 3.1. Computational design tools for synthetic biology

Circuit design and implementation	
Biojade	http://web.mit.edu/jagoler/www/biojade/
Tinkercell	www.tinkercell.com/Home
Asmparts	http://soft.synth-bio.org/asmparts.html
ProMoT	www.mpimagdeburg.mpg.de/projects/promot
GenoCAD	www.genocad.org/genocad/
GEC	http://research.microsoft.com/gec
TABASCO	http://openwetware.org/wiki/TABASCO#TabascoSimulator
Hy3S	http://hysss.sourceforge.net/index.shtml
Circuit optimisation	
Genetdes	http://soft.synth-bio.org/genetdes.html
RoVerGeNe	http://iasi.bu.edu/_batt/rovergene/rovergene.htm
DNA and RNA design	
Gene Designer	www.dna20.com/index.php?pageID=220
GeneDesign	www.genedesign.org
UNAFold	www.bioinfo.rpi.edu/applications/hybrid/download.php
Mfold	http://mfold.bioinfo.rpi.edu/download/
DINAMelt	http://dinamelt.bioinfo.rpi.edu/
Vienna RNA package	www.tbi.univie.ac.at/~ivo/RNA/
Vienna RNA web servers	http://rna.tbi.univie.ac.at/
Zinc Finger Tools	www.scripps.edu/mb/barbas/zfdesign/zfdesignhome.php
Protein design	
Rosetta	www.rosettacommons.org/main.html
RAPTOR	www.bioinformaticssolutions.com/products/raptor/index.php
Hhpred	http://toolkit.lmb.uni-muenchen.de/hhpred
Modeler	http://salilab.org/modeller/
PFP	http://dragon.bio.purdue.edu/pfp/
Autodock 4.2	http://autodock.scripps.edu/
HEX 5.1	http://webloria.loria.fr/~ritchied/hex/
Integrated workflows	
SynBioSS	http://synbioss.sourceforge.net/
Clotho	http://biocad-server.eecs.berkeley.edu/wiki/index.php/Tools
Biskit	http://biskit.sf.net

Source: Marchisio, M.M. and J. Stelling (2009), "Computational design tools for synthetic biology", *Current Opinion in Biotechnology,* Vol. 20, pp. 479-485.

Standardisation and interoperability

Active efforts to develop synthetic biology tools have raised questions regarding standardisation and interoperability. In the field of synthetic biology, standardisation aims to allow researchers to exchange designs electronically, to send designs to fabrication centres for assembly, and to allow storage of designs in repositories and for publication purposes.

Building synthetic circuits involves design and simulation tools that combine standard parts to introduce or modify biological functions, akin to the way in which engineers design new machines. One of the defining missions of the MIT Registry of Standard Biological Parts is to store and share the list of standard parts and devices to make this process easier.

Standardisation in engineering disciplines allows components to be combined easily to form larger systems, an approach that relies on the modularity of those components. A prevailing assumption in synthetic biology is that biological components should be modular as well. However, characterisation, standardisation and modularity are affected by cellular context (Purnick and Weiss, 2009), and it cannot be assumed that a functional module in one cell type will work the same way even in a closely related cell type (Bagh et al., 2008). Therefore, quantitative characterisations of component functions are necessary for efficient network design (Canton et al., 2008). However, biological knowledge and design capabilities are not yet at the level of sophistication needed for *a priori* design and production of a prototype with a reasonable chance of success (Alterovitz et al., 2010).

In synthetic biology, network standardisation should be given equal weighting with component-centred standards. Systems Biology Markup Language (SBML) is a machine-readable format for representing computational tools in systems biology. It was developed to exchange biological process information in the systems biology community (Hucka et al., 2003). Many other standards such as Cellular Markup Language (CellML) (Lloyd et al., 2004), MIRIAM (Novere et al., 2005) and Systems Biology Graphical Notation (SBGN) (Novere et al., 2009) represent a set of conventions to depict biological processes in graphical notation to facilitate efficient and clear communication among biologists. The heterogeneity of approaches to addressing network standards by using specialised formats for data management within synthetic biology sub-groups must be addressed.

Interoperability is a somewhat vague term, but it is generally regarded as necessary for the diffusion of innovation. As used in information and communications technology (ICT), it may be described as the ability to transfer data and other information across systems (which may include organisations), applications or components (Gasser and Palfrey, 2007). The benefits for synthetic biology are clear: standard parts that, when put together in a

working system, will function across different systems and organisations. It is analogous to digital music that can be played by different music players.

The public sector is likely to play a limited role in bringing interoperability to synthetic biology. In ICT cases, the private sector largely can and does achieve a high level of interoperability on its own. The public sector may help by playing a convening role, or even in mandating a standard on which there is widespread agreement within industry after a collaborative process. In a very few cases, the public sector may need to ensure that market actors do not abuse their positions.

Biological noise control

Biological noise is a problem both at component and network level. Genetic circuits tend to mutate rapidly and become non-functional (Tucker and Zilinskas, 2006). In general, combining disparate components requires the tuning of biochemical parameters such as affinities or rate constants, which is often difficult to do in biological circuits. The development of synthetic gene networks is still difficult and most newly created genes are non-functioning owing to intrinsic parameter fluctuation, external disturbances and functional variations of intra- and extra- cellular environments. The design methodology for a robust synthetic gene network that works properly in a host cell under these conditions of noise and fluctuation is therefore a high priority (Lee and Chen, 2010).

International distributed research infrastructures

These infrastructures tend to be large, expensive international facilities such as CERN, the European Organisation for Nuclear Research.[8] While such an experimental facility for synthetic biology would be hard to envisage, the case for a central facility to house publicly available databases from which data can be distributed is easier to justify. For example, the National Center for Biotechnology Information[9] facility, and in particular its BLAST facility,[10] provides a harmonised method for searching a large range of genomes. Box 3.1 describes the fundamental requirements that governments need to be aware of (also see OECD Global Science Forum, 2010).

Box 3.1. Requirements for an international distributed research infrastructure (IDRIS)

An IDRIS should have:

- An identity and a name.
- A set of international partners that are, typically, research institutes, academic institutions, foundations or other research-oriented organisations from the public or private sectors. Often, only parts of these entities make up the infrastructure.
- A formal agreement by the partners to contribute resources, expertise, equipment, services or personnel to achieving a common scientific purpose. The agreement does not necessarily need to define a new legal entity or be legally binding.
- A strategic plan, or work programme, that conveys the rationale for establishing the IDRIS and its added value over and above the separate activities of the partners.
- A governance scheme (for decision making, at a minimum) and a set of officers (not necessarily salaried staff) with well-defined responsibilities.
- A focus on the provision of services to members and users.

In addition, an IDRIS may have:

- An independent legal status (or an equivalent legal identity under the terms of an existing intergovernmental agreement).
- A common fund and rules for acquisition/spending of funds.
- A secretariat.
- A host institution.
- A central entry point for users.
- Explicit policies for access by users to research resources and to data and for managing any generated intellectual property.

Source: Michalowski, S. (2013), presentation at the OECD Marine Biotechnology workshop, Paris, 7 November.

The reason why a computational and not an experimental IDRIS would be important in synthetic biology is the drive towards parity of price and delivery time between DNA sequencing and DNA synthesis. Achieving the tipping point would bring the costs of synthetic biology research to a spectrum of researchers well beyond the initial centres of excellence. However, even now, the bigger infrastructure challenge is electronic storage and distribution of the huge quantities of data being produced (National Academy of Sciences, 2013).

Conclusion

The biggest challenge – that of long, accurate DNA synthesis – is gradually being addressed, although the latest figures on cost show that the price may be starting to plateau. In fact, both synthesis and sequencing costs have stopped falling precipitously. Owing to the technical similarities between wet biotechnology and wet synthetic biology, many other infrastructural challenges can be said to have been overcome (at the laboratory level). The vast amount of sequence data is now shifting the bottleneck towards data storage and management. This mirrors what practitioners also regard as training and educational bottlenecks; the future synthetic biologist will be more skilled in mathematics and data handling, and more familiar with engineering concepts than focused on biotechnology laboratory skills.

Notes

1. www.synthesis.cc/.
2. www.blueheronbio.com/Services/Gene-Synthesis.aspx.
3. http://gen9bio.com/.
4. www.dna20.com/.
5. A prokaryote (bacteria) has no nucleus to contain its genetic material. A eukaryote, a higher form of life, has a nucleus.
6. www.genome.gov/12513210.
7. http://research.microsoft.com/en-us/groups/biology/.
8. http://home.web.cern.ch/.
9. www.ncbi.nlm.nih.gov/.
10. http://blast.ncbi.nlm.nih.gov/Blast.cgi?CMD=Web&PAGE_TYPE=BlastHome.

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Annex 3.A1

Synthetic biology part types

The following selection of typical parts was taken from the iGEM Registry of Standard Biological Parts (http://parts.igem.org/Catalog?title=Catalog).

Composite parts: Composite parts are combinations of two or more BioBrick parts.

DNA: DNA parts provide functionality to the DNA itself. DNA parts include cloning sites, scars, primer binding sites, spacers, recombination sites, conjugative transfer elements and transposons.

Plasmid backbones: A plasmid backbone is defined as the plasmid sequence beginning with the BioBrick suffix, including the replication origin and antibiotic resistance marker, and ending with the BioBrick prefix.

Plasmids: A plasmid is a circular, double-stranded DNA (dsDNA) molecule typically containing a few thousand base pairs that replicates within the cell independently of the chromosomal DNA.

Primers: A primer is a short single-stranded DNA sequence used as a starting point for PCR amplification or sequencing.

Promoters: A promoter is a DNA sequence that tends to recruit transcriptional machinery and lead to transcription of the downstream DNA sequence.

Protein coding sequences: Protein coding sequences encode the amino acid sequence of a particular protein. Some protein coding sequences only encode a protein domain or half a protein. Others encode a full-length protein from start codon to stop codon.

Protein domains: Protein domains are portions of proteins cloned in-frame with other proteins domains to make up a protein coding sequence. Some protein domains might change the location of the protein, alter its degradation rate, target the protein for cleavage, or enable it to be readily purified.

Ribosome binding sites: A ribosome binding site (RBS) is an RNA sequence found in mRNA to which ribosomes can bind and initiate translation.

Terminators: A terminator is an RNA sequence that usually occurs at the end of a gene or operon mRNA and causes transcription to stop.

Translational units: Translational units are composed of a ribosome binding site and a protein coding sequence. They begin at the site of translational initiation, the RBS, and end at the site of translational termination, the stop codon.

Chapter 4

Changing investment patterns in synthetic biology

Over the last decade or so, there has been a marked increase in public and private investment in synthetic biology. Several countries have been particularly prompt to invest, and the effects are easier to see in the United States. The pattern of investment shows that the technology is also appealing to several key developing nations, and clearly China has strong ambitions. Several countries have also recognised a need to develop international funding mechanisms for student exchange and for reducing wasteful research overlap and duplication. Several key foundational companies have gone through favourable initial public offerings, most of them in the biofuels and bio-based chemicals sectors. However, such companies struggle with the complexities of scale-up to commercial production, especially in transport fuels. There has been a recent shift from biofuels to bio-based chemicals, which have lower production volumes. There may be a case for countries to offer specialised support to small and medium-sized enterprises, such as provision of access to demonstrator plants, testing and certification facilities.

The statistical data for Israel are supplied by and under the responsibility of the relevant Israeli authorities. The use of such data by the OECD is without prejudice to the status of the Golan Heights, East Jerusalem and Israeli settlements in the West Bank under the terms of international law.

> "Investment in research and innovation is the only smart and lasting way out of crisis and towards sustainable and socially equitable growth."
>
> European Commissioner Máire Geoghegan-Quinn, when announcing EUR 6.4 billion for research and innovation to be allocated by the end of 2011 (Fletcher and Bastin, 2010).

Introduction

For high-technology start-ups, the difficulty of attracting investments has always been one of the largest barriers to success. It may be easier for synthetic biology than for more traditional biotechnologies to attract investments, because of its cross-disciplinary nature and its applicability to health, chemicals, energy and environment. Nevertheless, governments aiming at an industry with a significant synthetic biology platform must prepare for this difficulty. Among the companies currently taking a synthetic biology approach to biofuels or bio-based chemicals production, for example, the big financial issue is not the technology but full-scale production.

Future synthetic biology companies will have various profiles. Many will be industrial-scale gene (and genome) synthesis companies. Already by 2005, there were at least 39 gene synthesis companies located around the world, including in Boston, Hong Kong (China), Moscow, San Francisco, Seattle, Shanghai and Tehran (Bügl, 2007). Once the cost tipping point in gene synthesis is reached (see Chapter 3), small companies offering software-driven services (similar to software design houses) may proliferate. Their investment requirements will be very different (and less of a concern) from those of the formative companies at the current cutting edge of synthetic biology. Today, the challenge is particularly acute for biotechnology entrepreneurs. Many biotechnology firms are years away from any significant revenue stream, have very few tangible assets, usually have significant accounting losses, and require large amounts of capital (Burill and Lee, 1992).

A mature synthetic biology industry sector may have companies ranging from very small software providers and developers to large dedicated and diversified (typically chemical or agricultural) multinational enterprises that act as manufacturers and provide manu-services, and have large customer bases to grow the market for synthetic biology products.

The allure of drug discovery is lessened for venture capitalists by the duration, risks and high costs of clinical trials. The distributed partnering business model described by Roth and Cuatrecasas (2010) may offer a solution. They argue that neither the vertically integrated pharmaceutical company nor the co-partnering biotechnology company is an appropriate model for drug

discovery. Under the distributed partnering model, the product definition company would license discoveries from research institutions and raise the money to advance the research to the product development stage. It would then sell the research to pharmaceutical companies, which would complete the development process. Synthetic biology's rational design approach will find a niche in drug discovery and development by decreasing lead times through the efficiencies gained in design. Synthetic biology companies involved in drug discovery may be an intermediate link in the chain between product definition company and large pharmaceutical, potentially invested in by both and also by venture capitalists.

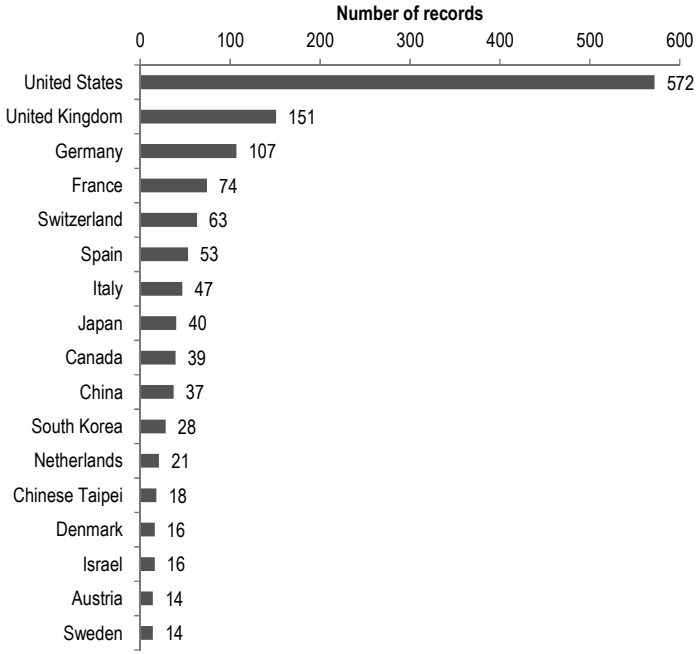
Industrial biotechnology, until the start of the biofuels era, struggled to attract investment, especially from venture capital funds. In 2003 R&D expenditure on industrial biotechnology in OECD countries was 2% of total biotechnology investments, but the OECD expects industrial biotechnology to contribute 39% to gross value added in the biotechnology sector (OECD, 2009). By 2010, the situation was 6% of R&D expenditure on industrial biotechnology compared with over 80% on the health sector. There is a gross mismatch in R&D funding if the OECD's expectations are to be realised.

Public funding

Since 2005, synthetic biology funding has risen significantly in the United States and Europe, roughly coinciding with the growth of the biofuels sector. Driving this increase is the potential to transform world industry in areas such as energy, health and the environment, to produce a new era of wealth generation, and to create large numbers of new jobs (Royal Academy of Engineering, 2009). Among the different emerging trends in biotechnology, synthetic biology may have the most potential to influence, or even transform, economies and society (Cichocka et al., 2011).

There are compelling reasons to believe that synthetic biology will strongly influence the biosciences research agenda in the 21st century and in fact may move biotechnology into the economic mainstream (Newcomb et al., 2007). The discipline arose in the United States, which has established a substantial lead over the rest of the world. Between 2005 and 2010, the US government spent approximately USD 430 million on research related to synthetic biology. The United States has therefore established a favourable intellectual property (IP) position, making it more difficult for the rest of the world to catch up, and will reap commercial rewards. This early lead is apparent from the figures cited in Figure 4.1. Well over half a billion dollars of government funding in the United States and Europe alone has been allocated to synthetic biology research in more than 200 locations.

Figure 4.1. Economies working on synthetic biology, ranked by the number of authors from a country appearing in publications in Web of Science



Source: Adapted from Oldham, P., S. Hall and G. Burton (2012), "Synthetic biology: Mapping the scientific landscape", *PLoS ONE*, Vol. 7.

A diversity of public research funding mechanisms

Different countries have taken different approaches to funding synthetic biology research. Funding mechanisms also differ, and the examples given here are not exhaustive. From 2008, the US Department of Energy has generously funded synthetic biology research on energy applications. The philanthropic Bill and Melinda Gates Foundation awards grants for health and medical applications, especially with a view to supporting health initiatives in developing countries (see Annex A). In the United States, public funding comes from diverse sources, and Europe has also taken various paths to synthetic biology funding. In France and Germany, funding has come from general biotechnology programmes, while Switzerland and the United Kingdom have set up dedicated programmes. Things to be borne in mind when setting up public research funding include the need for multidisciplinarity, for public engagement, for international outreach, and, increasingly, for support to start-up companies.

The dynamics of public funding are likely to be affected by a country's size. Small countries with a single research council may find it easier to monitor their spending. Larger countries with multiple research councils run the risk that, without inter-council co-ordination, overlaps and even duplication of spending may occur. This is especially a risk for synthetic biology, which cuts across biological, physical, environmental and chemical sciences, computing, social sciences and the humanities. Ideally, in times of austerity, co-ordination at international level would avoid the inefficiencies of duplicate spending.

For countries with multiple research councils that award grants in synthetic biology, one way to circumvent inefficiencies is to pool financial resources so that the grants are awarded by more than one research council. This is most likely to be effective for joint biological-physical sciences awards. The biotechnology-computer software interface is particularly important. A panel of representatives of the biological, chemical, physical, social and environmental sciences would have positive effects; a diversity of peer reviewers can stimulate healthy competition/collaboration between and within councils.

