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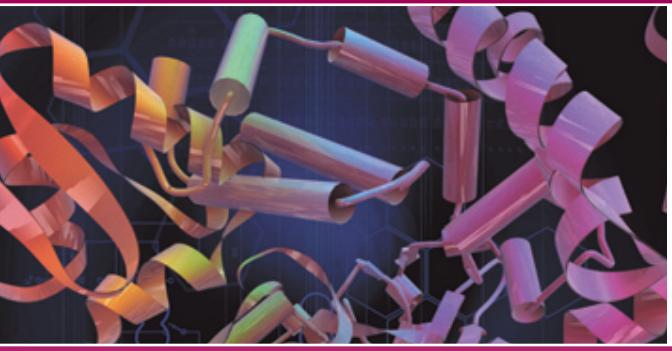
Synthetic biology

2 and 3 June 2008



scientific

DISCUSSION MEETING SUMMARY

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Contents

1 Introduction

Synthetic biology is broadly understood as the deliberate design of novel biological systems and organisms that draws on principles elucidated by biologists, chemists, physicists and engineers. It is an emerging field of increasing scientific and public policy interest, and the UK synthetic biology community is growing. To capture the enthusiasm surrounding synthetic biology, the Royal Society held a Discussion Meeting to showcase some of the most exciting research in the field. Participants discussed: technical advances; applications including novel ways to produce bioenergy, materials and drugs; and the social contexts of this research.

2 Key points

- Synthetic biology is concerned with producing biological based entities (e.g. parts, devices, systems, organisms) which perform a new function. From these entities, applications in areas such as medicine, energy, environment and materials may be developed
- Synthetic biology also aims to increase our understanding of biology
- Research reported at the Meeting illustrated the viability, power and potential of synthetic biology
- The UK has a growing synthetic biology community, and is already strong in related areas such as systems biology
- Healthy numbers of undergraduate and postgraduate students are choosing to study synthetic biology
- The continued development of synthetic biology requires synergy amongst a range of disciplines including biology, engineering, chemistry and information technology
- Development also requires advances in the automation and scaling of enabling technologies such as low cost DNA synthesis and genome assembly. *In silico* (computer-based) technologies and modelling should be increasingly useful
- Synthetic biology will be aided by understanding the cell response to engineering. Organisms may react to oppose engineering and this is currently a significant challenge to synthetic biologists
- Fully characterized, standardized, modular parts that have defined properties or perform defined functions independent of context will be useful, as will orthogonal parts that are invisible to the organism
- There are likely to be intellectual property and ownership issues around key technologies and processes
- Synthetic biology raises important ethical and social issues which need to be widely discussed in the short term and as the field matures
- The dual-use potential of synthetic biology (that is, the technology and knowledge could be used for and against public health and national security) may require the development of governance and oversight frameworks
- Public dialogue will assist policy makers and scientists develop synthetic biology, and the field will be served by open and accurate communication with the public.

3 The discussion meeting

Around 120 leading academics, policy makers and other stakeholders from the UK, USA and Europe participated in the Meeting. Presentations and discussion explored: the general principles and scope of synthetic biology; specific research programmes including the design of genetic switches, circuits and networks; broader applications, from rewriting the genetic code to producing materials and pharmaceuticals; enabling technologies; engineering challenges; insights for synthetic biology from systems biology; and current and planned UK research funding opportunities. A plenary session widened discussion to issues such as the continued development of the synthetic biology community, governance and oversight, and public dialogue.

This report summarises key issues raised during the course of the Meeting. It is, in the main, a summary of the technical work presented. Wider issues that arose in discussions and the plenary are also described.

The report describes views expressed at the Meeting. It does not necessarily represent the views of the Royal Society or a consensus opinion of participants. We are extremely grateful to: Professor Brian Spratt FRS (Imperial College London); Professor Richard Kitney FREng (Imperial College London); Professor Paul Freemont (Imperial College London); and Dr Jason Chin (MRC LMB, University of Cambridge) who organised the Meeting and reviewed this report. The Meeting programme is at Appendix A.

