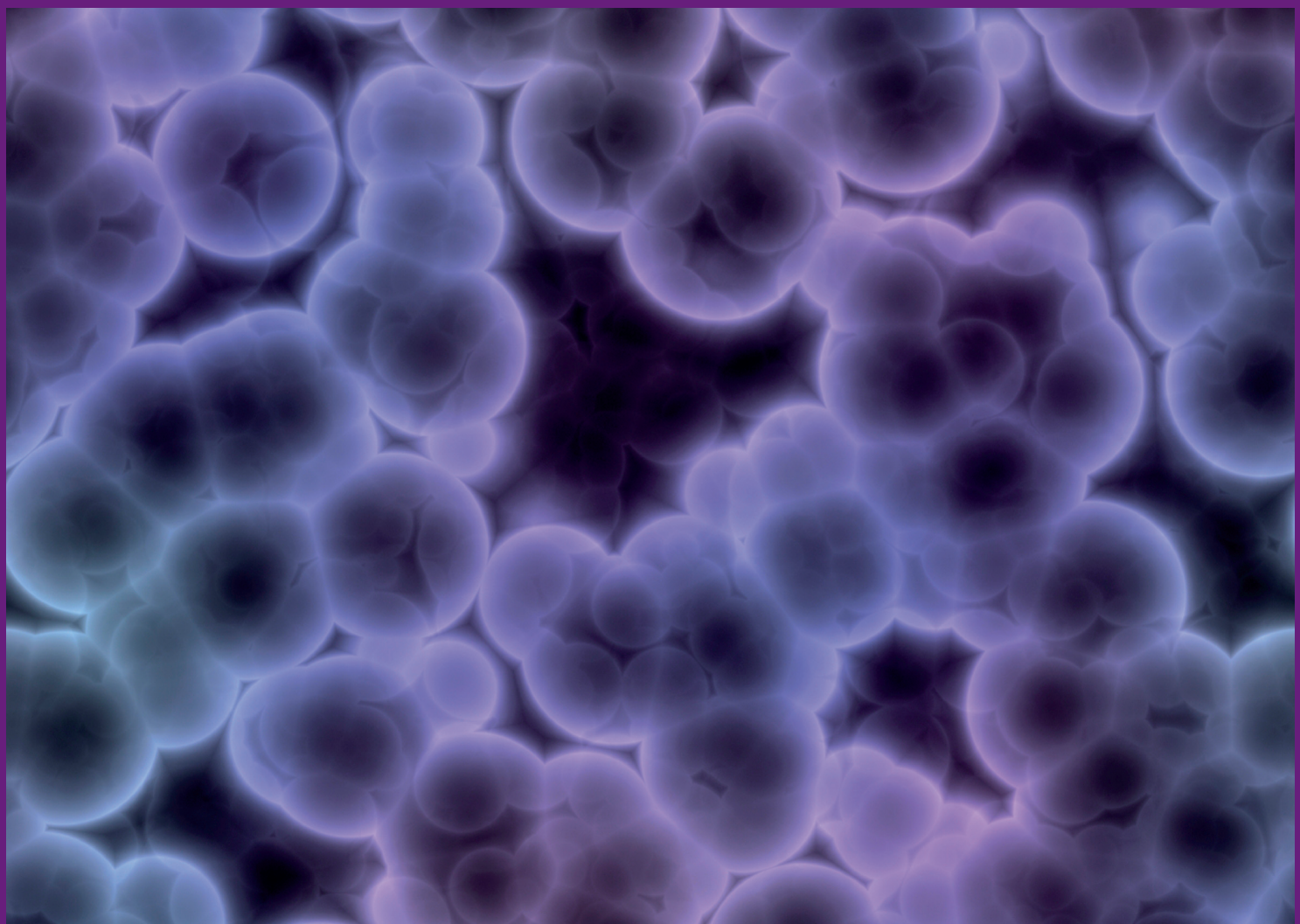
Engineering Life
The emerging field of synthetic biology



RSC | Advancing the Chemical Sciences

INSTITUTE OF BIOLOGY

IOP Institute of Physics

www.rsc.org

Synthetic biology is a new, rapidly developing and potentially controversial area of interdisciplinary research. A quantitative field that aims to design, model and construct new biological systems to carry out novel tasks, synthetic biology takes a rigorous engineering approach to biological systems.

