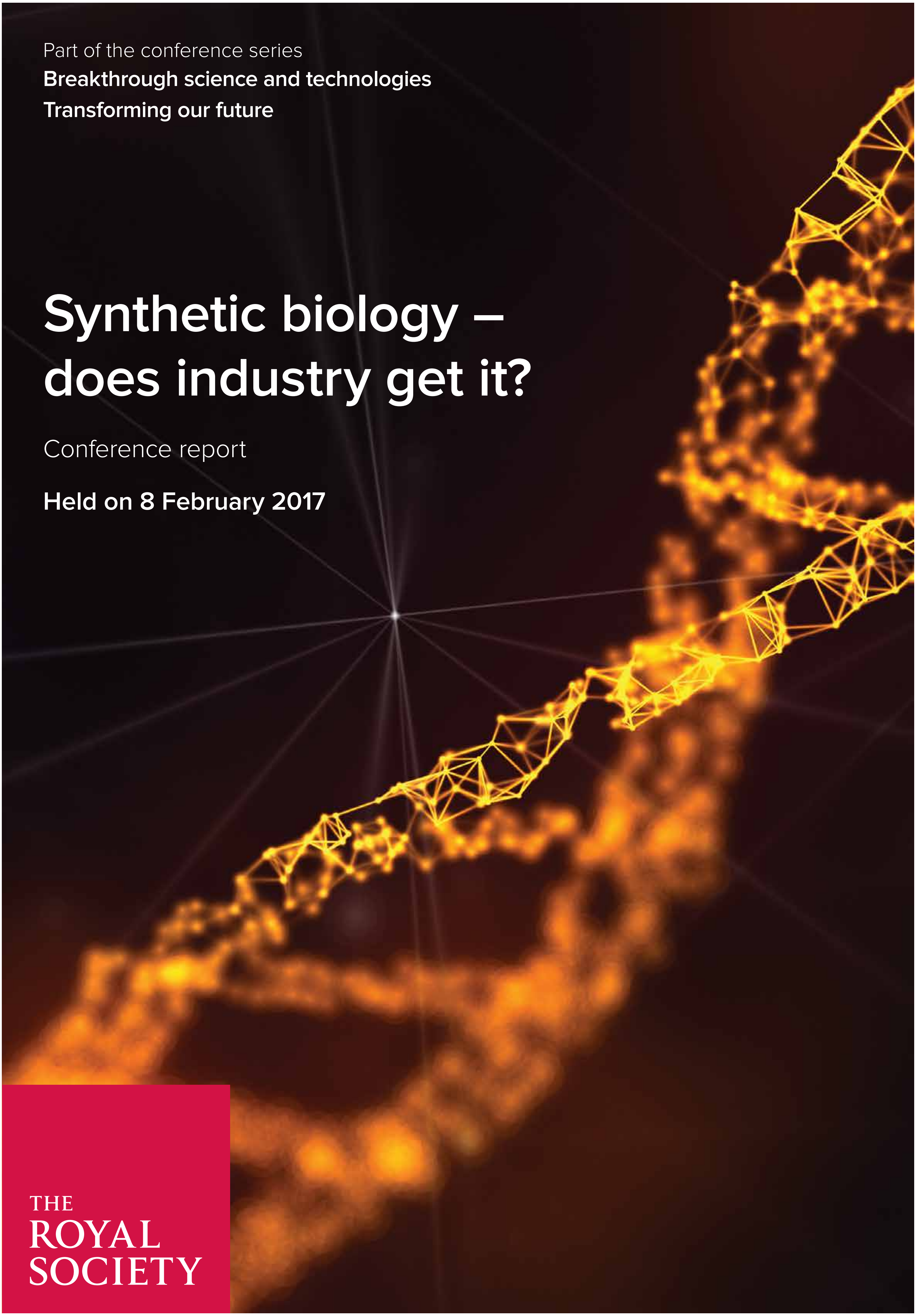
Part of the conference series
Breakthrough science and technologies
Transforming our future

Synthetic biology – does industry get it?