4 Introducing synthetic biology

Synthetic biology covers an increasingly wide area of modern biology and although difficult to define, in essence it is about redesigning life. Synthetic biology draws in the main on two established disciplines: engineering and bioscience. Engineering provides much of the conceptual framework and the material to which this is applied is biological. Knowledge of key properties of cells and sub-cellular processes is then essential, and additional disciplines such as chemistry and information and communication technology (ICT) facilitate the endeavour. The broad aim of this convergence of tools and knowledge is the (re)design and (re) assembly of biological systems which may lead to applications in areas such as healthcare, energy and environment (see Box 1).

Marrying an engineering approach to biology follows from parallel developments in both parent disciples. Fifty or more years of a sub-cellular molecular and genetic understanding of life, including the elucidation of the structure of DNA, gene regulation, genetic engineering, rapid DNA sequencing and advances in synthesis of DNA, have converged with parallel developments in engineering and information technology, in particular miniaturisation and computer chip design.

Like most emerging technologies, the boundaries between synthetic biology and other technologies and disciplines are blurred. A synthetic biology approach can be usefully distinguished from systems biology and genetic engineering. Systems biology can be understood as a top-down approach to the description and analysis of the dynamic interactions between components of a biological system in order to understand the behaviour of that system. Synthetic biology takes a bottom-up approach and seeks to understand and engineer genetic networks and systems by constructing and altering basic components (such as genetic switches and circuits). It is this bottom-up approach that facilitates the major aim of synthetic biology: the design of novel organisms or cells, including totally synthetic organisms, that provide new devices and materials with applications in areas that include health, materials, the environment, defence and energy production. As described below, mutual understanding and collaborative research between systems and synthetic biology communities benefits both individually.

Genetic engineering similarly seeks to change some aspect of biological function, yet does so with relatively poorly defined and characterised components, and with relatively weak control over inputs and outputs. Synthetic biology, in contrast, builds switches, networks and systems from components and modules that are well characterised and easily connected, and which encode for properties with known functions. Controlling design, characterisation and construction aims to increase the predictability of the properties of the designed systems.

In short then, the synthetic biologist seeks to build a bespoke system (such as an organism) by re-designing an existing system or constructing one from scratch using parts taken from nature or specially designed. This approach can lead to organisms, networks and systems with properties not found in nature (such as bacteria that produce spider silk or cells that change colour when they divide).

Box 1: Applying synthetic biology

Applications discussed at the Meeting, some near to market, some in the very earliest stages of development, included:

- Molecular computers (see 5.2)
- DNA-like polymers for novel materials (see 6.3)
- New protein therapeutics, e.g. human growth hormone (see 6.4)
- Production of the antimalarial artimisinin from yeast (see 8.1)
- Salmonella engineered to secrete spider silk (see 8.1)
- Gene therapies (see 8.2)
- Microbial 'factories' for generating energy and fuel (see 8.1 and 8.2)
- Development of drugs for tuberculosis (see 8.2) and trypanosomiasis (sleeping sickness; see 9.2)

5 Designing genetic switches, circuits and networks

Work was described that sought to construct integrated rationally designed molecular circuits that emulate electronic circuits. This requires well characterised and predictable molecular components and a method of programming biological behaviours. Simple synthetic model systems are a useful tool for learning about component parts and how they interact. Reported research demonstrated molecular switches, biological memory and the linking of component parts to perform computing operations.

5.1 Molecular switches and biological memory

Work was described in which two positive feedback loops, each exhibiting weak hysteresis, were added together to produce strong hysteresis. (Hysteresis is a property of a system where the present state of that system depends on its immediate history.) The first of these two positive feedback loops was for a LacY transporter that transports the inducer that increases its expression. The second of these was a synthetic genetic clock which produced sustained damped oscillations in *Escherichia coli* (*E. coli*) populations. By linking these two positive feedback loops, a 'double toggle switch' was created which resulted in biological memory. It was also shown that the hysteresis exhibited by the positive feedback loop could be eliminated by the addition of a negative feedback loop.