Definitions and guidance

The early rush to nanotechnology grant applications led to questions about whether applications truly addressed research at the nano scale or were simply sub-micro. In that case, the simple solution was to define nanotechnology in terms of size. In synthetic biology there is no such clear distinction. Various organisations are presently involved in refining a definition of synthetic biology (see Chapter 1). This is one of the tasks of the European Union's recently formed Scientific Committee on Emerging and Newly Identified Health Risks working group on synthetic biology.[1] Guidance for grant applications could adopt a definition and set boundaries to define qualifying criteria so that applications meet national views of synthetic biology research. This would allow for filtering applications before the lengthy process of peer review, preventing waste of time and resources.

Avoiding institutional bias

Public research funding should be available to all qualified researchers. For strategic purposes it makes sense to have funding ring-fenced or targeted to known centres of excellence. National centres of excellence can be expected to make the large technological breakthroughs, but a discipline is not developing freely until it can be rolled out to institutions with more modest funding. As in any discipline, it is necessary to foster talent by making sure that sufficient funds are available outside these strongholds so as

not to stifle the discipline. This is especially important in synthetic biology, which is likely to be attractive to young faculty with undergraduate and postgraduate training in genomics and other -omics technologies who are ready to embrace the open innovation culture.

Centres of excellence

Because synthetic biology is a young discipline that is costly in terms of equipment, people and consumables, the early establishment of national or regional centres of excellence through public funding is a sensible decision. It is in these hubs that success can be bred and rolled out. While the equipment of synthetic biology is not inordinately expensive or fundamentally different from that of routine molecular biology, the crucial link to genomics and other -omics technologies, and their associated computing power requirements, creates a strong imperative to build initial synthetic biology centres of excellence in close proximity to genomics centres. Proteomics, for example, may soon assume a greater role as advances in mass spectrometry bring it to a wider audience. Mass spectrometry has some specific infrastructure requirements and a need for a cadre of specialists who are not readily found in the life sciences.

This clustering of facilities and talent is common in the United States and other developed countries with advanced biotechnology capabilities. Co-location with business facilities, such as business incubators to support start-up companies, as well as the proximity of larger companies, provides an optimum research-to-application environment. Global Bioenergies, one of the few synthetic biology companies in Europe involved in biofuels, is located in Evry, France, close to one of the French synthetic biology strongholds at Genopole. Centres of excellence cost millions of US dollars if created at an existing facility. They would cost much more if built separately. In these early days of synthetic biology, the safer, less expensive solution is to equip existing facilities. Moreover, the companies supplying essential materials, such as oligonucleotides and synthetic genes, are likely to want to be nearby.

Synthetic biology consortium-building workshops

In countries with a highly developed biotechnology community, it may not be easy to identify the academic and industrial stakeholders with an interest in synthetic biology. Industrial stakeholders can come from various sectors, and academics span many disciplines. The public sector can fund workshops to bring interested stakeholders together. Such venues could also be used to discuss legal, ethical and societal issues. Events of this sort can take any number of forms, e.g. delegates could give very short presentations

to pitch their expertise, so as to leave time for networking opportunities. It would be important to take such workshops on the road, and not limit them to capital cities or known centres of excellence.

Internet-based knowledge transfer networks

Internet-based networks can rapidly build a community of like-minded professionals, whatever the discipline. The UK Synthetic Biology Special Interest Group (SynBio SIG) is hosted and co-ordinated by the Biosciences Knowledge Transfer Network, in partnership with other relevant knowledge transfer networks (KTNs): HealthTech and Medicine; Nanotechnology; Electronics, Sensors and Photonics; Chemistry Innovation; Environmental Sustainability; Information and Communications Technologies. Building capacity and interest in this manner is relatively inexpensive and puts the synthetic biology community in touch with a wide range of potentially interested stakeholders and *vice versa*. Such KTNs could be open to public interest groups, and may help non-specialists understand other issues at stake, such as biosecurity and biosafety. In the non-digital past, this effort would have meant road shows the length and breadth of a country. It was more expensive and had little chance of capturing the audiences that can be reached with a KTN. In addition, a KTN activity brings in interested parties from other countries.

International funding

Many countries express the need for an international effort to create efficiencies in synthetic biology and bring stakeholders together. Indeed, there is increasing evidence of international co-operation for public funding. Small countries with limited funds, human capital and facilities would benefit from public grants that encourage international collaboration with larger countries with more mature infrastructure. OECD countries with advanced biotechnology infrastructure would also benefit from grants to form ties with developing countries. This would help break down international barriers, ease the development of international regulation, make oversight of biosecurity and biosafety measures more transparent and easier to execute, as well as building capacity in research, human capital and business internationally.

The UK Biotechnology and Biological Sciences Research Council has set up a grant scheme to allow UK research institutions to partner with other countries. For example, it seeks to forge partnerships with Brazil in synthetic biology. Funds can only be used for travel, subsistence and activities such as workshops or exchanges. They cannot cover salary costs, consumables, items of equipment or other research costs or link on-going collaborative projects. The amounts vary from GBP 50 000 for single partner collaborations and up to GBP 100 000 for applications from consortia with several partners from the United Kingdom and Brazil. Additionally, applicants are encouraged to seek

additional funding from either the São Paulo Research Foundation[2] or the National Council for Scientific and Technological Development.[3] Under this scheme, partnerships can also be forged with India, China, Japan and the United States.

The European Union Framework Programmes offer the best opportunity for co-operation to prevent duplication of effort in European countries. A new ERA-NET[4] in synthetic biology (ERASynBio) was launched in January 2012. This three-year project is funded by Framework Programme 7 (FP7) and aims to enhance synthetic biology across Europe by co-ordinating national funding, community building, training and by addressing ethical, legal, social and infrastructural needs. As part of the ERA-NET's community-building activities, the ERASynBio Twinning Programme (SynBio TWIN) was launched to provide funding to initiate and develop synthetic biology collaborations between research groups in the ERA-NET partner countries. Other synthetic biology projects funded through the Framework Programmes are listed in Chapter 7.

In September 2012, the US Office of Naval Research advertised a research opportunity entitled "Synthetic Biology Tools for Sensing and Bioprocessing".[5] Research groups in both business and academia outside the United States were invited to apply.

At the "Forum on Synthetic Biology: Challenges and Opportunities for Australia", held in co-operation with the OECD in Sydney, on 13 March 2012, the Australian synthetic biology research community voiced the opinion that Australia suffers from a lack of overseas students and needs to find ways to join the international research community to make synthetic biology grow. This could be addressed by federal international research facilitation funds. In Australia, cultural dynamics exercise a "tyranny of distance" by favouring traditional ties with the United States and United Kingdom over ties with Japan and Korea. In this context, creating a viable biotechnology cluster is an immense challenge, calling for imaginative and finely directed public policy measures (Guilding, 2008). To specialise in synthetic biology, Australia could also look more to the growing Asian genomics and synthetic biology communities, such as the emerging centres of excellence in China (Pei et al., 2011), Japan (Mori and Yoshizawa, 2011) and Korea (Lee et al., 2011).

The route from the laboratory to the market

The value chain

All stages of the value chain are essential for bringing synthetic biology applications from the research laboratory to the market place. Governments are working to develop policies that achieve a balance between the different

supports being requested. These include the need for: personnel at all levels (research to testing and assessment to marketing); national and international collaboration and networks; critical mass in R&D; funding (for public- and private-sector research, for development, demonstration and deployment, for infrastructure, for knowledge acquisition and intellectual property management); routes to commercialisation; dissemination and communication with stakeholders; and access to markets, including public acceptance of products. While these needs are not specific to synthetic biology, there are particular challenges for developing the technology and bringing it to the market place. For example, synthetic biology is expected to be applicable in very specific ways in many disciplines and business sectors and an appropriate policy environment needs to be developed.

Co-operation between the public and private sectors

Co-operation between the public and private sectors can take the form of shared projects, technology transfer and public-private partnerships (PPPs). For the outputs of publicly funded research to reach the market place, some form of technology transfer is required. Technology transfer mechanisms can provide academic researchers and those in public research organisations the means to do so through licences and patents). Industry can benefit from technology transfer to renew its processes and products. For synthetic biology, there are technology transfer issues related to the novelty of the discipline, its multidisciplinary nature and the wide range of sectors in which it may prove to be applicable.

Partnerships are another area of co-operation between the public and private sectors. PPPs are one way to fund the large investments needed for the application of synthetic biology to industrial biotechnology (for example, for the construction of demonstrator plants or larger biorefineries). In 2007, the Energy Biosciences Institute,[6] the largest PPP of its kind in the world, was formed, at a cost of USD 500 million, to use advanced biological knowledge to develop bioenergy. The partner institutions are: the University of California, Berkeley; the University of Illinois at Urbana-Champaign; the Department of Energy's Lawrence Berkeley National Laboratory; and the international energy company BP.

PPPs in Europe include BE-Basic[7] in the Netherlands, which develops industrial bio-based solutions for a sustainable society. It has an R&D budget of more than EUR 120 million, half of it from the Dutch Ministry of Economic Affairs, Agriculture and Innovation. BE-Basic was founded early in 2010, and puts its international focus into practice through strategic partnerships in Brazil, Malaysia, the United States and Viet Nam.

Company creation and development

Like start-ups in other areas of the life sciences, synthetic biology start-up companies are likely to be years from their first products and revenue streams. Their only tangible assets may be some intellectual property and their personnel. During periods of economic austerity these companies are financially vulnerable because they need the high early-stage investments characteristic of life sciences research. They are likely to be dependent on genomics services and to require large numbers of consumables, especially the (as yet) relatively expensive synthetic genes. They also may require access to computing facilities beyond their means.

Access to public funding

When small companies seek funding from governments or from the European Union via the European Commission, they often lack the staff and expertise to deal with the bureaucratic hurdles. This is a long-standing problem and also affects synthetic biology companies, but is increasingly being addressed, for example in the upcoming Horizon 2020 Framework Programme for Research and Technological Development.[8]

Other opportunities for synthetic biology companies to access public funding include, in some countries, programmes for academic-industrial collaboration. However, within such programmes, the sums available are often quite small and the eligible costs are limited. They are also generally project-related.

Venture capital funding

Company growth requires injections of funding at various stages. In many countries, the venture capital (VC) route is not well developed, particularly for companies for which the rewards are long-term such as those in synthetic biology. Some countries have tried to develop policies to support this type of investment, particularly as financial support to companies from public sources, such as that mentioned above, is likely to be limited by state aid rules, for example. Nevertheless, direct support mechanisms are becoming more diverse.

The clearest evidence of a growing industry based on synthetic biology is found in the United States. A number of US companies have been founded from VC investments in synthetic biology platform technologies. They are mostly involved in bioenergy and bio-based materials production and target the boom in bioenergy in the United States from around 2005. Several of these companies have had initial public offerings (IPOs) (Table 3.2), and some have raised over USD 100 million.

Table 4.1. IPOs of some recent synthetic biology-based companies in the United States

Company	IPO (USD millions)	Product description
Codexis	78	Evolved biocatalysts
Amyris	84	Isoprenoids
Gevo	107	Isobutanol
Solazyme	227	Plant-based oils
KiOR	138	Crude oil from wood chips and switchgrass
Myriant	150	Succinic acid
Elevance	100	Specialty chemicals from biomass-based oils
BioAmber	150	Succinic acid

Source: Various sources.

Extensive VC investment in the life sciences, including synthetic biology, is much less common in other countries. Only a small number of European companies have been able to raise significant VC investment in the life sciences. While some support may be available in the early stages for some synthetic biology companies, later-stage investment generally requires much higher sums and is less attractive to investors. In addition, VC is not tailored to the innovation cycle of agro-industrial biotechnology companies, for example, since the return period is too long (7-13 years) and the risks too high. Some governments are taking measures to stimulate VC investments, using existing resources to leverage private funding.

Other financing mechanisms

Indirect mechanisms to support industry R&D include tax incentives such as tax credits. Unlike grants, they are generally available to all companies and are therefore neutral in terms of region and industry. The number of countries using R&D tax incentives is increasing, often with generous terms and conditions. Over 20 OECD countries use this indirect mechanism.[9] Consideration should be given to using these financing mechanisms for synthetic biology.

One example of such financing is France's young innovative companies (YIC) scheme (*Jeune Enterprise Innovante*),[10] which provides incentives for eligible companies by reducing social costs (social security, unemployment and pensions) and tax burdens and also provides incentives for investors. In France, more than 2 000 companies now benefit from this scheme. They are, by definition, research-intensive, and some 20% are active in the life sciences (EuropaBio, 2007). Detailed information about the benefits available through the scheme can be found at the French Ministry of Higher Education and Research website.[11]

Uruguay has very recently approved strong tax incentives for biotechnology companies.[12] The new law is a milestone in the implementation of the national strategic plan for the rapidly growing biotechnology industry, which has been officially declared strategic to the country's future industrial development. Under the new law, biotechnology start-ups can benefit from tax breaks of 50-90% of corporate tax until 2021.

Another example is the R&D tax incentive introduced in Australia (July 2011), which aims to encourage companies to invest in R&D. It provides small and medium-sized enterprises (SMEs) with an aggregate turnover of less than AUD 20 million a year with a 45% refundable tax offset. This reduces the cost and risk of undertaking R&D, and can improve cash flow for firms in a tax loss situation. As of early 2013, almost AUD 2 billion of innovative R&D had been registered by businesses since the incentive began.[13]

Joint ventures are being used by some synthetic biology companies (for example, certain companies developing biofuels and bio-based products) to overcome the challenge of large-scale production, which requires high levels of investment. For example, in Italy a 50/50 joint venture between Polimeri Europa/ENI and Novamont is converting a former ENI chemical plant into a third-generation biorefinery for the production of bioplastics and other bio-based products.

A specialised support infrastructure for SMEs across regions is a public measure worthy of consideration. It could advise interested stakeholders on the strategic use of instruments (e.g. standards, labels, certificates) and provide access to demonstration, testing and certification facilities. A region-wide approach bringing together suppliers and potential users downstream in the value chain would increase the probability of avoiding market failures and earn societal benefits earlier, contributing to a lead market advantage.

Conclusion

The linking of synthetic biology to a future manufacturing base clearly changes the dynamics of investment. Compared to basic research, taking biotechnology from the laboratory to the market increases the need for investment many-fold. The earliest synthetic biology investments at the company level have been mostly related to biofuels applications, and as a result many of the tools for high-throughput strain construction are being developed this way. Countries that are making public investments in synthetic biology are devising a variety of ways to do so. One aspect that arises frequently is the need for international funding to build lasting partnerships. It is hoped that this will make for more efficient public spending by cutting down on duplication. It is also a way to bring different countries with different problems together and could be especially important for bringing developed and developing countries into alignment.

Notes

1. http://ec.europa.eu/health/scientific_committees/consultations/calls_experts/scenihr_exp_07_en.htm.
2. www.fapesp.br/en/.
3. www.cnpq.br/.
4. The objective of the ERA-NET scheme is to step up co-operation and the co-ordination of research activities carried out at national or regional level in member and associated states through networking of research activities conducted at national or regional level and mutual opening of national and regional research programmes.
5. www.fbo.gov/index?s=opportunityandmode=formandid=4d0a0d102395ed78014629e71aa58468 andtab=coreand_cview=1.
6. www.energybiosciencesinstitute.org/.
7. www.be-basic.org/.
8. http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=h2020.
9. www.oecd.org/sti/ind/46352862.pdf.
10. www.aread.eu/jeune-entreprise-innovante.html.
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Chapter 5

Intellectual property issues and synthetic biology

Business models for synthetic biology need to address intellectual property. There is an apparent tension between the desire for "openness" and freedom of access to new parts and the need for intellectual property (IP) protection to allow companies to protect their investments and form the basis for developing their business. Patenting has for decades been a difficult area for life science business. Some envisage that synthetic biology will require a broader range of instruments: trademarks and industrial designs, copyrights, materials transfer agreements and database protection. However, a clear message from the IP community is that, although synthetic biology may present its own challenges, the global IP system is likely to be able to cope and is not under any serious threat. There are identifiable roles for government policies, especially in improvements to access and technology transfer.

The statistical data for Israel are supplied by and under the responsibility of the relevant Israeli authorities. The use of such data by the OECD is without prejudice to the status of the Golan Heights, East Jerusalem and Israeli settlements in the West Bank under the terms of international law.

> "Today the United States Supreme Court ruled on the validity of BRAC1 and BRAC2 human gene patents stating that, 'A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring,' is consistent with our views on gene patents and is one we support. This ruling is good news for the biotech industry as it clarifies the rules and reduces uncertainty."
>
> J. Craig Venter, Ph.D., Founder and CEO, Synthetic Genomics Inc. and Founder and CEO, the J. Craig Venter Institute
> www.syntheticgenomics.com/media/press/061313.html, 13 June 2013

Introduction

Business models in synthetic biology will have to address the question of intellectual property (IP), especially, but not exclusively, patenting. Biotechnology patents emerged from the pharmaceutical field, an unusual technological field that draws heavily on university science, venture capital financing, the production and marketing capabilities of global pharmaceutical firms, and skills in translational science developed by smaller, more nimble, science-based start-ups (Ebers and Powell, 2007). The field is characterised by rapid growth, complexity and comparative youth, and the participants tend to attach a high degree of importance to IP (Arora et al., 2008). Also, venture financing in biotechnology appears to be linked to patents (Kumar and Rai, 2007). The industry collectively submits a large number of difficult, highly technical patent applications, which makes it hard for patent examiners to pare down broad claims and weed out applications that do not meet statutory patentability criteria (OECD, 2005). Moreover, patents making very broad, prophetic claims have the potential to stifle innovation.

Companies can and do use trade secrets and first-mover advantages, or lead time, as alternative strategies to formal patenting. Even though a patent is supposed to protect against imitation, in practice it does so imperfectly, and secrecy may be a preferred strategy. In a survey conducted by Arundel (2001), although secrecy was the leading strategy, a substantial number of companies rated patents more highly than secrecy and many rated patents and secrecy as equally important. The semiconductor industry is a suitable comparative test case for synthetic biology as it is characterised by technological sophistication and extremely short product life cycles. Hall and Ziedonis (2001) noted that US companies in the semiconductor industry tend to rely more on measures such as lead time, secrecy and design capability than on patents. In terms of patenting, synthetic biology may resemble the semiconductor industry and other complex engineering industries more than biotechnology.

