Biology
by design

With our ever-increasing understanding of biochemistry and cell biology, scientists now have the tools to design complicated biological molecules, systems and devices to act as sensors, tissues or to produce useful chemicals. This document highlights the work of some of the UK’s leading synthetic biology researchers and how their work could deliver advances in a wide range of fields including medicine, biofuels and renewable materials.
The artificial leaf

More energy hits the surface of the Earth in the form of sunlight in the space of one hour than the entire human race uses in a whole year. This abundant energy is given away for free but making use of it is tricky. We can use solar panels to make electricity but it’s intermittent and difficult to store – you can’t fly an aeroplane or send a ship round the world using batteries, you need a fuel.

Only plants, algae and some bacteria have the amazing ability to capture and store the sun’s rays as sugars using photosynthesis. While amazing, photosynthesis is actually quite an inefficient process. Scientists, including Professor Richard Cogdell at the University of Glasgow, think that they might be able to tweak photosynthesis to produce fuel more efficiently.

Professor Cogdell’s team are trying to create an artificial system, using a chemical reaction similar to photosynthesis. “By stripping back photosynthesis to a level of basic reactions, much higher levels of energy conversion could be possible,” he says.

Ultimately, success in this research could allow the development of a sustainable carbon neutral economy, arresting the increasing carbon dioxide levels in the atmosphere caused by burning fossil fuels. In fact, if successful, this research could allow for carbon to be harvested from the atmosphere and returned to the ground, reversing the accumulation of carbon caused by burning fossil fuels.

The research is funded through a joint EU funding scheme ‘EuroSolarFuels’ which aims to produce fuels from light, BBSRC funds the UK part of this research.

Flat pack proteins

Professor Dek Woolfson and his team at the University of Bristol are working on a toolkit of newly designed proteins that could be used as building blocks to produce biological machines. The aim of scientists like Prof. Woolfson is to create catalogues of modular parts so that biological structures can be built from flat pack rather than being crafted from scratch each time.

One such structure that Woolfson’s team is working on is a synthetic version of the extracellular matrix, the scaffold that surrounds our cells. A synthetic extracellular matrix could be used in regenerative medicine to help generate tissues like skin, nerves or bone in the test tube, which could then be transplanted into patients. Prof. Woolfson is currently working with clinical scientists exploring applications for the technology in wound repair.

Another project in Woolfson’s lab is attempting to use rational protein design to produce new technologies for water purification and desalination. The team has discovered a new cylindrical protein structure, called CC-Hex, which they think could be engineered into biological membranes to filter water.

“These devices would be particularly valuable for producing small scale products that could be used easily by people who do not have access to clean water in the developing world,” says Woolfson. They are now working with the University of Oxford and an Australian water consortium, with the aim of developing a working prototype.

Designer tissues

Professor Jamie Davies at the University of Edinburgh is developing ways to control cell and tissue shape, an approach that he calls ‘synthetic morphology’. Although still in its infancy, this research could lead to a future where cells can be programmed to self-assemble into new structures and tissues. You could imagine, for example, that tissues grown in this way could provide an interface to allow a person to control movement in an artificial hand or even to see through an artificial eye.

These developments are still some way off. However in the medium term Prof. Davies hopes to be able to improve medical technologies, like dialysis, by developing tissues that can live happily inside medical machinery. Dialysis machines are very good at replicating the mechanical functions of a kidney but they cannot perform the biochemical functions that are important in properly filtering blood. By designing tissues that could grow along the tubes of a dialysis machine, researchers could produce a more effective artificial kidney.

And by developing synthetic systems that cause cells to organise and assemble themselves, the researchers can begin to understand how it happens in nature. This might, for example, give scientists insights that could help prevent developmental abnormalities like conjoined twinning.

What’s more, Davies believes that his approach is not just limited to human or animal cells:

“It should be possible to programme bacteria, yeast or plant cells to form new multicellular structures which could have an enormous range of uses in medicine and industry.”
Test-tube viruses

A research team, led by Professor Polly Roy of the London School of Hygiene and Tropical Medicine, has recently reconstructed bluetongue virus (BTV) in a test tube. This virus is responsible for an important disease of livestock that is transmitted by midges.

Bluetongue has a high mortality rate (up to 70% in sheep) and has a severe economic impact on European agriculture. Bluetongue was first detected in the UK in 2007 and there are fears that it could become a more regular threat.

Prof. Roy and her team synthesised BTV’s gene and protein building blocks separately and then combined them in the right order in order to produce a functional virus particle. By virus standards, bluetongue is quite architecturally complex and it has a relatively difficult genome to work with, so assembling it in a test tube was a significant challenge. To check whether they had been successful, they infected some midge cells with the newly synthesized virus and observed that the particles started behaving and replicating just as a wild-type virus would.

Prof. Roy said, “This was a really exciting moment. What had previously been a complex of proteins and other molecules whirred into activity and started making copies of itself.”