5.2 Biological computing

Designing and characterising simple systems, such as the above, assists the development of a library of interchangeable and transferable parts with predictable properties. These can then be used to construct more complex systems. Research was reported that constructed simple circuits with around ten components, including DNA-based gates and logic circuits. These share features of electronic circuits such as Boolean logic functions and signal restoration by threshold and amplifier gates. Gate design and circuit construction are modular and use single stranded nucleic acids as inputs and outputs. Although circuit activation is substantially slower than seen in electronic circuits, it is unlikely that this will be a limiting factor in all foreseeable uses of the technology. Potential applications are envisaged in bioengineering and biotechnology – for example in the construction of smart drugs and biomedical diagnostics. Next steps include the construction of a molecular compiler for logic circuits and chemical reactions.

6 Genome evolution and expanding the genetic code

Synthetic biology can be used to understand genome evolution and to harness selection to rapidly evolve organisms and systems.

6.1 Genome evolution

Synthetic model systems can be used to understand genome evolution. Deletion, rearrangement and duplication play important roles in the evolution of gene networks. Large-scale insertions usually involve the duplication of part of the genome. Research was reported that experimentally duplicated genes to better understand the effect of adding new regulatory links to gene networks and consequent effect on network evolvability.

Around 600 new regulatory links were added to a wild-type *E. coli*. The bacteria tolerated 95% of new networks, including rewired transcription hubs, and most were expressed. Very few altered growth. This result might be surprising from a bioinformatics perspective, which may suggest that rewiring hubs would be lethal. Selection pressure was applied to the rewired gene networks and certain networks consistently survived over wild type. This demonstrates the potential for evolution from acquired network connections. Similar experiments in other organisms, including mammals, have not been undertaken, but would indicate whether tolerance towards rewiring is a general feature of evolved biological networks.

6.2 Expanding the genetic code

As well as work with material taken from nature, a distinguishing ambition of synthetic biology is to expand natural genetic chemistry for novel applications. Participants at the meeting discussed work that sought to expand chemistry linked to polymerases and ribosomes.

6.3 Expanding polymerases

Research was reported that sought to engineer polymerases by directed evolution. Directed evolution develops molecules with desired traits through successive rounds of isolated replication and mutation. Compartmentalised self-replication (CSR) has been used to evolve new forms of polymerase (an enzyme that catalyzes the formation of new DNA or RNA from an existing strand of DNA or RNA). Based on a simple feedback loop consisting of a polymerase that replicates only its own encoding gene, CSR can be used to modify polymerase function in order to read or write genetic material in new ways. For example, polymerase can be engineered to amplify templates that could not otherwise be read, such as the recovery of ancient DNA sequences from archaeological and paleontological specimens. The technique has been used to obtain informative DNA sequences from cave bear bones around 45,000 years old.

Designer polymerases may also allow the 'writing' of novel, DNA-like polymers. The programmability of DNA makes it an ideal material for nanotechnology and the production of interesting and exciting materials.

6.4 Expanding Ribosomes

Ribosomes, organelles found in the cytoplasm of living cells, are made of protein and RNA subunits and catalyze the synthesis of proteins guided by a messenger RNA (mRNA) template. Reported research aimed to create ribosomes with expanded chemical scope to act as novel cellular translation systems able to synthesise unnatural proteins. If successful, the end goal of encoding amino acids which do not occur in nature will be to assist scientists in re-writing the genetic code.

To date, experiments have demonstrated sets of ribosome-mRNA pairs which are able to translate new proteins, and that it is possible to create ribosomes which can be switched on and off. This is the first demonstration of creating a

parallel translational machinery which evolves new functions and modifies how it reads genetic information.

The next stage of this work is to create new and expanded ribosome functions which will allow scientists to evolve components within cells to aid the study of molecular biology. This methodology could also be used to look at protein interactions. In addition, this technology would enable the expansion of genetic codes and allow the creation of more efficacious protein therapeutics, for example, human growth hormone.

7 Foundation technologies

Like synthetic biology, the research field of genetic engineering seeks to alter genetic codes. Genetic engineering typically involves serial changes in the genome by inserting or removing one or a few short sequences of DNA. In contrast, synthetic biology typically considers engineering at the whole cell (or organism) level and seeks greater efficiency. Engineering at the level of the genome for example aims to change as much as all nucleotide sequences in the genome of an organism in order to produce cells with new functions. To do this predictably and with control requires comprehensive understanding of cell behaviour and the development of technologies to efficiently and predictably alter the properties of genetic and biochemical molecules in interaction.