Because patents are used to derive measures of innovative capability, there is a danger that it is the propensity of a firm to patent rather than its ability to innovate that is measured (Zheng et al., 2010). However, a strong IP background is an important draw for venture capital investors. There is also some evidence to show that innovative capability is highly correlated with the growth potential and long-term performance of high-technology start-ups. In a Canadian study, Baum and Silverman (2004) showed that biotechnology start-ups with more patents, both recent and older, obtained significantly more VC financing. VC therefore appears more likely to be invested in start-ups with a strong history of patenting. Patents are also important for attracting finance for universities and research institutions specialised in research.

The question of patentability in synthetic biology

The patentability of genetic materials was examined by the United States Supreme Court and the Board of Appeal of the European Patent Office (EPO) between the 1970s and the 1980s. The issue ignited a heated political debate, with the involvement of citizen groups. The core issue is whether substances that exist in nature, such as DNA and genes, should be patentable.

Substances existing in nature are patentable in the United States, Europe and other OECD countries. However, the patentability of "substances existing in nature" falls under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities and is subject to different interpretations. It means that World Trade Organization (WTO) member countries are not obliged to grant a patent to substances from nature, even if they are isolated and purified (Correa, 2000).

Table 5.1. Patentability of substances existing in nature

Non-patentable "substances existing in nature" are excluded from patentability	Specific provision on the patentability of subject matter consisting of or deriving from naturally occurring products	
	excluding	allowing
Argentina, Brazil, Chile, Djibouti, Dominican Republic, Egypt, Guatemala, Honduras, India, Israel, Laos People Democratic Republic, Mexico, Nicaragua, Oman, Pakistan, Panama, Portugal, Thailand, Tunisia, Uruguay, Zambia, Zimbabwe, Andean Community, OAPI (African Intellectual Property Organisation)	Argentina, Brazil, Chile, Costa Rica, Egypt, Pakistan, Panama, Rwanda, Uruguay, Andean Community	Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, San Marino, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Former Yugoslav Republic of Macedonia, United Kingdom, European Union

Source: Adapted from WIPO (2011), "Patent-related flexibilities in the multilateral legal framework and their legislative implementation at the national and regional levels" , Part II, CDIP/7/3, Geneva.

Concerning the TRIPS flexibilities on the patentability of substances existing in nature, the Committee on Development and Intellectual Property (CDIP) of the World Intellectual Property Organization (WIPO) conducted a survey and provided a sample of TRIPS flexibilities in use (WIPO, 2011). The survey targeted 185 WIPO member countries and regional patent offices, and asked whether substances existing in nature are explicitly excluded as patentable inventions (Table 5.1), and whether there are specific provisions on the patentability of subject matter consisting of, or deriving from, naturally occurring products (allowing or excluding).

Synthetic DNA sequences are therefore more easily patentable than DNA sequences derived from natural sources. One of the main criticisms of the patent system in biotechnology was whether patents should be granted to products of nature, because products of nature are "discoveries", which are not patentable. In synthetic biology, however, DNA sequences, systems, cells and organisms are designed by humans. Human-made DNA sequences can therefore receive patent protection without touching on the issue of discovery from nature. According to Torrance (2010), "Genes constructed using synthetic biological techniques will have their origins in human imagination and will, thus, not be products of nature… synthetic genes would remain patentable subject due to their non-natural origins." While the ethical justification of DNA synthesis may be debatable, synthetic biology does not fall under the scope of general exclusion from patentability, such as "inventions contrary to public order or morality".

Complexity of the synthetic biology patent landscape

The J. Craig Venter Institute patent on the minimal genome bacterium (US Patent Application 20070122826),[1] i.e. the smallest genome needed for a living organism, is an example of a fundamental patent. The fundamental patent covers the basic starting point of technology and could frustrate follow-on research. Such fundamental patents can have detrimental effects on associated research. An early warning system at patent offices that would check for the emergence of such broad patents would be a useful tool (see Box 5.2).

Patents have already been granted on many of the products and processes involved in synthetic biology. For example, a report of the ETC group (2007) shows examples of patented inventions in synthetic biology: patents on methods of building synthetic DNA strands;[2] patents on synthetic cell machinery such as modified ribosomes;[3] patents for the engineering of biosynthetic pathways;[4] patents on new and existing proteins and amino acids;[5] patents on nucleotides that augment and replace the letters of DNA.[6]

Software infrastructure in the synthetic biology laboratory deserves special attention from the patent perspective. Currently, synthetic biologists use multifaceted software: there is software for circuit design and implementation, circuit optimisation, DNA and RNA design, protein design, and integrated workflows. Software patents are a problem not only because their number is increasing,[7] but also because patent laws in jurisdictions around the world are not clear on the scope of patent protection on software.

Discussions among lawyers to define the boundary between software that is or is not patentable have reached no clear conclusion. The starting point of deciding on the patentability of computer-related inventions is the rule that abstract mathematical methods and algorithms are outside the scope of patentable subject matter. However, pressure to patent software-related inventions emerged, especially when a patent was granted for business method inventions based on software in the United States.[8]

Software patents are often cumulative and prevent other people from using the patented technologies. However, as innovation in synthetic biology is inclined to be open, the software infrastructure needs to be accessible to researchers. Software patents in synthetic biology need to be analysed in terms of enhancing transfer of knowledge.

Open innovation and open source

The open innovation paradigm is built on the assumption that individual companies do not have the financial resources and personnel to carry out certain complex innovation projects on their own and must share knowledge, ideas and inventions with other companies (Chesbrough, 2006). Open innovation is usually contrasted with closed innovation, supposedly its predecessor, where companies generate their own innovation ideas and then develop, build, market, distribute, service, finance and support them on their own (Chesbrough, 2003). While truly closed innovation was never the rule, trends such as outsourcing, agility and flexibility have forced companies to become network organisations. With the rise of globalisation and the development of improved market institutions for trading ideas, and the appearance of new technologies for collaborating across geographical distances (Dahlander and Gann, 2010), the do-it-yourself mentality in innovation management became obsolete. Even a company of the size and resource intensity of IBM sometimes relies on open innovation and open source.

In synthetic biology, the massive infrastructure and business tasks involved in getting a product to market calls for an open innovation model ranging from engineering at the nano level to building refineries and large-scale plant to getting customers to buy the products. As a result, investors often respond positively to alliances with other firms who possess comple-

mentary resources such as financial, research and marketing capabilities (Chang, 2004). This complementarity is likely to be a defining feature of synthetic biology open innovation.

A high degree of complementarity (e.g. a synthetic biology biocatalyst producer and a large-scale chemical process technology company) and a blend of small and large organisations (e.g. for the small company to gain access to a large customer base and new geographical markets) seem critical to the new synthetic biology companies. Moreover, biotechnology is notorious for long lead times to market, and open innovation could reduce development times by allowing small companies access to the resources of large ones. For example, GlaxoSmithKline's Open Lab Initiative is designed to host 60 visiting scientists from academia or the biotechnology industry and provides access to the corporate compound collection (So et al., 2011).

However, a fundamental contradiction in openness has significant implications for synthetic biology. Kumar and Rai (2007) called it the Synthetic Biology IP Puzzle. On the one hand, intellectual property law insists that certain types of material remain in the public domain. On the other, individuals attempt to use intellectual property rights (IPRs) to create a commons, just as developers of free and open-source software use the leverage of software copyright to impose openness requirements on future programmers. Intellectual property policy specifies items, such as abstract ideas or compilations of unoriginal facts, that cannot be covered by IPRs precisely in order to leave them open to all. Yet many open source techniques require property rights so that future users and third parties will be bound by the terms of the licence. Kumar and Rai ask if this indicates a need to rethink the boundary between intellectual property and the public domain.

As it concerns software development, open source means that people have access to the source (fundamental) software code and can use it to modify, sell or give away new products without paying license fees. These new products, however, must also make their source code available and extend the same licence agreement to others. In effect, open source is covered by a specific, open form of IP, which is often called a public licence. For example, Netscape released its browser source code under the Netscape Public License, which in turn was developed into Firefox. Other examples of important products developed using the open source innovation method are Linux, Apache HTTP Server and Internet Protocol. Far from being unregulated, the system relies on existing IP and legal contracts, as copyright exists in the source code and the contract to ensure that a free licence is itself a legal tool.

The peculiarities of the parts agenda

Nowhere else in the life sciences is the ambition to standardise parts as pronounced as in synthetic biology. There is a frequent, almost universal, comparison to the electronics industry. However, while the technological benefits of introducing electronics methods to biology are clear, the economic benefits of standardising parts are less so. The cost of parts is at the heart of the matter, as well as the rate at which their cost drops the more they are used. A danger for the industry is the creation of a parts monopolist, which has been a feature of the electronics industry. Synthetic biology companies would have no desire to share their earnings with a parts monopolist. Henkel and Maurer (2007) argue that this is good reason for synthetic biology companies to donate resources to a Linux-style "open parts" collaboration. But they also note that there would be circumstances in which the simple Linux model based on own-use incentives would not work.

Because there are different levels in the hierarchy of biological structures, from individual molecules to whole cells, tissues and organisms, the patented information and tangible materials may cover different levels of the hierarchy, from DNA to parts, devices and systems. As a consequence, synthetic biology products could involve hundreds of different parts protected by different patents or copyright held by different rights holders. The situation is similar to a technical area such as semiconductors, and raises issues such as patent thickets. To the extent that they cover standards that synthetic biologists wish to establish, both foundational patents and patent thickets are likely to be problematic. Companies using their IP can also acquire related IP in order to create a patent thicket and a barrier to entry to potential rivals. Even assuming appropriate enforcement of foundational patents, a proliferation of patents on basic parts and devices puts high transaction costs on such thickets. Also, patents can compound the tendency of network markets to tip into monopoly, technically inferior products or other pitfalls (Henkel and Maurer, 2007).

Of interest to the MIT Parts Registry is non-assertion statements by other patentees. Recent non-assertion statements have been made by IBM, Sun Microsystems and other companies to indicate that they will not assert their patents against anyone working on open source software. In the IBM Statement of Non-Assertion of Named Patents Against OSS, IBM pledged the free use of 500 of their US patents, as well as all counterparts of these patents issued in other countries for the development, distribution and use of open source software, owing to their belief that the open source community has been at the forefront of innovation (www.ibm.com/ibm/licensing/patents/pledgedpatents.pdf).

Another potentially problematic issue is the 20-year protection period. However, a much more limited, metered protection already exists. Indeed, the available maximum patent life is not relevant for the majority of patents because the value of the intellectual property falls to zero, either because of technical redundancy or commercial non-viability (Greenhalgh and Rogers, 2010). The Linux General Public Licence does not require software companies to disclose their code to the general public until the devices containing it have reached the mass market. This creates an 18-month window in which the code remains proprietary. With a similar model for synthetic biology, the part maker would get protection long enough to get the reward before the protection disappeared. This seems to work as a reward model in Linux, and adaptations may work in synthetic biology (e.g. adjustment of the metered protection period).

Patent pools

The essential premise of the patent pool is that a series of patents relating to the use of a particular technology are collected so that they can be efficiently licensed to those making, using or selling the technology. The distinctive feature of the patent pool is the bundling of IP rights.

Patenting in various industries led to the idea that patenting can ultimately discourage innovation. The patent pool phenomenon arose from the need to overcome strategic behaviour by patent holders that blocked the development and sale of a new product. Patent pooling evolved with time, and a form of patent pool arose when companies wished to create common technological standards for an industry. This form of patent pool became common in the electronics industry, which now has clear technological standards. The relevance to synthetic biology, with the often-repeated need to create standardised parts, is obvious.

In the pharmaceutical industry, by contrast, it is argued that patents are particularly effective because there is typically a one-to-one mapping between chemical structure and the action of a given drug that makes inventing around difficult (Levin et al., 1987). Synthetic biology may fall between these categories. While there has been broad interest in patent pools in the life sciences, it has been difficult to create and maintain them. The life sciences and their translation into biotechnology products still require as broad a flow of basic scientific information as possible. But the need for standardisation in synthetic biology shows that patent pooling and other forms of knowledge networks and markets have a significant role to play and may shape the business models of synthetic biology companies.

The difficulties for life sciences patent pools appear to be particularly acute in human health biotechnology. The best-known life sciences patent pools have had a clear philanthropic purpose. In these early days of the development of synthetic biology companies, a clear lead seems to have been gained by those operating in industrial biotechnology, in particular those that are creating novel biofuels products or processes. This again may favour a particular type of behaviour. It has been previously opined (OECD, 2002) that patent pools may only be effective in the life sciences if there is a limited field of application and essential patents can be defined. In applying synthetic biology to biofuel products and processes, or more widely to bio-based products, those conditions may be met, but there are also situations where they may not. Therefore alternative mechanisms are essential for synthetic biology.

Open licensing, standardised licensing and licensing principles

Licensing guidelines can be published to streamline licensing activities in the life sciences, and licensing practice remains the most effective means of providing access to IP-protected technologies.

BioBrick Public Agreement (BPA)

The BioBrick Public Agreement[9] is a free standardised legal contract that allows individuals, companies and institutions to make their standardised biological parts free for others to use. According to the Foundation, "the BioBrick Public Agreement was developed for sharing the uses of standardised genetically encoded functions (e.g. BioBrick parts) but, in practice, can be used to make free the sharing of any genetically encoded function that you might already own or make anew". The agreement clearly states that the mission is to promote the development of synthetic biology as a field under the principle of openness in ways that benefit the world.

The BioBrick Public Agreement attempts to minimise legal uncertainty and to avoid disputes arising over ownership, IPRs and attributions, such as open source and free software licensing. According to Torrance (2010), this agreement could be seen as an "initial effort to draft a legal constitution to guide the beneficial development of the field of synthetic biology".

Creative Commons

RIKEN uses the Creative Commons licensing scheme for its gene design competition GenoCON. RIKEN licenses the newly designed DNA information through Creative Commons licensing "CC BY-SA (Attribution-Share Alike)". Licensees can use or alter the information, even for commercial purposes, as long as they identify the licensor and license their new inventions under identical terms.

BiOS

Biological Innovation for Open Society (BiOS)[10] promotes open source, open science, and open society. A BiOS licence is a legal framework to share patented and non-patented technology, including materials and methods. BiOS created a patent-based commons, called protected commons. The members of BiOS agree to responsible sharing and agree not to assert IP rights against other members of the commons for the use of technology for their research and further improvements.

Freemium

Toyoda (2011) extended the application of the so-called "freemium platform" to synthetic biology. A freemium platform takes different forms, with varying tiers from free to premium services, hence the term freemium. A free version of the service needs to be provided to contributors such as scientific and educational communities, while a premium or expensive version of the service will be required of those who receive the benefits from open innovation on the platform. For digital products, the ratio of free-to-paid services is very large in terms of the number of users. A typical online suite follows the rule that a small percentage of users support all the rest. In the freemium model, this means that the beneficiary pays for the premium version to support the platform, while many external contributors receive free access to the online services. The reason this works is that the cost of providing the online services is close enough to zero to be considered negligible. Thus, in a suitable freemium model, only a premium user can organise an open innovation project on the information platform, while free users cannot do so, but can participate as contributors to the project.

Influence on the licensing conditions by the funding agencies and the philanthropic organisations

Governments and philanthropic organisations (e.g. the Bill and Melinda Gates Foundation, see Annex A) financially support research and commercialisation of synthetic biology. IPRs are handled by the legal team of the Gates Foundation and are negotiated as part of the contractual agreement. The basic principle is that all scientific and technological advances should be distributed and disseminated as widely as possible. The intellectual property arrangements should contribute to this goal.

The Gates Foundation makes no claim on the IPR and is not opposed to companies profiting from the results as long as the desired impact is achieved. Pharmaceutical companies, for instance, can profit from selling the drugs they have agreed to sell at marginal prices in developing countries by selling them at market price in developed countries. In other words, IPR

policy is flexible but based on certain principles related to global access. The Foundation discusses this with the technology transfer office or lawyer, which then negotiates with the company or the university.

Patent clearing houses

In a field such as synthetic biology, in which one engineered microorganism might involve hundreds of different parts and processes and therefore various IPRs and stakeholders, freedom to operate (FTO) may be unclear and therefore hinder innovation. Specific problems include high transaction costs (identification, negotiation, enforcement), legal uncertainty, high royalties and royalties stacking (van Zimmeren et al., 2011). Determining what is already covered by patent rights is a particularly acute problem, but there is some hope that modern text mining and computer-search technologies will help to make analysis of FTO easier and economically more feasible (Rutz, 2009).

The notion of an FTO survey, which arose in the United States, is a sort of patent clearance search to confirm compliance with IP law. A clearance survey on the possibility of infringing a third party's patent is traditionally conducted when planning to put commercial projects on the market, but it is frequently conducted much earlier, even at the R&D stage.

In June 2010, the symposium of the National Academy of Sciences and the National Academy of Engineering, "Synthetic Biology for the Next Generation", made recommendations on IP management for the synthetic biology community. One of their recommendations was the creation of clearing houses. The idea is that a patent clearing house, organised by a third party, accepts the registration of synthetic biology inventions, both sequence and functional claims. Typically the functions of the clearing house would be to match licensees with licensors, offer standardised licences, collect and distribute royalties, enforce patents, and offer dispute resolution via mediation and arbitration. The incentives for users are safe harbours. Users of synthetic biology inventions though the clearing house would be exempted from patent infringement. The incentive for patent owners is assurance of their right to claim royalty fees and lower transaction costs. The recommendation came from a stakeholder group comprising government, industry and scholars that had met in Stanford in the previous year. Box 5.1 shows some other recommendations from the symposium.

Box 5.1. Synthetic biology for the next generation

At the "Synthetic Biology for the Next Generation" symposium (12-13 June 2012), legal scholars Farahany and Lemley proposed IP schemes for synthetic biology:

1. Creation of third-party patent clearing houses.
2. Refining statutory governing schemes: make exemption from patent infringement liabilities for: i) mere information providers who offer or sell synthetic biology inventions; and ii) third parties that assemble tangible materials based on the instruction provided by others, and iii) statutory research and educational use exceptions.
3. Introduction of petty patents (utility models) in synthetic biology: Under the current patent system, the high costs of obtaining IP protection and long prosecution processes may have a detrimental effect on synthetic biology and the biotechnology industry. Utility models may work well for synthetic biology, because they can be registered quickly without examination and may save costs, without royalties stacking.

Source: NAS (2012), "Synthetic Biology for the Next Generation" symposium held on 12-13 June 2012, transcript from online video: http://events.tvworldwide.com/Events/IOM/NAS120612.aspx.

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Open access, open publishing policy

US National Institutes of Health PubMed Central

In April 2008, the National Institutes of Health (NIH) implemented a policy requiring all NIH-funded researchers to make available to the public an electronic version of their final, peer-reviewed manuscripts accepted for publication by depositing the manuscripts in the National Library of Medicine's PubMed Central within 12 months of the journal's publication. Recent research on the NIH's policy confirms that "openness" has positive impacts on follow-on research, innovation and commercialisation (Committee for Economic Development, 2012).