Researchers suggest that this emerging field could offer societal, medical and environmental benefits. However, the ethical and social implications are considerable, and there is an ongoing discussion regarding whether current regulations are sufficient to address all potential outcomes of work in this area.

Scientists from engineering, physics, chemistry and biology are increasingly engaged in synthetic biology. For synthetic biology research and industry to flourish in the UK, research capacity, education and training need considerable expansion.

To understand the emerging field of synthetic biology, the Royal Society of Chemistry held a seminar, in collaboration with the Institute of Physics and the Institute of Biology, to discuss the evidence on 24 April 2008. Professor John McCarthy, chair of the RSC's Chemistry Biology Interface Forum and Director of the Manchester Interdisciplinary Biocentre, chaired the meeting.

Dr Philipp Holliger, Programme Leader at the MRC Laboratory of Molecular Biology outlined the science behind synthetic biology. Professor Richard Kitney OBE, Professor of BioMedical Systems Engineering and Chairman of the Institute of Systems and Synthetic Biology at Imperial College London, discussed current research capacity, funding and support for synthetic biology in the UK. Professor Brian Wynne, Associate Director of the ESRC Centre for Economic and Social Aspects of Genomics addressed the social and ethical issues.

The origins of synthetic biology

Watson and Crick's publication of the structure of DNA in *Nature* in 1953 marked the first phase of the molecular biology revolution. The sequencing of the human genome in 2001 represented a further major milestone, although already in 1978, the Nobel Prize in Physiology or Medicine was awarded to Werner Arber, Dan Nathans and Hamilton Smith for the discovery of restriction enzymes, "chemical knives" that can be used to cut DNA into defined fragments and are a key tool for synthetic biologists. Polish geneticist Waclaw Szybalski commented that their discovery opened up *"the new era of synthetic biology where not only existing genes are described and analysed but also new gene arrangements can be constructed and evaluated."* [1]

'Potential applications likely to benefit from synthetic biology include biofuels, biosensors, biomaterials, therapeutics'

A quantitative approach

Historically, biology has been a descriptive, qualitative science, using a reductionist approach to categorize and explain living systems. Emerging during the 20th century, quantitative biology has more in common with physical science and engineering in its approach to modelling systems. Indeed, the most pervasive manifestation of this trend, systems biology, evaluates the emergent properties of biological systems in terms of integrative computational models.

Synthetic biology aims to go beyond this analysis to the synthesis of complex biological based or biologically inspired systems to display functions that either mimic nature or that go beyond nature. Paraphrasing G.B. Shaw's *Back to Methusalem,* Holliger says that where traditional biology looks at things that are, and ask the question: "Why?" Synthetic biologists like to dream of things that never were, and say: "Why not?"

Models derived from systems biology form the basis for engineering novel systems, i.e. synthetic biology. To understand living systems in detail, it is fundamental that the models should predict behaviour that researchers can test, according to McCarthy. Biosystems studies increasingly depend on inputs from computing to the physical sciences and engineering.

Living systems comprise diverse molecules engaged in interactions that give rise to various levels of complexity. Small molecules and macromolecules

Escherichia coli (E.coli) a bacterium found in the lower intestine

interact to form complexes. These interact structurally and functionally forming pathways and circuits responsible, for example, for metabolic reactions catalysed by enzymes. At the next level, huge gene networks form between biological molecules in living cells. A quantitative approach goes beyond categorising these molecules and instead studies their complex interactions. The combined effect is often greater than the sum of individual interactions – this is known as "emergent behaviour."

