BBSRC SYNTHETIC BIOLOGY WORKSHOP
8-9 FEBRUARY 2007
Held at Alexandra House, Wroughton, Wiltshire

BACKGROUND

The area of synthetic biology has gained increasing attention in the scientific sphere in recent years. In 2005 the EU New and Emerging Science and Technology (NEST) programme published the report 'Synthetic Biology – Applying Engineering to Biology'. The Report described synthetic biology as:

> 'the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. In essence, synthetic biology will enable the design of biological systems in a rational and systematic way'

In early 2007, BBSRC held a synthetic biology workshop with the following aims:

- to showcase leading synthetic biology research to the UK science base;
- to assist in the development of an interdisciplinary synthetic biology research community; and
- to provide an opportunity to consider the societal and ethical issues raised by synthetic biology.

Participants were from a range of disciplines including biology, bioinformatics, chemistry, mathematics, physics and engineering, as well as ethicists and sociologists.

WORKSHOP STRUCTURE

The workshop comprised the following sessions:

- Keynote lectures demonstrating the utility of synthetic biology based approaches and related ethical / societal issues
- Two sessions of talks on (a) building blocks and engineering principles of modular design (b) engineering minimal biological systems
- Introductory networking session
- Breakout sessions on (a) potential research projects and (b) design challenges
- Closing discussion summarising the workshops findings and also covering funding opportunities and potential future directions.

The workshop agenda is at **Annex 1** and details of each session are provided in the following sections.

KEYNOTE PRESENTATIONS

Jay Keasling, Synthetic Biology Engineering Centre at Berkeley (SynBERC): *Engineering microbes for production of low cost, effective anti-malarial drugs*
Artemisinin-based drugs are fast-acting and effective, but are currently very expensive to produce. Professor Keasling's group has successfully metabolically engineered *E.coli* to produce high levels of a precursor to artemisinin, amorphadiene. This has enabled the *E.coli* to produce 1,000,000-fold higher levels of amorphadiene than previously used strains. In addition, the group has engineered yeast to enable artemisinic acid biosynthesis at high levels. This technology will eventually reduce the cost of artemisinin-based therapies.

Mark Bedau, Protlife SRL and ECLT: *Social and ethical aspects / implications in the synthesis of living entities*
In principle, living entities could be synthesised by two approaches: top down or bottom up. The interest in synthetic biology may be two fold: firstly, to learn 'the secrets of life'; secondly, for the vast array of potential applications, such as alternative energy, intelligent biosensors etc. He advises that society should avoid extremes and polarity of opinions, and instead pursue technological opportunities within a societal context with courage and wisdom.

Frederick Blattner, University of Wisconsin: *From genomes to designed genomes:* E. coli *and the synthetic biology challenge*
Sequencing and annotation of the *Escherichia coli* K-12 has included the use of a form of synthetic biology to trim the *E. coli* K-12 genome by making a series of planned, precise deletions, synthesizing them, and them crossing them into the genome. A genetically stable *tabula rasa* strain with robust metabolic performance has been constructed, to which genes for practical applications may be added.

PRESENTATIONS ON BUILDING BLOCKS AND THE ENGINEERING PRINCIPLES OF MODULAR DESIGN

Jason Chin, Medical Research Council Laboratory of Molecular Biology, Cambridge: *Expanding the functions of living matter*
Incorporation of unnatural amino acids into polypeptides would have applications in photo-cross-linking protein interactions, adding fluorescent labels and producing homogeneously PEGylated protein therapeutics. Building orthogonal ribosome mRNA pairs, in which the interaction between the mRNA and the ribosome could be controlled, could be used as a tool to investigate natural biology, for example, the functional subunits of a ribosome, in a manner that was previously unachievable.

Ben Davis, University of Oxford: *Chemical Biology – carbohydrates and proteins*
Development of synthetic biology from origin-of-life research may be compared to research that led to the development of synthetic organic chemistry from the natural origins of that subject (Isolation>Characterization>Total Synthesis>Redesign). Modular design principles to create synthetic proteins can be used in, for example, the design of drug delivery systems, such as LEAPT: Lectin-directed Enzyme Activated Prodrug Therapy. Proteins and carbohydrates could also serve as powerful 'biobricks'.

Vitor A.P Martins dos Santos, Helmholtz Centre for Infection Research, Germany: *Programmable bacterial catalysis*
Constructing a functioning, streamlined bacterial cell devoid of most of its genome, and endowed with a series of highly coordinated, newly assembled genetic circuits for the biotransformation of a range of chloroaromatics into high added-value compounds: this research is relevant to the field of engineering minimal living systems, an area usually considered to be allied to both synthetic biology and systems biology.