Similar policies to increase public access have been implemented in other OECD countries: European Research Council (European Union); Medical Research Council (United Kingdom); Biotechnology and Biological Science Research Council (United Kingdom); Wellcome Trust (United Kingdom); Hungarian Scientific Research Fund (Hungary); Austrian Science Fund (Austria).

Improving technology transfer

The Lambert Toolkit

National patent offices may facilitate technology transfer by providing standardised licensing models. For example, the United Kingdom Intellectual Property Office was involved in creating the Lambert Toolkit to enhance business–university collaboration (www.ipo.gov.uk/lambert). The toolkit is a set of model agreements and governance structures prepared by the Lambert Working Group on Intellectual Property to highlight opportunities for business–university collaboration, identify successful business–university collaborations that could serve as role models, and offer ideas to stimulate debate and shape policy. The United Kingdom Intellectual Property Office hosts the Lambert Toolkit on its website. This collaboration takes advantage of national regulatory infrastructures and is a model that policy makers can refer to when designing technology transfer systems.

The objectives of the toolkit are to facilitate negotiations between potential collaborators, reduce the time and effort required to secure agreements, and provide examples of best practice. The toolkit consists of a set of five model research collaboration agreements (one-to-one collaborations) and four consortium agreements (multi-party projects). The five research collaboration agreements provide different approaches in terms of ownership or the right to exploit the intellectual property and the contributions (financial or other research assets) that result from the collaborative project. The model agreements also address issues such as liability, state aid, tax credits, confidentiality and publication.

Competition policy: A new form of mandatory license

When universities and companies manage their IP on an exclusive basis and do not contribute to the dissemination of technology, other centres, genetic testing laboratories, and low-margin national laboratories may be excluded from the market (Carbone et al., 2010). Compulsory licensing, which gives non-voluntary authorisation to use patents to accelerate the diffusion of technologies, is rarely used by OECD governments. Recently, however, France and Belgium drew up national laws giving government statutory authority to force patent owners to license patents, if failure to do so would threaten public health (Carbone et al., 2010).

Other forms of IPR relevant to synthetic biology

For synthetic biology, IPR issues extend well beyond patenting and increasingly include copyright, design rights, trademarks and data exclusivity.

Copyright

Copyright may be applicable to two of the main technologies of synthetic biology. First, software receives copyright protection in addition to patent protection, although the basic rule is that an "idea" is not copyrightable, but that the "expression" of an idea should be within the scope of copyright protection. Despite this basic rule, software is considered to meet the "expression" requirement and to be protected under copyright law.

Second, copyright may be applied to DNA sequences, although the products of synthetic biology are not yet discussed as copyrightable subject matter in the courts (Kumar and Rai, 2007). Torrance (2010) reports that DNA, genes, arrays of genes and genomes fit into the "literary works" category, both generally and as computer programmes, in several significant ways. A synthetic biologist might consider DNA sequences to be a form of computer software. Given that one of the primary goals of synthetic biology is to engineer cells and genes to become ever more like computer software, DNA sequences will likely move towards copyright by analogy to computer software. An implication for synthetic biology research is that the exceptions to copyright, such as fair use or research use exceptions, need to have clear boundaries and offer safe harbours for free research.

Protection of databases

Databases receive legal protection that varies from country to country. Databases may be protected under copyright law, laws on prevention of unfair competition, or *sui generis* data protection laws. When companies invest time, costs and effort in gathering and storing data, the results of such efforts deserve legal protection. However, data need to be shared in the research community.

For example, the information biology group of RIKEN (Japan) maintains databases for genomes and proteins (Scientists' Networking System, SciNES), and opens them for research purposes, including research competitions organised by RIKEN. RIKEN aims to provide a basic database for rational genome design based on the RIKEN SciNES and offers programmes for designing the sequence of genomes as "open source programmes".[11]

Trademarks and industrial designs

Trademarks can play a role in synthetic biology by distinguishing the scientific, technological and research services offered by certain institutions. For example, BioBricks® is a registered trademark. When scientists, students or the general public seek biological parts under the "Biobrick" word and logo, they expect the parts to come from the BioBricks Foundation, and consider that the Foundation controls their quality. In this way, trademarks associated with certain services in synthetic biology have value.

Johnson (2009) pointed out that industrial design rights may be relevant to synthetic biology when interoperability is required. In Europe, however, industrial design protection is not applied to "must-fit" parts that need to fit to work together, e.g. plugs and sockets, or to "must-match" parts, where the appearance of an article is an integral part of the other object, e.g. a door and a car body.

Protection of confidential information and material transfer agreements

Undisclosed information, also known as trade secrets, is an integral part of intellectual property protection in the life sciences. Undisclosed information on research, data and methods can be protected by *sui generis* trade secret law, which prevents the unauthorised transfer of undisclosed information. Undisclosed information is often a critical part of technology transfer between scientists and companies.

In addition, materials that are covered or not covered by patents are often transferred through material transfer agreements (MTAs). In such cases, undisclosed information can be protected through contractual provisions, such as confidentiality agreements. However, gathering and analysing the information required to guarantee freedom to operate for an MTA has become prohibitively expensive for a single part, and would economically unviable for complete devices. This is becoming a burden for commercialisation. What is needed is a minimal and universal MTA so that the flow of parts is easy and cheap.

At a workshop on "Synthetic Biology, Innovation, and Intellectual Property: Towards a UK Strategy Workshop Report", IP issues associated with synthetic biology were discussed and a small number of targeted recommendations were made (Box 5.2).

Box 5.2. "Synthetic Biology, Innovation, and Intellectual Property: Towards a UK Strategy" Workshop, London, June 2013

At this workshop it was generally agreed that there was nothing about synthetic biology that would necessitate an overhaul of the IP system. Three specific recommendations can be carried forward by the UK Synthetic Biology Leadership Council to the Technology Strategy Board and the Department for Business, Innovation and Skills.

1. *Synthetic biology IP watching function*

   The United Kingdom could benefit from a synthetic biology IP watching function that is similar to IP Watch (www.ip-watch.org/) or sector-supported consortia but focused on synthetic biology issues in the United Kingdom. The synthetic biology IP watch would perform several functions. First, it would provide timely reports on synthetic biology patent applications and patents granted in the relevant jurisdictions (UKIPO, EPO, USPTO, JPO). Second, applications with the potential to become blocking patents could be identified and comments submitted to patent offices. Third, the IP watch would periodically present consolidated reports on what is considered non-obvious in synthetic biology IP and how multidisciplinary teams in IP offices are being organised to examine applications. Fourth, it could identify and track emerging issues in synthetic biology IP, including changes in patent prosecution and patent challenges. It could develop education and outreach mechanisms to benefit researchers, institutions of higher education, funding councils and firms through the collection and dissemination of information relevant to innovation in synthetic biology. It could be established on the initiative of the Technology Strategy Board, with the expectation that it would ultimately be supported through a public-private partnership.

2. *Identification of synthetic biology value chains*

   Work on the identification of value chains for synthetic biology needs to be undertaken immediately. In fields such as pharmaceuticals and fine chemicals there are established value chain models in which the role of IP is reasonably well understood, even if that role is viewed as problematic or in need of optimisation. Inventions and discoveries in synthetic biology will introduce new opportunities for commercialisation, yet it is unclear if value chain archetypes for other technologies will apply. Adoption of information and communication technology archetypes in the context of biotechnology innovation has proven unsuccessful, and it is now apparent that the R&D and firm strategies for innovation in the life sciences are different. The development of examples of value creation in synthetic biology, ideally concentrating on UK firms, would generate synthetic biology archetypes. These would be useful in exploring links between IP and synthetic biology innovation, and would provide a context for interpreting open access and innovation policies arising in UK and Horizon 2020 synthetic biology initiatives.

…/…

Box 5.2. "Synthetic Biology, Innovation, and Intellectual Property: Towards a UK Strategy" Workshop, London, June 2013 *(continued)*

3. *Evaluating potential strategies for blended IPRs*

   A consequence of the recognition of biology as an information science is the temptation to think of ways to apply copyright to biological information. Although this was previously not feasible as an alternative to patenting genes, creating and transcribing synthetic sequences raises questions about copyright of "biological expressions". As synthetic biology develops, the integration of biological with automated machine systems increases the importance of software IP. Envisioned, then, is a future in which commercialisation of synthetic biology involves the stacking of different kinds of IP rights in single products in ways that do not have obvious correlations in contemporary technology. Although this may not occur until sometime in the future, it is serious enough to warrant consideration, perhaps in a scenarios format, of the implications for open access and innovation policies, behaviour of institutions of higher education, venture capital and firm strategies.

Source: Workshop summary document, Innogen, Edinburgh.

Conclusion

This chapter may give the impression that IP issues in synthetic biology are very difficult. This is not the case. There are specific problems or potential problems, but there are also solutions or potential solutions. There is no need to reform the IP regime. The synthetic biology community and IP professionals can learn from the semiconductor and other industries that have solved similar problems. But the issues will have to be tackled in a systematic and timely manner to prevent the formation of commercial barriers at a time when many stakeholders are watching synthetic biology closely. The toughest issue will be achieving international agreement on allowing the free flow of information to maximise progress.

Notes

1. US 20070122826: Minimal bacterial genome. Assigned to J. Craig Venter Institute, Inc.
2. For example, US 6, 521, 427: Method for the complete chemical synthesis and assembly of genes and genomes. Assigned to Egea Biosciences, a subsidiary of Johnson and Johnson.
3. For example, WIPO Patent WO05123766A2: Methods of making nanotechnological and macromolecular biomimetic structures. Awarded to Alexander Sunguroff.
4. For example, WIPO Patent WO05033287A3: Methods for identifying a biosynthetic pathway gene product. Claimed by The Regents of the University of California, or US 20060079476A1, US patent application entitled, "Method for enhancing production of isoprenoid comoonds."
5. For example, WIPO Patent WO 06091231A2: Bio-synthetic polypeptides utilising non-naturally encoded amino acids (2006). Awarded to Ambrix, Inc.
6. For example, US 5, 126, 439, "Artificial DNA base pair analogues," awarded to Harry P. Rappaport; and S. Benner, U. Patent 6, 617, 106, "Methods for preparing oligonucleotides containing non-standard nucleotides."
7. The number of registered computer-related patents (G06F17/60 and G06Q) was around 288 in 2000, but increased to 2 562 in 2009. Bessen and Hunt (2004) say that the number of software patents issued in the United States was 765 in 1976 and increased to 24 891 in 2002.
8. State St. Bank and Trust Co. v. Signature Fin. Group, 149 F. 3d 1368 (Fed. Cir. 1998).
9. https://biobricks.org/bpa/.
10. www.patentlens.net/daisy/bios/home.html.
11. RIKEN's SciNES is a cloud web system built on the next-generation web standard "semantic web" which offers the research community a networking system. SciNES contains many virtual laboratories and researchers can create their own database without creating and maintaining a web server themselves. The SciNES virtual laboratories aim to enhance international research collaboration among researchers. RIKEN's GenoCon offers SciNES to participants in the competition (www.riken.go.jp).

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Chapter 6

Governance, regulation and risk management in synthetic biology

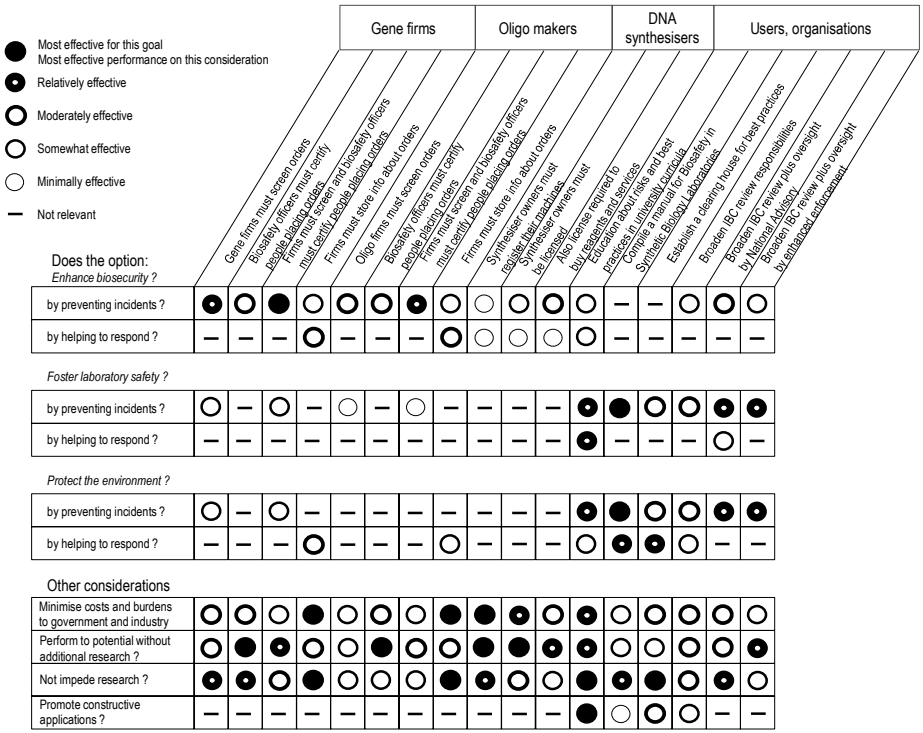
To date the regulation of synthetic biology is effectively the regulation of genetically modified organisms (GMOs). The thinking on whether this is adequate is polarised. The over-riding opinion of the synthetic biology community itself is that regulation is currently sufficient: it is felt that GMO regulation is already onerous and that further regulation may stifle research. Nevertheless, vigilance is required to ensure that any additional biosafety and biosecurity issues are discovered as early as possible and dealt with both rationally and rigorously. The main difference with GMO regulation may be the ability to order tailor-made DNA sequences. While the vast majority of these will be created for valid reasons by responsible individuals and institutions, the risk of mal-intentioned use calls for an inspection process and oversight. Governance and regulation must also take account of public opinion regarding synthetic biology, and the need for early and sustained public engagement is increasingly recognised. Potential international regulatory and governance conflicts could damage legitimate international trade. Therefore, even in parts of the world where there is little controversy, there would still be international trade issues.

Introduction

Many experts consider that synthetic biology is not significantly different from genetic engineering in terms of regulatory needs and that current regulation and the principles of risk assessment as applied to genetic engineering may be adequate for synthetic biology. For contained use (as opposed to deliberate release), synthetic biology in general is not expected to raise fundamentally new questions, even in the medium term (EPTA, 2011). However, a growing body of literature on how the nascent synthetic biology industry could be regulated (e.g. Kelle, 2009) can help to inform policy development.

The governance and regulation of synthetic biology concerns a wide range of potential stakeholders. Figure 6.1 summarises issues raised and some policy options. It covers DNA synthesis and synthesiser companies through to end users, as well as biosecurity, safety and environmental protection.

Figure 6.1. Summary of policy options in the regulation of synthetic biology



Source: Garfinkel, M.S., D. Endy, G.L. Epstein and R.M. Friedman (2007), "Synthetic Genomics Options for Governance", www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf.

Biosafety and biosecurity

Biosafety covers the range of policies and practices designed to protect workers and the environment from *unintentional* misapplications or the *accidental* release of hazardous laboratory agents or materials. Biosecurity is usually associated with the control of critical biological materials and information, to prevent *unauthorised* possession, misuse or *intentional* release.[1] More simply, the European Parliamentary Technology Assessment (EPTA, 2011) briefing note on synthetic biology terms biosafety as "keeping bad bugs from people" and biosecurity as "keeping bad people from bugs". Even though the difference between the two definitions may appear clear in theory, in practice the two tend to overlap. With the advance of synthetic biology, governments face biosafety and biosecurity challenges raised by synthetic biology.

For example, there are particular concerns about the use of software infrastructure to design parts by non-experts working from a home computer. While this does not engender any risk in itself, subsequent construction of a designed part may. Software use by the non-expert is not under the control of a laboratory or research environment and represents a challenging regulatory situation, as it will be difficult to monitor.

Biosafety and the user community

Synthetic biology is a scientific field that cannot be linked to a single professional branch. In addition to synthetic biologists, chemists, engineers, physicists and computer scientists are also involved in synthetic biology projects.

The biosafety problem in this respect is not necessarily related to a potentially malevolent intent, but rather to the lack of proper biosafety training or attitude (Schmidt et al., 2009). There is therefore a need for training programmes especially designed for non-synthetic biologist practitioners, such as standard microbiologists, synthetic chemists or computer engineers. In this respect the National Science Advisory Board for Biosecurity (NSABB) and the Industry Association Synthetic Biology (IASB) envisaged the development of a web-accessible advice portal for "experiments of concern", in order to provide scientific and biosafety-related advice for companies or single practitioners (IASB, 2008).

Biosafety and the eventual decentralisation of synthetic biology

The open source nature of synthetic biology creates both biosafety and biosecurity concerns. In the last two decades, the Internet has enormously expanded the potential to diffuse information "from the laboratory to the basement". In parallel, synthetic biologists have extensively used the Internet to increase the openness of this new life science, in line with an approach that favours openness, communication and innovation. The primary goals of this new approach were new ideas and better-informed public opin-

ion. As this eventually led to the release of scientific information outside the academic and scientific sphere, an increasing number of amateur practitioners are now likely to have little notion of biosafety (NSABB, 2010). The initial aim of enhancing innovation through public diffusion has therefore been slowly leading to a phenomenon now known as "garage biology" (Schmidt, 2008). At present a contained and relatively small issue, its importance may increase over time. At the very least, it requires monitoring by policy makers.

The potential for improper or malicious use of synthetic biology challenges the need for regulation, at least at the level of DNA synthesis. Among the greatest challenges facing those who develop such regulations will be weighing the costs and benefits of rules and developing an effective enforcement system. The situation in the United States and the European Union is described by Bar-Yam et al. (2012), bearing in mind that many other countries have their own procedures. Policies for regulating synthetic biology should aim to ensure the implementation of well-crafted regulations that do not hinder beneficial research.