Synthetic biology has a value as a pure science in adding to the fundamental understanding of biological systems. Potential applications likely to benefit from synthetic biology include biofuels, biosensors, biomaterials, therapeutics, and ultimately, hybrid devices - engineered systems that integrate biological and non-biological components. In the next decade, organisms and biomolecules with greatly expanded chemistry will provide materials and even evolutionary processes to nanotechnology and materials science, and allow the synthesis of novel nucleic acid and protein-based drugs. Other applications include bioremediation for the cleanup of toxic spills, targeted tissue regeneration, and search and destroy vehicles to target disease.

Exponential progress

The rate of progress in DNA sequencing and synthesis has been likened to the computer industry, where processor capacity per unit cost doubles roughly every two years - a phenomenon known as Moore's Law. Sequencing the first human genome took ten years and cost $3 billion. In February 2008, the Californian company Illumina claimed it had sequenced a human genome in less than four weeks for approximately $100,000[2].

'known as biobricks or bioparts, parts are typically placed in cells like *E. coli*, to produce devices'

Although the computing analogy is helpful in developing hierarchies and breaking down complex systems into manageable subsystems, it has limitations. Holliger suggests we know much less about complex dependency and how parts really function together within a cell than we do about computer chips. How a biosynthetic device functions, and if it functions at all, may depend heavily on the genetic make up of the host cell, its metabolic state, and even on the location of various elements within the genome.

Technological advances in high throughput sequencing and gene synthesis provide the building blocks for synthetic biology. One example of a new property engineered by rearranging the building blocks from two organisms is bacterial photography. *E. coli* is a gut bacterium used to living in the dark, but researchers added a light sensor from the photosynthetic cyanobacterium, *Synechosystis*. A further *E. coli* gene was swapped for one that triggers enzyme expression leading to synthesis of a black pigment. A layer of these bacteria now forms photographic film with resolution of up to 100 mega pixels when the bacterial switches are triggered by light.

Further examples of the building block approach include work towards creating cancer invading bacteria or "biobots." The low oxygen environments typical of tumours in the body switch on an invasion gene, prompting the bacteria to invade cancer cells. This potential selective delivery mechanism for anti-cancer drugs shows how cellular behaviour can be programmed through signalling cascades

