Meeting report

A brave new synthetic world

Farren J Isaacs* and Lingchong You†

Addresses: *Department of Genetics, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115, USA. †Department of Biomedical Engineering and Institute for Genome Sciences and Policy, Duke University, 101 Science Drive, Durham, NC 27708, USA.

Correspondence: Farren J Issacs. Email: farren@genetics.med.harvard.edu; Lingchong You. Email: you@duke.edu

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A report of the first meeting on 'Frontiers in Synthetic Biology', Boston, USA, 1-2 December 2008.

Like Aldous Huxley's *Brave New World* at the time of its publication, the field of synthetic biology currently has skeptics and critics among both scientists and non-scientists. But in contrast to Huxley's pessimistic outlook, synthetic biology has the opportunity to highlight the good to society that can be derived from biotechnological breakthroughs. This naturally begs the question: what exactly is synthetic biology? A meeting at Harvard Medical School last December revisited this frequently posed question. Keynote speaker Clyde Hutchison (J Craig Venter Institute, Rockville, USA) offered his perspective: "while some have a strong desire to sort this out, I'm not interested in this question, as it is largely about semantics and not in itself a scientific question".

Nevertheless, an analogy to computer science provides a good basis to describe synthetic biology. If we think of the cell as a computer, the work of synthetic biologists can be simplified into three main approaches: the creation of a minimal computer from basic building blocks; software to program a working computer; and the application of these devices or knowledge gained in the engineering process. We describe here a few of the highlights of the meeting. Presentations covered a wide spectrum of topics, ranging from the engineering of artificial cells and the creation of gene circuits in cell-free, prokaryotic and mammalian systems to the direct synthesis and recoding of whole genomes.

Protocells and cell-free systems

In his keynote address, Jack Szostak (Harvard Medical School, Boston, USA) discussed his group's efforts to create lipid-vesicle-based protocells using basic chemical substrates as building blocks. When starting from scratch, many cellular processes perceived as simple become formidable challenges. For example, a cell not only has to produce a cell wall and replicate intracellular biomolecules (nucleic acids, proteins, lipids), but these processes need to occur in a coordinated manner to produce growth. Szostak gave an interesting example of one problem. Large vesicles were forced through pores of a smaller diameter to try and divide them. This simple strategy worked, but each round of division resulted in significant loss of intravesicular materials: a large sphere holds approximately 40% more material than two smaller, equal-sized spheres with the same total surface area as the large sphere. In this context, Giovanni Murtas (Enrico Fermi Center, Rome, Italy) described his group's efforts to achieve coupling between vesicle growth and synthesis of intracellular materials. They have encapsulated enzymatic reactions for synthesizing vesicle materials within a liposome vesicle.

Given the multitude of technical challenges, the functionality of such 'protocells' remains limited. Researchers in this area predict that the engineering of protocells could eventually lead to insights that will explain the emergence of life billions of years ago. But protocells are more likely to find a use sooner as nano-scale reactors for producing molecules that are difficult to produce in cells, such as cytotoxic proteins.

Components, circuits and cell populations

The dominant flavor of synthetic biology is arguably the integration of non-natural, or synthetic, gene networks into existing cellular pathways to better understand or program cellular behavior. These approaches are analogous to the design and implementation of software that programs customized functions in a working computer, with the distinction that engineering of biological systems is performed in the dynamic context of evolution. Yet, despite the physical access to cellular machinery, programming complex behavior inside cells remains a challenge.

Addressing such a challenge requires not only the development of well-characterized parts (as advocated by the BioBricks Foundation [http://bbf.openwetware.org]), but also a better understanding of different control strategies. Addressing the latter point, James Collins (Boston University, USA) described a series of synthetic gene circuits of diverse function, such as the toggle switch and RNA-based switches, and the integration of simple circuits to generate more complex systems. He described the introduction of one RNA-based switch to give tight control of the expression of a toxin (CcdB) in the bacterium *Escherichia coli*. This enabled precise mapping of the death pathway initiated by the toxin and revealed a common death pathway in *E. coli* exposed to bactericidal agents. Timothy Lu (Harvard-MIT Health Sciences and Technology, Cambridge, USA), from the same group, described the practical application of two re-engineered T7 phages: one encodes a protein that disrupts bacterial biofilm formation and the other encodes a protein that targets an antibiotic resistance mechanism in *E. coli*, improving the efficacy of antibiotics against the bacteria it infects.