DNA synthesis and biosecurity

The most critical difference for regulation between synthetic biology and genetic modification (GM) lies in the ability to make tailored DNA sequences. GM technology is restricted to complex laboratory operations. In synthetic biology, the design of DNA can theoretically be done from a computer in any location, without organisational regulation. Bügl (2007) argues that modern DNA synthesis challenges the existing recombinant DNA safety framework on two fronts:

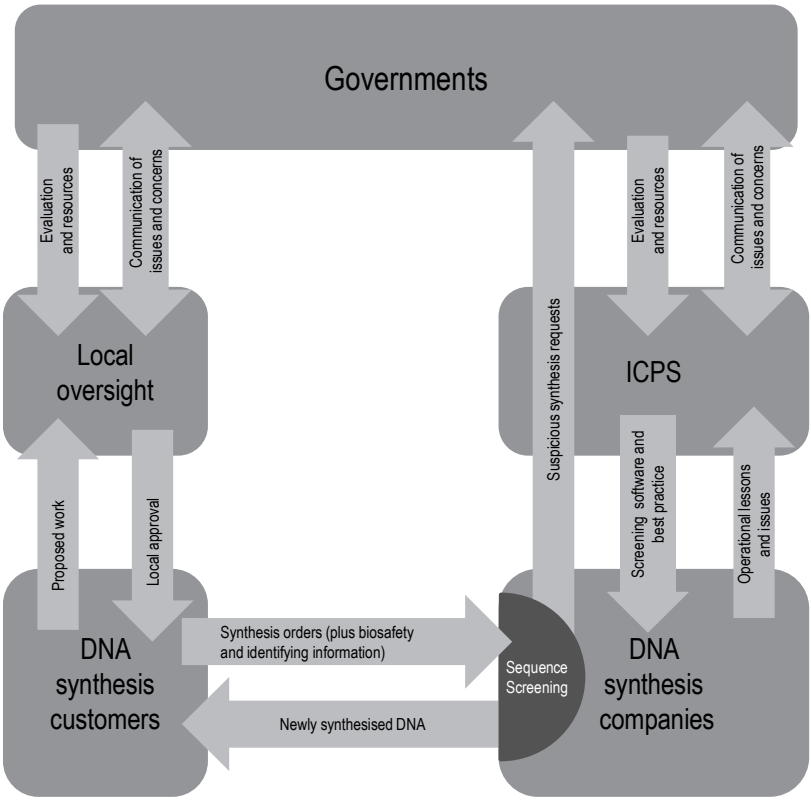
1. DNA can be readily designed in one location, constructed in a second and delivered to a third. The resulting use of the material can therefore take place far from its originators.
2. Synthesis may provide an effective alternative route for those who seek to obtain specific pathogens in order to cause harm, thereby circumnavigating national or international approaches to ensuring biosecurity.

Although much additional expertise would be needed to produce infectious agents from the resulting genetic material, such work may not be subject to review or oversight. The DNA synthesis industry requires regulatory protocols to ensure that it does not become a vehicle for biosafety/biosecurity violations. The industry can only continue to advance and realise the potential of synthetic biology if it supports best practices in biological safety and security. See, for example, IASB on the effective deterrence and investigation of criminal uses of synthetic DNA. [2]

International regulation

A broader role for government policy is the achievement of international consensus. Harmonisation among countries is important. Otherwise potential violators of biosecurity regulations may simply transfer their design and construction activities to a less regulated country. Means of obtaining regulatory interaction among governments, synthesis companies and customers are summarised in Figure 6.2. It represents the collective views of all founding members of the International Consortium for Polynucleotide Synthesis as well as the individual opinions of members of the US Federal Bureau of Investigation, executives of several leading synthetic biology companies and members of academia.

Figure 6.2. A proposed framework for DNA synthesis regulation and oversight



Note: ICPS: International Consortium for Polynucleotide Synthesis.

Source: Bügl, H. (2007), "DNA synthesis and biological security", *Nature Biotechnology*, Vol. 25, pp. 627-629.

Comparisons of the regulatory instruments employed in the United States and the European Union help to see how broader international regulation may evolve. Table 6.1 shows that international regulation is virtually at the level of the Cartagena Protocol, which governs the trans-boundary movement of genetically modified organisms (GMOs).

Table 6.1. Analysis of regulatory coverage of safety and environmental risks of synthetic biology

Risk	International	United States	European Union
Transfer of genes	Cartagena Protocol on Biosafety	EPA and APHIS	Directive 2001/18/EC
Mutations, evolution and proliferation		EPA	Directive 2001/18/EC
Effects on ecosystem and other species	Cartagena Protocol on Biosafety	EPA and APHIS	Directive 2001/18/EC
Effect on biodiversity	Convention on Biological Diversity, Cartagena Protocol on Biosafety		Directive 2001/18/EC
Consumption risks		EPA (only for plant-incorporated pesticides)	Regulation 1829/2003
Risks to laboratory workers		NIH Guidelines	Directive 2009/41/EC Directive 2000/54/EC
Accidental release of laboratory strains		NIH Guidelines	Directive 2009/41/EC

APHIS: Animal and Plant Health Inspection Service, USDA; EPA: Environmental Protection Agency.

Source: Bar-Yam, S., J. et al., (2012), "The regulation of synthetic biology: a guide to United States and European Union regulations, rules and guidelines", SynBERC and iGEM Version 9.1, 10 January 2012.

Most GMO-exporting countries have not ratified the Cartagena Protocol. However, given that importing countries increasingly place restrictions on imports that are in line with the rules in the Protocol, the rules may have an impact on policies in exporting countries even if they have not ratified the agreement (Falkner, 2007). There is a body of opinion arguing that Annex III of the Cartagena Protocol should be modified to allow comparative safety assessments based on the properties of the introduced trait, rather than the current testing requirements (OECD, 2013).

A screening process for synthetic DNA manufacture and sale

The aim of a screening process is to avoid the intentional or unintentional sale of synthetic DNA to unreliable costumers.

By analysing US biological companies, Schmidt and Giersch (2011) concluded that the main aspects to be controlled are sequence screening for select agents to avoid synthesis of known pathogens or toxin-related DNA, customer screening to avoid shipment to dubious clients, and licensing of equipment and substances required for the synthesis of oligonucleotides.

Until recently, the role of governmental institutions in controlling synthetic DNA trade and production has been relatively marginal. However, this has changed slightly since US administrative bodies such as the NSABB have started to take a proactive role in promoting security standards in gene synthesis companies.

Documents such as the NSABB *Addressing Bio-security Concerns Related to the Synthesis of Select Agents* (NSABB, 2010) represent government efforts to try to address security at the institutional level. Nevertheless, government involvement is currently limited to recommendations.

The engagement of US governmental agencies could represent a step towards a more global approach to synthetic biology security. In explaining the objectives of its *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,*[3] the US Department of Health and Human Services (HHS) pointed out that "the Guidance was composed so that fundamental goals, provider responsibilities, and the screening framework could be considered for application by the international community". Box 6.1 lists some of the screening recommendations made by the HHS, as well those of a working paper co-ordinated by the Berkeley SynBio Policy Group.

Besides customer screening practices, a fairly new challenge needs regulatory attention: the phenomenon called "split orders". These are the alleged action of a mal-intentioned person or organisation that tries to circumvent the detection systems of DNA synthesis companies by splitting up one piece of DNA into many smaller, harmless-looking pieces and ordering them from a variety of companies (Schmidt and Giersch 2011). However, one of the barriers to this scenario is represented by synthetic biology itself: the complexity of assembling the pieces, along with transport uncertainties and environmental conditions, are considered serious obstacles. However, the split orders issue remains a potential problem that needs to be monitored, most of all at the international level.

Box 6.1. Synthetic DNA companies' screening processes

Following the guidance of the Department of Health and Human Services, the US government recommends that for every order companies should gather the following information: customer's full name and contact information; billing address and shipping address; and customer's institutional or corporate affiliation.

If the last of these is not relevant, providers are requested to pursue a follow-up screening process to verify the legitimacy of both the customer and the end user (if different).

In addition to these general requirements, the Berkeley working paper tries to identify procedures for improving the screening of customers and orders by gene synthesis companies. Once the traditional identification process has been carried out (e.g. nationality, employment or academic affiliation) companies should look at:

- Intended use: to confirm that the experiment is genuine and not a cover story; the customer should provide documents that can be used to judge the potential results of the experiment.
- Legitimacy: companies should evaluate the potential dual use of the gene requested.

Gene synthesis companies may rely on different investigative techniques:

- Direct evidence: direct contact with the customer to analyse the experiment, preferably in person, but most likely by telephone or email.
- Indirect evidence: companies can consult trusted contacts who know the researcher and his work.
- Signalling: The customer should provide evidence of the impracticability for terrorists to perform the same type of experiment. These assurances could include financial capability; proof that the work would be performed openly, so that a large number of scientists could scrutinise its developments; affiliation to a large, well-established and trustworthy company.
- Institutional control: companies might ask researchers' home institutions to monitor and report on the results of an experiment.

Source: Adapted from Maurer et al. (2009), "Making commercial biology safer: What the gene synthesis industry has learned about screening customers and orders", working paper, http://gspp.berkeley.edu/iths/Maurer_IASB_Screening.pdf.

Regulation and public opinion and engagement

Societal aspects of synthetic biology

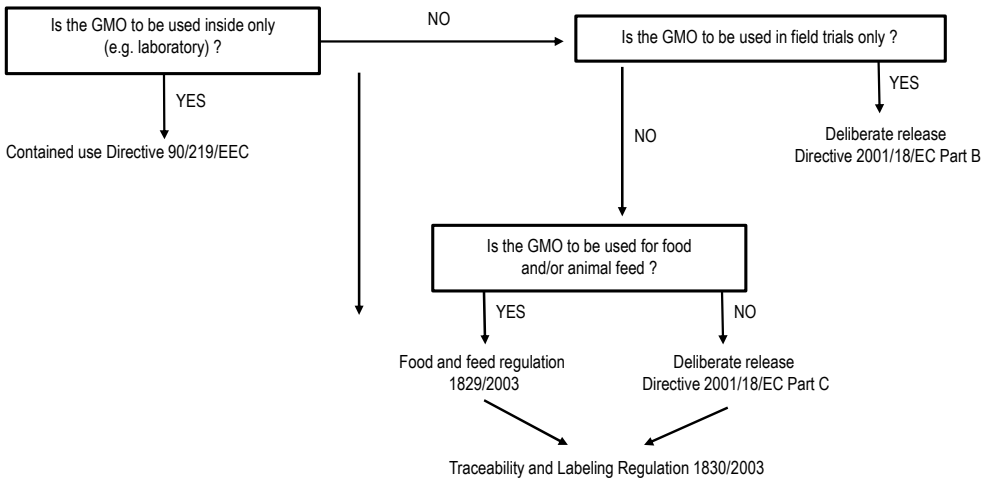
> "…if ever there were a science guaranteed to cause public alarm and outrage, this is it. Compared with conventional biotechnology and genetic engineering, the risks involved in synthetic biology are far scarier." (Ball, 2004, consultant editor for Nature)

> "Much of what is currently called synthetic biology is congruent with recombinant DNA technology discussed in Asilomar 30 years ago. This includes bacteria that express heterologous genes, proteins in which amino acids have been replaced, and cells with altered regulatory pathways. Placing a new name on an old technology does not create a new hazard." (Benner and Sismour, 2005)

These two quotations highlight an issue at the heart of the public engagement and acceptance debate that has shadowed GM technology. There has been an enduring disconnect between the scientific community, government and the public. Public and stakeholder pressures tend to reinforce demands for more regulation and stricter governance, related in the case of synthetic biology to biosafety, biosecurity, trade, global justice, and the morality of creating novel life forms (Tait, 2009). However, governance in the life sciences has led to an increasingly onerous and lengthy regulatory process that may eventually stultify innovation.

Given the serious concerns of public opinion regarding GMOs, Europe has adopted very stringent provisions. The legal framework is very complex and is based, among others, on EC directive 90/220/CEE (contained use) and EC Directive 2001/18/EC (deliberate release), (Figure 6.3).

Figure 6.3. Basic structure of EU GMO regulations



Source: Bar-Yam, S., J. et al., (2012), "The regulation of synthetic biology: a guide to United States and European Union regulations, rules and guidelines", SynBERC and iGEM Version 9.1, 10 January.

In the on-going debate about whether or not there is already enough regulation, it is worth re-emphasising that GM concerns have been much more of an issue in Europe than in other regions. It is not a significant issue in much of Asia, the Americas and the partner economies, and it is not clear whether these regions would agree that new or more regulation is required. The voice of civil society has traditionally been much stronger on the issue of GM in Europe; this is likely to be the case for synthetic biology as well. It is weaker in the United States, let alone in Asia or other parts of the Americas, where it barely registers as a political factor.

EU and US GMO regulations differ fundamentally in terms of the conceptual bases upon which they were established. In the United States, environmental legislation has been based on regulatory impact analysis which, by and large, is founded on the idea that "regulation must be based on learning: once more is known about a certain risk, regulation must be adjusted accordingly" (Aerni, 2006).

By contrast, in the European Union, environmental legislation has adopted the precautionary principle as the basis for evaluating the applicability of life science innovations. The principle relies on the premise that, if scientific data do not permit a full evaluation of the environmental risks of the introduction of a substance into the environment, the relevant authorities should block its diffusion (Aerni, 2006).

Yet, a recent EC report (European Commission, 2010) concluded that biotechnology, and in particular GMOs, are not *per se* more risky than conventional plant breeding technologies, after having spent more than EUR 300 million on more than 130 biosafety research projects, covering a period of more than 25 years, and involving more than 500 independent research groups.

As in the European Union, regulations in the United States do not deal with synthetic biology as such; typically, the processes and products of synthetic biology are covered by regulations that deal with GMOs. While it is often said that European regulations tend to be stricter than their US counterparts, the US situation is also complex and involves multiple agencies (National Institutes of Health, Environmental Protection Agency, US Department of Agriculture, Food and Drug Administration).

New agriculture and forestry: The defining public concerns?

The contained use of synthetic biology in research laboratories and in industrial bioreactors is much less likely to raise public concerns than deliberate or accidental release to the environment. After all, GM strategies for the production of new medicines have been used for decades (Goeddel et al.,

1979) and create little controversy. Fears arise when GM is moved beyond controlled environments and into the outdoors.

The forest products sector is looking for new opportunities to produce value-added products while securing access to emerging carbon capture markets (Sheppard et al., 2011). Extending the limits of conventional breeding of trees, a very slow and inefficient process, to realise faster and more accurate trait improvement for application in plantation forests (such as faster growth, improved pest and disease control), has the potential to lead to easier and cheaper development of goods, such as second-generation biofuels. However, because of public sentiment against GMOs, researchers and companies have used conventional and less efficient technologies (e.g. marker-assisted selection).

Synthetic biology, sustainability and the bioeconomy

Several countries and international bodies are developing the concept of a bioeconomy,[4] as evidenced by the publication of strategies, in the early months of 2012, by the United States (The White House, 2012) and the European Union (European Commission, 2012), and by earlier work by the OECD (2009). Bioeconomy strategies at national (e.g. Sweden and South Africa) and regional levels (e.g. Flanders) (Sormann, 2012) are under development. R&D in synthetic biology has initially addressed biofuels, which are themselves contentious, and products such as bio-based chemicals and plastics, which are hallmark products of a bioeconomy. A second phase, which involves a much broader spectrum of industry sectors, such as food, cosmetics, pharmaceuticals and medicine, is now emerging for synthetic biology.

Bioeconomy strategies focus on sustainability and the application of biotechnology to grand and societal challenges such as climate change mitigation, and energy and food security. The one indicator of sustainability that seems to be universally accepted is reduction of greenhouse gas (GHG) emissions. Many of the products of industrial biotechnology are designed to move away from dependence on fossil fuels and to reduce GHG emissions. A particular concern associated with industrial biotechnology, however, is the impact on land use of the large amounts of biomass required for non-food purposes. With the increasing number of applications of synthetic biology techniques to the manufacture of these products, the land use issue can be addressed by improving crop resistance to pests and drought, increasing yields of crops, using gas fermentations that do not require land for the production of biomass, and the industrialisation of photosynthesis (Pavanan et al., 2013).

Regulation of crops as bioreactors

For the controlled release of GM technology into the environment (fields, unless the plant cultivation is performed indoors), regulation is going to involve controversial policy decisions. Synthetic biology applications to plants in the field will inevitably face the same acceptance problems as GM, and the problems are similar to those already described for GM technologies. To the extent that the general public already has a negative opinion of transgenic plants, the notion that genetic engineering is against nature makes itself felt on regulators (Streiffer and Hedemann, 2005). Lack of communication among the regulatory bodies involved in research, biosafety and trade also hampers developments in this field (Ramessar et al., 2008).

The regulatory challenges for molecular farming and how they differ from those for first-generation transgenic crops were reviewed by Spok et al. (2008). The most important issue is to segregate GM crops from non-GM crops to prevent intermixing. It is very difficult to maintain complete segregation of GM and non-GM crops in open fields (USDA, 2006), even with stringent confinement. The European Parliament and the Council of the European Union have allowed GM presence of up to 0.5% in non-GM food or feed where the presence of the genetically modified material in non-GM material is technically unavoidable (European Parliament, 2003). For plant-made substances other than pharmaceuticals that do not pose hazardous risks, the threshold limit for contamination of non-GM crops is 0.9% (Spok, 2007).

Another important issue is labelling of GM products. However, mandatory labelling may not be economically justifiable and may not provide the consumer with the required information. Alternatively, information domains can be built to provide consumers with essential information related to GM content. A system that traces products in the market to their source and a good strategy for post-market monitoring and surveillance may also be a solution.

Regulatory conflicts and disconnects

Regulatory conflicts and disconnects are likely to be significant on at least three levels:

1. Between countries and regions, such as the EU, that apply the precautionary principle, with a focus on process as well as product and a presumption in favour of regulations, and the United States, where regulation is risk-based/evidence-based, the precautionary principle is not dominant, and there is no willingness to regulate process as well as product ("equivalence", which the European Union does not accept).

2. Within countries and regions depending on the mission and biases of different regulatory authorities (e.g. in the United States, the Environmental Protection Agency is likely to take a different approach to governance/regulation from that of the Food and Drug Administration or the Department of Agriculture).
3. At different levels within countries for countries with federal systems (such as the United States, Canada, Australia), where there could be regulatory conflicts between the federal government and the states/provinces, and between these and local jurisdictions.

Conclusion

As a public acceptance/perception issue synthetic biology is so closely related to the GM issue in Europe that it is impossible for synthetic biology to have a fresh start. It inevitably carries the GM baggage, but this has both positive and negative aspects. On the positive side, there are decades of experience in dealing with GM in terms of regulation and public engagement. Attempts to unblock the GM debate in various countries will also apply to synthetic biology, although progress in many locations has been extremely slow. The negative reaction to GM technology is not gradually disappearing as was expected and excessively demanding regulatory systems are not being modified on the basis of experience. The GM quagmire is to a great extent a European issue, and if it encompasses synthetic biology, it is very likely that its benefits will not be realised in Europe but in other regions.