Jim Ajioka, University of Cambridge: *Genetic Machines*
Engineering principles can be applied to synthetic biology; this is being put into practice through the annual international Genetically Engineered Machines (iGEM) competition. Simple biological systems could be built from standard, interchangeable parts, and therefore, it was possible to design and construct new biological parts, devices and systems and use these to redesign existing natural biological systems for useful purposes.

PRESENTATIONS ON ENGINEERING MINIMAL BIOLOGICAL SYSTEMS

David Gilbert, University of Glasgow: *Modelling and analysis of the* MAPK *signalling pathway: a case study*
Modelling biochemical networks and development of an associated computational system to facilitate the analysis of the behaviour of these networks: research has focused on the MAPK signalling pathway, investigated by continuously cross-checking between the model and real experimental data generated in-house. Specifically we have been investigating the Negative Feedback Amplifier characteristics of this pathway, as well as developing novel computational techniques. This research was carried out as part of a DTI-funded 'Beacons' Bioscience project.

Jim Haseloff, University of Cambridge: *Tools for bioengineering of plants*
Development of a library of phytobricks provides interchangeable parts that could be used for the biological engineering of plant systems. These parts included promoter elements, transcription regulators, reporter genes and effectors of plant cell behaviour. CellModeller has been used for the construction of a mathematical model for the physical basis of plant cell growth and interaction within a multicellular tissue.

Prasanna de Silva, Queen's University of Belfast: *Switchable molecular systems*
Chemically-switchable luminescent systems control the competition between fluorescence and photo-induced electron transfer (PET) with chemical species, which is the key to the success of such systems. Various switches had been constructed which were now on the market, including a sensor to monitor acidic compartments in cells, and another for blood diagnostics.

BREAKOUT SESSION: SYNTHETIC BIOLOGY RESEARCH

The aim of the breakout sessions was to consider synthetic biology research prompted by the following questions:

- What do we understand by the term synthetic biology and where does my research fit in?
- What is the applicability of the 'modular concept' to biological systems?
- Are there any disciplinary 'language barriers'?
- What do we know of the potential wider impact of synthetic biology?
- How can the Research Councils support and foster this area?

The outcomes of these discussions were reported back to a plenary session, as follows:

What do we understand by the term synthetic biology?

- There may or may not be a need to define synthetic biology. However, there is still confusion about what the term actually means, e.g., to some clinicians synthetic biology is about prosthetic devices.
- There is no agreed definition: it could be 'Engineering new function in living systems and their interactions with physical and chemical systems' or 'Rational design of biological systems for a specific application'. The NEST definition (see background section) was considered appropriate by some groups, but not others.
- The term represents a continuum and the area could become a catch all.
- Synthetic biology is not a new science; rather it is an extension of what has already been done.
- Synthetic biology is a multidisciplinary enterprise and should involve biologists and engineers, as well as others.

- There is a question about whether top-down approaches could be considered synthetic biology, since they would not involve as much forward planning and rational design as would be ideal.
- Synthetic biology covers more than entities that 'do not exist in nature'.

What is the applicability of the "modular concept" to biological systems?

- There was some agreement that modularity was important. However, it was also recognised that better solutions for dealing with synergistic effects were required, such as a better understanding by using computational models or indirect approaches (e.g., design and mutate). The modular concept is a useful, but potentially limited, analogy.
- Re-design of modules to control interactions would make them truly modular.
- There is still a debate to be had about whether biological systems were modular. If not, this would bring the utility of the modular concept into question.
- There is a need to use rational design in applying a modular model: how generic could a module be?
- The modular concept could be expanded to include chemistries other than nucleic acids – e.g. proteins.

Are there any disciplinary 'language barriers'?

- In bridging the disciplines, there is a serious gap in language and expectation; language barriers were observed in breakout discussions.
- Definitions and new vocabulary are required.
- Asking 'dumb questions' is a good way to start getting over the language barrier.
- Different types of explanation are intellectually satisfying for biologists and engineers.

What do we know of the potential wider impact of synthetic biology?

- Synthetic biology can be considered an extension of biotechnology.
- Explaining such research to society should use examples of actual applications; wild analogies and outrageous claims needed to be avoided.
- Risks and fears should be acknowledged and dealt with in a safe, sensitive and effective way.
- Understanding what constitutes a living organism was an interesting undertaking in itself and synthetic biology would enable this.
- Renewable energy was an area of potentially wide positive impact; also other 'green' applications.

How can the Research Councils support and foster this area?

- This was covered under the closing discussion.