For eukaryotes, Pamela Silver (Harvard Medical School, Boston, USA) described a number of artificial gene-control circuits she and her colleagues have devised to carry out predefined functions in eukaryotic cells. One is a eukaryote-specific negative feedback oscillator based on intron-mediated time delay. Transcription of the intron introduces a time delay, enabling the generation of oscillations by the repressor. Interestingly, Silver and colleagues observed that the oscillation characteristics could be modulated by using introns of varying length. She suggested that such intron-mediated oscillations might underlie cell-fate decisions in development.

Beyond single cells, increasing effort is being devoted to programming population dynamics. One of us (LY) described the use of bacterial communication (quorum sensing) to program interactions between two populations of *E. coli*, which resulted in a synthetic predator-prey ecosystem that can generate oscillations in the two populations. This synthetic ecosystem has been used to explore the interplay of cellular motility, population segregation and signal diffusion in the maintenance of biodiversity in microbial ecosystems. In addition to temporal dynamics, cell-cell communication can also be used to generate self-organized spatial patterns, and two such examples were presented at the conference. Jian-dong Huang (University of Hong Kong, Hong Kong) described a system where cell-cell communication in *E. coli* was coupled with cellular motility. The modified bacteria generated a near-perfect, self-organized ring pattern on an agar plate. Ron Weiss (Princeton University, Princeton, USA) described another circuit in *E. coli* designed to generate a Turing pattern (for example, hexagonal arrays of spots) in a lawn of bacteria. These cells synthesize two signals, one serving as an activator and the second as an inhibitor. Under appropriate conditions, the system was able to generate regular spot-like patterns.

In addition to exploring the limits of programming complex dynamics, Weiss proposed that these systems could offer insight into the dynamics of natural systems, such as whether self-organization underlies developmental processes or pigmentation patterns in animal skin.

Emerging technologies and genome engineering

Traditional genetic engineering technologies devised 20 or more years ago are now insufficient for the complex engineering of biological systems required by synthetic biology. Streamlining of DNA synthesis and the development of strategies for efficiently introducing synthetic DNA *in vivo* were discussed by a number of speakers.

Peter Carr (Massachusetts Institute of Technology, Cambridge, USA) described work with the goal of automating the entire DNA synthesis process. He is working towards a pipeline that can integrate oligonucleotide assembly for any desired DNA sequence from high-density microchips on microfluidic devices with optimized DNA error-correction strategies, yielding the required DNA fragment rapidly and at significantly reduced cost. With a similar goal, Heinz Schwer (Sloning Biotechnology, Puchheim, Germany) presented a new method of making DNA sequences for use in protein engineering. Using a library of pre-made double-stranded DNA triplets that act as universal building blocks, Schwer and his colleagues are able to assemble any desired DNA fragment with high fidelity compared to existing DNA synthesis and cloning methods.

Clyde Hutchison described the Venter Institute's "quest for a minimal cell". With the goal of identifying the minimal set of genes that are needed for life, this work pursues two main tracks of research that Hutchison termed synthetic genomics. First, the group obtained 101 fragments of around 5 kb each from commercial suppliers of synthetic DNA and assembled the entire genome of *Mycoplasma genitalium* through a series of *in vitro*, bacteria- and yeast-based strategies. Concurrently, they developed a strategy for replacing the genome of a bacterial cell with one from another species, inserting a genome isolated from *M. mycoides* into *M. capricolum* cells. Hutchison described the merging of these two efforts by transplanting the synthesized *M. genitalium* genome into native *M. genitalium* strains as challenging work in progress.

In complementary research, one of us (FI) described work on genome engineering in *E. coli* aimed at introducing increased genetic diversity into cell populations using a combination of bioengineering and evolution. Our group has developed a highly efficient recombination method that gives large numbers of desired mutations across whole genomes. In one experiment, a new genetic code in *E. coli* is being constructed to facilitate the incorporation of non-natural amino acids and to create safe genetically modified

organisms. The same approach is being applied to obtain genetic diversity for applications in metabolic pathway engineering. On the theme of creating strains with many mutations, Fritz Roth (Harvard Medical School, Boston, USA) described a new high-throughput approach for creating yeast strains with increased combinations of gene knockouts or insertions. This strategy may facilitate introduction of complex genetic circuits into the yeast chromosome.

While a clear and concise definition has yet to emerge, synthetic biology may simply be part of the natural maturation of biotechnology, in which the engineering of biological systems is becoming a formal discipline. Great expectations exist for biotechnology's potential in addressing global challenges in medicine, energy supply and the environment. Can synthetic biology meet these challenges and be embraced by its present skeptics and critics? With hindsight, Huxley's book shows that anticipating how developments will change society is probably unreliable; only time will tell if synthetic biology can channel biotechnology advances to the greater good of society.