

Symposium on Opportunities and Challenges in the Emerging Field of Synthetic Biology

SYNTHESIS REPORT



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Introduction

Synthetic biology is a dynamic, innovative and highly promising blend of science and engineering which aims to construct novel biological entities and to redesign existing ones. It is a new field, but one that has already stimulated substantial discussion regarding its technical possibilities, its role in addressing global challenges, and its use in increasing our understanding of biology. Discussion has also focused on burgeoning social, ethical and regulatory questions, as well as on the field's economic potential. Attention is also being given to synthetic biology's position in national and international science and governance strategies.

The myriad of issues raised by synthetic biology are likely to be viewed differently and to receive differing levels of attention across the international landscape. This can affect the development of the field and the realisation of its potential benefits. It is therefore important to understand and to address globally the opportunities and challenges presented by synthetic biology. This report, and the symposium on which it draws, aim to contribute to this process.

Key points

- Synthetic biology is a set of tools and techniques which mix engineering and biology and support the development of new functions or applications. New applications may be found in medicine, energy, environment and materials. Synthetic biology also aims to increase our understanding of biological systems; in particular, it may offer an approach to managing their complexity.
- It is crucial to invest in underpinning technologies, science, education and policy in order to ensure the safe and efficient development of synthetic biology. Investments in automated technologies such as DNA synthesisers and combinatorial technologies are important to enhance research and optimise the use of researchers' time. Rewarding and publishing advances in synthetic biology would also be a strong stimulus for the field.
- The gap between applications and tools and techniques must be bridged. This calls for investments to develop tools and techniques.

- The degree to which experience and knowledge gained from other emerging technologies are being drawn upon and used is not clear.
- Issues raised during the symposium that would benefit from further investigation and, in some cases, policy interventions at multiple levels, include:
 - standardisation, for example of biological parts;
 - the shaping of an intellectual property model;
 - international collaboration and co-operation in the regulation and governance of synthetic biology, as well as scientific and technical development.
- Opportunities for public debate and discussion of synthetic biology need to be created. Part of the challenge will be to develop a common, widely understood language for discussing ethical and social, as well as technical aspects of synthetic biology. The public should be involved in a healthy and open dialogue. What is needed is real dialogue and engagement with the public rather than a simple communication strategy.
- Communication between the many stakeholders involved in novel technologies and science depends on a variety of complex factors and is context-dependent.

The symposium

Under the auspices of the United States National Academies, the Organisation for Economic Co-operation and Development and the Royal Society, an international symposium entitled “Opportunities and Challenges in the Emerging Field of Synthetic Biology” was held in Washington, DC, on 9-10 July 2009.

This symposium brought together the various communities – scientific, engineering, policy, public, legal – that are involved in synthetic biology and explored the opportunities and challenges raised by this emerging field. The symposium was organised around expert talks and discussions on issues such as: the state of the field and its commercial and scientific potential; scientific, educational and commercial infrastructure needs; emerging financial and business models for its commercial development; the challenges synthetic biology may present to legal and regulatory arrangements (*e.g.* biosafety, biosecurity, intellectual property rights); and the related ethical dimensions.

One of the aims of the symposium was to identify issues and areas for future study and help generate policy-level discussions of synthetic biology.

The symposium agenda is included as an annex to this report. Presentation slides, audio recordings and an unedited transcript of discussions are available at:

http://sites.nationalacademies.org/pga/stl/PGA_050738.

This report, prepared by the OECD and the Royal Society, aims to summarise the discussions and key messages from the symposium. It does not necessarily represent the views of the Royal Society, the OECD, the National Academies, or a consensus among participants. Nor does it necessarily represent the views of the sponsoring organisations, the Alfred P. Sloan Foundation, the Biotechnology Industry Organisation (BIO), and the National Science Foundation. The OECD and the Royal Society are grateful to those who gave their time to review this report.

Synthetic biology: an overview

Over the last five years there has been much discussion of opportunities and challenges in synthetic biology. The symposium aimed to evoke a wide-ranging discussion of the value of synthetic biology rather than carry out a traditional risk-benefit analysis. Risk-benefit analyses are important, but examining wider opportunities and challenges helps draw attention to the evolving nature of synthetic biology, to the surrounding public and policy dialogue and to the fact that risks and benefits shift and reconfigure over time: what is an opportunity one day may become a challenge the next.

Synthetic biology arrives at a time when science's role and position in society face increased public scrutiny. Difficult questions are raised, including: Who is to imagine the future of science? How do we decide which scientific and technological interventions to undertake for society? Who is responsible for the consequences of innovation whether positive or negative? In thinking about such questions, Shelia Jasanoff (Pforzheimer Professor of Science and Technology Studies, Harvard University, United States) argued at the symposium that synthetic biology's potential power requires us to explore ways to be "more in charge of the process by which imaginative futures enter our lives".

The scope of synthetic biology

In his presentation, Drew Endy (Assistant Professor, Department of Bioengineering, Stanford University, United States) suggested that descriptions of synthetic biology tend to be limited. They typically emphasise one or more of the following elements: synthetic biology is a natural science that contributes to expanding our knowledge of biology; it is a synthetic science, analogous to synthetic chemistry, which seeks to construct novel molecules and systems for useful purposes; or it is a technology available to engineers, again to put to useful purposes. It was argued that although accurate, descriptions in these terms are partial and tend to underplay aspects of this work's wider context.

Following Jasanoff's call to expand our imagination, it was pointed out that synthetic biology raises opportunities for humanity and at the same time raises the question of what it means to be human. Synthetic biology can help address key challenges facing the planet and its population, such as food security, sustainable energy and health. This potential raises questions such as how we should (and how we will) change ourselves and our environments. Synthetic biology may be especially powerful in this respect because it frees the design of biological systems from the process of natural evolution. The ability to sequence and then synthesise DNA (and even to invent new base code) adds a new layer to the power of nature: giving humans the ability to design and redesign the biological systems of which they themselves are part.

Synthetic biology has already made some significant contributions to the need to meet global challenges. The best known is the synthesis of artemisinic acid in *E. coli* and yeast. Artemisinic acid is needed for artemisinin, the most effective known anti-malarial drug. However, this achievement also represents the high-water mark of metabolic engineering. Relying on the tools of biotechnology and genetic engineering which changed little in three decades, this effort took several years and USD 25 million. There are already reports of resistance to artemisinin and the yeast-derived alternative has not yet reached the market. More efficient and flexible biotechnology in the future will require new tools.

Synthetic biology could offer this "tool revolution". Established techniques – recombinant DNA technology, polymerase chain reactions, DNA sequencing and DNA synthesis – are supplemented by synthetic biology tools including abstraction (reducing information content to what is required to work with parts, devices, etc.) and standardisation (consistent definition and production of biological functions and

biological parts). Synthetic biology may go some way to refining and extending metabolic and genetic engineering to develop “off-the-shelf” components and reduce the need for lengthy and bespoke biotechnology projects.

Thinking and language for synthetic biology

Paul Rabinow (Director of Human Practice, Synthetic Biology Engineering Research Center, United States) proposed further technical and non-technical features that may distinguish synthetic biology from previous developments in the life sciences including: its emphasis on instrumental goods; its shift of attention away from the molecule and the gene as primary objects of interest; its attempt to make biology an engineering discipline; and its endeavour to establish new collaborative “venues” for scientific research. “Venue” here means the organising concepts and forms of knowledge used, as well as the physical space in which they might be brought together and assembled.

Rabinow argued that synthetic biology requires “refreshed venues” – a radical rethink of how we think about the significance of work done in this area, particularly the relative contributions of ethics and science. Frameworks developed for thinking about recombinant DNA in the 1970s and the genome sequencing effort of the 1990s fall short of the task, in part because the science and technology have evolved, but also because the social and political environment for this work has changed. Synthetic biology comes at a time of increased global exchange and connectivity via the Internet and a challenging security landscape. This, it was argued, obliges us to renew our investigation of the technical, ethical and social aspects of synthetic biology rather than rely on earlier conclusions.

The US Synthetic Biology Engineering Research Center (SynBERC) is examining critically the role synthetic biology plays in promoting human well-being. It does so less in terms of technical optimisation than of what counts as a good life and what the biosciences may contribute. This metric (termed “flourishing”) takes over from previous metrics applied to the life sciences, including autonomy, security and responsibility. While these are important, they are not sufficient given the far-reaching potential of synthetic biology.

Going further, other delegates felt that established categories such as biotechnology, genetics, society and the public may no longer apply, although most discussants were hesitant to abandon them. It was generally agreed that the meaning of such terms is not fixed across natural language boundaries. The international character of synthetic

biology sometimes makes it difficult to find a common language and consistent vocabulary. For instances, definitions of concepts such as risk, public good and ethics vary significantly across countries and public sectors. This is a challenge which will require attention.