BREAKOUT SESSION: DESIGN CHALLENGE

The Design Challenge exercise was devised in order to give delegates a practical opportunity to consider the various aspects of synthetic biology in greater depth. The overall aim was for each group to design novel biological functionality; it was stipulated that the agreed challenge should include the concept of BioBricks (http://parts.mit.edu/registry/index.php/Main_Page) and engineering principles. An important aspect of the Design Challenge was for delegates to give due consideration to the ethical / societal issues that might be raised.

The outputs from the Design Challenge groups are listed below:

- Population-based computing using bacteria

- A carbon dioxide sensor to monitor greenhouse gas sequestration
- Measuring bacterial sound: using quorum sensing mechanisms and a MEMS pressure transducer.
- A bacterial exposure meter for UV light detection
- A bacterial biosensor to detect UV light or DNA damage
- A microbial nitric oxide sensor

CLOSING DISCUSSION

Presentations were made by BBSRC and EPSRC representatives, in which the following points were made:

- Synthetic biology research project applications should be directed to responsive mode. The most likely home for such applications was the Engineering & Biological Systems (EBS) Committee, as synthetic approaches were specifically cited under the systems biology theme. The Biomolecular Sciences (BMS) Committee also covered relevant work. Both BMS and EBS Committees had a standing arrangement with EPSRC to co-fund research projects that spanned the remit of the two Councils.

- Delegates were informed that the workshop report would be submitted to the EBS Committee and drawn to the attention of several BBSRC Strategy Panels. This would lead to BBSRC receiving advice on how synthetic biology should be strategically supported and developed.

- EPSRC stated that synthetic biology was emerging as an important area for future development within the Engineering Directorate. For example, EPSRC had co-sponsored the recent BioSysBio conference at Manchester, and supported Summer Vacation Bursaries for graduates to participate in iGEM last year (both activities were similarly supported by BBSRC). The primary route for synthetic biology applications in EPSRC was responsive mode, but the support for synthetic biology through other activities, such as workshops, networks, etc. was also possible.

- BBSRC commented on the societal and ethical implications of synthetic biology. The role of the BBSRC Bioscience for Society (BSS) Panel was explained, and it was noted that a member of that Panel was also present at the workshop. It was emphasised that BBSRC was giving serious consideration to the potential ethical, moral and societal impacts of synthetic biology. BBSRC has subsequently set up a working group under the BSS Panel to explore this further.

The presentations were followed by a general discussion in which the following points were made:

<u>How can the research councils support and foster this area?</u>

It was agreed that building a community was vital, especially as the gap between disciplines was large. Practical suggestions to encourage this were:

- Research Councils should develop a generic method for building new scientific communities, by drawing upon what has worked well in the past (e.g. networks, ‘sandpits’).
- Research Council-sponsored networks could help develop synthetic biology through forging multidisciplinary collaborations and exposing the UK community to international developments.

- Feasibility studies and responsive mode grants could be generated by networks and future workshops.
- Fostering disciplinary cohesion through the Discipline Hopping scheme.

Communication/meetings:
- A regular network meeting or conference – not necessarily organised by the Research Councils.
- An internet-based consortium, which would be useful for finding collaborators as well as disseminating information.
- Network meeting funding from the Research Councils.
- Organise a meeting based on the *Nanomedicine Canada* conference, where anyone who was interested could attend and research consortia could be formed at the meeting.
- A repeat of this workshop would be helpful.
- Meetings should cover trans-national aspects.

There was agreement that a thematic programme / research initiative was premature for synthetic biology, at this stage, in the UK. There was still much to be done to define the area and bring disciplines together. Comments made were:

- Research Councils should be careful to avoid premature 'professionalisation' of this area (to its longer term detriment) and be cautious about how synthetic biology is defined – how much relevant work is already being done, for example?
- If a thematic programme were launched, it would be important not be restrictive or prescriptive, since synthetic biology was still developing. It would need to include bottom-up approaches.
- Referees/reviewers capable of handling interdisciplinary research were vital in assessment processes.
- High risk fundamental projects should be funded.
- Training was vital – physical scientists would need training in biology and *vice versa*. Biologists stood to gain from the engineer's input to answer biological questions in new ways.
- Research Councils involved would need to ensure that any gaps between disciplines were bridged.
- More industrial partnerships may be beneficial
- iGEM was a valuable entry-level activity in synthetic biology, particularly for drawing in early career researchers.

<u>The wider impacts: incorporating ethics into science</u>

The ethicists / social science delegates were in agreement that participation in the workshop had been worthwhile. Their comments are summarised below:

- Ethicists / social sciences should be involved at early stage in synthetic biology but were unsure how to achieve this. Could ethics/societal issues be integrated at the project development stage?