Conference report

Held on 8 February 2017



THE ROYAL SOCIETY

Introduction

On 8 February 2017, the Royal Society hosted a conference that posed the question *Synthetic biology – does industry get it?* It brought together nearly 200 experts from academia, industry and government to provide an honest and open appraisal of how industry is using synthetic biology, acknowledging successes and strengths but also looking at what barriers still need to be overcome.

This conference is part of a series organised by the Royal Society, entitled Breakthrough science and technologies: transforming our future, which is addressing the major scientific and technical challenges of the next decade. Each conference focuses on one or more technologies and covers key issues including the current state of the UK industry sector, future direction of research and the wider social and economic implications. The conference series is being organised through the Royal Society's Science and Industry programme, which demonstrates our commitment to reintegrate science and industry at the Society and to promote science and its value, build relationships and foster translation.

This report is not a verbatim record, but summarises the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society.

Executive summary

Synthetic biology is creating ground-breaking new technologies and applications across a wide variety of industry sectors, from pharmaceuticals to energy. However, challenges remain to the wider industrial uptake of synthetic biology, including the need to demonstrate profitability, concerns over public acceptance, and difficulties with the language and definitions used.

Being able to redesign and modify the internal architecture of the cell is leading to the creation of new approaches in therapeutics, natural product synthesis, biological computing, industrial biotechnology and the energy system. It is also leading to novel commercial opportunities from synthetic peptides for clothing to fighting mosquito-borne diseases.

The ability to rationally design synthetic biological systems to ensure they are reliable and predictable will be key to success. Convergence of science and engineering is, therefore, playing a pivotal role in the field. Not only will this rational design approach encourage investors and established industry to take up synthetic biology to a greater extent, it will also help allay the concerns of the public and regulators.

However, as synthetic biology advances, it will require a workforce with new skills – for example, biology will need more computer science, and computer science more biology – while those in jobs at the risk of being lost will need support through the transition to new business models.

In answer to the question, "Does industry get it?", there was a clear sense that industry is very interested in synthetic biology but that there remains a conservativism that holds back its wider implementation. Industry speakers encouraged synthetic biologists to look at solving the unmet needs of industry and demonstrate the benefits that future products will bring. Researchers should avoid the risk of overselling their new and exciting science - there needs to be a balance between ambitious, long-term scientific targets and working within the existing product development lifetimes in industry.

Even though there remain unanswered questions that demand considerable effort in fundamental research, particularly in chemistry and biology, there is reason to be cautiously optimistic. Synthetic biology stands on the cusp – as the costs of processes fall, the moment where rapid growth in industrialisation will take place is nearly upon us.

Image

Professor Ben Davis, University of Oxford, introduces *Synthetic biology – does industry get it?*

Programming and reprogramming biology

Nature builds a diverse array of polymers from a highly conservative tool box – just 20 natural amino acids are synthesised from the translation of 64 triplet codons. Reprogramming this system to generate polymers from new building blocks will be facilitated by advances in our ability to engineer how the natural biological system works.

Professor Jason Chin, MRC Laboratory of Molecular Biology, described how his team has created organisms that synthesise proteins and polymers from non-natural amino acids through the engineering of new components of the translational process, including ribosomes and aminoacyl-tRNA synthetases. He highlighted the value of building orthogonal systems in biology, that can be co-opted for new purposes. Recent applications were discussed, including optical remote control of intracellular protein function and the development of protein therapeutics.

Professor Chin also talked about how his research goals have led him to tackle 'known unknowns', such as whether codons can be replaced by synonyms without disturbing protein interactions and disrupting cell function. Chin's research is addressing these questions through the development and application of methods to rapidly redesign and replace whole genomes; using these approaches he is uncovering the hidden layers of regulation that may underpin natural biological function.