Some argue that there is a need to reconsider how science is presented in communications with the public. Focus group research involving ordinary citizens in five European countries shows that the public resents decision-making procedures more than they oppose GM products as such (Levindow and Marris, 2001). The scientific community must take, and be seen to be taking, a lead in debating the implications of their research and must engage with society on the issues raised by synthetic biology (Balmer and Martin, 2008). For example, amateur scientists are stakeholders who are not often considered in the literature. In terms of dealing with risk, careful attention must be paid to the way synthetic biology skills diffuse to such groups. The consequences of this broader diffusion of biotechnology are not clear and should be investigated (Schmidt et al., 2009). In particular, ease of access to research tools and concepts increases the likelihood of unintentional effects by well-meaning institutionally based scientists or amateur biologists (Cho and Relman, 2010).

Notes

1. http://oba.od.nih.gov/biosecurity/pdf/NSABB%20SynBio%20DRAFT%20Report-FINAL%20(2)_6-7-10.pdf.
2. www.ia-sb.eu/go/synthetic-biology/.
3. www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf.
4. http://bioeconomy.dk/news/besides-eu-usa-and-germany-several-countries-have-published-bioeconomy-strategies.

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Chapter 7

National policies for the development and application of synthetic biology

The lack of policy development reflects two things: synthetic biology is still very young, and it may still be too indistinct from genetic modification and recombinant DNA technology to warrant specific policy developments and interventions. Countries are taking different approaches to public funding of synthetic biology R&D. Educational initiatives are key to the future of the field, as the need for an interdisciplinary approach in higher education is a challenge to science education, owing to the need for sufficient depth and breadth in both the biological sciences and engineering. Public engagement to date has been limited and this requires serious consideration. A noticeable development is the spread of interest in competitions to countries outside of the United States. Some consider that the most pressing near-term need is to develop technology roadmaps for synthetic biology. There is even a feeling that a global roadmap might be enabling and a key element of policy. It is clear that a technology roadmap can also serve as a policy roadmap, with the inclusion of strategies for public engagement and educational priorities.

Introduction

Countries are taking different approaches to public funding of synthetic biology R&D. Because synthetic biology is still very young, many countries have not yet begun to address this issue. This chapter presents relevant efforts by several countries that have seen the need for public engagement. Some consider that the most pressing near-term need is to develop technology roadmaps for synthetic biology. It is clear that a technology roadmap can also serve as a policy roadmap, with the inclusion of strategies for public engagement and educational priorities.

Australia

Infrastructure

Infrastructure is being developed mainly through CSIRO[1] projects. These are mostly based on applications, especially platforms. A project on crop biofactories has been under way for eight years and may continue for another eight. The target is the production of novel oils and oleochemicals in plants (e.g. nutraceuticals, biodiesel, lubricants and polymers). One of the reasons for doing this work in plants is that it is scalable, constrained simply by the availability of land, and versatile. Compared to fermentation, however, it lacks a fine degree of process control. Sunflower is one of the target crops. It is not a major food crop in Australia, but it is suited to marginal land, which is abundant there.

An objective of the relatively new Molecular Machines project is making metabolic pathways outside cells. This offers several advantages, especially in specificity and noise reduction. Another major part of the work is the development of flow cells, which are intended to be modular and scalable and to operate in parallel fashion. If it achieves industry buy-in, this could be a 16-year project.

Regulation

The main legislation in force is the *Gene Technology Act* (2000).[2] Its objectives are to protect the health and safety of people and to protect the environment. It aims to do this by identifying risks posed by, or as a result of, gene technology, and by managing those risks through the regulation of certain utilisations of genetically modified organisms (GMOs). The Australian philosophy, as in other countries, is based on risk analysis and risk management.

The main message is that Australian regulators are aware of synthetic biology, are maintaining a watching brief on it, but in practical terms existing regulation adequately covers current activities. Regulation should be commensurate with risk and Australia's regulatory frameworks seek to ensure protection of human health and the environment while allowing application of technologies and products with the least impact on businesses and R&D.

The Office of Gene Technology and Regulation (OGTR) has disseminated information about Australia's regulatory system to individuals aligned with the DIY bio- movement, and also posted these on its website. The Gene Technology Ethics and Community Consultative Committee (GTECCC) has also considered the question of whether synthetic biology raises new ethical issues and concluded that issues are qualitatively similar to those raised by gene technology. GTECCC recommended maintaining a watching brief on developments in synthetic biology.

There was an independent review of the Gene Technology Act 2000 in 2011 which noted that scientific and technological advances in gene technology and biotechnology continue to be rapid. The 2013 All of Governments Response to the review agreed to undertaking further investigation of ways to ensure that the Act remains up to date with advances, including in relation to mechanisms to expeditiously amend legislative definitions and exclusions but also in relation to the scope of regulation. The review report and government response are available from the Department of Health website[3].

Ethics

GTECCC has also produced a guidance document – "National Framework of Ethical Principles in Gene Technology"[4] – which could also be applied to synthetic biology.

Public engagement

As in other countries, different applications of synthetic biology produce different reactions. People respond to the applications rather than to synthetic biology itself. Early results show that 60% of the Australian public have not heard of synthetic biology (OECD, 2012). Of those who have, there is strong support for synthetic biology to move forward. Results are largely comparable with those in the United States and the United Kingdom, which show "conditional" support for synthetic biology. As in most countries, there is very limited public attention to synthetic biology in Australia.

China

As there are few private investors in China, the government plays an important role in fostering new areas of science and technology, such as synthetic biology. In 2008, a dedicated research funding scheme for synthetic biology was proposed to encourage research on the development of new biofuels and biomaterials and to find novel approaches to bioremediation and medical applications. However, it has been delayed (Pei et al., 2011a).

Long-term support for industrial biotechnology is reflected in China's 11th Five-Year Plan (Wang et al., 2009), with planned spending on biofuels and renewable energy in the billions of US dollars. China is the world's third largest producer of ethanol. Existing bio-based production includes vitamin C and citric acid. The Chinese chemicals industry makes increasing use of industrial biotechnology, particularly in biopolymers. Pei et al. (2011a) describe many synthetic biology applications and numerous institutions involved in research. In the 12th Five-Year Plan, China will spend USD 308.5 billion on science and technology, with biotechnology a major priority,[5,] specifically biopharmacy, bio-engineering, bio-agriculture and bio-manufacturing.

A draft roadmap for China

China is developing its synthetic biology strategy through a roadmap that sets out targets over 5, 10 and 20 years (Zhang, 2012). The five-year targets concentrate on technologies and industrial, medical and agricultural applications. By the 20-year stage, the technology targets are: databases of full ranges of parts and devices for chassis organisms; and integrated technology platforms for design, modelling and validation of biosystems.

The products envisaged at the 20-year stage include: commercial production of a range of natural compounds, drugs, chemicals and biofuels; clinical applications of devices and biosystems for surveillance, control and treatment of selected major diseases; commercial plants and crops with high tolerances and improved photosynthesis, and engineered microbes with improved nitrogen fixation capabilities; microorganisms with enhanced capabilities for the bioremediation of environmental pollutants; and artificial microbial life forms. China is currently developing synthetic biology capabilities through a number of projects (Table 7.1).

Table 7.1. Current synthetic biology research projects in China, 2010

Project	Cost (million RMB)
Artificial cell factory	80
Photosynthesis and the artificial leaf	50
High-yield production of microbial drugs	30
New functional biodevices	40
New pathways for biological materials	2.5
Standardisation of biological components (under review)	30-40
Industrial, agricultural or medicine applications (under review)	20-40

Source: Zhang, X.-E. (2012), "Synthetic biology: China's perspective", Presentation at the Six-Party Joint Symposium on Synthetic Biology for the Next Generation, under the auspices of the NAS/NAE, Washington DC, 12-13 June.

Regulation

Like other countries, China currently regulates synthetic biology through genetic modification regulations, e.g. Order No. 304 (2001), The State Council of the People's Republic of China, Safety regulations for agricultural genetically modified organisms.[6] For the majority of the Chinese population, synthetic biology is an unknown concept, and discussions of the social issues are for the moment confined to the scientific community (Pei et al., 2011b). Most researchers believe that regulation is sufficient to cope with the current status of synthetic biology. According to a series of interviews with researchers (Pei et al., 2011b):

- Four interviewees out of 20 considered that the current institutional review of research regulation was sufficient.
- Seven out of 20 thought that regulations at a national level would be better, whereas three preferred an international framework.
- Four suggested that regulation should be either targeted at risk prevention or based on research objectives.
- One considered that the current regulation on recombinant DNA was sufficient.
- Two were worried that further regulation specific to synthetic biology would harm the development of the field.

Denmark

Denmark has identified synthetic biology as a field with enormous potential to create innovation and growth. Research in synthetic biology began around 2005 with some small projects. In 2008, funding of EUR 16 million was given to the UNIK Synthetic Biology Research Centre by the Danish Ministry of Science, Technology and Innovation. In 2010, the Novo Nordisk Foundation provided EUR 100 million for the establishment of the Novo Nordisk Foundation Centre for Biosustainability, a basic research centre with a focus on synthetic biology. Today, research in synthetic biology is taking place at most Danish universities and in a number of Danish companies (ERASynBio, 2012).

The Danish Council for Strategic Research has prioritised synthetic biology and will encourage scientists to work in international networks in order to pool competences and resources. In addition to supporting research in synthetic biology, an education programme at the undergraduate, postgraduate and doctoral levels is to be developed.

Finland

As in most countries, synthetic biology is in its infancy in Finland and synergies are being sought through the pooling of researchers' resources in the various -omics technologies, bioinformatics and systems biology. Networking will be a key feature of the development of synthetic biology and may be fostered by public policy.

To capture the multidisciplinarity of synthetic biology, Finland has created FinSynBio, a national research programme in synthetic biology (Academy of Finland, 2012). The stated aims of the programme are to: support high-level synthetic biology research in Finland; promote co-operation among scientists and researchers based in Finland and working in different fields to facilitate the achievement of critical mass in the research community and international competitiveness in the synthetic biology field; increase international collaboration to support the achievement of other programme objectives; foster dialogue between the research community and the rest of society on socio-cultural concerns and issues related to synthetic biology; and promote public understanding of synthetic biology research. The programme is to run from 2013 to 2017.

France

Educational initiatives

The European Master in Systems and Synthetic Biology (University of Evry-Val-d'Essonne) aims to provide students from the life sciences, mathematics, engineering and physical sciences with a means to engage fruitfully in collaborative work across disciplinary boundaries, with applications in systems and synthetic biology. Students undertaking the course gain hands-on experience in experimental biology, modelling and design.

Infrastructure

Synthetic biology currently has two main centres in France, one in Evry (Paris area) around Genopole,[7] Evry University and the Centre National de la Recherche Scientifique (CNRS),[8] and one in Toulouse around INSA,[9] INRA[10] and the CNRS. The CNRS is the largest basic research organisation in Europe. It encourages multidisciplinarity and the opening up of new fields of enquiry to meet social and economic needs. One of the stated aims of CNRS multi-disciplinary programmes is to support the emergence of new research themes at the interface of traditional fields relevant to synthetic biology.

Five strategic recommendations have been made to support the development of synthetic biology in France (*Ministére de l'Enseignement Supérieur et de la Recherche*, 2011):

1. promotion of dialogue between science and all relevant stakeholders to enable the involvement of society in the direction of synthetic biology in France;
2. facilitation of the emergence of multidisciplinary centres of excellence and creation of a national forum on synthetic biology to facilitate exchanges of best practice;
3. mobilisation of public-private institutions in a co-ordinated fashion;
4. development of a strategy to reach critical mass for synthetic biology not seen elsewhere in Europe;
5. harmonisation of political aspects internationally and control of risks.

Commercialisation and venture capital

The only well-known European enterprise working on biofuel production by a synthetic biology route is Global Bioenergies[11] in Evry, France. In February 2009, the company raised EUR 3.2 million from Masseran Gestion, the venture capital subsidiary of *Caisse d'Epargne* (now BPCE), one of the three largest banks in France. In March 2012, Global Bioenergies announced that they would be receiving EUR 740 000 of financing from OSEO, a French state SME-funding agency, in the form of an interest-free loan to be reimbursed from 2016 onwards. The loan will be used to support the creation of an isobutene production strain compatible with industrial pilot testing. This brings OSEO's financing of various development stages of Global Bioenergies' isobutene programme to a total of EUR 2 million since 2009.[12]

India

India is including plans for developing synthetic biology in its 12th Five-Year Plan. The following recommendations were made by the Task Force on Synthetic and Systems Biology Resource Network:[13] augment capacity in India through the creation of institutions; augment human resource development; build translational capabilities; evolve multi-modal and fast-track funding options; build international linkages; create training centres, network centres, dedicated seminar circuits for synthetic and systems biology research; create fellowships and facilities for micro-fluidics, high-throughput genome sequencing, and engineering and "-omics"-scale data generation; and create plug-and-play facilities and creation of open knowledge-ware. The indicative budget for this in the 12th Five Year Plan (2012-17) is INR 19 700 million (approximately EUR 277 million).

Japan

Competitions

RoboCon is a well-known robot contest in which individually developed robots compete on the basis of excellence in certain skills. GenoCon is the life science version, and expects researchers to compete on the basis of their skills in the rational design of genome-based sequences. The competition also hopes to attract researchers familiar with bioinformatics who may lack the experimental resources to build what they design.

GenoCon expects small-scale business groups and academics with patented DNA sequences to use the platform to find optimised versions of the sequences claimed in the patents. Results will normally be made public, but

participating companies will have the option to keep sequences secret if they are negotiating joint patent or licensing agreements with other businesses, a strategy that has been coined open-optimisation research. Like the annual international Genetically Engineered Machine (iGEM)[14] competition (see Chapter 1), the organisers hope that GenoCon will attract budding scientists through a separate category for high-school students. Currently, the GenoCon2[15] biannual international competition focuses on modifying the genome of the thale cress plant *Arabidopsis thaliana*.

Infrastructure

A comprehensive approach to building synthetic biology infrastructure is being taken at the RIKEN BASE (Bioinformatics and Systems Engineering) division.[16] The following activities and projects are being developed: international cyber-infrastructure standards; database integration; common platform uniting projects; RIKEN SciNeS: life science networking system; scalable platform incubating databases; strengthening bioinformatics; and genome design.

United Kingdom

Roadmap

The United Kingdom Technology Strategy Board published their roadmap in July 2012 (UK Synthetic Biology Coordination Group, 2012). It maps to 2030 the timeframe for the development of a bioeconomy. It has five core themes: foundational science and engineering: the need for sufficient capabilities for the United Kingdom to maintain a leading edge; continuing responsible research and innovation: including the need for awareness, training and adherence to regulatory frameworks; developing technology for commercial use; applications and markets: identifying growth markets and developing applications; and international co-operation.

A crucial element of the roadmap proposal is the establishment of a leadership council. The range of potential synthetic biology applications and the corresponding number of bodies involved in different aspects of synthetic biology show the need for one body to be a visible point of co-ordination. The government has proposed that this leadership council would own and oversee the development and delivery of the vision and roadmap. A recommendation in the UK Synthetic Biology Roadmap is the creation of a network of multidisciplinary centres, including a dedicated innovation and knowledge centre. An announcement to this effect was made on 11 September 2012 (EPSRC, 2012).

Innovation and knowledge centres were established by the Engineering and Physical Sciences Research Council (EPSRC) as centres of excellence with five years' funding to accelerate and promote business exploitation of an emerging research and technology field. Educational initiatives

Synthetic Biology, Imperial College, London: A final-year option in synthetic biology is available to undergraduates wishing to study for a BSc in Biochemistry or Biology or a BEng or MEng in Biomedical Engineering. In the undergraduate synthetic biology course, students learn about the foundational technologies and theory behind engineering biology and real-world situations in which synthetic biology is being applied. The course contains an introduction to the moral and ethical issues associated with synthetic biology, as well as practical sessions on experimental molecular biology and biological modelling. The course culminates with a "mini iGEM" project, a two-week task to develop a synthetic biology idea and outline the design, modelling, experimental work and data analysis required to bring this to reality.

MRes at Imperial College, London: The Master in Research course, at the Institute of Systems and Synthetic Biology, consists of an eight-month multidisciplinary research project, as well as case studies, practicums and taught courses in advanced molecular biology, genetics, synthetic biology, biophysics, bioengineering, systems biology, physiological systems, advanced imaging technology and data analysis. The degree is designed to prepare students for doctoral course work or for a career in research, by placing emphasis on a significant dissertation.

Infrastructure

The cross-cutting nature of synthetic biology is exemplified by a joint initiative between four UK research funding councils – the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, the Arts and Humanities Research Council and the Economic and Social Research Council. Together, they have provided funding totalling GBP 970 000 to finance seven networks in synthetic biology (Table 7.2). Annex B presents individual synthetic biology research projects funded by two UK research councils. They cover a diversity of types of projects and university departments.

Table 7.2. Synthetic biology research networks in the United Kingdom funded by public money

Network title	Lead university
Synthetic components network: towards synthetic biology from the bottom up	Bristol
Standards for the design and engineering of modular biological devices	Edinburgh
A synthetic biology network for modelling and programming cell-cell interactions	Nottingham
From robust synthetic biological parts to whole systems: theoretical, practical and ethical challenges	Oxford
SPPI-NET: A network for synthetic plant products for industry	Durham
The UCL network in synthetic biology	University College London, Birkbeck
MATEs – microbial applications to tissue engineering: an exemplar of synthetic biology.	Sheffield

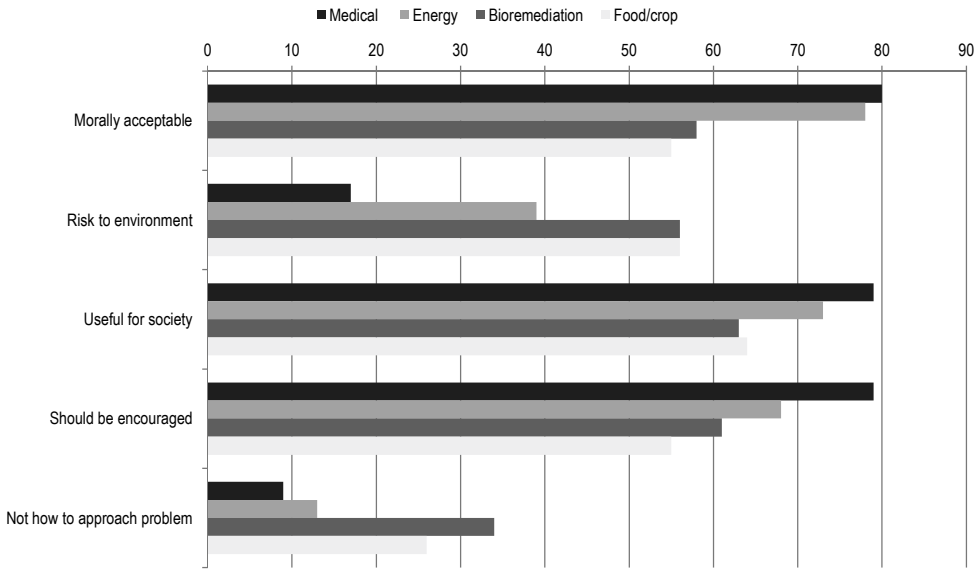
Source: Royal Academy of Engineering (2009), "Synthetic Biology: scope, applications and implications", ISBN: 1-903496-44-6.