As the language and terms continue to evolve, the importance of starting and sustaining discussions of synthetic biology was described in stark terms: we are at the point at which we could fashion our own version of the living world but we must take collective responsibility for this. We need a “post DNA-synthesis” discussion that takes account of the progress made in various fields of technology, but is also sensitive to the historical framework this work may now have outgrown.

Participants discussed the difficulties in enabling the public to understand and influence the development of synthetic biology; science is global, uncertain, contested and not currently part of popular culture and discourse. It was suggested that public discussion needed to begin with a realistic appraisal of the promise of synthetic biology, and that current visions take too much account of ill-founded assertions. In reply, it was pointed out that it can be difficult to secure research resources without claiming that the work will help solve important problems. Moreover, such claims can help build interest and excitement in the public space beyond the research and funding communities. The role of public engagement in discussions of synthetic biology was a recurrent theme throughout the symposium, and is further discussed below.

National and international public policy

Emerging national strategies and policies will play a role in the development of synthetic biology, but how they will affect research, grass-roots activity and international exchange is not currently clear. What is certain is that different countries will intervene in different ways in the development of synthetic biology. A richer comparative understanding of national cultures of innovation can help to recognise international differences as well as opportunities for collaboration. In this respect, three national perspectives were highlighted at the symposium.

United States

The US National Science Foundation (NSF) is a major federal supporter of basic research. The NSF has identified synthetic biology as a transformative field which has the potential to deliver great knowledge

and benefits to society, revolutionise and disrupt accepted research and theory, and destabilise markets. The NSF recognises that investigating and understanding social, ethical and public aspects of synthetic biology is essential for what Arden Bement, Jr. (Director, National Science Foundation, United States) described as “sophisticated and subtle solutions, the very best we can devise” to the challenges presented by synthetic biology. The NSF funds research into these wider aspects of synthetic biology at SynBERC in addition to SynBERC’s basic and applied research on synthetic biology. The NSF has also collaborated with the UK Engineering and Physical Sciences Research Council (EPSRC) in an intensive workshop (or “sandpit”) to develop and allocate funds to innovative projects in synthetic biology.

United Kingdom

Central funding for specific research projects is just one of a range of possible government interventions in synthetic biology. In the United Kingdom, the government sets the overall strategy for funding and research. However, once the funding has been distributed to the seven UK research councils, the government plays no further part in determining the particulars of research spending. The UK government distributes around USD 4.5 billion (GBP 3 billion) a year in this manner – added to by other funding partners such as The Wellcome Trust.

Synthetic biology is beginning to feature in the funding distributed by the research councils. Overall, around USD 27.6 million (GBP 17 million) has been allocated to synthetic biology projects and related activities. In line with much of the discussion at the symposium, Adrian Smith (Director General for Science and Research, Department of Business Innovation and Skills, United Kingdom) stated that “the science and thinking about the science must continue in parallel”. In addition to the EPSRC/NSF “sandpit”, Smith cited the EPSRC-funded Centre for Synthetic Biology and Innovation (CSynBI), which brings together the scientific research labs at Imperial College London and the BIOS Centre at the London School of Economics, which focuses on social science. Like SynBERC, CSynBI will integrate scientific and social scientific research from the outset.

In a separate initiative, four UK research councils came together to put just under GBP 1 million into seven synthetic biology networks. Spread across eight institutions, the networks aim at facilitating multi-disciplinary work and finding a “common language” between bioscience and engineering research groups. Some networks address the development of basic tools, and others explore specific technical challenges and

applications. Some institutions involved in the networks, in particular the University of Edinburgh, the University of Cambridge and Imperial College, are developing education and training opportunities at undergraduate and postgraduate level.

The UK activities benefit from, and are often part of, activities taking place at the European level. The European Union (EU) funds synthetic biology research through its Framework Programmes and specific initiatives. The latter include the New and Emerging Science and Technology programme, which provided early-stage funding for 18 synthetic biology research and policy projects, and Towards a European Strategy for Synthetic Biology (TESSY), which developed a research roadmap for Europe.

For Adrian Smith, it remained an open question whether the UK government should or needs to develop a centralised innovation strategy for synthetic biology, over and above the types of activities noted here. Investment in synthetic biology needs to be considered against competing investment opportunities. Moreover, the balance of responsibility between the government and other actors in the development of security policy, ethical frameworks and public dialogue needs to be found. Interaction with business and industry will be crucial, especially as they are often the source of tools and applications. The UK government regularly engages with business leaders on a range of science and technology issues, and has done so increasingly over the last few years.

The regulatory implications of the field are currently closer to the government's immediate concerns. It was noted that the official UK view is that most synthetic biology research will be covered by current regulations on genetically modified organisms (GMOs) and that there is no need, at present, for new regulations relating specifically to synthetic biology. However, in the discussion, it was noted that it is commonly assumed that current regulations are suitable for new technologies because it is not possible to define new fields neatly and draw boundaries around what is included or excluded. It was argued that this pattern holds for synthetic biology. In contrast, it was argued that in the early days of genetic engineering, regulators and others were quite clear on the nature of the science and its boundaries. This facilitated the establishment of regulations. It was suggested that since the situation of synthetic biology is not clear, self-regulation is likely to prevail.

China

In China, synthetic biology has only recently gained ground. Haunming Yang (Director, Beijing Genomics Institute, China) described China as a latecomer to the field, as it was for genomics. From a search of public databases of all Chinese funding agencies, the first synthetic biology project to involve Chinese researchers was funded by the European Commission in 2006. The project – PROBACTYS: Programmable Bacterial Catalysts – involved scientists from the Beijing Genomics Institute in partnership with researchers from across the EU. Three further synthetic biology projects with centralised funding are currently under way. Most research is undertaken at government laboratories in Shanghai, Tianjin, Chengdu and Taipei and focuses on metabolic pathway analysis.

Although early Chinese research in genomics and synthetic biology benefited from international collaboration stimulated by partners outside China, China is increasingly in a position to lead partnerships. For example, the Beijing Genomics Institute is the world's third biggest sequencing centre and is an integral part of international sequencing efforts. If synthetic biology is conceived as a natural extension of genomics – from the reading to the writing of genome sequences – then China is well placed to take an active part.

Prospects for international collaboration

Delegates discussed the challenges of international collaboration on several levels, from individual scientists and research groups to countries and wider geographic areas. It was noted that the United Kingdom, along with other countries in Europe and the United States, is positioning science and technology at the centre of the national strategy for recovery from the current economic downturn. But narrow national strategies might risk deterring international collaboration. Discussants pointed out that the link between science and innovation and economic growth is well founded, but it was suggested that emphasising science's economic potential may lead to investments in areas that promise short-term economic gain. Realising the benefits of synthetic biology is likely to require sustained long-term investment. It was further suggested that international collaboration thrives on bottom-up, researcher-led activity that is not determined by centralised policies.

International communication and collaboration by scientists, including those from emerging economies, will be a key part of the successful development of synthetic biology, but there are system factors that

work against this. For example, collaboration might be affected by intellectual property protection and security threats. International cultural and regulatory differences may also present challenges. It was further mentioned that China may lack an international forum for stating its views. However, there are notable examples of successful collaboration; collaboration played an important role in completing the human genome project and, although it is painfully slow and difficult, international co-operation to mitigate climate change has made progress. Yang proposed the founding of an international synthetic biology consortium, which could promote communication and exchange, co-ordinate efforts and resources, explore data sharing and consider international responses to biosafety and biosecurity challenges.

Innovation in synthetic biology

Enabling innovation: tools and techniques

Synthetic biology was presented as a set of tools and techniques that bring together engineering and biology and support the development of new entities, functions or applications. Caroline Ajo-Franklin (Staff Scientist, Biological Nanostructures Facility, University of California, Berkeley, United States) described new functions including the ability to create new ecosystems by enabling intercellular communication, as well as novel regulatory networks that monitor the development of gene products. The development of these tools and techniques underpins synthetic biology's potential to tackle challenges such as greener energy production (*e.g.* development of alternative energy sources such as bio-fuels), the environment and better health.

A gap between tools and applications

Synthetic biology promises to advance smart therapeutics. However, Christina Smolke (Assistant Professor, Department of Bioengineering, Stanford University, United States) described hurdles that still impede the use of synthetic biology for innovation in health or other domains. Mainly, there is a gap between the development of technology and tools and their applications. Bridging this gap is an important step in ensuring the growth of the field, but it represents a significant challenge which is not well appreciated. It was argued that the difficulty of translating tools into applications is due to the following:

- First, the development of a tool, its refinement and optimisation (*e.g.* going from the conceptual design of a function to a genetic sequence that fully implements the function) represents a significant technical challenge and a significant investment of time and money.
- Second, the invention and implementation of engineering design principles in biology is critical for effective tool development and thus for moving more applications forward. However, the culture of biological research traditionally rewards novelty to a much greater extent than the contributions of engineering. To ensure that synthetic biology can make its full contribution, it is critical to recognise the part that engineering plays.
- Third, from a technology development standpoint, it is important to develop computer-aided design tools that support the design and programming of devices and their implementation in systems. Such tools are currently insufficiently developed and accessible.
- Fourth, to address scalability, public libraries of refined parts would have to be set up. These libraries could also include many different classes of molecules such as: metabolites for research on biosynthesis; disease biomarkers for biomedical research; and exogenous chemicals for research on agricultural biotechnology.
- Finally, applications generally focus narrowly on the end product rather than on developing a technology base to support many different products. Companies often base their strategy on the end product they plan to distribute. Investing in or integrating new tools and technologies is often not a priority when this does not lead directly to a specific product.