> "Intelligent combinations of chemical and biological synthesis… provide many new opportunities for synthetic biology"
>
> **Professor Jason Chin**

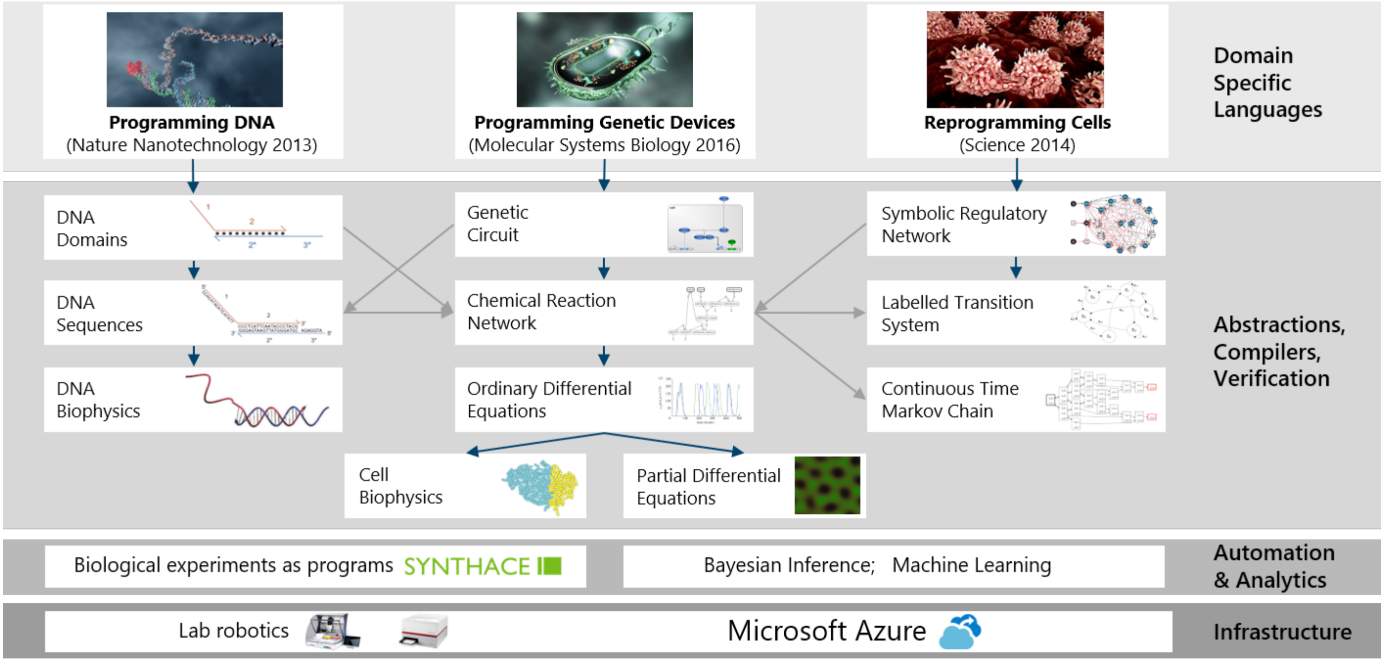
In declaring that programming biology could enable the greatest revolution in technology this century, Dr Andrew Phillips, Microsoft Research, compared the speed of development in reading and writing genomes with Moore's Law. He then laid out Microsoft's approach to developing a biological computation platform (see Figure 1):

- Improve our understanding of how biological systems compute, by uncovering the molecular data structures, biological algorithms and fundamental principles of computation in biology.
- Develop the relevant biological programming languages and compilers, together with characterised components that can be used to design more complex systems.
- Develop methods for digitally encoding biological experiments, to improve automation and reproducibility, and integrate these with an in-house wet lab.

Programming DNA through DNA Strand Displacement (DSD) is being used to develop a language for designing DNA devices and circuits. Dr Phillips illustrated their DSD language approach through the development of a biological consensus algorithm in DNA, in collaboration with the University of Washington. The speeding up of molecular circuits through localisation was also discussed as was the logical next step of molecular circuits embedded within cells for disease detection and ultimately treatment. Phillips also presented a language for programming genetic devices and the development of independent receiver and sender devices that allow precise cell communication in cell populations.