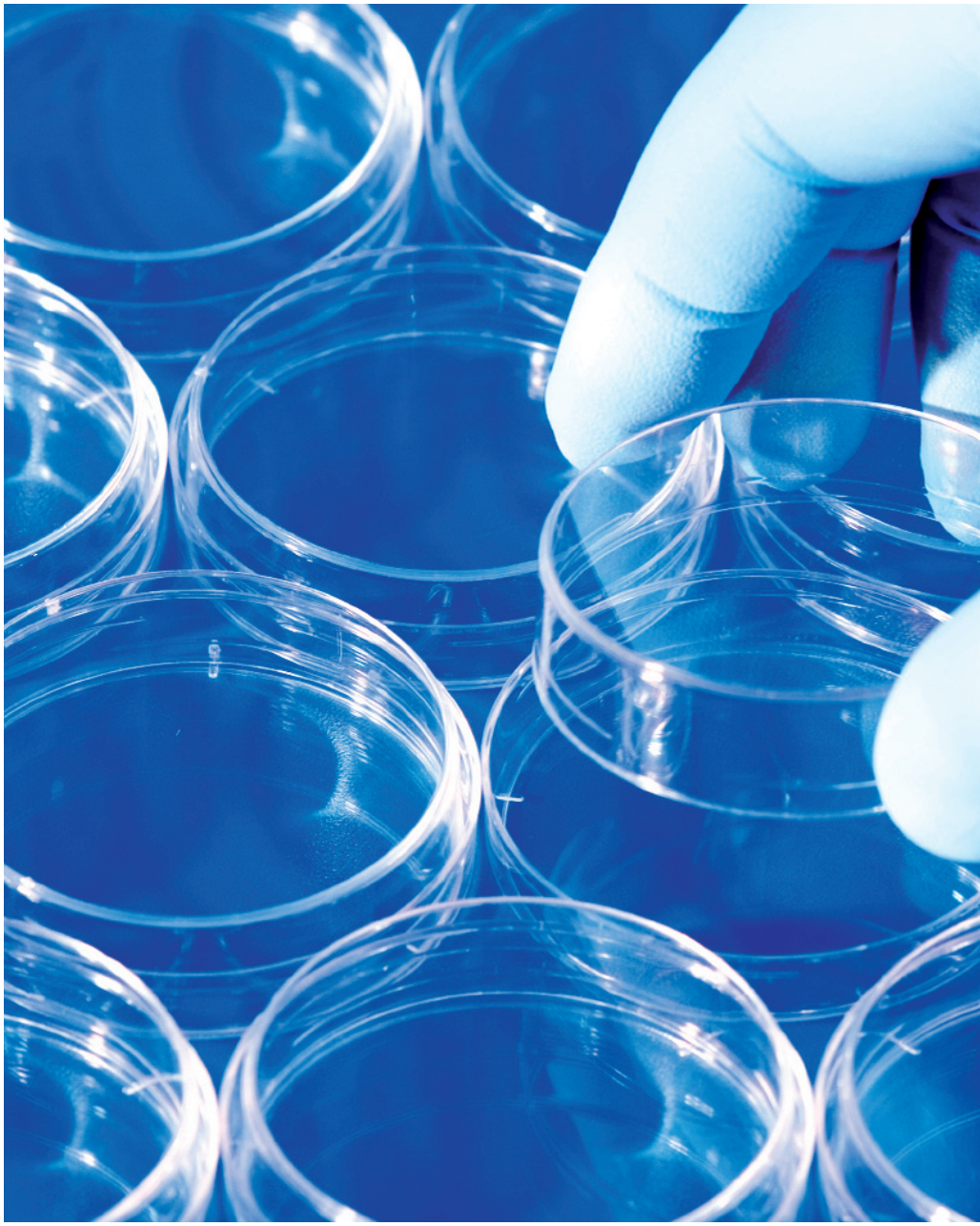
triggered by environmental cues. Other applications include tissue remodelling with genetic programmes that might be integrated into stem cells.

Drugs synthesised by engineered microbes could be cheaper to produce. The anti-malarial drug artemisinin derived from sweet wormwood is expensive and difficult to obtain by conventional organic chemistry. *E. coli* and bakers' yeast can provide a faster path to precursor artemesic acid in ever increasing yields, greatly reducing artemesinin production costs.

To overcome complex dependence on the host organism, synthetic biologists employ several strategies. One is to decouple a genetic system or device from host-cell interactions and is known as orthogonality. A functionally orthogonal pair - a tRNA/synthetase pair that react together but not with endogenous organism pairs - is evolved to selectively accept unnatural amino acids. Almost all known forms of life use the same common 20 amino acids to make proteins. Such technologies allow the chemistry set of proteins to be expanded from 20 amino acids to many more. Synthesis of proteins with unnatural amino acids has many applications both in scientific investigation and pharmacology. Using these building blocks, researchers can reprogramme cell behaviour to create new phenotypes.

A more radical, "top down" approach to reduce complex dependence involves stripping unnecessary elements from a genome. For instance, researchers have reduced the *E. coli* genome by about 15 percent. The result is a strain much more stable for genetic experiments.

"Bottom up" approaches include building systems with lifelike properties such as growth, reproduction and adaptation from simple components. Directed evolution is an approach that allows synthetic biologists to explore functions that don't require a natural environment, for which they may not even understand the molecular basis. A powerful technique, directed evolution creates novel functions in synthetic biology, and is central to efforts to expand the chemistry that can be encoded within DNA. Examples include compartmentalized self-replication (CSR), where a polymerase replicates only its own encoding gene. The reactions take place in an emulsion comprised of water droplets suspended in oil, creating compartments akin to artificial cells. This technique can be used to create new forms of DNA such as those soluble in liquids other than water. Holliger suggests that expanding the chemistry of the molecules of life has exciting applications, for example, in nanotechnology and materials science.