These arguments highlight the importance of investing in the development of tools to generate more applications. A key point is the need to think through strategies and mindsets that support the implementation of underpinning technologies and tools. Funding is also important to support the development of tools and technologies in synthetic biology at scales and time frames that are appropriate for the challenges that synthetic biology seeks to address.

Issues linked to intellectual property (IP) models and regulatory frameworks were also raised. The current IP model for biotechnology is quite heavy; an approach that may be inappropriate for synthetic biology as it is developing today. Current regulatory frameworks may be similarly inappropriate. Given the ease with which DNA sequences are produced today, Cord Staehler (Chief Executive Officer and President, Febit Biomed GmbH, Germany) called for companies such as genetic tool providers to be involved in developing risk management guidance. Groups such as the International Association for Synthetic Biology in Europe and the Synthetic Biology Industry Agency in the United States have taken a step towards bringing companies together and developing instruments such as a code of conduct for facilitating risk management in tools development.

Eco-innovation

Industrial and environmental biotechnology was described as the third wave of biotechnology innovation (following health care and agriculture). James Greenwood (President and CEO, Biotechnology Industry Organisation, United States) pointed out that the increasing attention to innovation in industrial biotechnology is partly due to major challenges that this century is starting to face: How do we reduce our dependence on petroleum? How do we decrease pollution? How can we improve manufacturing processes so we generate less hazardous waste and use less energy? How can these processes serve the developing world as well as they do the developed world? These and many other questions were raised, and it was proposed that synthetic biology was able to help find the answers.

Synthetic biology, biotechnology and the chemical industry

Sven Panke (Associate Professor of Bioprocess Engineering, Department for Biosystems Science and Engineering, ETHZ-Basel, Switzerland) argued that biotechnology is increasingly used in the chemical industry for the following reasons:

- First, it improves the chemical industry's sustainability and offers recyclability, stability and biodegradability of bio-based products as well as increased safety and sustainability of the production process itself. A good example of the latter is production of vitamin B12, in which bioprocesses have made it possible to reduce some 12 steps of reactions to one-step fermentation. Another example is the use of biotechnology in the production of amoxicillin to reduce the production of 50 kilo-

grams of waste per kilogram of product in the 1970s to two to five kilograms today.

- A second driver is the ease and efficiency of using biotechnology processes instead of chemistry to obtain certain end products. For example, a product marketed under the name Sorona® and developed by Dupont is a polymer composed of propanediol, a monomer that is easily made biotechnologically but is difficult to synthesise chemically. The life cycle analysis for this particular product shows that 35% less energy is required to produce a kilogram of propanediol using biotechnology, but both biological and chemical methods have similar energy balances. The main interest in using biotechnology therefore is that propanediol is simply much more easily produced by biotechnology.

What can synthetic biology bring to the chemical industry? Today, biotechnology in the chemical industry is mainly about metabolic engineering. However, “traditional” metabolic engineering is raising important challenges because of the complexity of metabolic pathways. The production of a pharmaceutical composed of five precursors illustrates this complexity. The easiest way to produce such a molecule is to identify the enzymes that help convert glucose to these five precursors in a certain number of steps and to put them together in a reactor and obtain the end product. However, it is difficult to control reaction pathways and there is, for example, the possibility of an accumulation of particular intermediates which creates an imbalance that may be toxic for the cell, making the system collapse. Because of the complexity of biological systems, chemical processes are sometimes considered more reliable than biotechnology. This accounts for some of the delays in delivering the promise of biotechnology in this industry.

The complexity of biological systems frustrates their engineering. As Endy put it: “Engineers hate complexity. I hate emergent properties. I like simplicity. I don’t want the plane I take tomorrow to have some emergent properties while it is flying.” It was argued that synthetic biology could reduce complex networks to smaller, more manageable ones and rationalise the design of reaction pathways. Pathways can be fitted to a “chassis strain” of micro-organism (host cell) that runs particular pathways orthogonally and avoids extensive interactions with the remaining metabolism. The production of the drug Artemisin by Amyris is the first such example of the successful combination of synthetic biology techniques with traditional chemical processes. Artemisin is now produced faster and more cheaply.

It was argued that for biotechnology to reach its full potential in the chemical industry, synthetic biology is essential. It would allow more predictable and faster chemical development. It would also allow the development of more complex production pathways and novel products. However, certain issues stand in the way of broader use of synthetic biology in the chemical sector. For example, the development of chassis strains is still in its infancy and there is a lack of registries of high-quality parts. Access to materials is not always straightforward, in part because of compartmentalised intellectual property structures.

Kinkead Reiling (Co-founder and Senior VP, Corporate Development, Amyris, United States) also pointed out that the scalability of synthetic biology tools has yet to be tested. Currently, synthetic biology works at very small scales, but industry needs to produce large amounts of products, especially for biofuels. How can synthetic biology processes be scaled up? How can low-cost, profitable end products be achieved from an innovative front-end microbe? These and many other questions will need to be answered to ensure the uptake of synthetic biology tools and techniques by industry.

Synthetic biology for bioremediation

The 1970s and 1980s saw the emergence of genetic engineering for environmental purposes. Bacteria with superior catalytic activities were produced and a bacterium able to digest petroleum or petroleum components was developed.

Genetic engineering, and to an even greater extent synthetic biology, can now be used in many different ways to tackle environmental challenges:

- for mobilisation, such as modification of bacteria to increase their ability to absorb metal;
- for detection through biosensors;
- for transformation, such as setting up catalytic reactions to convert industry waste to CO₂ or water;
- for bioremediation or biodegradation.

This last point raises difficult issues. Genetic engineering for bioremediation purposes generated great enthusiasm in the mid-1980s. However, Victor de Lorenzo (Research Professor, Spanish National Research Council, National Centre of Biotechnology, Spain) noted that many issues arise when putting modified bacteria in a contaminated

environment. For example, the bacteria developed in laboratories were not robust enough to survive in the environment, and their capacity for bioremediation developed in a laboratory did not transfer readily to the natural environment.

As in the chemical industry, the complexity of biological systems has hampered their use in bioremediation; engineering bacteria that are predictable when released in the environment has proved difficult. Here again synthetic biology was shown to be able to help tackle the problem conceptually by emphasising the importance of engineering principles (such as standardisation of parts or plasmids) blended with principles of biology.

Synthetic biology and the food industry

At present, the use of synthetic biology in the food industry is limited to incremental modifications in current processes or applications. Vitor Martins Dos Santos (Systems and Synthetic Biology Group, Helmholtz Centre for Infection Research, Germany) showed that key contributions are likely to be made in the areas of health and nutrition. Five areas of the food industry particularly likely to profit from synthetic biology tools and techniques were described:

- metabolites, health products (*e.g.* vitamins) and processing aids in the manufacture of food and food derivatives, such as nutraceuticals, probiotics and glycol nutrients used to raise the value of certain foods or nutrient-enriched plants;
- preservatives, an area already largely based on genetic engineering;
- flavours and fragrances;
- biosensors, for example to replace the human “nose” in the food industry with an artificial nose;
- food waste processing.

A great deal of money is invested in these fields, and synthetic biology is seen as able to facilitate, enhance and reduce the cost of production processes. An example given was the food preservative Nisin. This molecule is traditionally obtained by natural fermentation of *Lactobacillus plantarum*. Fermentation can be relatively inefficient, especially for these kinds of compounds from the lantibiotics family. A synthetic biology approach can facilitate the design of compounds that may be produced more efficiently than by the usual fermentation. The design of compounds beyond those found in nature will also be

possible. This will enable the food industry to enlarge its portfolio of products.

Biosensors are another example of efficiency gains that may be achieved through synthetic biology. For example, it is expensive to employ a human nose to test aromas; the industry would therefore profit from automation of this activity. Researchers are working on the development of an artificial nose composed of thousands of micro-sensors, each based on particular bacteria or enzyme systems to allow the detection of a specific compound.

Challenges for developing these advances in the food industry are similar to those described for the chemical industry and bioremediation. Technology platform development was seen as a crucial issue for structuring the field. Intellectual property is also an issue: in complex systems there are worries about the protection of all of the parts needed to construct a system.