FIGURE 1

Microsoft's biological computation platform focuses on three main application areas: programming computation in DNA molecules; programming genetic devices that are inserted into cells to modify cell behaviour and reverse-engineering specific cell types so that they can be reprogrammed for targeted applications.



Rational design and bio-based supply chains for new medicines

Both Professor Christina Smolke, Stanford University, and Dr Edmund Graziani, Pfizer, acknowledged the debt that modern medicines owe to natural products.

Smolke observed that while more than 50% of current medicines are derived from plants, problems associated with pests, climate and complex downstream processing lead to unreliable supply.

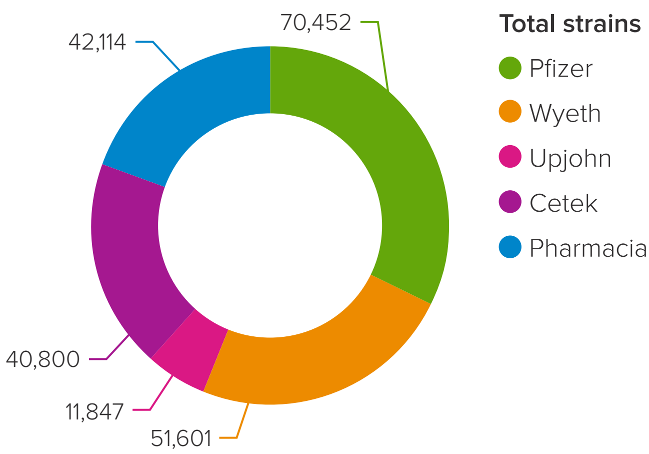
By outlining her work on microbial biosynthesis steps, Smolke gave an alternative vision to drug production. Barriers that need to be addressed were also described, including the gaps in our knowledge of plants' biochemical pathways and the loss of functionality that may occur when plant enzymes are put into yeasts cells. Emulating the way plants split intracellular processes across different cell types, Smolke has compartmentalised enzymes within the yeast cell to direct specificity.

Professor Smolke stressed the need to understand biosynthetic pathways and establish the building block toolbox of common platform molecules and organism strains to take forward into production. Recent developments in research leading to common building blocks are allowing efficient access to structural and functional diversity. For her team, it was a 10 year process to develop the first end product but it has taken just 12 months to get the second.

Graziani argued that since microbial secondary metabolites are the products of natural selection, they a priori possess biological activity, but not necessarily against pathways important in human disease. The pharmaceutical industry has had many successes with natural products and as it is possible to design organisms capable of making drug-like small molecules, Graziani believes the goal for the synthetic biology community should be to design a system that can evolve small molecules under the selective pressure of a biological assay.

FIGURE 2

Pfizer's strain collections.



Adapted from the presentation of Dr Edmund Graziani, Pfizer

From his own work, Graziani noted the improvements in long-term stroke treatments provided by ILS-920, achieved by the synthetic modification of rapamycin, which helped identify new binding partners. In another example, Graziani explained how engineering an antibody-drug conjugate payload allows it to remain benign until the payload is released in the target tumour. Recent successes through metabolic engineering of a wild-type strain have delivered a fifty-fold yield improvement.

In the future, Graziani hopes to be able to take advantage of the huge potential locked up in Pfizer's large microbe collection (Figure 2) and, through genome sequencing and analysis, identify biosynthetic gene clusters and predict the compounds they can make.

The energy challenge and synthetic biology

Outlining the multiple challenges facing the energy industry by 2050, Dr Jeremy Shears, Shell, pointed out that while energy demand will have doubled its 2000 level, carbon dioxide emissions must be halved.