- The scientific delegates demonstrated awareness of the ethical issues surrounding synthetic biology, and showed a lot of respect and common sense in this regard.

- Based on the design challenge exercise, it appeared that synthetic biology was not yet close to producing real life applications in the main – what could one do with the iGEM toolkits and why? However, thinking of potential applications for environment and health was a good starting point.

- Applications for public good should be sought early in the development of synthetic biology research.

General

Several other points were made in the general discussion, as set out below.

- Synthetic biology was sometimes conflated with *systems biology*. However, there was a different starting point to the former, because a ready-to-engage cadre of researchers was not available at present for the 'dry work': there was no nascent community on the dry side for synthetic biology, as there was for systems biology, because such a community needs engineers, who were, largely, not yet sufficiently engaged with life science research.

- The BBSRC/EPSRC *Centres for Integrative Systems Biology* might be able to help, simply by increasing the future supply of scientists trained in interdisciplinary research - however, that would not solve the problem of bridging disciplinary gaps apparent for today's generation of research leaders, and this needed to be given due consideration.

- Many biologists wanted to engage in synthetic biology research because knowledge from other disciplines would help answer some of the most important questions which are currently intractable, e.g., noise, transcription, the source of stability. Synthetic biology abstractions would help test models of complex systems.

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- All keynote and session speakers
- Session chairs: Professor Alistair Elfick, Professor David Fell and Dr Jay Keasling.
- EPSRC and AHRC for supporting the workshop through attendance

DISCLAIMER

This report was produced by BBSRC in consultation with others, as a result of a workshop attended by independent researchers. The report communicates a range of views, which are not necessarily those of BBSRC.

ANNEX 1

BBSRC SYNTHETIC BIOLOGY WORKSHOP AGENDA

DAY ONE

Session 1: Introducing Synthetic Biology
Chair: Rob Beynon (University of Liverpool)

10.30-10.40	Welcome Rob Beynon, University of Liverpool
10.40-11.30	Keynote Lecture 1 Jay Keasling, Synthetic Biology Engineering Centre at Berkeley (SynBERC) *Engineering microbes for production of low-cost, effective, anti-malarial drugs*
11.30-12.10	Keynote Lecture 2 Mark Bedau, European Centre for Living Technology, Venice. *Social and ethical aspects/implications in the synthesis of living entities*
12.10-12.30	Discussion of keynotes

Session 2: Breakout Discussions
Chair: Rob Beynon (University of Liverpool)

13.20-13.30	Introduction to Breakout Session
13.30-14.30	Breakout Session
14.30-15.00	Reports from Breakout Session

Session 3: Building Blocks & Engineering Principles of Modular Design
Chair: Alistair Elfick (University of Edinburgh)

15.00-15.20	Jason Chin, MRC Laboratory of Molecular Biology, Cambridge *Expanding the functions of living matter*
15.20-15.40	Ben Davis, University of Oxford *Chemical Biology - carbohydrates and proteins*
15.40-16.00	Vitor Martins dos Santos, Helmholtz Centre, Braunschweig *Programmable bacterial catalysts*
16.00-16.20	Jim Ajioka, University of Cambridge *Genetic machines*
16.20-16.40	Discussion of Session 3 presentations

Session 4: Networking Exercise
Led by BBSRC

17.00-17.05	Introduction to Networking Exercise

17.05-18.15 Networking Exercise

Session 5: Design Challenge
Chair: Rob Beynon (University of Liverpool)

18.15-19.00 Design Challenge

DAY 2

Design Challenge - continued

08.45-09.15 Design Challenge: final heads-together for groups

09:15-09.45 Design Challenge presentations

09.45-10.15 Discussion of Design Challenge outcomes

Session 6: Engineering Minimal Biological Systems
Chair: Jay Keasling (University of California, Berkeley)

10.45-11.05 David Gilbert, University of Glasgow
Modelling and analysis of the MAPK *signalling pathway: a case study*

11.05-11.25 Jim Haseloff, University of Cambridge
Tools for bioengineering of plants

11.25-11.45 Prasanna de Silva, Queen's University of Belfast
Switchable molecular systems

11.45-12.20 Discussion of Session 6 presentations

Session 7: Closing Keynote
Chair: David Fell (Oxford Brookes University)

13.15-13.55 Keynote Lecture 3
Frederick Blattner, University of Wisconsin
From genomes to designed genomes: E. coli *and the Synthetic Biology Challenge*

13.55-14.05 Discussion of Keynote 3

Session 8: Funding and Future Directions
Chair: David Fell (Oxford Brookes University)

14.05-14.35 Research Councils' presentation
Supporting Synthetic Biology

14.35-15.00 Discussion and Closing Remarks