Research reported at the Meeting described technologies that assist the pursuit of controlled, efficient molecular changes. Two particular enabling technologies relate to new methods to change the DNA of cells efficiently and at scale, and new ways of changing and controlling gene expression.

Toward the former, researchers are working on new methods that combine large-scale DNA synthesis techniques with engineered recombination strategies to manipulate native genomes and introduce synthetic DNA elements. *E. coli* has proved a useful test bed for this work. An engineered strain of *E. coli*, in which the entire genome has been recoded, opens this microbe to a broad set of applications, such as the incorporation of non-natural amino acids with novel biochemical properties. Techniques are being developed to automate the simultaneous introduction of libraries of DNA constructs into cells, making the process 'hands-off' and efficient.

As well as improving techniques for making large-scale, site-specific direct manipulations of genomes, researchers are working toward tight expression control of introduced DNA. RNA based molecular switches are an attractive route to control. Work was reported on engineered RNA switches which allow tuneable control of the expressions of target genes. Researchers are now working toward a modular library of RNA switches.

8 Designing organisms and systems

A large part of discussion at the Meeting revolved around the design and redesign of organisms and systems for better understanding of biology and for constructing organisms with useful functions.

8.1 Designing organisms

Work was reported on developing technologies to design and synthesise bacterial cells. The initial goal of this research is to construct a synthetic cell, the minimal version of *Mycoplasma genitalium*. *M. genitalium* was taken as the model of choice since it has a small genome and minimal metabolic complexity and may become the platform of choice for understanding how the simplest possible cell works. Two key technologies for the design of

synthetic cells are genome assembly (assembly of overlapping 'cassettes' of genome segments) and genome transplantation (the installation of the synthesized genome into a receptive cytoplasm, such that the donor genome becomes the new operating system of the cell). Work was described that used these techniques to demonstrate synthesis and transplantation into host bacteria of the largest chemically derived molecule to date. Next steps for this work include construction of a true 'minimal cell' by taking away all of the non-essential genes of *M. genitalium*. This would enable scientists to learn more about the essential basics of cellular life. End goals for this work include creating useful bacteria, for example, with applications in areas such as energy and the environment. The work with *M. genitalium* presently uses the known genome sequence. The extent to which the genome can be redesigned to produce a radically novel synthetic organism by this method is of considerable interest.

Rather than stripping away dispensable genes to produce a minimal chassis, other striking work in synthetic biology seeks to add to natural organisms and engineer them to produce useful materials and substances that they do not in their wild type form. For example, the pathogen *Salmonella typhimurium* transports some proteins completely out of the cell via a needle-like biomachine know as the type three secretion system (T3SS). Experiments were described that harnessed this system to produce proteins of industrial interest, in this case spider silk.

Attempts have been made to engineer bacteria to produce spider silk before, but it is toxic to the cell. The advantage of the T3SS is that it reduces the period of time the protein is resident in the cell. It also avoids difficulties in extracting and preserving the protein of interest. By creating synthetic spider silk gene sequences, inserting these into *S. typhimurium* and controlling the T3SS, researchers have experimentally produced spider silk that can be drawn into threads. The system appears to have no negative effects on the growth and viability of the cell; indeed toxicity impedes growth and viability only when secretion is prevented. Spider silk is as strong as Kevlar and ten times more elastic and has significant industrial potential. The challenge now is to scale up production to an industrially useful level.

Isoprenoids are another class of naturally occurring organic chemicals of interest to synthetic biologists and industry. Isoprenoids include chemicals used as flavours, fragrances, fuels and therapeutics including artemisinin, the most effective known anti-malarial drug.

Derived from the plant *Artemisia annua*, the varied therapeutic benefits of artemisinin have been known to the Chinese since at least 150BC. Artemisinin is currently considered prohibitively expensive for treating the majority of the malaria sufferers in the world. It is estimated that 700 tons of artimisinin would be sufficient to treat all malaria sufferers, and synthetic biologists are investigating ways to engineer microbes to produce this quantity of the drug cheaply.