Health and medicine

Richard Kitney (Chairman of the Institute of Systems and Synthetic Biology, Professor of Biomedical Systems Engineering, Department of Bioengineering, Imperial College, United Kingdom) mentioned that synthetic biology is expected to bring important advances in the field of biomedical research with the development of biosensors, vaccines and the optimisation of drug development processes. For example, synthetic biology is expected to help reproduce and improve natural therapies. Synthetic biology should make it possible to scale up and improve pharmaceutical production processes, as in the case of Artemisin. Synthetic biology may also have a part to play in developing novel, more efficient biosensors, that could be useful, for example, in tackling poorly understood, complex diseases by allowing the collection of dynamic quantitative data in minimally invasive ways. Further, it may influence the development of personalised medicine, which aims to identify groups with a better chance of responding to particular therapies by using markers and other techniques to segment patient groups with confidence.

Synthetic biology in immunology

Several applications of synthetic biology for detecting viruses, triggering antiviral activities or developing vaccines were presented.

Frank Notka (Manager, Research and Development, Geneart, Germany) showed the opportunities that gene synthesis can offer synthetic biology. According to Notka, gene optimisation (codon choice, sequence modification) and gene synthesis can contribute significantly to the development of synthetic biology. The example given was development of a vaccine. In this case, the objective was to develop an HIV vaccine based on HIV genes, a highly difficult task. HIV genes are not expressed to a high level in human cells. In order to increase gene expression, the codons used by the HIV were exchanged with codons used in human genes.

The following steps were taken to define which virus strains to use, which targets to include in the vaccine, and which delivery systems to use. The main strain used was the C virus whose genetic sequence was almost integrally kept in order to include as many relevant epitopes as possible in the antigen. For safety reasons, parts of the proteins were split, the active sites were removed and additional modifications were introduced to enhance the efficiency of the production and secretion of the antigen. An algorithm was developed to optimise a given gene expression for a specific host. Negative elements such as repeated sequences, RNA secondary structure and splice sites were removed. Naked DNA and viral vectors were chosen as delivery systems: the New York *Vaccinia Ankara* viral system. The final step was the clinical trial: one-half of the volunteers received the vaccinia virus only, the other half the synthetic DNA expressions construct. Patient response to the synthetic construct was good; responders had a greater capacity to induce memory immune cells.

Roman Jerala (Head, Department of Biotechnology, National Institute of Chemistry, Slovenia) presented two other possible applications of synthetic biology in the immunology domain. The first is a device able to recognise a viral infection, in this case HIV infection, and trigger antiviral activity once the infection is detected. The device is designed to detect a specific viral function (attachment of the virus to cells or HIV-specific protease activity) rather than to detect specific viral proteins, which frequently mutate in the case of HIV and could compromise the functioning of the device. Once the infection is detected, the device triggers mechanisms that prevent, for example, further spread of infection or prime neighbouring cells against the virus.

The second application concerns the design of vaccines able to uncover the stealth of bacteria by making bacterial components visible to the immune system. The example given was *Helicobacter pylori*. The flagellin (a specific protein contained in the flagella of bacteria) of *H. pylori* is not recognised by the immune system but the flagellin of *E. coli* is. A vaccine was designed based on a chimeric flagellin composed of a segment from *E. coli* and a segment from *H. pylori*. This chimeric protein is able to activate the immune system and make it produce antigens that will recognise a future infection by *H. pylori*. Jerala underlined that the combination of immunology knowledge with synthetic biology tools show great promise for developing novel therapeutics, vaccines or detection tests.

Developing smart therapeutics

Christina Smolke described the use of synthetic biology tools in the field of cellular therapeutics. The example given showed how synthetic biology can help engineer the immune system to treat different diseases. Normally, T cells (one type of immune system cell) work by binding through receptors to a pathologic cell. Once bound, T cells release cytolytic proteins to kill the disease cell and release different types of proteins that will send a signal to amplify the immune response as other disease cells are detected. In the case presented, the goal was to engineer receptors that would allow T cells to recognise disease cells that they would not normally recognise, such as cancerous cells and to build a synthetic system control that can induce the amplification mechanism that does not exist in *ex vivo* engineered cells.

The system is based on a biosensing device built through RNA construction (input/output tools). The device is able to recognise a drug once it is administered to a patient. Once the drug is recognised, the device establishes the circuit that tells T cells to bind to target cells (*e.g.* cancerous cells), activate and proliferate. This circuit system principle can be used for many different purposes; for example, it could recognise a biomarker of a certain disease and release a specific drug once it recognises the marker.

Developing the field: the needs of academia and industry

To move forward, synthetic biology requires the development of a better environment, including research infrastructures, education and intellectual property.

Research infrastructures

The symposium emphasised that for synthetic biology to become an innovation-enabling technology, strategies and mindsets that support the implementation of underpinning technologies, adequate research infrastructures, and technology platforms had to exist. Francois Képès (Research Director, French National Centre for Scientific Research, and Founding Director, The Epigenomics Project, Genopole, France) suggested steps to follow to develop these supportive infrastructures:

- **Fund blue-sky projects and ensure efficient co-operation between academia and industry.** Synthetic biology was presented as lying between exploration and exploitation. Currently, exploration needs to be strengthened and the funding of underpinning studies and blue-sky projects is especially important. As research in synthetic biology has both basic and applied aspects, small and medium-sized companies will be increasingly involved in this baseline research. Synthetic biology is seen as an area in which collaboration between academia and industry will be particularly enriched by true scientific co-operation. This co-operation could suggest that academia should have the capacity to retain and capture intellectual property in the spirit of not “doing industry’s job”, but rather maintaining balanced relations between academia and industry.
- **Establish technology transfer units.** There remains some uncertainty over the best way to establish technology transfer units and where to locate them. In discussions, it was suggested that these units should be located within academic laboratories.
- **Develop full-stream translational research.** There is a need to encourage multidisciplinary training of students, for example by having PhD supervisors from biology, mathematics and physics, and by facilitating student mobility across borders.
- **Develop technology platforms.** Developing capabilities such as DNA synthesisers and DNA robotic assembly that are available to both industry and academia was viewed as an important step in ensuring efficient synthetic biology research. These capabilities can be augmented by biological resource centres (*e.g.* DNA banks, cell banks, biological models). However, it was pointed out that work is still required to adapt existing repositories to the needs of synthetic biology research (*e.g.* good practice, standards). These platforms can also act as a good meeting point for academia and industry. Képès remarked that developing

such technology platforms requires initial financial support. Such platforms could become self-sustaining by charging customers for services. It was suggested that these platforms should be located near or within centres of excellence.

- **Develop standards for biological parts.** Standardisation is important for measurement with “omics” techniques. For DNA parts, it was noted that better standards, characterisation and annotation would be welcome. An iGEM standard already exists and others are possible, but it may be too early to set up a universal standard.

Developing the field: case study

Synthetic biology in the health industry

Adriano Henney (Director, Obsidian Biomedical Consulting, United Kingdom) pointed out that major pharmaceutical companies are not yet involved in synthetic biology to any great extent although they already consider its sister field “systems biology” as crucial to tackling complex diseases. Synthetic and systems biology are particularly tightly linked in the context of human biology and medicine.

Synthetic biologists are confident that their work is of interest and importance to industry. However, Henney suggested that industry needs more proof of utility before making significant use of synthetic biology in health innovation. Proposals to shape a more persuasive position for synthetic and systems biology were put forward. For example, it was noted that from December 2000 to February 2008 the top 15 companies in the industry lost approximately USD 850 billion in stakeholder value and that that current processes and approaches to generating pharmaceuticals would not be sustainable in future. The pharmaceutical industry needs to find new ways to innovate, and systems and synthetic biology have a part to play.

Why is the pharmaceutical industry facing this crisis? Post-genome biology is focused on entities: isolated proteins and engineered cell lines which are outside of any physiological context. It then tries to translate the data obtained to humans by using associative models which may or may not have a relation to human physiology. To complicate the issue, patients may be taking other drugs that can affect the action of the target entity, but such models do not take this into account. Henney suggested that to understand why a biological network shifts into pathology requires understanding a dynamic and complex series of network interactions, but these cannot be understood by studying entities separately. A systems biology approach is needed to rationalise and model a specific biological system in order to extract strong hypotheses that will lead to progress in treating patients.

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Developing the field: case study (*continued*)

A possible solution to current problems in health innovation in the pharmaceutical industry could be to combine synthetic biology's innovative tools with a holistic understanding of human physiology and novel therapies. These key developments in synthetic and systems biology will largely be driven by academia, but Henney emphasised that it is important for academia and industry to start working closely together. Academia would have to be ready to demonstrate the applicability of its knowledge in an industrial and commercially relevant context, as industry increasingly faces economic and regulatory hurdles which reduce its willingness to invest in blue-sky research. To bring the benefits of synthetic and systems biology to industry, it is crucial to draw the different communities and stakeholders together to drive change. Better co-ordination is needed to create a significant impact and mechanisms need to be found to get industry on board.

