A new approach in biology is emerging and gathering a broad band of advocates. Synthetic biology aims to improve our abilities to engineer biological molecules, assemblies and systems; to design and develop biomimetic systems; and to apply these to useful ends. It brings together the biological and physical sciences, applying engineering and mathematical principles. Currently, a number of different approaches are being explored in synthetic biology, which are meeting with different levels of success. In the present article, we outline these efforts in general terms giving just a few examples for each; unfortunately, space does not for allow in-depth reviews, for which we apologize.

**Origins of the field**

Although others were clearly thinking about, and indeed actively engaged in tinkering with biology for some time beforehand, the first use of the term synthetic biology is attributed to Waclaw Szybalski in 1974. He asked what might follow the more-descriptive phase of molecular biology, and raised possibilities such as synthetic genomes and, consequently, engineering new and “improved organisms”. Indeed, the 1970s and the two subsequent decades saw the rise of recombinant DNA technology with its many and varied applications in basic and applied molecular biology. These are generally referred to from the bottom-up as protein, metabolic and genetic engineering, i.e. in terms of (protein) molecules, pathways and organisms respectively. Over the last decade, an expanding group of researchers have adopted the name synthetic biologists; taken up Feynman’s epitaph “what I cannot create, I do not understand” as their mantra; and are working to the broad definition that “synthetic biology refers to both: (a) the design and fabrication of biological components and systems that do not already exist in the natural world; and (b) the re-design and fabrication of existing biological systems” (see Box 1).

Such a broad and potentially inclusive definition serves a new and emerging field well; it prevents it from being stifled at birth. However, it also raises the questions what is synthetic biology, and how is it different from what has gone before? True, the majority of the currently high-profile work on synthetic genomes, contemporary metabolic engineering and the BioBricks and iGEM (international Genetically Engineered Machine) projects (Box 1) do bear a strong resemblance to the field’s origins in the more traditional disciplines of genetic, metabolic and protein engineering. However, we believe the true strength of the emerging field is formed from the synergy of developing concepts, knowledge and technologies drawn from other diverse disciplines, including bioengineering, conventional engineering, protein and nucleic acid design and systems biology. Synthetic biology is also differentiated by a new fearlessness in setting ambitious and ground-breaking research targets. To give just a few diverse examples of the wave of ambitious goal-driven projects that are being undertaken, researchers are: chemically synthesizing whole genomes for viruses, bacteria and mammals; transplanting whole biosynthetic pathways from higher organisms into more tractable ones to facilitate the production of small molecules as biofuels, biomaterials and drugs; constructing molecular motors spanning a range of sizes, to mimic those that Nature presents; and attempting to create self-sustaining encapsulated entities, to capture the main defining features of living cells.

We believe that this combination of practicality, ability and ambition sets synthetic biology apart, and that we are witnessing the birth of a new field. How far this will advance and develop truly new science is still not clear, but, even looking through some of the hype, the initial signs are encouraging.

**Synthetic biology space**

In this section, we attempt to give a flavour of the various approaches to achieving some of the aforementioned ambitious goals in synthetic biology. To help to illustrate and navigate the broad possibilities, in Figure 1 we have plotted our own representation of synthetic biology space, and the current approaches within it. Essentially, the y-axis represents the biomolecular and systems hierarchies in natural biology: that is, it starts with basic building blocks, such as the nucleotides, amino acids, carbohydrates and lipids; moves through
oligonucleotides and polypeptides, what we term \textit{tectons}; on to folded, assembled and functional biomolecules, including nucleic acids, proteins and assemblies thereof, and lipid vesicles; and up to cells, in which these various \textit{components} are brought together, or encapsulated, organized and orchestrated. The \textit{x}-axis represents increasing diversity from Nature. Thus the route that runs parallel to the \textit{y}-axis, but furthest along the \textit{x}-axis, represents the development of synthetic cell-like entities based on non-natural chemistries, so-called \textit{protocells}; whereas the various routes emanating from the left-hand side and moving out towards the top right of the plot represent various ways of \textit{engineering} or \textit{designing} biomolecules. Here, we distinguish \textit{engineering} and \textit{design}, as the processes of adapting or mutating natural biomolecules and systems, and of creating new examples of these from first principles (also referred to as \textit{de novo} design), respectively.