The development of both *E. coli* and yeast engineered to produce artemisinic acid was described. A precursor to artimisinin, artemisinic acid falls under a different regulatory burden to the drug itself: the acid is regulated as a chemical, not a pharmaceutical. This means that the process of production can be changed without again triggering the regulatory process. Increased efficiencies in the process can therefore be applied as they arise. This will assist researchers achieve their target of enough affordable artimisinin for all malaria sufferers. Artimisinin derived from yeast is likely to be on the market in 2-3 years, initially at a price directly comparable but soon undercutting the traditionally derived version.

It was reported that no one is making a profit from this production of artimisinin from yeast and it is anticipated that artimisinin sold to

western tourists will subsidise that delivered to the developing world. The chassis constructed for the production of anti-malarial drugs may now be adapted to produce profitable biofuels. This is in line with the engineering ethos of synthetic biology, where tools and techniques developed for one application can be transferred to another.

Work elsewhere is already underway to engineer microorganisms for energy production. Work was reported with the long term goal of creating microbial 'solar cells' that produce hydrogen. Choosing cyanobacteria as the model organism, research to date has concentrated on gene level analysis of responses to light. Ultimately it is hoped that this and other properties of the organism can be harnessed to produce hydrogen from sunlight.

8.2 Designing systems

Because most biological functions result from interplay of components and modules, synthetic biology requires knowledge beyond individual molecular function. As described above, assembling networks from individual modules increases understanding of natural processes and facilitates hypothesis testing. Synthetic gene networks are designed to emulate natural gene expression behaviour, and may open up new pathways to engineer therapeutics and foster progress in gene therapy and tissue engineering initiatives. Research was described that used a synthetic gene network to assemble and test human-compatible transgene control technologies. Success has been obtained with upstream gas inducible transcription control in mice, and with epigenetic toggle switches that lock transgene expression in response to administration of inducer molecule concentration.

The latest synthetic mammalian gene networks imitate ecosystems and reveal cross-talk dynamics between species sharing the same habitat. Work was reported that constructed a network containing mammalian cells and *Mycobacterium tuberculosis* (the cause of tuberculosis) which was then used to screen for efficient tuberculosis treatments. For example, ethionamide is an antibiotic used in the treatment of malaria, but has side-effects for humans. The synthetic circuit was successfully used to explore ways to knock down the ethionamide-resistance pathway of *M. tuberculosis*. This increased its sensitivity to ethionamide which could then be delivered in lower dosage. Next steps involve testing this intervention in animal and then human models.

Synthetic constructs, such as gene control circuits, need to be well interconnected with the host cell's existing networks. Moreover, these interconnections need to be well characterised and predictable. It is possible to test this understanding by building an artificial system and comparing its behaviour with its natural counterpart. Synthetic gene circuits have been used in such a manner over the last eight years. In most cases, the scientist has tried to simplify the system in order to insulate it from the underlying cell physiology. In taking this approach, the host cell is considered to be an invariable 'chassis', with a well-defined interface between the circuit and the host. The dominant observed function is usually attributed to circuit design. However, simplified circuits do not always reflect what is observed in the natural state where there may be hidden interactions between the circuit and the cell. For instance, there may be cross-talk between the circuit and endogenous compounds, or the circuit may modulate cell physiology to produce unexpected behaviour. This may be thought of as faulty circuit design. However, using two simple circuits, it was shown that the unexpected behaviour can be explained by cell interactions impacting on circuit dynamics.

The first example given was a circuit which generates bistable gene expression in *E. coli*, for a protein which determines cell cycle entry. A very simple circuit consisted of a positive feedback loop alone. It was expected that this

circuit would exhibit monostability, and that an additional protein titration component would be needed for the circuit to show bistability. However, even the minimal circuit generated bistable gene expression. It was found that this could be explained by circuit activation inhibiting cell growth, with the combination of growth modulation and the positive feedback loop resulting in bistability. The interaction between the circuit and the cell physiology can therefore explain the dynamics of the circuit.