Drugs synthesised by engineered microbes could be cheaper to produce

DNA is a particularly attractive material to construct nanostructures and devices, because synthetic biologists can control its make-up with atomic precision.

Engineering synthetic life

An important question concerns whether we can synthesise life itself, and if so whether this would provide answers about how life began. Experiments to make prototype cells (protocells) containing self-replicating RNA address this question. These quasi-biological systems would be capable of growth, division, and evolution. These would still be greatly dependent on being "fed" chemicals, but might manifest certain features of living systems.

'...considerable investment over the last five years puts the US at the forefront of synthetic biology'

Kitney outlined how synthetic biologists apply engineering and physical science design approaches to biology. Engineering systems are built from a hierarchy comprising parts, devices and systems. Characteristics at each of these levels are well defined and reproducible.

The engineering cycle involving detailed modelling, design, implementation, testing and then further modelling is now being applied in synthetic biology. Synthetic biologists aim to build a device, or system, from standard parts. Sometimes known as biobricks or bioparts, these parts are typically placed in cells like *E. coli*, to produce devices, all of which are currently relatively simple and on the nanoscale.

Biobricks:

- Parts – encode biological functions (often modified bacterial DNA)
- Devices – made from a collection of

parts, these encode human-defined functions (e.g. logic gates)
- Systems – perform tasks (e.g. counting)

Specification sheets for standard parts are listed on the MIT registry website[3]. Currently there are some 800 standard parts listed. The international Genetically Engineered Machine competition (iGEM) is an international arena where student teams compete to design and assemble engineered machines using advanced genetic components and technologies[4].

'Academic organisation, funding streams and research assessment mechanisms must evolve to encourage the growth of interdisciplinary research...'

Funding

Synthetic biology research within US universities is particularly strong and considerable investment over the last five years puts the US at the forefront of synthetic biology. For instance, the National Science Foundation contributed funding worth $16 million over five years for a new synthetic biology centre at the University of California at Berkeley[5], launched in 2006. BP has invested $500 million to fund research into new forms of energy, using synthetic biology, through a consortium led by UC Berkeley, to which the Gates Foundation is another contributor. Research at the Whitehead Institute at the Massachusetts Institute of Technology is also notable[6].

US biologist and businessman J. Craig Venter was instrumental in mapping the human genome. Venter's own DNA is the subject of the first complete (six-billion-letter) genome of an individual human. He is also seeking to patent the first human-created life form. The new J. Craig Venter Institute was formed in October 2006 through the merger of several affiliated and legacy organizations. In addition to genomics, the Institute studies the societal implications of its research. Research involves clean energy, synthetic biology, ethics, law, and economics. The Institute employs over 400 people, including Nobel laureate Hamilton Smith.

In the UK a three-year inquiry into systems biology (also incorporating synthetic biology) by the Academy of Medical Sciences and The Royal Academy of Engineering[7] published in 2007 had four main recommendations.

These were:
- to establish a number of new major systems and synthetic biology centres in the UK;
- additional investment;
- to create an interdisciplinary research environment;
- to foster interdisciplinary skills and create interdisciplinary research environments.

The new centres should be located within leading universities internationally competitive in biology, medicine, engineering and physical sciences research. They must be a focus of activity effectively networked to smaller centres in other universities, including those currently being established by the BBSRC and the EPSRC, and linked to international initiatives. An investment of approximately £325 million is required over a period of 10 years to establish three to five new centres.

The interdisciplinarity of systems biology poses a challenge to the traditional university department structures and the current arrangements of research grants committees in the public, private and charity sectors. Academic organisation, funding streams and research assessment mechanisms must evolve to encourage growth of interdisciplinary research activities such as systems biology. This means a substantial change in culture, in which biology and medicine become more quantitative. *"Universities must break down barriers between disciplines and consider new methods of organisation that promote novel scientific approaches,"* Kitney suggests.

Given the urgent need to develop the necessary skills required for systems and synthetic biology, universities should create new postgraduate courses and expand postdoctoral opportunities. Undergraduates, including medical students, should be offered options in the core disciplines that support systems biology, as well as increased exposure to interdisciplinary problems and modules.