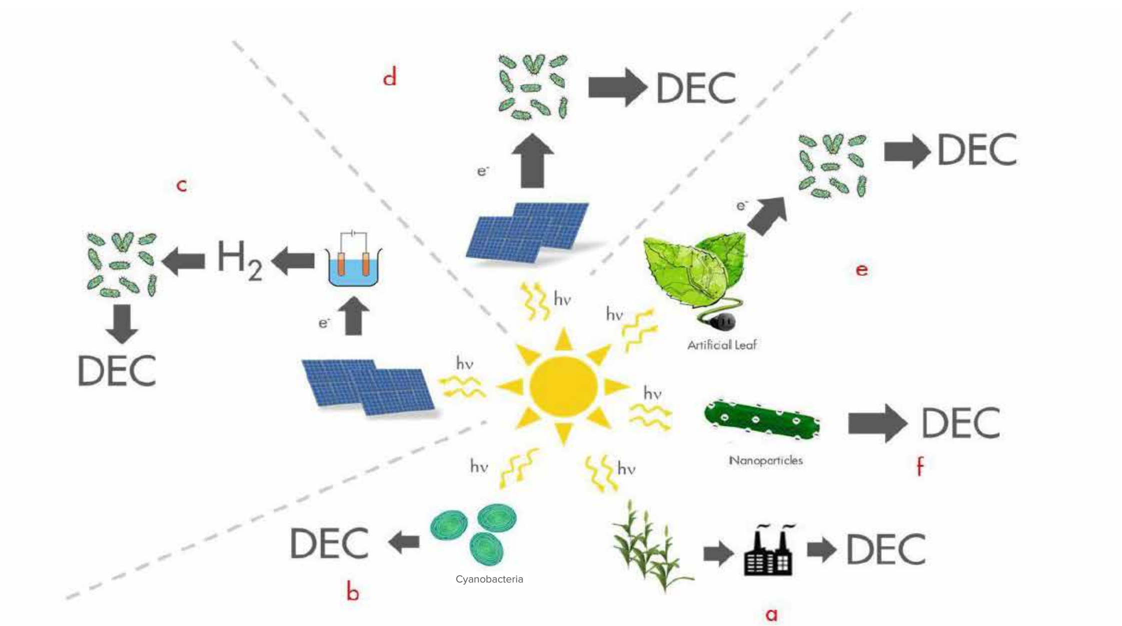
Taking the long view, Dr Shears presented an optimistic vision where synthetic biology will be a key technology to help in the energy transition to renewables and meet our global energy needs. However, for this photonic future to arrive, there is an urgent need for dense energy carriers (DECs) that enable the long distance transport of energy, long term and large scale energy storage, and convenient use in high-performance transportation (Figure 3).

> "It is challenges around capital costs and processes… that's preventing a massive roll-out of biology in the energy sector"
>
> **Dr Jeremy Shears, Shell**

Shears gave conceptual bio-pathways to DECs, including photovoltaic panels, artificial leaves and nanoparticles, with the most likely success being suggested as a combination of solid state and biological systems. However, the design of this bio/solid-state interface will be a major obstacle. He also suggested that the ideal DEC may still be diesel, illustrating a proof of concept developed in partnership with the University of Exeter Microbial Biofuels Group using engineered *E. coli* to produce biodiesel. Another possible way forward is using synthetic biology to increase the efficiency of known pathways for methane activation and alkane chain elongation, an area of sustained research interest that has yet to translate into commercial success.

FIGURE 3

Conceptual biological pathways to dense energy carriers (DECs).



The emerging synthetic biology industrial ecosystem

Covering 'shoes from spider silk', 'Moore's Law for the SynBio industry', and 'biologists as rock-star designers', Dr Jason Kelly, Ginkgo BioWorks, highlighted synthetic biology's progress into new markets, thanks to biology's fundamental programmability.

Examples included artificial leather, major-brand sports shoes and designer clothing ranges incorporating artificial spider silk peptides, and yeasts that produce the fragrances of roses or the flavours of mint. Ginkgo BioWorks, which now has ten flavour and fragrance cultured products, is making its own move into a total market for all plant extracted ingredients worth in excess of $56 billion.