The second example described the insertion into cells of a simple cell suicide circuit containing a quorum sensing module. Bacteria employ quorum sensing (a form of cell-cell communication) to sense changes in population density and control bacterial population size by regulating gene expression. At high levels, the protein produced (ePop) blocks cell wall synthesis and induces cell death ('popping'). In small populations of bacteria, synchronised popping is seen which leads to sustained oscillations in population size in macroscopic batch cultures. However, oscillations were also observed without the quorum sensing module in the circuit. The oscillations must be produced via hidden interactions with the cell. This can be explained by diffusible factors produced by the cell which accumulate at high density and induce expression of the ePop protein.

These two examples illustrate the challenge of constructing fully predictable biological parts and systems, and show that unintended interactions between the synthetic circuit and underlying cell physiology can impact circuit function. These problems are likely to get worse as network complexity increases and will be a challenge to the design of biological circuits that have anything like the precision and durability of electronic circuits.

9 Synthetic and systems biology

Discussion at the Meeting confirmed close affinity between the disciplines of synthetic and systems biology; indeed the design and construction of systems that exhibit complex dynamic behaviour remain major goals of synthetic biology. Work was reported at the Meeting on new methods for modelling gene interactions, and on techniques to engineer recalcitrant systems.

9.1 Modelling gene interactions

Work was described in which metabolic models were used to identify functional models within networks and predict interactions between genes. A list of all metabolic reactions for *Saccharomyces cerevisiae* (a species of yeast) has been defined and analysis of deletion mutants used to describe functional modules for the organism. Specific lethal interactions between genes were sought to isolate functional modules. These are cases where knocking out two different genes results in a sick organism. Such lethality can be the result of either redundant gene duplicates or the existence of alternate cellular pathways. Computer simulation of all possible double and triple gene deletions of non-essential genes can be used to predict cases of synthetic gene lethality with a success rate of approximately 56%.

Further experiments have been carried out on the metabolism of *Buchnera aphidicola*, a relative of *E. coli*. Using *in silico* modelling, genes were deleted at random and if this had no impact, another was deleted and so on. This predicted with around 80% accuracy the metabolic network of the actual organism.

A 'robot scientist', which can generate a hypothesis, design a test and analyse results,

has also been used to design modules. Novel modules or pathways can be introduced and their performance observed. In a model of aromatic amino acid biosynthesis in yeast, a robot was given deletion mutants and background knowledge of the metabolic pathway. The robot was set the task of discovering which genes encode enzymes for metabolic reactions which it did not yet know. Sometimes this approach cast new light on the known gene, sometimes the robot was wrong, and sometimes it confirmed what was already known.

9.2 Engineering recalcitrant systems

Perhaps one of the more significant challenges for synthetic biology is that living systems actively oppose engineering. They are robust and have evolved to be self-sustaining, responding to perturbations through adaptation, mutation, reproduction and self-repair. This presents a strong challenge to efforts to 'redesign' existing life. One approach to meet the challenge is to turn to systems thinking and try to 'motivate' a system to produce the required behaviour or product by asking what is preferable from the perspective of the recalcitrant system. In one experiment, researchers disabled lactic acid pathways and engineered diacetyl production in bacteria *Lactococcus lactis*. Initial steps included quantifying the importance of each step in the lactic acid pathway to determine which may be inactivated with least overall effect on the organism.

In silico modelling can help determine the degree to which one can interfere with molecular processes without reducing overall system function. Experiments have shown that impairing robustness at some point in a network reduces overall robustness: robustness is not conserved. However, network fragility turns out to be a conserved property and this has been exploited to develop drugs to combat trypanosomiasis (sleeping sickness). This parasitic disease is caused by protozoa of species *Trypanosoma brucei* and transmitted by the tsetse fly. One possible novel intervention interferes with the glucose transport system of *T. brucei* whilst resident in its mammalian host. It is fooled into reacting as if in the tsetse fly (where ambient glucose levels are lower) and this apparently robust response is instead turned into fragility. This intervention waits testing within host tissue, but demonstrates that auto-robustness mechanisms can be used to re-make networks successfully for biotechnological and therapeutic benefit.