Public opinion and engagement

Findings from a UK public dialogue showed conditional support for synthetic biology (Bhattachary et al., 2010). While there was great enthusiasm for the possibilities of the science, there were also fears about control, who benefits, health or environmental impacts, misuse, and how to govern the science under uncertainty. There was broadly greater support for medical applications (Figure 7.1) than for food/crop applications, with a perception of greater risk to the environment associated with the latter, combined with relatively lower societal benefit.

Figure 7.1. Public attitudes in the United Kingdom to synthetic biology in different applications

Percentage of responses



Source: Bhattachary, D., J.P. Calitz and A. Hunter (2010), "Synthetic biology dialogue", for the BBSRC, United Kingdom.

United States

Educational initiatives

The United States has synthetic biology education programmes ranging from high school to postgraduate. A few representative initiatives are:

- Massachusetts Institute of Technology (MIT) high-school enrichment programme: The course, intended for 12th grade, demonstrates the process of cloning a gene from start to finish, including use of polymerase chain reaction (PCR) to amplify a gene of interest, BioBrick assembly of DNA fragments, transformation of DNA into a host bacterium strain, and controlled expression through a variety of expression systems.[17] MIT is also developing integrated, interdisciplinary graduate courses that are accessible to students from different backgrounds. MIT synthetic biology education is discussed in detail by Tadmor and Tidor (2005).

- Brown University 1 BIOL 1940T (CRN 14871) Synthetic Biological Systems: This course builds on recent work in systems biology involving the modelling of biological systems, but goes further in that it involves the construction and standardisation of biological parts that fit together to form more complex systems. It covers fundamental principles of engineering such as abstraction, modularity, standardisation and composition and how these are being applied to biology.
- Harvard University Systems Biology 204: Biomolecular Engineering and Synthetic Biology: This is a course focusing on the rational design, construction and applications of nucleic acid and protein-based synthetic molecular and cellular machinery and systems. Students are mentored to produce substantial term projects. It is intended for graduate students in Systems Biology, Biophysics, Engineering, Biology and related disciplines.
- University of California Berkeley Implications and Applications of Synthetic Biology: This is different from other courses in that, not only does it have scientific and engineering aspects, it also covers aspects of policy making (e.g. policy recommendations) and business (e.g. market trends, intellectual property, hypothetical balance sheets for projects).
- Genome Consortium for Active Teaching (GCAT): Davidson College uses the MIT iGEM competition to expose undergraduates to complex research questions at the interface of mathematics, computer science and biology (Haynes et al., 2008). The course, which combines lectures in the theoretical foundations of biology and mathematics with intensive laboratory work, was recently awarded a multi-year NSF grant to develop the programme as the Genome Consortium for Active Teaching.[18] GCAT aims to make genomics education and research opportunities available to undergraduates, to provide a summer synthetic biology workshop for pairs of interdisciplinary faculty from colleges and universities around the United States and to introduce faculty members to the field of synthetic biology research.
- SynBERC: The Synthetic Biology Engineering Research Centre[19] sponsors a number of educational programmes. One of their sponsored projects is BioBuilder, a website filled with interactive and animated educational resources. Though it is geared towards students, the animations, which provide an introduction to the mechanics of engineering biology, are for any audience. There are also resources for teachers, a synthetic biology glossary and walkthroughs for a number of laboratory activities to introduce students to synthetic biology.

Roadmap

A comprehensive technical roadmap process has been proposed in the United States that would address key technological challenges, the development of common measurements and standards, and shared foundational elements such as tools, techniques, and platforms. The American synthetic biology research community, the National Academies and the business community have all expressed strong interest in a technical, pre-competitive roadmap focused on key challenges to be overcome in synthetic biology. Planning processes are under way at the National Academy of Sciences, the BioBricks Foundation and several industry-university coalitions.

The roadmap will likely represent a multi-year effort focused on overcoming the major technological, measurement, standards and scientific barriers. It is likely to take a very different form from that of the UK roadmap and others. It will not be an overview of the field or a strategy planning document but is much more likely to resemble the Semiconductor Roadmap, an on-going and comprehensive technical and scientific process involving working groups, measurements, technical challenges and benchmarks to drive progress in the field. Also, it is likely to focus more on the key building blocks for synthetic biology (tools, technology platforms, data, metrology) than on applications.

Research

Between 2005 and 2010, the US government spent approximately USD 430 million on research related to synthetic biology, with the Department of Energy funding the majority of this research.

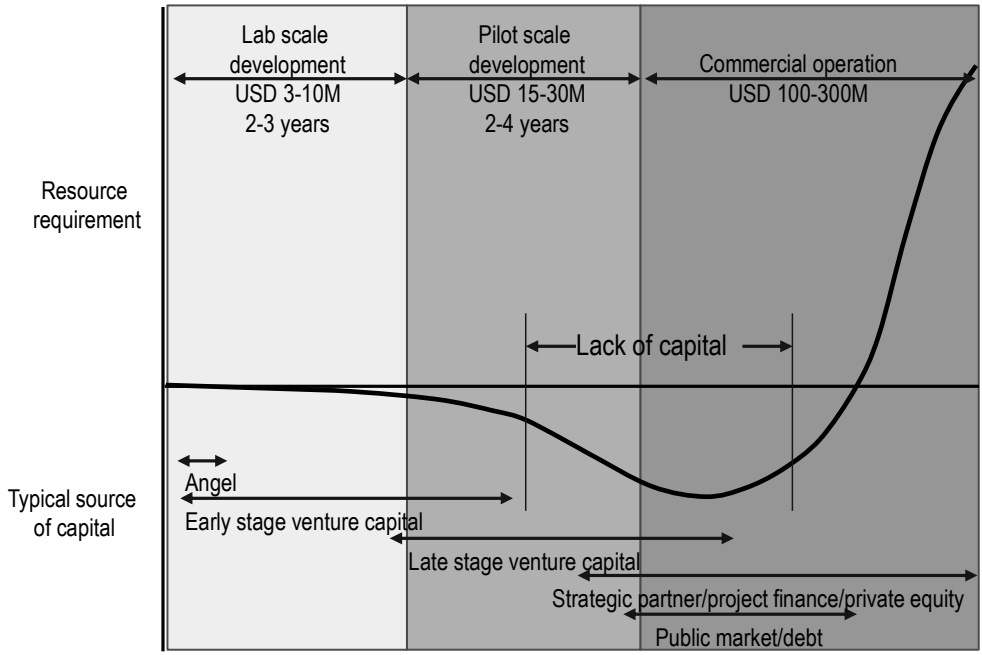
Intellectual property

The BioBrick Public Agreement is a free standardised legal contract that allows individuals, companies and institutions to use their standardised biological parts for free. According to the BioBrick Foundation,[20] "the BioBrick Public Agreement was developed for sharing the uses of standardised genetically encoded functions (e.g. BioBrick parts) but, in practice, can be used to make free the sharing of any genetically encoded function that you might already own or make anew". The BioBrick Public Agreement attempts to minimise legal uncertainty and to avoid disputes arising over ownership, intellectual property rights and attributions, like open source and free software licensing. According to Torrance (2010), this agreement could be seen as an "initial effort to draft a legal constitution to guide the beneficial development of the field of synthetic biology".

Commercialisation and venture capital

In the United States, a new wave of university funding may further stimulate synthetic biology through the commercialisation of near-market research. While MIT, Stanford and Caltech have long provided infrastructure to nurture new companies, other universities are now seeking to do the same. New York University, for example, announced a new USD 20 million venture fund to commercialise internal research (Belz, 2010). For university professors, access to internal sources of funds, instead of external venture capital, is attractive as it is likely to be accompanied by institutional support. University administrators can retain faculty members with the promise of funding their future enterprises. However, experience in the United States has shown that such spin-outs are resource-intensive, can take years to achieve sales and typically require financial support at levels beyond university funds. Figure 7.2 shows typical cash requirements for a young high-technology company in the United States.

Figure 7.2. Typical capital requirements for a biotechnology company



Source: Wyse, R. (2011), "Challenges to financing a global bio-based economy: opportunities for emerging economies", Presented at the European Forum for Industrial Biotechnology, 19 October 2011, Amsterdam.

In the United States, some synthetic biology companies with flexible platform technologies have seen significant investment. Among the biofuels processing technologies, synthetic biology start-ups have attracted increased funding since 2004.[21]

Lab-scale R&D is the least expensive phase of the development of a spin-out. Pilot-scale development has been lacking, but this is now being addressed. For example, the US biofuels industry is currently relying on pilot plants to develop efficient processes to produce cellulosic biofuel and verify its economic viability (An et al., 2011).

Regulation

The United States' approach to regulation of synthetic biology is premised on the assumption that regulation should focus not on the production process *per se* but on the properties of products as regulated under existing statutes. Consequently, synthetic biology products are currently covered by three different US agencies operating under four separate statutes (Bar-Yam et al., 2012).

Until recently, the role of governmental institutions in controlling synthetic DNA trade and production has been relatively marginal. However, this has changed slightly since US administrative bodies such as the National Science Advisory Board for Biosecurity (NSABB) have started to take a proactive role in promoting security standards in gene synthesis companies.

Documents such as the NSABB's Addressing Bio-security Concerns Related to the Synthesis of Select Agents[22] or the National Institutes of Health's Guidelines for Research Involving Recombinant DNA Molecules[23] represent government efforts to address the security aspect at the institutional level. Nevertheless, the involvement of government at this stage is limited to making recommendations.

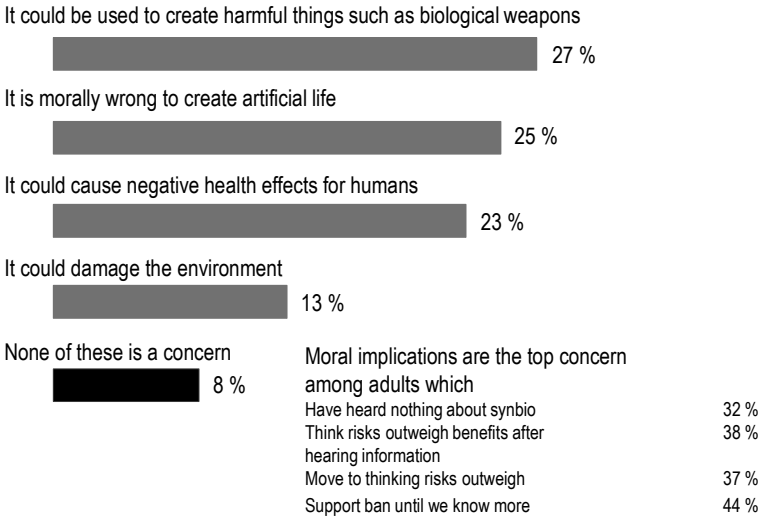
The engagement of US governmental agencies could represent a step towards a more global approach to synthetic biology security. This goal is also shared by the US Department of Health and Human Services. In explaining the objectives of its *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,*[24] it pointed out that "the Guidance was composed so that fundamental goals, provider responsibilities, and the screening framework could be considered for application by the international community".

Public opinion and engagement

During 2010, Hart Research Associates conducted a nationwide survey of 1 000 American adults about attitudes towards nanotechnology, and awareness of, and attitudes towards, synthetic biology. Awareness of synthetic biology grew significantly over three years from 9% in 2008 to 26 %. Figure 7.3 may be revealing if these opinions are widespread. It would appear that, in the United States at least, the negative association of synthetic biology with agriculture is not yet a concern. In a presentation to the European Commission, Michele Garfinkel stated that the five key societal concerns regarding synthetic biology in the United States are: bioterrorism; laboratory safety; harm to the environment; distribution of benefits; and ethical and religious concerns.

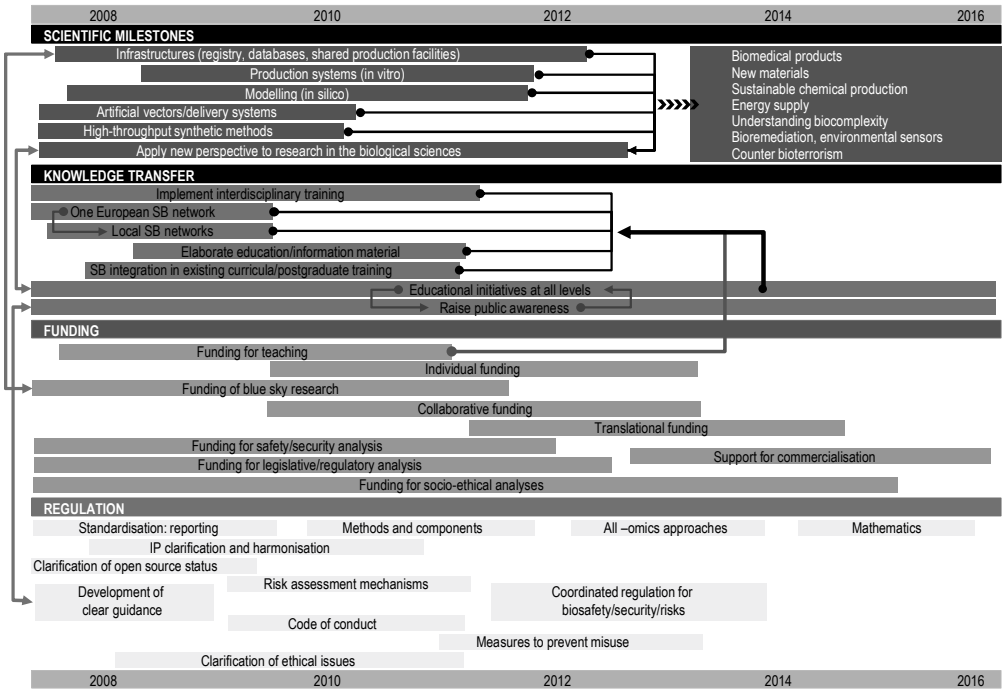
Interestingly, there was no concern about synthetic DNA itself; rather there was concern about whether specific engineered organisms pose risks to the environment; this is a link to concerns surrounding agriculture and forestry. In this regard, the debate has been on-going since the 1970s and is far from a new issue. The concerns over the distribution of benefits revolve around intellectual property and the concentration of benefits in a small number of companies. This is a concern for any new technology and is not specific to synthetic biology. Less tractable, however, are moral and ethical concerns over the changing relationship of humans to nature.

Figure 7.3. Top concerns about synthetic biology among US adults



Source: Hart Research Associates (2010), "Awareness and impressions of synthetic biology: a report of findings based on a national survey among adults", Hart Research Associates, Washington, DC.

Figure 7.4. A vision of an EU roadmap for synthetic biology



Source: Gaisser, S. (2009), "Making the most of synthetic biology. Strategies for synthetic biology development in Europe", *EMBO Reports* 10, S5-S8.

European Union

Roadmap

Research activities in synthetic biology are scattered across Europe and are still concentrated in a relatively small number of working groups. To strengthen European competitiveness in synthetic biology, it is necessary to integrate the various activities and to draft a comprehensive strategy for the field. This situation lends itself to a roadmapping exercise, and in 2008, an EU project outlined a synthetic biology roadmap to 2016, with individual roadmaps for regulation, funding and technology transfer. The exercise was performed in three phases:

1. co-ordinating roadmap committee workshops with representatives from on-going synthetic biology projects and funding agencies in the United Kingdom, France, Spain, Germany and Italy;

2. fact-finding workshops with representatives from European research projects in synthetic biology, in which milestones and possible scientific and/or political measures were discussed;
3. once the two workshop series were completed and a draft roadmap was written, an online survey of the broader scientific community was conducted, designed to involve as many persons with an interest in synthetic biology as possible.

The results were published in 2009 (Gaisser et al., 2009), and the resulting roadmap summary diagram is shown in Figure 7.4. It is clearly as much a policy roadmap as a technology roadmap. Such an exercise can be extremely useful for governments by framing the issues and placing them in a time-constrained context.

The rapid technological developments that characterise synthetic biology can change the situation rapidly so that roadmaps must be continuously updated as new technology is developed.

Infrastructure

The fragmented nature of EU research in synthetic biology, alluded to above, requires the involvement of groups in different countries working in various disciplines in infrastructure projects. FP6 and FP7, DG Research and Innovation, have financed 27 synthetic biology projects (Box 7.1).

Regulation

All European Union regulations on genetic engineering pertain to synthetic biology. As with genetic engineering, the contained use of microorganisms in closed systems (regulated by EU Directive 2009/41/EC)[25] has to be distinguished from the deliberate release (EU Directive 2001/18/EC)[26] of organisms into the environment. The European regulations tend to be stricter than their US counterparts, especially with respect to labelling and traceability requirements. The more stringent European rules can be attributed to public concern about the potential dangers of GMOs and food. SYNBIOSAFE[27] was the first project in Europe to research the safety and ethical aspects of synthetic biology and aimed to stimulate debate on these issues.

Box 7.1. Synthetic biology projects under the Framework Programmes

FP6

SYNBIOLOGY: A European perspective on synthetic biology

BIOMODULARH2: Energy project promises a new biotechnology

TESSY: Foundations for a European synthetic biology

SYNPLEXITY: Dynamics and complexity in synthetic protein networks (MOBILITY)

CELLCOMPUT: – Biological computation built on cell communication systems (NEST)

SYNBIOSAFE: Safety and Ethical Aspects of Synthetic Biology

FP7

KBBE-2007-3-3-01 Synthetic Biology for the Environment (CSA-CA): Targeting environmental pollution with engineered microbial systems a la carte (TARPOL)

KBBE-2009-3-6-05: Synthetic biology for biotechnological applications (CP-FP): Bacterial Synthetic Minimal Genomes for Biotechnology (BASYNTHEC)

KBBE.2011.3.6-03: Towards standardisation in Synthetic Biology (CP-IP): Standardization and orthogonalisation of the gene expression flow for robust engineering of NTN (new-tonature) biological properties (ST-FLOW)

KBBE.2011.3.6-04: Applying Synthetic Biology principles towards the cell factory notion in biotechnology (CP-FP): Products from methanol by synthetic cell factories (PROMYSE) and Code-engineered new-to-nature microbial cell factories for novel and safety enhanced bioproduction (METACODE)

KBBE.2011.3.6-06: Synthetic biology – ERA-NET. Call FP7-ERANET-2011-RTD: Development and Coordination of Synthetic Biology in the European Research Area (ERASynBio)

SiS-2008-1.1.2.1: Ethics and new and emerging fields of science and technology: SYNTHETICS and SYBHEL

SiS.2012.1.2-1. Mobilisation and Mutual Learning Action Plans; Acronym: SYN-ENERGY

Conclusion

It will be clear that the policy landscape for synthetic biology reflects the youth of the field. Not all countries have detailed policy agendas. However, synthetic biology also takes advantage of the several decades of policy development associated with biotechnology more generally. So there are familiarities in, for example, R&D subsidy approaches, biosafety and biosecurity. Policy may diverge if countries believe that synthetic biology is the start of a manufacturing revolution in which biotechnology takes its place in mass production. The earliest synthetic biology technology roadmaps have begun to appear. Roadmaps are considered to have been instrumental in the development of the semiconductor industry, and they can also be powerful instruments for policy makers, when considering, for example, the applications that are most important to a particular country or region, and how to go about public engagement. There have even been voices calling for a global synthetic biology roadmap.