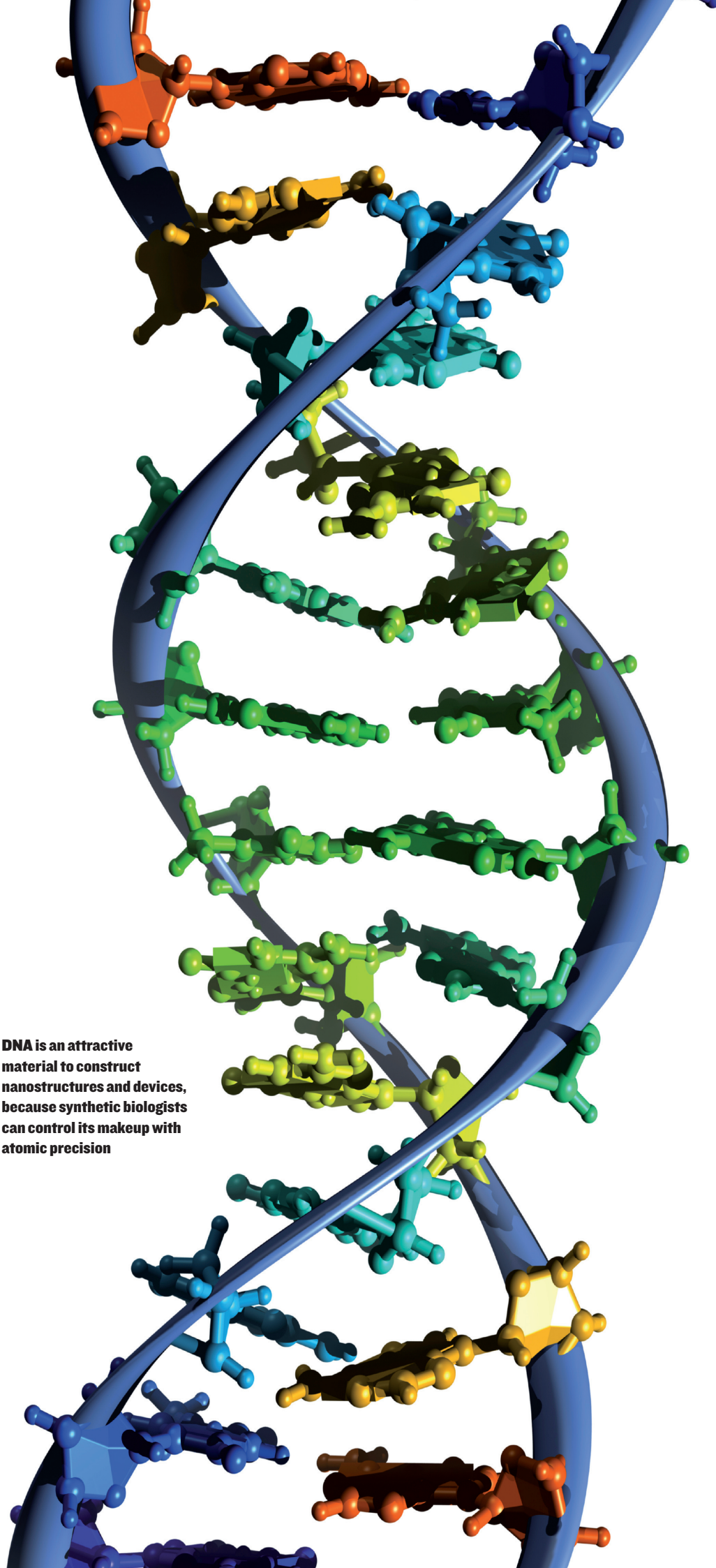
Courses in biology and medicine for engineers, mathematicians and physical scientists must be combined with an expansion of mathematical training for biological and medical scientists to develop multi-skilled, interdisciplinary teams. In view of the shortage of trained personnel in the UK, overseas recruitment may be necessary.