10 The future development of synthetic biology

The meeting included a plenary session that widened discussion on synthetic biology beyond technical foundations and achievements. The following section summarises key aspects of this discussion.

10.1 Engineering biology

The many successful research projects and experiments reported at the meeting were taken to show that biology is open to engineering. One goal of synthetic biology is to make biology easier to engineer, and it does this through better characterisation and predictability of easily connected parts and modules, and better understanding of these in interaction. Synthetic biology may then be considered the full conceptual realisation of an engineering approach to biology.

There was a suggestion that the 'newness' of synthetic biology is sometimes presented in ambivalent ways. For example, sometimes it is presented as something very new, sometimes as a continuation of some 25+ years of engineering biology (for example, insulin production by *E. coli* was achieved in the late 1970s using recombinant DNA technology). Discussion tended toward suggesting that synthetic biology is both old and new: old in the sense

that it builds on accumulated knowledge and understanding, new in the sense that it is the first full application to biology of engineering principles.

This new approach is leading to developments that are genuinely novel; for example, the very notion of a 'box of parts' from which can be assembled synthetic bespoke organisms. Biologists and engineers have not had that expansive capacity before.

A step change in synthetic biology productivity, particularly parts and organisms, may be pushed by quicker, cheaper and easier synthesis of accurate nucleotide sequences. The amount of DNA that can be synthesised per day has increased rapidly and looks likely to continue to do so for the next decade.

10.2 Community matters

The continued development of synthetic biology requires synergy between researchers in all disciplines involved, including but not limited to the core disciplines biology and engineering. Engagement with and between communities will be served by demonstrating mutual benefits, for example that synthetic biology offers biologists, engineers and others technologies and concepts that they may not have encountered before. It will also be facilitated by the development of libraries of techniques, tools and standard parts for rapid take-up and deployment by diverse researchers.

Demonstration of success is likely to engage specialist and lay audiences. There was some debate on what might constitute the best form of success. Completed work on new ways to make therapeutic drugs is a considerable achievement, but target audiences may not see this as a discrete success of synthetic biology, especially if success is defined in terms of previous approaches or paradigms. For example, to publicise the construction of a synthetic gene network may gain little notice over the production of a new drug, even if that new drug was a consequence of such a network.

It was suggested that synthetic biology too often seems to focus on the cellular or sub-cellular level and that this constrains the development of the field. This bias may derive from the early domination of the field by researchers used to working with bacteria. Nonetheless, work presented at the meeting showed that biology can be engineered at a more complex level. It was suggested that communication with even wider communities, such as population biologists and policy makers, may stimulate complex integrated projects such as the design of ecosystems for pest management.

One measure of engagement success is student uptake. Participants at the meeting reported healthy student numbers entering undergraduate and postgraduate training and that it is a popular option for women.

10.3 Communication and dialogue

Participants discussed public perception of synthetic biology. It was suggested that this may be the moment to offer the public a new promise, for example that synthetic biology will allow an understanding of disease at a level not previously possible. Others noted that, again, there may be no discrete appreciation of synthetic biology: people are more likely to be interested in the ways of tackling disease rather than means by which any intervention was developed.

Participants considered the need to continue to open up synthetic biology to public discussion, and debated the nature and timing of public engagement activities. It was suggested that basic science is less controversial than application and that debate on synthetic biology may intensify along with any increased number of products. Perceived benefits of continued public dialogue included: demonstrating positive and genuinely beneficial scientific developments; assisting governments and others develop measures against misuse of this powerful technology; and understanding societal issues.

Another suggested area for public discussion was whether synthetic biology may become 'too successful', for example by endowing humans with new functional capacities with profound societal implications. Such considerations have been the subject of recent reports by the military.

10.4 Control and oversight

Participants further discussed that synthetic biology could be used to develop harmful and nefarious applications. This possibility means that oversight and control cannot be overlooked. The control of radioactive material shows that potentially harmful knowledge and technology can be successfully regulated. The burden of ensuring the aversion of potential danger falls in part on the synthetic biology community and the successful approach of risk assessment of experiments in genetic engineering provides a useful model.