Notes

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3. www.health.gov.au/internet/main/publishing.nsf/Content/gene-techact-review
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10. www.inra.fr/.
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Annex 7.A1

Recent grants of the Gates Foundation for synthetic biology applications to health

A microbial platform for the biosynthesis of new drugs

The development of synthetic biology platforms to improve the scale and efficiency of microbial systems used to discover, develop, and produce drugs based on natural products. Such new biosynthesis approaches could lead to new and less expensive drugs for global health.

A predictive model for vaccine testing based on aptamers

The use of synthetic nucleic acid molecules known as aptamers to develop a model that can be used to predict the success or failure of new vaccines in clinical trials. This work could help to remove some of the uncertainty in the early-stage development of new vaccines.

A synthetic biosensor to find drugs targeting TB persistence

The use of a synthetic biosensor strain and high-throughput screening to discover compounds that inhibit tuberculosis persistence. Study of these compounds may lead to new drugs that limit the establishment of chronic tuberculosis infections.

Development of a microorganism to produce artemisinin

The production by an endophytic fungus of artemisinin, a key ingredient in malaria treatments. If the fungus produces artemisinin in the absence of light, an enzymatic mechanism is likely involved. This mechanism could be harnessed for a new production method to reduce treatment costs for malaria patients in developing countries.

Discovering new anti-microbial peptides against mycobacteria

The design and production of a large library of antimicrobial peptides (AMPS) that will be tested against *Mycobacterium tuberculosis* strains to identify potential new drugs that can damage the bacterial membrane and be less susceptible to evasion by the development of resistance.

The construction of an inexpensive and robust nanodevice that uses DNA as a scaffold to interact with proteins and nucleic acid markers of target pathogens. When this interaction occurs, the movement will be detected by a reader embedded in the device to create a visual readout of pathogen detection. Nature-inspired nanoswitches for HIV antibodies detection

The development of molecular nanoswitches that provide a visual cue when they bind to HIV antibodies for use in a rapid (one minute) diagnostic test to detect and quantify HIV antibodies in serum samples.

Plant-produced synthetic RNA vaccines

Testing of the ability of a low-cost plant-based synthetic biology method to produce a combined viral protein epitope with an antigen RNA expression system for use in an RNA malaria vaccine. Using plants for this viral transfection system could make RNA vaccine production scalable and cost effective.

DNA nanodevice for pathogen detection

The construction of an inexpensive and robust nanodevice that uses DNA as a scaffold to interact with proteins and nucleic acid markers of target pathogens. When this interaction occurs, the movement will be detected by a reader embedded in the device to create a visual readout of pathogen detection. Nature-inspired nanoswitches for HIV antibodies detection

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Plant-produced synthetic RNA vaccines

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Protein-based low-cost metabolite biosensors for pneumonia

The use of synthetic biology to develop protein-based metabolite biosensors. These biosensors will be used to create a simple, low-cost diagnostic test for pneumonia that is based on specific metabolite signatures found in urine.

Reconstitution of a synthetic Mycobacterium tuberculosis system

The synthetic reconstruction of essential biological processes of *Mycobacterium tuberculosis* and the use of this system as a drug-testing platform for the screening of small-molecule therapeutics against multi-drug resistant *M. tuberculosis*.

Synthetic probiotic to identify and prevent cholera

The engineering of the probiotic bacterium *Lactobacillus gasseri* to detect and kill *Vibrio cholerae* in the human intestine. The probiotic could be supplied as an inexpensive lyophilised powder to endemic populations to prevent cholera.

Synthetic signals to eliminate essential Plasmodium proteins

The development of synthetic compounds that target essential proteins in the *Plasmodium* parasite for destruction by its own protein degradation mechanisms. This strategy could aid new small molecule drug development efforts to combat malaria.

Transcription factor screening for P. falciparum therapy

The development of a high-throughput screen to search for artificial transcription factors (ATF) that are candidates to treat *P. falciparum* infections. ATFs could be a gene-regulating drug resource for the study and treatment of malaria.

Wolbachia as a back door to synthetic entomology

The use of synthetic DNA techniques to transform *Wolbachia*, a bacterial parasite that infects most insect species, in an effort to engineer mosquitoes to be immune to malaria parasites.

Yeast receptors for a generic biomarker detection platform

Engineering of yeast-based biosensors that identify protein biomarkers in samples such as blood and urine. An array of yeast strains could serve as a low-cost, in-home device providing patients with a panel of diagnostics to improve treatment and diagnosis in resource-poor settings.

Source:
www.grandchallenges.org/explorations/pages/grantsawarded.aspx?Topic=SyntheticbiologyandRound=8andPhase=all

Annex 7.A2

Synthetic biology research grants awarded in the United Kingdom by two research councils (BBSRC and EPSRC)

Holding organisation	Grant title	Total grant value (GBP)
Imperial College London	Data-based optimal control of synthetic biology gene circuitsa	99 918
University of Glasgow	Developing theory on the formation, composition and structure of open microbial communities that can be used in engineering design	518 536
University of Glasgow	The CHELL : A Bottom-Up approach to in vitro and in silico Minimal Life-like Constructs	373 250
University of Oxford	The CHELL : A Bottom-Up approach to in vitro and in silico Minimal Life-like Constructs	573 990
University of Nottingham	The CHELL : A Bottom-Up approach to in vitro and in silico Minimal Life-like Constructs	729 420
Imperial College London	Centre for Synthetic Biology and Innovation at Imperial College	4 710 140
University of Leeds	Self-assembling virus-like particles	489 951
King's College London	Molecular mechanisms of antimicrobial peptides: phase changes induced in endotoxic bacterial lipopolysaccharide.	195 662
Newcastle University	Sandpit: Cyberplasm	298 311
University of Bristol	Sandpit: Engineering genetically augmented polymers (GAPS)	628 055
University of Glasgow	Sandpit: Synthetic integrons for continuous directed evolution of complex genetic ensembles	907 086
University of Cambridge	Sandpit: The Programmable Rhizosphere	972 909
University of Cambridge	Towards Industrial Applications of Modular Languages for Biology	250 340
University of Edinburgh	Enabling Tools & Technologies for Synthetic Biology	807 438
University of Southampton	Engineering a semi-biotic immune system	1 031 745
University of Exeter	Evolving controllers and controlling evolution	416 929
London School of Economics & Pol Sci	Synthetic Biology: Generativity and the Limits of Intellectual Property	86 014
University of Oxford	Control Engineering Inspired Design Tools for Synthetic Biology	363 101
University of Cambridge	Control Engineering Inspired Design Tools for Synthetic Biology	313 139
Imperial College London	Control Engineering Inspired Design Tools for Synthetic Biology	429 418

Holding organisation	Grant title	Total grant value (GBP)
University of Glasgow	Bio-desalination: from cell to tap	1 040 620
University of Nottingham	ROADBLOCK: Towards programmable defensive bacterial coatings and skins	899 798
University of Warwick	ROADBLOCK: Towards programmable defensive bacterial coatings and skins	259 428
University of Sheffield	ROADBLOCK: Towards programmable defensive bacterial coatings and skins	601 135
University of Nottingham	Towards a Universal Biological-Cell Operating System (AUdACiOuS)	1 026 408
University of Glasgow	A synthetic biology approach to optimisation of microbial fuel cell electricity production	960 593
Imperial College London	An infrastructure for platform technology in synthetic biology	5 007 845
University of Sheffield	From Molecules to Systems: Towards an Integrated Heuristic for Understanding the Physics of Life	247 084
Imperial College London	Assessment of Integrated Microalgal-Bacterial Ecosystems for Bioenergy Production - Optimization-based Methodology	99 382
Imperial College London	Engineered burden-based feedback for robust and optimised synthetic biology	436 947
University of Kent	Bioengineering of complex metabolic pathways	742 283
Imperial College London	Investigation of water oxidising catalysis for renewable energy	490 684
John Innes Centre	The exploitation of viruses for bionanoscience and synthetic biology approaches to new materials and devices	519 797
Rothamsted Research	Rational metabolic engineering of oilseed fatty acid composition	1 178 692
Cardiff University	High-throughput engineering of proteins: Sampling extended chemical diversity by combining directed evolution with an expanded genetic code	314 171
University of Bristol	Synthetic components network: Towards synthetic biology from the bottom-up	125 833
John Innes Centre	Rational design of plant systems for sustainable generation of value-added industrial products (SmartCell)	261 357
University College London	Exploitation of Tat export machinery for protein production by bacteria	331 103
University of Warwick	Exploitation of Tat export machinery for protein production by bacteria	343 575
University of Edinburgh	Creating and evaluating a library of effector modules for synthetic morphology	418 263
University of Reading	A synthetic and recombinant approach to the production and characterisation of IAPV an associated agent of honey bee Colony Collapse Disorder	320 689
Imperial College London	Mapping combinatorial stress responses in bacteria using chimeric proteins and probabilistic modelling	2 900 932

…/…

Holding organisation	Grant title	Total grant value (GBP)
University of Kent	Mechanism of dimethyenzimidazole (DMB) synthesis and the metabolic engineering of a dietary useful form of cobalamin in Lactobacillus	407 274
University College London	Synthetic biology pathways of isoquinoline alkaloids	713 221
John Innes Centre	Plant production of vaccines	426 895
University of Bristol	A biomolecular-design approach to synthetic biology: towards synthetic cytoskeletons	673 294
University of Nottingham	Second generation sustainable bacterial biofuels	2 127 704
University of Dundee	Bacterial hydrogenases for biohydrogen technology	365 058
University of Oxford	Bacterial hydrogenases for biohydrogen technology	524 205
Plymouth Marine Laboratory	Integrated approach to cost effective production of biodiesel from photosynthetic microbes	823 495
Durham University	Integrated approach to cost effective production of biodiesel from photosynthetic microbes	844 536
University of Cambridge	SYNAPTA: An artificial genetic system and its application for the generation of novel nucleic acid therapeutics	275 007
University of Kent	Synthetic biology approaches to compartmentalisation in bacteria and the construction of novel bioreactors	874 606
University of Southampton	Modifying nucleic acid nanostructures using triplex formation	346 022
University of Oxford	Synthetic biology of bacterial cell division	355 946
University of Oxford	NANOCELL	319 781
Rothamsted Research	Engineering oilseeds to synthesise designer wax esters	444 370
University of Nottingham	Systems biology of the butanol-producing Clostridium acetobutylicum: new source of biofuels and chemicals / COSMIC2	452 694
University of Nottingham	Systems biology of the butanol-producing Clostridium acetobutylicum: new source of biofuels and chemicals / COSMIC2	230 848
University of Birmingham	Engineering biofilm catalysts	407 420
University of Bristol	Development of a systems biology for Bordetella pertussis metabolism	576 513
The University of Manchester	Conformational switching for trans-membrane communication	609 437
University of East Anglia	Engineered biofilm catalysts	313 977
University of Cambridge	Collaborative project MAGIC: A multi-tiered approach to generating increased carbon dioxide for photosynthesis	400 261
University of Glasgow	Collaborative project MAGIC: A multi-tiered approach to generating increased carbon dioxide for photosynthesis	401 332
University of Warwick	Collaborative project MAGIC: A multi-tiered approach to generating increased carbon dioxide for photosynthesis	199 054
Cardiff University	Design of bioactive sesquiterpene-based chemical signals with enhanced stability	390 616

…/…

Holding organisation	Grant title	Total grant value (GBP)
Rothamsted Research	Design of bioactive sesquiterpene-based chemical signals with enhanced stability	479 026
University College London	Characterisation of cellular assemblies in microfluidic systems (synthetic biology to obtain novel antibiotics and optimised production systems)	403 051
University of Oxford	Developing and investigating an ultra-stable molecular hub for bionanotechnology	339 378
University of Cambridge	Production of isoprenoid-based biofuel in algae using a synthetic biology approach	313 780
University College London	Production of isoprenoid-based biofuel in algae using a synthetic biology approach	408 529
University of Southampton	Plug 'n play photosynthesis for Rubisco independent fuels	300 609
Imperial College London	Plug 'n play photosynthesis for Rubisco independent fuels	339 879
University of York	Biotransforming phenylpropanoids derived from biorefining: A toolkit approach	352 972
University of Nottingham	Quantification of promoter activity using Lux read-outs and mathematical models.	606 738
University of Southampton	Extending the boundaries of nucleic acid chemistry	1 829 817
University of Oxford	Extending the boundaries of nucleic acid chemistry	1 659 227
University of Sheffield	Design synthesis and evaluation of novel nucleotides for use in nanowire-based DNA analysis and diagnostic devices	91 932
The University of Manchester	A synthetic biology approach for engineering the biosynthesis of new friulimicin lipopeptide antibiotics	75 281
University of Birmingham	Selective biochemical and synthetic biology approaches for improved delivery of recombinant proteins to the extracellular milieu	444 102
Rothamsted Research	Collaborative Research: Exploiting prokaryotic proteins to improve plant photosynthetic efficiency (EPP)	210 284
John Innes Centre	CAPP: Combining Algal and Plant Photosynthesis	313 802
Oxford Brookes University	CAPP: Combining Algal and Plant Photosynthesis	159 329
University of Cambridge	CAPP: Combining Plant and Algal Photosynthesis	372 138
The University of Manchester	Bioorthogonal site-selective protein immobilisation and labelling	475 116
University of Bristol	Alpha-helical peptide hydrogels as instructive scaffolds for 3D cell culture and tissue engineering	659 988
University of Nottingham	Engineering biobutanol production in a cellulosic clostridium using synthetic biology principles	74 410
University College London	MRes in Synthetic Biology	247 204
John Innes Centre	Sandpit: Synthetic integrons for continuous directed evolution of complex genetic ensembles	43 340

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Holding organisation	Grant title	Total grant value (GBP)
Imperial College London	Modular design of a bioinspired tandem cell for direct solar-to-fuel conversion (Solarfueltandem)	175 476
Rothamsted Research	Engineering oilseeds to synthesise designer wax esters	79 704
University of Exeter	Decreasing the oxygenase activity of Rubisco: a synthetic biology approach	174 567
The University of Manchester	Orthogonal riboswitches as tools for controlling gene expression in bacteria	639 275
University of Glasgow	Plug'n Play Photosynthesis for Rubisco Independent Fuels	327 929
Rothamsted Research	Design of bioactive sesquiterpene-based chemical signals with enhanced stability	39 326
University of Bristol	Engineering purple bacterial photovoltaic complexes for device applications	360 080
University of Bristol	Assembly of Artificial Oxidoreductases	294 752
Cardiff University	Controlling cell death and proliferation with encodable visible light responsive proteins	441 375
University of Essex	Metabolic engineering to enhance photosynthesis based on empirical data and in silico modelling	352 167
University of Warwick	Studying stochasticity in eukaryotic gene expression using novel tools of synthetic biology modelling and analytical science	1 150 283
University of Sheffield	Development of an integrated platform for transient production of recombinant protein biopharmaceuticals using disposable processing technology	72 540
University of Cambridge	Mimetic IgG binding ligands	72 540
University of Reading	The Biosynthesis of Artemisinin	387 616
University College London	Use of transaminase enzymes for the synthesis of pharmaceutical intermediates	83 281
University of York	Exploiting the genomic diversity of bayer-villiger monooxygenases for new industrial oxidation reactions	75 281
University of Edinburgh	Biosensors for real-time monitoring of waterborne pathogens and viability determination	75 281
University of Oxford	Bionanopore Function via In Silico Design: A Biomimetic Approach	91 932
University of St Andrews	Development of artificial metalloenzymes for highly efficient catalytic processes.	91 932
John Innes Centre	Integration and coordination within complex antibiotic biosynthetic pathways	462 572
University of Bristol	Novel hybrid anti-MRSA antibiotics from manipulation of the mupirocin and thiomarinol biosynthetic pathways	434 747
University of Birmingham	Novel hybrid anti-MRSA antibiotics from manipulation of the mupirocin and thiomarinol biosynthetic pathways	524 711
University of Leeds	Real-time high sensitivity detection of biological agents	129 242.76

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Holding organisation	Grant title	Total grant value (GBP)
Imperial College London	Engineered security systems for environmental synthetic biology	120 073.40
Imperial College London	Logic-directed evolution of new biosensor molecules in vivo	127 392.67
Cardiff University	Biological Amplification of Chemical Warfare Agent Sensors - Towards 'Deviceless Devices'	120 080.82
University of Reading	Smart Materials for Wound Healing: A New Fast Acting in situ Method to Treat Skin and Eye wounds	
Queen Mary, University of London	Site Directed Inactivation of Biological Agents	114 721.04
Cardiff University	The ostracod carapace window as a biomimetic basis for development of a novel eye shield.	119 583.50
University of York	Exposing explosives: novel synthetic gene circuits for explosive detection via innovative waveguide sensing	119 258.26
University of Bristol	A synthetic biology approach to fighting Francisella tularensis: Development of aptamer presenting DNA-nanorings	122 666.08
The University of Manchester	Exposing explosives: novel synthetic gene circuits for explosive detection via innovative waveguide sensing	44 773.89
University of Birmingham	A homogenous bimodal (immuno/PCR) pathogen detection system based on a bio-nanoparticle	119 898.38
University of Glasgow	Generation of a large family of genetic logic gates for applications in biosensing and information processing	120 185.17
Newcastle University	Surveillance of toxic threats by electronic supervision of synthetic neurons in 3D	100 186.48
University College London	Self-regenerating, suspended-phase whole-cell biosensor system employing micro-chemostat and cell engineering technologies	120 561.78
University of Oxford	Single-molecule DNA biosensors for rapid microbial detection	119 863.42

Source: Adapted from the UK Biotechnology and Biological Sciences Research Council (BBSRC), www.bbsrc.ac.uk/home/home.aspx.

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Emerging Policy Issues in Synthetic Biology

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