Education in synthetic biology: the iGEM

“Can simple biological systems be built from standard interchangeable parts and be operable in living cells?” This question, raised by Randy Rettberg (Director of the Registry of Standard Biological Parts, Director of the International Genetically Engineered Machine [iGEM] Competition, Principal Research Engineer in Biological Engineering, Massachusetts Institute of Technology, United States) in a biological system design class for undergraduate students at Massachusetts Institute of Technology (MIT), led to an innovative way to train students and interest them in biology and engineering.

The International Genetically Engineered Machine (iGEM) competition draws on this new course at MIT. It is an international design competition primarily for undergraduate students, although some high school teams are involved. The goal is to realise a synthetic biology design project using specific standard biological parts called biobricks. A kit of about 2 000 parts is given to each team at the beginning of the contest. The philosophy for iGEM is “get and give”. Parts developed by a team are made available to other teams. The iGEM registry now has about 3 500 parts. There is a standard method for assembly. Almost all the parts are compatible and can be attached to one another.

The iGEM programme includes a large number of students, instructors and schools (1 180 participants in 2008). The number of teams registered for the competition rose from 84 in 2008 to 211 in 2009. Final projects are presented during an annual jamboree. The projects

include ideas and inventions at the leading edge of synthetic biology (many iGEM projects have been published in academic journals) and some projects are very ambitious. An example is the introduction of a haemoglobin system in bacteria, a development called “bactoblood”. It was pointed out that centres for synthetic biology have been established at sites where iGEM teams were set up.

The iGEM competition is very aware of the societal aspects of synthetic biology. For the iGEM community “science can only work successfully and develop useful inventions if it is based on a high level of acceptance in the society”. iGEM competitors are deeply involved, as part of their projects, in interacting with the public, doing surveys and interacting with the press. The issue of safety is also central. Each iGEM team now has to write a report on how the safety of their project relates to the world around them.

Education can play a central role in ensuring advances in synthetic biology, and the very innovative iGEM competition illustrates how it can help the field develop. In terms of maintaining and enriching education for emerging fields, Pam Silver (Professor, Department of Systems Biology, Harvard University, United States) raised the following questions: How can we ensure that students at all levels of the engineering and science system become skilled? How can the training environment maintain the level of excitement with which students come into the field? How can students become more involved in moving from innovation to commercialisation?

Intellectual property challenges

iGEM’s open system makes parts freely accessible and exchangeable. What would happen to this contest if parts became patentable, or were patented? The answer is not clear, and indeed many questions regarding intellectual property in synthetic biology remains unanswered. Richard Johnson (Senior Counsel and Senior Partner (Ret.), Arnold & Porter LLP, and CEO of Global Helix LLC, United States) recalled that the patent landscape is complex, especially in synthetic biology because it deals with a cumulative and convergent set of technologies. There is a real risk that patent thickets will hinder the ability to do research and commercialise applications.

Much has been done to attempt to clarify how patenting should be organised in the field of synthetic biology. Many in the field advocate openness and minimal patenting, but others indicate that, in some cases, a strong intellectual property regime that can be controlled is the best way to protect openness. The major issues raised by Johnson were:

- **Patents.** The world of patents is complex, especially for a discipline like synthetic biology which relies on the convergence of multiple disciplines. Moreover, there is a range of unresolved patent issues that will have a major impact in shaping the future of synthetic biology (*e.g.* patentability, how prior art is applied, non-obviousness).
- **Material transfer agreements.** There are major concerns over ownership and access to material and information created through synthetic biology. There are unresolved questions, as has been recognised, about university technology transfer offices and how they operate.
- **Interaction and bundles of rights.** There are potentially some very interesting issues around design rights, especially in Europe. In the United Kingdom, 10 to 15 years ago, there was a series of cases concerning interoperability of parts, and there was a “must fit, must match” exemption to intellectual property rules for designs. Does this apply for synthetic biology?
- **Database operation.** Information and materials (*e.g.* parts) emerging from synthetic biology research are already being placed in registries or other types of database. There is concern about the operation of these databases. OECD publications on human genetic research databases, as well as the guidelines on biological resource centres, already address some of these issues.
- **Copyright.** Copyright protects originality and expression. In synthetic biology, an increasing decoupling of design from manufacturers and processes might increase the likelihood of copyright issues.
- **Trademark.** Biobricks have value. Logos and trademarks are important quality control tools.

An important point, often raised when talking about synthetic biology and intellectual property, is the question of openness. Competitive visions of openness were described:

- “Open source” is a term which is often misinterpreted. It relies on a very robust intellectual property system. To be effective, “copyleft” and other types of licences require a very efficient and effective intellectual property system.

- Open innovation is an important notion for industry and universities. Johnson mentioned that “you don’t have to do it all or to be vertically integrated”. One can, for example, take strategic opportunities that are not a core part of the business outside of the company.

In the synthetic biology community, the term “semi-commons” is increasingly used to emphasise that biological parts are interacting commons and at the same time for private use. These resources are dynamic, scalable and can adjust to different mechanisms.

Johnson pointed out a number of other IP issues in synthetic biology. A clash of cultures is likely to become an issue. A pharmaceutical company, a chemical industry, a university or a semiconductor company all see intellectual property rights differently, and it is difficult to align their interests. The synthetic biology community is also built around trust because the output volume is relatively small. As the community grows, there will be a transition from trust to contract, and the role of intellectual property will be particularly important.

Innovation in synthetic biology is going to be user-driven. Johnson emphasised that it is important to think of policies as user-focused rather than, as is commonly the case, producer-oriented. Open development is another important issue. It needs to be community-driven and align its needs with priorities in shared resources and open access.

As synthetic biology is an emerging field, comparison with other fields is useful when thinking about intellectual property. So far, analyses and analogies have typically focused on biotechnology and information technology. The analysis of semiconductors – and to some extent nanotechnology, where patent thickets have developed in the way they might also develop for synthetic biology devices – could be a viable means of anticipating intellectual property needs in synthetic biology. The work of the OECD and the National Academies on different types of collaborative mechanisms also offers good sources of references.

Investment model for synthetic biology

Government funding agencies, philanthropic foundations and private investors gave an overview of investments in synthetic biology and the challenges that could affect investment in the field.

Factors influencing investment

Investment in synthetic biology relies on different factors, and Mark Waxman (Partner and Chair of the Health Care Industry Team, Foley and Co., United States) noted the following: the perception of synthetic biology by the public; the regulatory regime that will be developed for synthetic biology; the need or not for product liability insurance; industry involvement; and patent thickets and intellectual property models.

The industry and the venture community are looking for wealth creation and sustainability. According to Greg Kisor (Vice President, Investor Relations, Intellectual Ventures, United States), the public good alone is not sufficient to attract venture funds, so innovation might have to rely on philanthropy and government funding. IP rights underpin the ability to create wealth, which is critical for attracting venture investments. Companies that work with venture investment models in intellectual property are currently little involved in synthetic biology. Kisor specified that synthetic biology is a small part of an investment in two of his company's funds. It was proposed that to help fund the next generation of research, governments might look at grants and consider whether they lead to intellectual property. If so, governments should take the IP rights and make them more generally available.

A further influence on the development of synthetic biology is the balance of investment between tools and applications. It is difficult to know whether more funding is currently allocated to build the next generation of applications or to enhance tool development directly. As a first impression, discussants felt that funding seems to be more oriented towards applications.

Philanthropic funding

Several grants from philanthropic organisations are directed towards synthetic biology. Paula Olsiewski (Program Director, Alfred P. Sloan Foundation, United States) stressed the significant involvement of the Alfred P. Sloan Foundation in synthetic biology, especially in governance issues. In order to improve understanding of ethical, social and policy issues by scientists and engineers and to improve understanding of science and engineering by policy makers, journalists and the public, the Sloan Foundation has invested at least USD 2 million in addressing societal issues raised by synthetic biology.

In 2005, the Sloan Foundation funded a grant which was a joint venture between the J. Craig Venter Institute and MIT and CSIS (Center of Strategic and International Studies). A report entitled “Synthetic Genomics: Options for Governance” resulted from this partnership. The Foundation also actively participates in Synthetic Biology #.0 meetings throughout the world, particularly in sessions on societal issues. Recent engagements of the Foundation include the present symposium, projects with the Hastings Center, the Woodrow Wilson International Center for Scholars, and the Venter Institute.

The European Commission funding plan

The European Commission is investing in synthetic biology as part of a wider structure of investment. Two sets of projects were launched and some continue through publications or public relations, such as Synbiosafe or TESSY. Ioannis Economidis (Principal Scientific Officer, European Commission) pointed out that the idea is to cover not only basic research linked to synthetic biology but also more applied topics such as medicine, new generations of pharmaceuticals, new chemicals, environment and energy.