Bodies such as the Royal Society are actively engaged in reviews and discussion groups on synthetic biology, and research councils are moving to ensure that funding is available.

The BBSRC has already set up six systems biology centres, along with Engineering and Biological Systems Grants and Synthetic Biology Network Grants 2008 (with EPSRC). The EPSRC will also invest £3-5 million in one or two universities to underpin synthetic biology, and fund grants. UK universities leading synthetic biology research include Imperial College London, and the Universities of Cambridge, Edinburgh, Glasgow and Manchester. A number of these are developing undergraduate and postgraduate courses in synthetic biology.

The ESRC also funds three centres on genomics-related social, scientific, and ethical scientific research: Centre for Social and Economic Research on Innovation in Genomics (Innogen) at the University of Edinburgh, Centre for Genomics in Society (Egenis) at the University of Exeter and Centre for Economic and Social Aspects of Genomics (CESAGen) at Lancaster and Cardiff Universities. In addition, it funds a Genomics forum and a considerable amount of responsive-mode research in various UK universities. Much of this and the Centre's research is with natural sciences partners.

The European Union has funded several projects under New and Emerging Science and Technologies[8] (NEST) within the Sixth Framework Programme (FP6), and further support is likely under FP7 as part of health and biotechnology themes. One example under NEST is TESSY[9], a series of expert workshops and other activities to coordinate research activities that are currently scattered across European regions and scientific disciplines.



DNA is an attractive material to construct nanostructures and devices, because synthetic biologists can control its makeup with atomic precision

A third industrial revolution?

Kitney argued that the confluence of biology, engineering, and physical science in synthetic biology will result in a third industrial revolution over the next 50 years. He cited strong parallels with the emergence of synthetic chemistry in the 19th century, when chemists moved from studying natural chemicals to creating synthetic chemicals, such as aspirin, quinine and mauve dye.

Although the complexity of biological

systems suggests extremely tough challenges for synthetic biologists to overcome, many engineering problems involve great complexity. For instance, the latest Intel chip features two billion transistors. The UK and Europe need to establish the required research capacity funding to meet these challenges.

Controversy and risk

Discussions about the possibility of creating living organisms have been aired in the media. In particular, excitement and concern surround Craig Venter's work in synthesising whole genomes, leading to comments in the press that he is "playing God."[10] This work involves synthesising a genome for an organism with just over 500 genes (a human cell has around 25,000 genes). However, although genes may represent the blueprint for a cell, it is important to draw a distinction between creating a genome and a living cell in its entirety.

'*What is synthetic biology*, is not only a technical scientific question, but also a social and public question'

Synthetic biology poses a new set of social and ethical concerns articulated by various parties, including some scientists, and examined by the social sciences and humanities. Some question the adequacy of scientific regulation and risk assessment as a means of understanding, anticipating and hopefully managing the kinds of futures synthetic biology is generating.

Wynne highlights the reasons for these questions about the intellectual capacity of risk assessment to predict the consequences of advances in fields like synthetic biology. Where the pace of scientific change, and particularly of attempts to commercialise it, is increasingly rapid; and where scientific research is increasingly driven by expectations and promises of imagined social benefits, unpredicted consequences become more likely. The convergence between fields of already dynamic innovation, such as nano-bio-info research, makes prediction and risk analysis more difficult. Moreover, informed public debate as to what social needs should be the priority for research to resolve becomes more important.

A public question

"What is synthetic biology?," is not only a technical scientific question, but also a social and public question. We need to define what we mean by the prospect of engineering life, and what we mean by "synthetic."

The rise of nanotechnology created pressure to re-label previous research activities for funding purposes, an issue that may arise with synthetic biology because this is also an emergent interdisciplinary field.

Without promising future social benefits resulting from their research, Wynne suggests, scientists are less likely to generate the necessary research funds. With an emphasis on evidence-based policy, it is important to render scientific promise and expectations realistic and accountable against evidence of outputs. With synthetic biology being used to promise non-agricultural carbon-free biofuels, for example, what effect do such "super-technical fix" promises have upon citizen commitment to lifestyle changes?