Starting from the middle of Figure 1, we define \textit{genome engineering} as the approach of constructing whole genomes synthetically and then introducing them into a host cell for ‘booting up’. In reality, this means chemically synthesizing small fragments of DNA, piecing them together using conventional \textit{in vitro} enzymatic ligation, followed by \textit{in vivo} recombination usually employing yeast to render the full-length chromosomes, with DNA sequencing at each stage to confirm the products. This is, of course, the province of Venter and his colleagues at the J. Craig Venter Institute (Box 1) who have, along with others, employed it to produce viral, bacterial and mammalian chromosomes. The research came to the attention of the world press on the eve of the publication of a paper in \textit{Science} in May 2010, which claimed the production of the first living organism whose parent is a computer\textsuperscript{3}. In essence, a modified version of the genome from one type of \textit{Mycoplasma} was chemically synthesized and transplanted into the cell of another, with the new DNA...
taking over such that the progeny only contain copies of the synthetic genome. The new organism has been nicknamed Synthia by some. Much of this work represents a technical achievement; it is a milestone in the development of this aspect of synthetic biology, rather than a landmark. The real questions remain: namely, what can be done with this approach and with the resulting organisms now that they are here and what transferable knowledge has been gained? True, whatever a researcher wants to place in a synthetic genome can be achieved within reason; for example, the Venter group introduced ‘watermarks’ in the synthetic Mycoplasma genome. The continued search for a minimal genome for an operative cell might be one useful and informative quest. This may pave the way to sharper experiments in systems biology, or provide a ‘chassis’ for the introduction and expression of genes and gene pathways.

This idea of a cell or an organism as a chassis to which further functional biomolecular components or pathways can be added takes us on to the next approach, which we term biomolecular engineering. The heralded example in this area is the production in yeast of a precursor for the plant natural product and anti-malarial drug artemisinin. This has been achieved by Keasling and colleagues at Berkeley, and involved the concomitant cloning of several biosynthetic enzymes for the small molecule from the plant into yeast. One of the non-profit aims of a spin-out company based on this work, Amyris Biotechnologies (Box 1), is to provide the drug as cheaply as possible to malaria sufferers in developing countries.

The key synthetic biology concept here is the idea that biological components – in this case genes and their products, functional protein assemblies – are modular and can be cut-and-pasted or plugged-and-played. The approach that biology is modular and rich in useful and transferable components is gathering momentum in several respects: the extreme is that transcriptional elements, and genes for particular cellular functions can be used to create a toolkit of so-called ‘BioBricks’ (Box 1). Once these components are fully characterized, standard protocols can be implemented to insert their function into new contexts. One important aim of this work is to provide tools that are reusable in achieving new goals and, as such, it provides an important step on the road to true engineering of biology. However, to date, our understanding of the fundamentals behind the modularity of biology and how cellular functions interact is insufficient to prevent unexpected, or emergent properties when different components and chassis are combined.

Nevertheless, the BioBricks approach, and the resulting Registry of Standard Biological Parts, has spawned the annual iGEM competition (Box 1), which

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**Box 1: Some useful websites in and around Synthetic Biology**

**General:**
http://syntheticbiology.org

**BioBricks, Registry of Standard Biological Parts and iGEM:**
http://bbf.openwetware.org/
http://partsregistry.org/Main_Page
http://2011.igem.org/Main_Page

**Companies and Institutes:**
J. Craig Venter Institute: www.jcvi.org/
Amyris: www.amyrisbiotech.com/

**UK SynBio Networks:**
CHELLnet (lead institutions: Nottingham and Oxford)
http://huey.cs.nott.ac.uk/wiki/index.php/Main_Page

**MATEs (lead institution: Sheffield)**
www.sheffield.ac.uk/synbio/mates

**RoSBNet (lead institution: Oxford)**
www.rosbnet.org/

**SCN (lead institution: Bristol)**
www.bristol.ac.uk/scn/network/

**SPPI-NET (lead institution: Durham)**
www.sppi-net.org/

**SynBio Standards (lead institution: Edinburgh)**
www.synbiostandards.co.uk/resources.php?type=networks

**Synbion (lead institution: UCL)**
www.ucl.ac.uk/synbion/

**SynBioNT (lead institution: Nottingham)**
www.synbiont.org/

**Upcoming conferences:**
www.biochemistry.org/Harden.aspx
Biochemical Society 70th Harden Conference, Synthetic biology: design and engineering through understanding, Keele, UK, 22–26 August 2011

**PE and ELSI links:**
www.raeng.org.uk/synbio
is inspiring a new breed of young researchers and drawing them into synthetic biology; a good thing for the future of engineering biology and science in general.