The current funding programme of the European Commission is the Seventh Framework Programme. It covers funding for seven years at a level of EUR 53 billion. This funding programme has several dimensions. One is linked to basic research and includes some projects on synthetic biology. Another deals with human resources, including student training. The major funding comes from the Cross Co-operation Programmes which encourage young scholars to exchange their experiences. Synthetic biology might also be funded under health, environment and nanomaterials development.

It was noted that in the context of the Knowledge-based Bioeconomy Programme of the European Commission, synthetic biology is considered an advanced tool, and a merging of biotechnology knowledge essential to promote bioeconomy. An investment of EUR 1 million has been dedicated to using synthetic biology to find solutions to environmental issues and aspects of bioremediation. This programme brings scholars together to create critical mass for work on these particular issues. A further investment of EUR 3 million is under discussion to broaden the issue and to try to understand how synthetic biology could advance biotechnology more broadly. Other investments from the European Commission aim to establish a network and help people to work together (*e.g.* the European Network of Semantic Work).

Company funding: the example of the genetic tool provider Febit

Febit is a company that provides genomic tools. Its goal is to help understand the issues raised by biological functions and processes. It does so by providing platform technologies, for example for resolving gene sequencing and expression profiling challenges.

Febit is financed by two types of investors. The first is Diet Hopp, founder of the software giant SAP. Cord Staehler noted that a number of well-known names in the software industry are now also investing in synthetic biology. The second investor and strategic partner is In-Q-Tel, especially the Central Intelligence Agency (CIA). The interest of this second is to ensure that Febit has access to the most advanced technologies and to have ready access to risk management for the risks that could result from the company's activity.

Outstanding issues: developing a roadmap for investment

The discussion made clear the need for a comprehensive study of investments in synthetic biology. Answers to a range of questions would help clarify how the field is organised. These include: Is funding directed more towards applications than towards tools? Who is investing in tools and who is investing in applications? Do countries differ in this respect? Is there a fundamental difference between the two types of investment, given that synthetic biology is still an emerging science and the link between applications and tools is still very tight?

Developing a roadmap for funding agencies and government to help them plan how and when to invest in synthetic biology was suggested as a useful outcome of the meeting and a next step. More than simply focusing on synthetic biology, the roadmap could help ensure that investments work to improve processes in engineering biology more broadly.

It was mentioned that the synthetic biology community would have to have all the tools and resources it needs to make this field move forward. The consensus seemed to be that this is currently not the case.

Governance issues related to synthetic biology

Biosafety

Robust regulations for the safe use of biotechnology and recombinant DNA technology are in place, and it was contended that no known incidents have occurred. However, synthetic biology is frequently conceived as an extension of these established technologies, and perhaps a step change, so it is frequently asked if current biosafety procedures and regulations are sufficient. In response, regulators and synthetic biologists typically argue that current regulatory regimes are adequate for the work they do. In contrast, it is more commonly acknowledged that adaptation may be required with regard to biosecurity. However, it was argued that biosafety and biosecurity should not be treated as separate issues. They face many of the same problems, including the same root issue: how to assess and respond to risk. The following difficulties concerning safety and security for synthetic biology were identified:

- **It is more difficult to identify agents of concern.** Taxonomy can act as a guide to pathogenicity, but it is less useful for synthetic biology. Novel organisms would present a particular challenge because of the lack of prior experience. Identifying sequences with pathogenic properties is also difficult, and conventional tools may no longer be appropriate.
- **Science and politics have changed since the initial rDNA regulations.** Things have moved on since Asilomar. Science and technology are increasingly available and easy to access, and the proliferation and distribution of knowledge makes oversight increasingly difficult. In the lab, the intermingling of disciplines helps synthetic biology progress, but awareness and training in biosafety issues differ across disciplines. Outside the lab, heightened security threats increase attention to biotechnologies as possible sources of harmful agents.
- **The context for biosafety may have changed.** Notions of “harm” – what should be prevented and how to do it – are fluid. For example, debate continues over the meaning of the “natural environment” that is under threat from biotechnological interventions.

- **The purpose of regulation may not be clear and needs to be examined.** For example, regulation may serve a technical need or may aim to allay public anxiety.

These challenges suggest that synthetic biology offers an opportunity to revisit established concepts in biosafety and biosecurity.

Learning from work on viruses

Prior experience with potentially hazardous materials such as RNA viruses can provide useful lessons for synthetic biology and assist in safety and security efforts. RNA viruses use RNA, rather than DNA, as their genetic material but reverse transcribe their RNA genome into DNA which is inserted into the host genome in order to be transcribed into RNA. RNA viruses include those responsible for influenza, mumps, measles, ebola and HIV. The first infectious cDNA clone of an RNA virus (polio) was reported in 1981 and work on infectious viruses has led to better understanding of their life cycle and pathogenesis and progress in anti-viral drug and vaccine development.

Work on RNA viruses is not without risk, including the accidental spread of artificial viruses to nature and the acquisition of virulent strains for bioterrorism. The likelihood of the latter varies somewhat according to the complexity of the target pathogen. In 2002 the first chemical synthesis of polio virus, using only sequence information, was achieved. The synthesis of polio is comparatively easy. If a virus can be synthesised using sequence information alone, there is an increased risk of construction for nefarious intent. The estimated cost of infectious virus production is just USD 7 500 using the types of labs typically present in universities.

Perhaps more than the threat of bioterrorism, the relative ease of production of viruses raises the chances of accident. There are documented cases of virus leaks from laboratories, including smallpox in the United Kingdom (1978), SARS in Singapore (2003) and China (2004), and several cases of accidental polio release, including the identification in 2003 of a laboratory strain circulating in the general population. This makes abundantly clear the importance of regulations and guidelines, their enforcement, and the vigilant containment of pathogens.

Reviewing the US National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules

Proposed updates to the NIH Guidelines for Research Involving Recombinant DNA Molecules to account for recent advances, including synthetic biology, are currently under consideration in the United States. The review was prompted in part by a report from the National Science Advisory Board for Biosecurity (NSABB) which suggested that the current guidelines are deficient in certain respects. In particular, the report *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* noted biosafety concerns arising from the diverse institutional settings and disciplinary backgrounds of practitioners of synthetic biology. Some of those undertaking research in synthetic biology are educated in disciplines that do not routinely conduct formal training in biosafety, and NSABB found some are unclear as to the circumstances under which they should consult their Institutional Biosafety Committees (IBC). Furthermore, some research is now undertaken in institutions such as high schools which do not have access to an IBC. Taken together with technical advances that fall outside the scope of the guidelines (such as synthesised RNA viruses and synthetic DNA that is synthesised *de novo*) a trans-federal policy co-ordination process took the decision to modify the NIH guidelines.

The NIH Recombinant DNA Advisory Committee (RAC), which advises the Director of the NIH on rDNA research, was charged with considering the application of the NIH guidelines to synthetic biology. The RAC looked at the degree to which this technology is covered, and whether the scope of the guidelines needs to be modified to capture synthetic biology research. The RAC made a series of proposed modifications including: a revised definition of rDNA molecules; an exemption for synthetic nucleic acids that cannot replicate, provided they are not used in human gene transfer; and an update of the “spirit clause”. This clause recognises that mitigating risk depends in large measure on the motivation and good judgement of individuals and that all conceivable experiments involving recombinant and synthetic DNA cannot be foreseen. It is therefore proposed to emphasise that new genetic manipulation techniques may enable work to be accomplished faster, more efficiently or at larger scale, and to reiterate that as the field develops, the guidelines may need to be updated.

It was noted that the NIH guidelines are not legally binding although adherence to them is a condition of obtaining a grant for research funded by the NIH, and other funding bodies have adopted the guidelines as best practice. Because the guidelines apply at the institutional

level, it is the responsibility of IBCs to ensure compliance. To facilitate their work, the NIH promotes observance of its guidelines and updates IBCs on developments through site visits and information on its website. The NIH is aware of IBCs that are reviewing their work in the light of synthetic biology. The approach taken by the NIH is therefore to work with practitioners and oversight committees toward shared goals rather than act as a sanctioning and regulatory body.

The NIH guidelines apply only to research, but synthetic biology is also covered by existing regulations, in particular when used for commercial purposes. It is not, or would not be, regulated as synthetic biology *per se* but according to its use, for example industrial biotechnology, consumer products or agriculture, by the relevant federal agency.

The NIH was noted for its foresight in updating its guidelines to accommodate advances in synthetic biology, and delegates discussed the situation in other countries. In Japan, researchers are required by law to notify the Ministry of Education of any research involving rDNA. In Europe, biosafety is captured within legally binding directives, and regulatory bodies in member states undertake compliance checks. A European Commission working group is currently exploring whether existing directives need updating to accommodate synthetic biology.

One issue was left hanging: Would we recognise the point at which evolving synthetic biology research posed a fundamental challenge to the current regulatory structure, a challenge that could not be met by modifying existing structures?