Ethics

The issue of creating life is a fundamental ethical issue, and enters as an object of technological enterprise and aspiration in synthetic biology.

One area of research focus has been the minimal functionality of a synthetic genome – stripped of "redundant" genes and synthesized for specific use in a variety of different potential applications. Wynne asks: "functional for what purpose?" The notion of a minimal genome function requires a definition of functionality. Do we mean replication or do we mean life? What social purpose is assumed in making such synthetic cells? And if these will be in practice turned to other attempted uses or "functions", and under different conditions, what are the risk and control implications of this? This distinction is still open to debate.

'A key shift in approach supported by scientists is a move to define the social and ethical issues before new science reaches the point of impact'

A key shift in approach supported by many scientists is a move to define the social and ethical issues before new science reaches the point of impact. Social and ethical considerations need to be incorporated early in the whole life cycle of research, development, potential application, and testing and final use, along with regulatory assessment.

Today, scientists are increasingly inviting social scientists to collaborate with them to better understand scientists' technical and scientific practice, and identify social issues to consider as public issues and to communicate these to policy makers. This represents an improved pathway to understanding through collaboration.

Onlookers often respond to scientific promises, and future visions with a certain amount of grounded scepticism. This response is actually evidence based, grounded in experience of sometimes few results delivered from previous scientific promises in spite of huge investment. Practitioners, policy makers and funders might all consider moves towards balance and accountability through applying organised scepticism (an essential principle of the scientific institution) to such promises.

Wynne advocates restraint in the face of pressure to race to translate cutting edge – yet arguably under-developed - science into full-scale social and commercial technologies, with associated unknowns and a lack of control.

The GM crops debate illustrated that the public were not necessarily exaggerating risk. Instead they were suggesting that risk assessment did not cover all of the potential consequences, because scientific knowledge was being translated into commercial technology in agriculture too fast. *"We need to be clear about what it is we think we control, and which questions we may inadvertently be failing to address because we did not know they needed to be asked,"* Wynne stated. Development of two-way engagement with all stakeholders is essential to listen to and act upon the public's concerns.

Summary

Synthetic biology is an emerging science with great potential and scope, which offers the tantalising prospect of engineering biological systems from component parts. As well as providing a potential path to less expensive and more efficient manufacturing, synthetic biology also offers academic tools and models with intrinsic value to biology as a research discipline.

The strategic significance of synthetic biology is not in doubt, and Europe and the UK must invest in developing skills and infrastructure to capture a share of the valuable intellectual property that is at stake.

Also at stake is the public's trust in those responsible for managing the development and exploitation of synthetic biology. Social, ethical and safety concerns, including the suitability of established risk assessment methodologies, must be addressed from the very beginning through dialogue within society as well as collaboration between scientists and social scientists.

References

1 Nobel prizes and restriction enzymes. Gene, Volume 4, Issue 3, November 1978, Pages 181-182
2 http://investor.illumina.com/phoenix.zhtml?c=121127&p=irol-newsArticle&ID=1105194&highlight=
3 http://partsregistry.org/Main_Page
4 http://parts2.mit.edu/wiki/index.php/Main_Page
5 www.QB3.org
6 www.wi.mit.edu
7 Systems Biology: a vision for engineering and medicine: A report from the Academy of Medical Sciences and The Royal Academy of Engineering (2007) http://www.raeng.org.uk/news/publications/list/reports/Systems_Biology_Report.pdf
8 Synthetic Biology: A NEST Pathfinder initiative. European Commission 2007: http://ec.europa.eu/research/fp6/nest/pdf/nest_synth_bio.pdf
9 http://www.tessy-europe.eu/
10 Newsweek, June 4 2007

Royal Society of Chemistry

Registered Charity Number: 207890

Burlington House
Piccadilly
London W1J 0BA
UK

Tel: +44 (0)20 7437 8656
Fax: +44 (0)20 7734 1227
Email: sciencepolicy@rsc.org
www.rsc.org