The next approach represented in Figure 1, *biomolecular design*, takes the view that stripped-down or *de novo* biomolecules also provide useful modular units for building structure and function. Here, those using nucleic acids as the fundamental building blocks are making the fastest headway. Both DNA and RNA are being used\(^1\),\(^2\), but, as might be expected, DNA is the preferred building material at present. The subfield dates back to the early 1980s when Seeman proposed and demonstrated that DNA could be used as a useful building material outside of traditional molecular biology. The area was later boosted by Rothemund’s introduction and beautiful single-handed demonstration of the concept of DNA *origami* (Figure 2). In essence, a single-stranded circular piece of DNA – at present, this is invariably a phagemid – is used as a template. *In silico*, this is configured as the desired two-dimensional shape or three-dimensional object. A series of small DNA fragments, called staples, are then designed, again computationally, to anneal to the DNA to form local double helices, and so fix the template in the prescribed structure. The staples are

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Figure 2. DNA origami from Rothemund’s 2006 paper\(^7\). (a) A shape (red) approximated by parallel double helices joined by periodic crossovers (blue). (b) A scaffold (black) runs through every helix and forms more crossovers (red). (c) As first designed, most staples bind two helices and are 16-mers. (d) Similar to (c) with strands drawn as helices. Red triangles point to scaffold crossovers, black triangles to periodic crossovers with minor grooves on the top face of the shape, and blue triangles to periodic crossovers with minor grooves on bottom. Cross-sections of crossovers (1, 2, viewed from left) indicate backbone positions with coloured lines, and major/minor grooves by large/small angles between them. Arrows in (c) point to nicks sealed to create green strands in (d). Yellow diamonds in (c) and (d) indicate a position at which staples may be cut and resealed to bridge the seam. (e) A finished design after merges and rearrangements along the seam. Most staples are 32-mers spanning three helices. Insets show a dumbbell hairpin (d) and a 4-T loop (e). Reprinted by permission from Macmillan Publishers Ltd: *Nature* **440**, 297–302, copyright 2006.
synthesized, then mixed and annealed with the template in a one-pot reaction. Annealing is required because the mixtures are complex often including hundreds of oligonucleotides: the sample is heated to denature all of the DNA, and then cooled slowly to pair and assemble the staples with their cognate sequences on the template. Given their size, which is on the order of hundreds of nanometres across, the resulting structures are usually observed by electron or atomic force microscopy. The results from this simple and elegant approach are stunning. Moreover, online applications are now available to help in the design of the sets of staples. Consequently, this approach has been adopted by many; for example, leading to the construction of a nanoscale DNA box with a DNA-based combination lock. This particular example takes DNA assembly in the direction of encapsulation, a key goal in synthetic biology. Other exciting areas being developed in DNA assembly are the construction of DNA-based motors and chemical assembly lines.

Arguably, however, with a richer set of natural structures, assemblies and functions for inspiration, a wide range of stabilities and the ease of production in bulk via recombinant DNA and heterologous gene expression, peptides and proteins present the preferred biomolecules for engineering and exploiting biology. There is a snag, of course: the wonderfully reproducible success of DNA-based applications is founded on our considerable understanding of the relationship between chemical and three-dimensional structure in terms of Watson-Crick base pairing. This allows one-dimensional sequences with predictable folding, assembly and stability simply to be written down, and, indeed, emailed off for synthesis. We do not have such straightforward links, or a set of rules for the folding of polypeptides, which rather limits de novo peptide and protein designs. However, and although a general solution to the protein folding problem remains elusive, there is hope: first, certain groups, notably those of Baker, DeGrado and Mayo, are getting better at designing peptides and proteins de novo using computers to tackle combinatorial problems in the design process, and more adventurous and novel structures; and specific protein falls – for example, the α-helical coiled coil, zinc fingers and collagen-like peptides – are amenable to design, synthesis and assembly. De novo designs of coiled-coil and collagen motifs in particular in providing new routes to new self-assembling biomaterials, a stated target of the synthetic biology community. In turn, these materials may prove useful as scaffolds for three-dimensional cell culture and tissue engineering.