10.5 Ownership and intellectual property

There are unresolved ownership and intellectual property issues. It was suggested that these must be addressed in the near term to avoid future difficulties. Participants relayed that there are already some tensions between scientists and universities around innovative academic research on for example biofuels. Many synthetic biologists prefer to reserve patents for products (e.g. the organism that produces a biofuel) rather than underlying technologies (e.g. genes, devices, parts, tools). The BioBricks Foundation, based at MIT, has a registry of standard DNA parts ('BioBricks') that encode biological functions. These are open access and free to use.

10.6 Funding

It was reported that the UK Research Councils have sharpened their focus on synthetic biology, recognising opportunities for improved understanding of biological systems, a wide range of potential applications and complex societal issues. As well as responsive mode funding for technical research, work is being undertaken across the Research Councils on ethical, legal and social aspects including regulatory frameworks and public concerns and aspirations.

To facilitate the development of synthetic biology, BBSRC and EPSRC, with ESRC and AHRC, are funding networks in synthetic biology. These will stimulate cross disciplinary networking and communication between researchers in the biosciences, engineering and the physical sciences, with input from the social sciences and humanities.

11 Further information and resources

Further information on synthetic biology can be accessed through the following Society web page:

royalsociety.org/syntheticbiology

This includes an online resource on synthetic biology. Updated regularly, the resource has information on policy activities in the UK, Europe and elsewhere as well as information on events and conferences, discussion forums, courses, journals and research centres. Suggest additional items for the resource to: synthetic.biology@royalsociety.org.

The synthetic biology web pages also contain information on the Synthetic Biology Policy Coordination Group. This multi-stakeholder group, convened by the Society, has been set up to: share information of synthetic biology related activities; identify gaps in current policy work; and stimulate activities in identified gap areas.

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12 Appendix A: Discussion Meeting programme

Day 1: Monday 2 June

Welcome and opening remarks
Mr Stephen Cox, Executive Secretary, the Royal Society
Professor Brian Spratt, Imperial College London

Session 1

Chair: Professor Richard Kitney, Imperial College London

Designing biological systems
Professor Pamela Silver, Harvard Medical School

Nucleic acid logic circuits for programming biology
Dr Georg Seelig, California Institute of Technology

A tale of two circuits: what I create, I may not understand
Dr Linchong You, Duke University

Building biological memory by the coherent linkage of positive feedback loops
Professor Alex Ninfa, University of Michigan

Session 2

Chair: Dr Jason Chin, University of Cambridge

Evolvability and hierarchy in rewired bacterial gene networks
Dr Mark Isalan, Centre for Genomic Regulation Barcelona

Synthetic mammalian gene networks
Professor Martin Fussenegger, Swiss Federal University of Switzerland

Engineering the secretion of spider silks from salmonella
Dr Danielle Tullman-Ercek, University of California San Francisco

Synthetic biology for synthetic chemistry
Professor Jay Keasling, University of California Berkeley

Day 2: Tuesday 3 June

Session 3

Chair: Professor Paul Freemont, Imperial College London

Ribosome engineering and new genetic codes
Dr Jason Chin, University of Cambridge

Design, synthesis and control of genetic and genomic systems
Dr Farren Isaacs, Harvard Medical School

Synthesis and replication of nucleic acids with expanded chemistry
Dr Phil Holliger, University of Cambridge

Synthetic genomics: progress on construction of a synthetic bacterial
Dr John Glass, J. Craig Venter Institute

Session 4

Chair: Professor Pam Silver, Harvard Medical School

Synthetic systems biology: engineering self-sustaining systems
Professor Hans Westerhoff, Manchester Interdisciplinary Biocentre

Synthetic and systems biology: simplicity and simplification
Professor Steve Oliver, University of Cambridge

Plenary Discussion
Synthetic biology: the Research Councils' perspective
Dr Amanda Collis, Biotechnology and Biological Sciences Research Council

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Founded in 1660, the Royal Society is the independent scientific academy of the UK, dedicated to promoting excellence in science.

As we prepare for our 350th anniversary in 2010, we are working to achieve five strategic priorities:

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- **Increase** access to the best science internationally
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