Roy’s team hopes to deliver more effective bluetongue vaccines, either by producing a virus-like particle that triggers an immune response but does not contain any genes, or by removing only certain genes so that the virus can raise an immune response but can’t reproduce outside of the lab. It should also be possible to build viruses with useful properties. For example, developing vaccines that are tagged with a marker gene to make it easier to distinguish animals that have been vaccinated from those that have recovered from an infection, which is difficult to do using current vaccines.

Plant vitamin factories

Professor Martin Warren at the University of Kent hopes to engineer plants to produce vitamin B12, which is essential for brain and blood health. Most people are able to get enough vitamin B12 in their diets by eating meat, fish and dairy, however people who are on strict vegetarian diets are prone to vitamin B12 deficiency and this can lead to anaemia, neurological disorders and developmental problems in unborn babies.

Deficiency is also a problem in the elderly and research suggests a link between a lack of the vitamin and the breakdown of the brain seen in Alzheimer’s sufferers.

At present, vitamin B12 supplements are produced industrially through a bacterial fermentation process but scientists want to see whether they can make this more efficient or produce plants that contain the vitamin. Vitamin B12 is the largest and most complicated vitamin that we know of. Thirty different enzymatic steps are required along the production line to produce the finished vitamin and scientists have been puzzling over how all of the pieces fit together for over 50 years, since its structure was first revealed by the famous scientist Dorothy Hodgkin.

Professor Martin Warren and his team want to take the complex biological pathways which some bacteria use to make the vitamin and transfer them into other organisms, like yeast and plants. But engineering an organism that can produce vitamin B12 from scratch requires a whole series of genes to be combined and inserted into a cell in a very specific order. “Transferring entire biological pathways across the large evolutionary distance that separates a bacterium from yeast or a plant is a considerable technical challenge but we are confident that it can be achieved,” says Warren.
Rapid diagnostics

The dreaded *E. coli* O157:H7 strain causes a serious infection, which can lead to acute kidney failure and death in up to 5% of cases. Worryingly, the number of outbreaks is on the rise. A critical stage in dealing with infection is in confirming which strain is causing the problem – current detection methods take between 12 and 14 hours.

Professor Tim Dafforn from the University of Birmingham is developing a rapid *E. coli* detection system using a novel spectroscopic technique called linear dichroism, which detects molecules when they line up in solution if you stir it – just like when you stir a bowl of spaghetti and the strands align around your fork.

He realised that the method could be used to detect long, thin nanoparticles formed from a filamentous virus called M13. M13 is a bacteriophage – a family of viruses that attack bacteria. Using synthetic biology, Dafforn has engineered M13 to ‘stick’ to chosen target molecules, in this case *E. coli*.

And, just as meatballs disturb aligned spaghetti, bacteria stuck to the virus particles causes them to separate and tangle, a change which can be detected in under two minutes. The method also has potential to be used for many different bacteria simply by changing the target binding site. A spin-out company, Linear Diagnostics, has been set up by the team to develop the technology.

“...This provides the basis for creating almost instantaneous diagnosis of what is causing an infection and what will be the best way to treat it,” continues Dafforn. “However, a lot of work is still needed to turn it into a routine procedure that will be found in every doctor’s surgery.”

Prof. Dafforn is also working with Professor John Ward at University College London to create novel bio-compatible nanoscale devices from phage. They are using genetically engineered filamentous phage particles as scaffolds to chemically link organic molecules and metal ions into regular assemblies, which could have a wide range of industrial applications including the production of chiral molecules and fuel cells.

Hybrid antibiotics

Professor Chris Thomas, also from the University of Birmingham is studying antibiotic production by microorganisms in a bid to recreate these biosynthetic factories in the lab and build new hybrid antibiotics that are significantly more potent than currently available drugs.

Thomas’s team has discovered how marine bacteria join together two antibiotics that they make independently to produce a potent chemical. This chemical can kill drug-resistant strains of MRSA.

Using synthetic biology, Thomas is working alongside chemists from the University of Bristol and pharmaceutical scientists in Japan to understand the modular steps involved in the assembly of antibiotic production. Once they understand the assembly line, which is quite complex, they can manipulate it.

“We’re working on how to exploit this research to generate families of new hybrids that will be screened for novel antibiotic activity,” explains Thomas. “The synthetic part is because we’re creating the blueprint: we’re reprogramming the genes so that they make a new factory. We’re creating new pathways and assembly lines to make new molecules.”

BBSRC has invested nearly £40M in synthetic biology research to date.

**Synthetic biology and society**

A synthetic biology approach offers incredible promise but also poses many ethical, legal and even existential questions for the scientific community, policymakers and for all of us to think about. Some of these questions were explored in a public dialogue carried out by BBSRC and the Engineering and Physical Sciences Research Council in 2010.

Read more at [www.bbsrc.ac.uk/syntheticbiologydialogue](http://www.bbsrc.ac.uk/syntheticbiologydialogue)