The big leap in the general area of rational protein design, however, is likely to be the design of the protein function; namely, specific and tailored binding, and enzymatic activity. Although there is hope here too; the best route forward at the moment appears to be advanced protein engineering using privileged scaffolds, i.e. a protein fold fit for purpose as indicated by its use in Nature; e.g. the TIM barrel as a sensible starting point for enzyme engineering, good intuition and state-of-the-art computational methods.

As with the BioBricks approach, one goal would be to create a toolkit of modular peptide units that can be mixed and matched at will. However, it is unlikely that this endeavour will succeed fully without an increased understanding of sequence-structure and sequence-function relationships in protein. The ultimate quest must be to match the precision of the DNA-folding rules, although that might be a bridge too far. Furthermore, any uncertainty in any design at this level of the synthetic biology hierarchy will be passed upwards, and can be expected to cause problems for higher-order combinations of biomolecules.

Proponents of the various protocell design projects include Rasmussen and Luisi, both of whom have edited or authored recent books on the subject. The basic idea is to capture the defining features of natural cells in biomimetic systems: i.e. (i) an encapsulated system, which (ii) is blueprinted by some molecular-based store of information, and (iii) transduces energy from its environment to perform some form of metabolism; ultimately, these might also have the ability to pass on their blueprint for the construction of successive generations. Ideally, although bioinspired, none of these aspects would use natural biomolecules: i.e. no DNA/RNA-based information stores or transfers; no carbohydrate-based or similar metabolism; no protein structures, binders or catalysts; and, although this appears to be a less stringent stipulation, no natural lipids as membrane components. Clearly, these are lofty goals, and the area is most notable for its books, modelling projects and discourses on the origin of life. Nonetheless, the production of a working protocell would be a landmark event in synthetic biology, indeed for the whole of science; how such entities might be put to use is another question.

The final general routes in Figure 1, tissue and protocell engineering, have been added since our original reviews of synthetic biology space. These were inspired by the comments and work of Hagan Bayley (see below), and by the recognition that, in many respects, three-dimensional cell culture and tissue engineering can be considered as part of the overall synthetic biology scheme. The goals here are, as expected from the subtitles, to bring together cells or protocells to make three-dimensional cell cultures or tissue in vivo, or to engineer and manipulate more complex synthetic networks respectively.
Synthetic Biology in the UK

On purpose, above we focused on examples from outside the UK. Not surprisingly, much of the effort in synthetic biology has been in the USA, but others are contributing and gathering speed, notably in continental Europe and Japan. The UK synthetic biology community is growing, and is particularly interesting for its breadth and energy, much of which builds on strong traditional foundations in many aspects of the basic science and engineering of biological systems.

Genome engineering in the UK includes work by Smith at Edinburgh and work being conducted at the Roslin Institute, Edinburgh. Biomolecular engineering has been a UK strength in terms of protein and genetic engineering for some time. Regarding new metabolic engineering, the obvious strengths are those groups working on polyketide synthases, notably Challis and colleagues (Warwick), Leadlay and colleagues (Cambridge) and Simpson and colleagues (Bristol). Chin's group (MRC Laboratory of Molecular Biology, Cambridge) is engineering the ribosome machinery to create orthogonal systems in cells to allow the introduction and expression of alternative genetic codes. More generally, groups at Cambridge (Haseloff), Edinburgh (Elfick) and Imperial (led by Freemont and Kitney) are leading the way on standardization, BioBricks- and iGEM-style approaches. Regarding biomolecular design, Turberfield's group (Oxford) is a world leader in the design of DNA-based structures, materials and motors; and our own groups are active in de novo peptide and protein design, particularly employing tractable and compliant coiled-coil protein-protein interaction domains. In terms of protocell design, the UK has collaborative activity in both theoretical and experimental aspects, notably through groups at Nottingham (Krasnogor) and Oxford (Davies) respectively, and the resulting chemical cell, CHELLNet, project (Box 1). As mentioned above, Bayley (Oxford) is combining aqueous droplets in oil to create networks linked by lipid bilayers with embedded functional protein pores. Finally, in terms of cell engineering, the UK tissue-engineering community is broad and thriving, and is too large to mention individual groups here.