Biosecurity

“Synthetic biology presents risks, but so does biology and in fact so does everything we do on a day-to-day basis”, said Michael Imperiale (Arthur F. Thurnau Professor of Microbiology and Immunology, University of Michigan, United States). Iain Gillespie (Head, Science and Technology Policy Division, Directorate for Science, Technology and Industry, OECD) pointed out that it is difficult to quantify the risk linked to synthetic biology but it is important to create governance systems which are sustainable, forward-looking and dynamic and which allow innovation in synthetic biology to emerge.

The risk factors

Imperiale presented four risks for synthetic biology: the technologies themselves, the practitioners of these technologies, the biology and the public.

- **Technologies.** Imperiale divided synthetic biology into two types of technologies: genome synthesis and engineering. Both sets of technologies present risks. As noted, genome synthesis allows the synthesis of virus genomes and, eventually, the derivation of a virus from this genome. It may also become possible to build *de novo* an organism which can escape current system controls. Engineering techniques include molecular shuffling or self-replicating systems which might also pose security threats. The following actions would help integrate all the components needed to evaluate risk and ensure an efficient regulatory framework for synthetic biology:
 - Develop uniform and standardised screening tools to determine what is dangerous and what is not, especially in the case of synthetic genomics.
 - Develop a rationalised list of agents to determine the most dangerous or risky and prioritise screening. This is difficult, however, and managing risk in this case is complex because the mechanisms of pathogenic agents are not fully understood and it is currently difficult to identify agents that may be hazardous.
 - Build a database of risky sequences or experiments to help stratify and keep track of risk.
- **Practitioners.** Practitioners include traditional scientists, other groups such as iGEM competitors and, perhaps at some point, terrorists. Although it is important to be mindful of risks associated with terrorism, the risks posed by the scientific enterprise itself were presented as needing immediate attention. Students from the synthetic biology community already discuss biosecurity issues among themselves. This is the case for the iGEM group but also for the “do it yourself” (DIY) bio community which has set up a safety and security working group.
- **Biology.** Biology can be more or less predictable or unpredictable. The behaviour of designed circuits, selection and virulence for example can be difficult to anticipate.

- **The public.** If hazards result from synthetic biology activities, there is a chance they will affect the public. The public has a voice in the acceptance of an emerging technology. It is important to engage the public in dialogue and discuss potential risks and benefits.

Debates are already taking place concerning the safety, security and ethical aspects of emerging technologies. The presentation pointed out that it is important to look into these debates and learn from the past.

It was suggested that industry should start a dialogue with the public and should engage in establishing a framework to regulate synthetic biology, especially in terms of providing relevant data. An important first step is to assess whether the current regulatory framework is able to deal with the challenges posed by synthetic biology. It was noted that there are more discussions about the adequacy of the regulatory framework in the United States than in Europe because the original network of regulations is somewhat stricter in Europe. Many ongoing initiatives and discussions deal with synthetic biology and security. The initiative taken by Berkeley was quoted as an example. It has developed a portal for submitting questions about whether an experiment may pose a risk. An anonymous group of experts discusses the question and provides advice. Discussions among scientists and the security community at national and international levels are ongoing.

The French approach

The generic tools to improve biosecurity are regulation, recommendation and awareness. Various recommendations to improve biosecurity have been published for governments and the authorities. Although the French Academy of Science has not published a specific report on synthetic biology, its report on biological constraints, biological security and scientific responsibility can be relevant for synthetic biology. A number of instruments which may be of interest for synthetic biology regulation were analysed (*e.g.* federal regulation to monitor and control DNA synthesis; guidelines; harmonisation and controls; education and training programmes; and a committee to check and control synthetic biology research). Nicolas Bécard (Project Manager, Secretariat of National Defence, France) presented four recommendations that emerged from this analysis:

- **Adaptation to limit malicious applications.** Instruments are already in place to limit malicious application. There is an international regulation with United Nation resolutions. The chemical Weapons Convention and the Biological Weapons Convention normally limit the risk of development of new agents. There are also European regulations for export control. The list of biological and chemical items is determined by the Australia group list. European regulations for biological risk and warfare are more oriented towards biosafety but deal with some issues raised by biosecurity. Specific regulations in place in different countries allow for control over the order of DNA parts (this includes DNA synthesis, DNA sequences, micro-organisms and toxins). However, according to Bécard, further analysis is required to ascertain whether these regulations are sufficient to cover all the risks that synthetic biology could raise. This work is ongoing in France.
- **Controlling DNA synthesis.** It seems difficult to control DNA synthesis directly from a biosecurity point of view. To have effective control calls for a good database and international oversight. This is not yet the case. Another approach aims to educate the gene synthesis industry on how to identify suspicious DNA orders and inform them about national points of contact they can report to. This is the approach taken in France and in the United States.
- **Awareness and education in the scientific community.** In France, the French Academy of Science has reported that by developing a good awareness and education programme for the scientific community, biosecurity could be significantly improved, and conferences and seminars are given on this topic to train and inform scientists. Some university degrees have modules dealing with biosecurity and biosafety issues and others are being developed.

Bécard said that these recommendations are not specifically directed at synthetic biology, but are for all emerging technologies. France will have guidelines specifically dealing with biosecurity for synthetic biology.

Public engagement and participation

A drive to engage with the public and promote discussion of the issues raised by synthetic biology has come both from within the synthetic biology community and from outside (for example from policy makers, civil society groups and research funders). It is not clear why some forms of science and technology provoke calls for public dialogue, while others do not, although it was suggested that one factor is the extent to which that science or technology is framed as new or emerging. Synthetic biology obviously falls into this category.

Accepting that public engagement and dialogue are important for synthetic biology, questions remain. These include: What is meant by “the public”, especially in a global environment? How is the public to be engaged and do we have successful models? Will engagement succeed with so few products to talk of? What is the role of the media? Delegates discussed studies on emerging public views of synthetic biology, the potential participants in engagement, and the functions and roles of the media.

Emerging public views on synthetic biology

A study undertaken by the Woodrow Wilson Center Synthetic Biology Project explored public awareness and views on synthetic biology in the United States. The research consisted of a representative national telephone poll and two focus groups (one with female and one with male participants). The results were compared with those of focus groups in the United Kingdom as part of the Royal Academy of Engineering inquiry into synthetic biology, and with earlier work undertaken on nanotechnologies.

In the poll, 67% had not heard of synthetic biology (nanotechnology is better known, with 49% having not heard the term before). In the focus groups, participants discussed which applications of synthetic biology they viewed as most promising. Both males and females considered biofuels the most promising potential application, a finding reflected in the UK research. Drugs for treating diseases, and new ways to treat cancer and clean up the environment were also well supported.

When asked who is best placed to regulate or manage risks associated with synthetic biology, participants did not think industry should have full responsibility for testing their products. The federal government was considered most appropriate for managing risks, but females also tended to favour the scientific community and others

involved in advancements to regulate synthetic biology. Some male participants favoured an immediate ban on further synthetic biology work. Generally, however, participants did not favour a moratorium, and recommendations for the road ahead, such as increasing trust through openness and transparency, were similar across the Atlantic.

The research also pointed to potential challenges for communication about synthetic biology to the public. For example, David Rejeski (Director, Foresight and Governance Project, Woodrow Wilson International Center for Scholars, United States) noted that the reaction of participants when first introduced to the term synthetic biology “pushed buttons that nanotech never pushed for them”. It may be that the term will be a liability in a way that “nanotechnology” is not. Added to this, a convergence of factors might mean that there is high potential for risk amplification. These factors include: greater public anxiety over biological issues and threats following the H1N1 pandemic; a general decline in the number of dedicated science journalists; a decline in trust in government agencies; and the possible rise of new opponents. The last of these factors is based on research by Kahan *et al.* who showed that a group known as “environmental risk naysayers”, who are typically unconcerned by potentially hazardous issues such as nuclear power, climate change and bovine spongiform encephalopathy (BSE), show concern for synthetic biology.

Why this should be requires further exploration, and this is just one suggested avenue for further research on the public and communication aspects of the field. Other near-term needs include applied research on public attitudes and perceptions, including international comparisons that may be used as a basis for a communication and engagement strategy. Differing reactions to synthetic biology across nations and regions can affect the future geography of synthetic biology. For example, the generally negative public reaction to genetically modified organisms (GMOs) in Europe is well documented and the economic loss to the US economy of the failure of GMOs on the European market may be some USD 300-400 million a year. However, research commissioned for the Royal Academy of Engineering inquiry into synthetic biology found a more positive reaction to synthetic biology, including the term itself, than from US counterparts. It was suggested that UK participants preferred to learn more about the science and technology before making a judgement.

The increasingly global nature of modern life sciences is an important consideration in discussions of the meaning and significance of synthetic biology. It will not be possible, nor would it be desirable, for public debate and dialogue to be restricted to a few countries and a few experts. Facilitated by information communication technologies, both the science and the debate about the science will be widely known.