Dr Kelly also contrasted synthetic biology with the electronics industry, highlighting the million fold drop in DNA sequencing prices over the last 15 years, equivalent to moving from desktop PCs to smartphones in less than five years. Highly automated bio-foundries, such as Ginkgo's own BioWorks, have rapidly expanded output and efficiency (Figure 4).

Dr Kelly concluded by pointing out the sophistication of plants compared to man-made machines, as they are self-repairing, self-assembling, self-replicating and self-renewing, and operate from the nanoscale to the continent scale.

> "The missing component is our ability to design biology"
>
> **Dr Jason Kelly**

FIGURE 4

Through improvements in automation and lab design, Ginkgo's BioWorks 1 increased output by 500% and efficiency by 200% in 2016. BioWorks 2 (shown) is now also open and BioWorks 3 will be on coming on stream in 2017.

Getting synthetic biology into industry

Has industry been sceptical of new advances in synthetic biology? There was an admission that there exists a conservatism within industry that stands in contrast to the more entrepreneurial spirit among the synthetic biology community. However, many sectors were engaging more with the field, although the term 'biotechnology' is still often preferred to 'synthetic biology'. This terminology mismatch runs the risk that the full potential of synthetic biology is missed, in particular the design elements it brings.

The future trajectory of synthetic biology in industry will depend on a number of factors, including:

- The growing awareness that it will be fundamental to helping us manage the Earth's resources.
- The impact it will have upon many other processes and industries.
- The massive challenge presented by moving up scale, especially the financial investment necessary.
- The ability of research leaders to champion synthetic biology within their companies and convince their senior management of the opportunities it offers.
- Focusing on what products synthetic biology will create, and the value through improved performance they bring, rather than the underpinning technology.
- Convergence between product development lifetimes of 18 months in some industry sectors and synthetic biology's longer-term horizons, supported by advances in bio-foundries and the boost to speed they provide.
- The need for predictability – design approaches, high throughput screening and careful data management will all be features of finessing the predictability of synthetic biological systems for industry.

"We're getting far more requests through our businesses than we've ever had before"

Neil Parry, Unilever

Interest in synthetic biology varies sector by sector. For example, while the broader chemicals industry is not yet engaged, speciality chemicals, with its heavy dependence on bio-based ingredients, has a greater understanding, especially when products are high value. In the pharmaceutical sector, synthetic biology offers opportunities from making manufacturing processes more efficient to delivering personalised medicine. However, the risk/reliability profile needs to be considered. It was noted that while artificial viruses and in-cell therapeutics are exciting, there are lots of less risky ways of developing new drugs and treatments.

Advances in academic research make companies' international networks of university collaborators essential in helping them develop disruptive new technologies. However, when working with industry, academics need to 'get in early' and identify what industrial unmet needs synthetic biology can address. They must also understand the whole value chain, from lab to pilot plant to production, and accept that industry can and does change its mind.

"Look less at the system and the technology, look more at the product"

Hadyn Parry, Oxitec

The example of the biotech boom and crash of the 1990s was used as a cautionary example for synthetic biology. Like biotech, synthetic biology will grow and be profitable as it picks off the low-hanging fruit, but sustainability will only come if it can successfully address the more difficult problems. In biotech, the US had amassed significant expertise and finance to survive the crash of the late-90s, whereas in the UK, which had invested in biotech later on, the sector was badly hit. There was optimism that the UK was better placed to avoid the same pitfalls with synthetic biology and that the benefits from the field will be spread more globally than with biotech's US dominance.