Through many of these centres and groups, the UK has strong and successful representation at the annual iGEM competition (Box 1).

Although space does not allow us to cover all of the exciting UK activity in synthetic biology in its broadest sense, this breadth and energy of on-going research is demonstrated further by the recently funded Research Council Networks in Synthetic Biology (Box 1). In alphabetical order by acronym and with the lead institutions in brackets, these include networks engaged in:

- microbial applications to tissue engineering (MATEs, Sheffield); systems-engineering approaches (RoSSBNet, Oxford); biomolecular design of synthetic components (SCN, Bristol); producing synthetic plant products for industry (SPPI-NET, Durham); modularization and standardization (SynBio Standards, Edinburgh);
- virus engineering and bionanotechnology applications (Synbion, UCL); and modelling and design of artificial cells (SynBioNT, Nottingham). These Networks provide forums for and scientific foci in UK synthetic biology. They are also working together to create a joined-up and collaborative UK community to cover all aspects of the field from the scientific, through Ethical Legal and Social Issues (ELSI), and on to public engagement (PE).

Synthetic Life, ELSI, and Public Engagement

Let's be clear, and we gauge that many agree, despite any claims or concerns to the contrary, Venter's genome synthesis and engineering experiments have not led to a new form of life yet. Also, the various protocell projects are considerably off from creating anything experimentally, let alone a self-sustaining system with some sort of metabolism and mechanism of reproduction. Putting aside the direct, although rather philosophical and oft-debated question of what is life?, synthetic biology does and will doubtless continue to raise similar issues of concern to the public and of interest to the media. As a result, philosophers, social scientists and those involved in engaging with public on science are taking an active interest in the growth and development of synthetic biology. Therefore practising synthetic biologists must be aware of these issues and be prepared to argue their corners both with the media and the public.

Venter's announcement in May 2010 is a good case in point. The UK scientific community responded extremely well with interviews for the national papers and magazines, local and national radio and mainstream TV. This served UK science well, and, in this case, played down the hype and addressed public concern surrounding the ‘creation of life’. This effort was co-ordinated very effectively and quickly through the Science Media Centre, the Research Councils (via the Synthetic Biology Networks) and learned societies such as the Royal Society.

This type of rapid and informed response is essential in modern-day science, as a large proportion of the public remain poorly formed about science and its many benefits; even though they pay for scientific research, and it is so vital for the development of society in all respects, i.e. in terms of education, technology, industry, commerce and culture. More generally, the Research Councils, and several learned societies have commis-
sioned and published reports on the public perception of synthetic biology (Box 1). Many scientists give their time to lead Science Cafés, make visits to schools, and contribute to science festivals. That they continue to do so is important for science as a whole. However, it may be particularly prudent in the emerging field of synthetic biology, with its potential for academic, industrial, medical and societal impacts.

Conclusions

The new field of synthetic biology offers much for both new academic and applied research. Although aspects of the field have emerged through technological advances – largely in DNA sequencing and synthesis – the field is much broader than genetic engineering itself, and the application of this technology alone will not enable the field to reach its full potential. In order to achieve true engineering of biology, synthetic biology must continue to expand and include related disciplines and mature from its current state of isolated successes to one in which general scientific principles underpinning applications are fully understood. This will require better knowledge of fundamental biological principles at all levels, but particularly in understanding how all types of biomolecule fold, interact and assemble, and function. Synthetic biology is not without hype, public and private interest, and, as a consequence, controversy. Therefore ethical, legal and social issues, so called ELSI, as well as public engagement are, and will be increasingly, important as the field grows up and, hopefully, blossoms.

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