Participants in engagement

Robert Cook-Deegan (Director, IGSP Center for Genome Ethics, Law and Policy, Duke University, United States) argued that emerging research points to a difficult public landscape for synthetic biology: it has an unfavourable name; no apparent communication strategy; no clear leadership; and no media channels through which to pass on information. Yet it was suggested that the issues raised by synthetic biology are shared by many new technologies, such as neuroscience, stem cells and agricultural biotechnology. It was argued, therefore, that the task is not to educate all the public so that anyone and everyone can enter policy discussions, but to determine which broad set of stakeholders is likely to be affected by this technology and bring them into discussions. This needs to be done with an awareness of the broad nature of the synthetic biology research base in terms of the range of research agendas that constitute “synthetic biology” and the fact that synthetic biology is being developed both within and outside of the traditional arenas of science and technology R&D. The iGEM competition and the rise of the “garage biotechnologist” illustrate this. A wide range of people therefore need to be engaged in policy discussions.

Media roles

Some see reasons for optimism in public communication regarding synthetic biology. Adam Bly (Founder, CEO and Editor in Chief, Seed Media) argued that synthetic biology arrives at a time when US government support for science is at an all-time high, and science is currently considered essential to the vitality of the nation. Synthetic biology can be part of this positive view of science. Furthermore, the synthetic biology community is quite ready to explore non-traditional media as a channel for communicating their work. This means that synthetic biologists could augment, even circumvent, traditional media sources and more closely control their messages.

Bly argued that traditional media may “fail” synthetic biologists because they lack the required scientific literacy to deal with a field that is this complex, challenging and developing at a rapid pace. Bly summed up his position by stating, “I wouldn’t even contemplate the need for mainstream media ...; bypass it and focus on new tools for scientific communication.” He argued that the synthetic biology community has an opportunity to revise and reform science communication and science literacy based on three factors: a shared sense of social responsibility within the synthetic biology community that will appeal to the wider public; synthetic biology has the potential to be a participatory science; the open and transparent forms of communication currently preferred by many within the community are readily transferable and already accessible to the public. Moreover, because it is characterised by unpredictability, synthetic biology can pave the way for a new form of debate about science, in which unpredictability and uncertainty are openly discussed. Bly suggested unpredictability is likely to be an increasing feature of future science.

The synthetic biology community is already undertaking some public engagement both passively (through researchers’ use of open access web-based tools) and actively. When added to initiatives undertaken and planned by other organisations (*e.g.* the Woodrow Wilson Center, the Royal Academy of Engineering, the UK research councils), the question arises whether communication and engagement call for a more detailed and co-ordinated strategy. It was even in fact asked whether it would make any difference if there were no public engagement effort at all.

Some participants felt that there was little need for a public engagement strategy. However, this was set against the examples of GMOs and human gene therapy (HGT). It was suggested that a better public engagement strategy in the early development of GMOs might have led to a more productive technology that better matched perceived needs. In the case of HGT, it was suggested that powerful religious groups in the United States lobbied the federal administration and influenced decision making. This was viewed as a narrow evidence base on which to base policy. Wider dialogue about emerging science and technology may lead to different outcomes.

It was also noted that in the United Kingdom and elsewhere there is a general move away from communication strategies that resemble marketing campaigns towards initiatives that foster dialogue among scientists, policy makers and the public with a view to feeding into decision making at the research and policy levels. This is the aim of

forthcoming efforts by the UK research councils. In the United States, engagement initiatives linked to policy processes already exist. For example, as part of the redraft of the above-mentioned NIH guidelines, proposed changes were considered at a conference involving stakeholders. However, the number of public participants was described as disappointing, although turn-out from civil society groups was better and led to rich discussion.

Annex

Agenda of the Symposium: Opportunities and Challenges in the Emerging Field of Synthetic Biology

Under the auspices of
The U.S. National Academies
The Organisation for Economic Co-Operation and Development (OECD)
The Royal Society

9-10 July 2009
The National Academies' Keck Center
500 5th Street, NW
Washington, DC

Thursday, 9 July

Welcome: Ralph J. Cicerone, President, National Academy of Sciences

Keynote Address: Arden Bement, Jr., Director, National Science Foundation

Session 1: Synthetic Biology Overview

Moderator: Sheila Jasanoff, Pforzheimer Professor of Science and Technology Studies, Harvard University

Speakers:

Drew Endy, Assistant Professor, Department of Bioengineering, Stanford University

Paul Rabinow, Director of Human Practice, Synthetic Biology Engineering Research Center

Session 2: Public Policy – Government Perspectives and Approaches

Moderator: James Wilsdon, Director, Science Policy Centre, The Royal Society

Speakers:

Adrian Smith FRS, Director General for Science and Research, Department for Business Innovation and Skills

Huanming Yang, Director, Beijing Genomics Institute

Session 3: Roundtable Discussions on Innovation in Synthetic Biology

Tools and Techniques – Enabling Innovation

Moderator: Caroline Ajo-Franklin, Staff Scientist, Biological Nanostructures Facility, University of California, Berkeley

Speakers:

Christina Smolke, Assistant Professor, Department of Bioengineering, Stanford University

Cord Straehler, Chief Executive Officer and President, Febit Biomed GmbH

Eco-Innovation

Moderator: James Greenwood, President and CEO, Biotechnology Industry Organization

Speakers:

Sven Panke, Associate Professor for Bioprocess Engineering, Department for Biosystems Science and Engineering, ETHZ-Basel

Victor De Lorenzo, Research Professor, Spanish National Research Council, National Center of Biotechnology

Kinkead Reiling, Co-Founder and Senior VP, Corporate Development, Amyris

Vitor Martins Dos Santos, Systems and Synthetic Biology Group, Helmholtz Center for Infection Research

Health and Medicine

Moderator: Richard I. Kitney, Director of the Graduate School of Engineering and Physical Sciences; Chairman of the Institute of Systems and Synthetic Biology; Professor of BioMedical Systems Engineering, Department of Bioengineering, Imperial College

Speakers:

Adriano Henney, Director, Obsidian Biomedical Consulting Ltd.

Frank Notka, Manager, Research and Development, Geneart

Roman Jerala, Head, Department of Biotechnology, National Institute of Chemistry – Slovenia

Friday, 10 July

Welcome: Charles M.Vest, President, National Academy of Engineering

Session 4: Developing the Field – Needs of Academia and Industry

Moderator: Pam Silver, Professor, Department of Systems Biology, Harvard University

Speakers:

Francois Kepes, Research Director, French National Center for Scientific Research and Founding Director, The Epigenomics Project, Genopole

Randy Rettberg, Director of the Registry of Standard Biological Parts; Director, The International Genetically Engineered Machine (iGEM) Competition; Principal Research Engineer in Biological Engineering, Massachusetts Institute of Technology

Richard A. Johnson, Senior Counsel and Senior Partner (Ret.), Arnold & Porter LLP and CEO, Global Helix LLC

Session 5: Roundtable on Investment Models for Synthetic Biology

Moderator: Ed Lazowska, Bill and Melinda Gates Chair in Computer Science, Department of Computer Science and Engineering, University of Washington

Speakers:

Mark Waxman, Partner and Chair of the Health Care Industry Team, Foley & Co

Greg Kisor, Vice President, Investor Relations, Intellectual Ventures

Paula J. Olsiewski, Program Director, Alfred P. Sloan Foundation

Ioannis Economidis, Principal Scientific Officer, European Commission

Session 6: Governance Issues Related to Synthetic Biology

Health / Safety / Environment

Moderator: Helge Torgersen, Senior Researcher, Institute of Technology Assessment, Austrian Academy of Sciences

Speakers:

Takuji Wakita, Director, Department of Virology II, National Institute of Infectious Disease

Jacqueline Corrigan-Curay, Acting Director, The Office of Biotechnology Activities, Office of Science Policy, National Institutes of Health; Executive Secretary, Recombinant DNA Advisory Committee

Security

Moderator: Iain Gillespie, Head, Science and Technology Policy Division, Directorate for Science, Technology and Industry, Organisation for Economic Cooperation and Development

Speakers:

Nicolas Bécard, Chargé de mission, Secrétariat de la Défense Nationale

Michael Imperiale, Arthur F. Thurnau Professor of Microbiology and Immunology, University of Michigan

Session 7: Public Engagement and Participation

Moderator: Mike Rodemeyer, Lecturer, Science, Technology, and Society,
University of Virginia

Speakers:

David Rejeski, Director, Foresight and Governance Project, Woodrow Wilson
International Center for Scholars

Robert Cook-Deegan, Director, IGSP Center for Genome Ethics, Law and Policy,
Duke University

Adam Bly, Founder, CEO and Editor-in-Chief, Seed Media Group

Session 8: The Path Forward

Roundtable of all session moderators

Adjourn