Regulation and public acceptance

Proportionate and appropriate regulation will play a major role in the development of synthetic biology, particularly as the experience of the public and regulatory response to GM crops still looms large in the memories of many working in the sector. A number of suggestions and examples were raised about how synthetic biology can avoid the same fate, especially as signs of a backlash are emerging in the US:

- The technology should be framed with what is possible now rather than what may be possible in the future.
- Regulation must be proactively and transparently addressed.
- Using a 'trial and error' approach, with a lack of data, carries a risk in a regulatory environment that presumes guilt until proof of innocence.
- There is a need for expert-led regulators that are non-political – Brazil's approach of a full risk/benefit assessment undertaken by expert-led regulatory panels was highlighted.
- In any situation where a high risk/high reliability profile exists, the regulatory environment must be friendly. Regulators are prepared to be sympathetic if a new technology is used to address an unmet medical need.
- If synthetic biology is considered digital encoding of biology rather than chemical processing, it was proposed that regulations be modelled on an electronics regime rather than chemicals. However, such an approach would not be suitable – whereas an electronic device, such as an iPhone, can be proved and developed within a consumer environment, the products of synthetic biology will face regulation before consumer contact.

"Regulation is also an issue and it needs to be more proportional and more adaptive, particularly for biological products."

Professor Joyce Tait

- EU over-regulation was felt by some to have damaged biotech, particularly in agriculture, where regulators and politicians have taken full account of the risks but not the benefits that might be derived. Leaving the EU may give the UK a chance to shift the argument more towards science.

Intrinsically linked to the issue of regulation are concerns about public acceptance. Again it was argued that synthetic biology must demonstrate that its products are better products not just better technology, and practitioners must take care not to make over-ambitious claims. If politicians fear that the public will not accept synthetic biology, it will be the responsibility of those in the field to transparently explain the technology and contribute to the regulatory environment.

"There is a whole movement in synthetic biology that wants to have this open source environment where you can democratise the technology."

Professor Paul Freemont, Imperial College

Reductionism – biology, computer science or engineering?

Synthetic biology has brought engineering concepts to the world of microbiology and this coming together of disciplines was discussed during the conference. Many biotech start-ups now have more engineers and computer scientists than biologists, highlighting that a good understanding of engineering is an advantage for biologists.

Rational design may be the driver for dry lab time at the expense of the wet lab. However, there is an incomplete understanding of the intricacies of complex biological systems and we do not yet have a complete toolbox that we can work with. Although the field utilises a significant amount of electronics and software, unlike most electronic circuitry, biological systems generate a lot of noise that is difficult to tune out. Furthermore, the possibility of evolution within synthetic biology systems cannot be ruled out. Reductionist views of genes as pipes and circuits, and biologists as plumbers and electrical engineers, were rejected.

> "The engineers are here."
>
> **Steve Bates OBE, BioIndustry Assocation**

Talent and skills

Advances in synthetic biology will result in changes to jobs, skills and careers paths, requiring thought about future education and training:

- Synthetic biology is creating a convergence in disciplines, and the UK, with its strength in IT, maths, chemistry and biology, is in a good position to take advantage. However, there is a shortage of computing courses in the UK that cover any aspect of biology.
- There is a need to inspire the next generation to be excited by and comfortable with advances in the science – expanding the model of the iGEM competition would be a good way of achieving this.
- Transitional help will be required for older industries like farming, where jobs and businesses will be affected by advances such as those outlined by Smolke and Kelly.

> "How do we reach out into education? I take that seriously… unless we do, that will be a rate limiter"
>
> **Dr Virginia Acha, ABPI**

Image
Dr Jason Kelly, Ginkgo BioWorks talks to student members of the University of Oxford's iGEM team.

Acknowledgements

Organisers

Professor Ben Davis FRS, University of Oxford
Professor Paul Freemont, Imperial College London
Steve Bates OBE, Chief Executive Officer, BioIndustry Association

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Dr Andrew Phillips, Head of Bio Computation Group at Microsoft
Dr Jeremy Shears, Global Manager, Innovation and New Energies, Shell Projects and Technology
Dr Edmund Graziani, Head, Synthetic Biology and Natural Products, Medicinal Design, Pfizer
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Hadyn Parry, CEO, Oxitec Limited
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- Supporting international collaboration
- Demonstrating the importance of science to everyone

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Registered Charity No 207043
Issued: May 2017 DES4433_4