Synthetic Biology: An Introduction

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Foreword

The European Academies Science Advisory Council (EASAC) is made up of the national science academies of the member states of the European Union. As such it offers European science a collective voice, enabling member academies to collaborate in providing advice to European policy makers.

Mindful of the need to capitalise on emerging innovations, and conscious of the scientific and commercial potential of synthetic biology, EASAC assembled a working group of independent experts on the topic. Drawn from across the EU and chaired by the Council's president Volker ter Meulen, it compiled a report titled *Realising European Potential in Synthetic Biology: Scientific Opportunities and Good Governance*. Drawing in part on previous work published by individual member academies, the report reviews the current state of synthetic biology, and suggests why and how the countries of the EU could and should contribute to its further development. It is available on the EASAC website.

The present document – a summary of the full EASAC report – offers readers a non-technical account of its principal content and conclusions.

Introduction

Artificial life breakthrough announced by scientists

BBC News, 2010

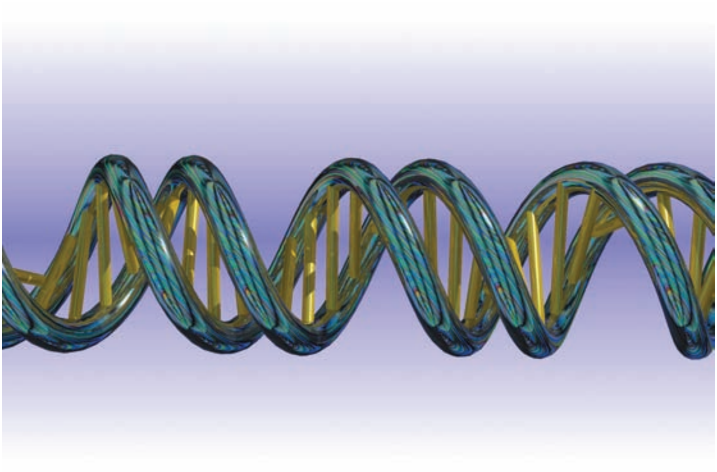
"Frankenstein" lab creates life in a test tube

Daily Express (London), 2010

Scientist accused of playing God after making artificial life by making designer microbe from scratch – but could it wipe out humanity?

Daily Mail (London), 2010

Many developments in biology over the past decade have prompted not only public interest, but also suspicion, hostility and occasionally alarm. In some cases – *in vitro* fertilisation, for example – these advances have gone on to achieve widespread if not universal acceptance. In others, such as genetically manipulated organisms and work on human embryonic stem cells, much of the public has yet to be persuaded that the techniques are variously safe, necessary or even desirable. The advent of synthetic biology, with its aim of creating living systems out of non-living materials, is as exciting as any biological advance of recent decades, and has much to offer, socially as well as scientifically. But as some recent headlines demonstrate, it has already generated antagonistic questioning and pejorative comment. And if the volume of press coverage has so far been relatively modest, this may reflect nothing more than the infancy of the field and the consequently limited extent of the attendant publicity. The more progress that synthetic biology research makes, the more controversy it is likely to generate. Which is one reason why the authors of the EASAC report favour the establishment of a dialogue between scientists and the public on the future of the technology and its potential benefits. Such an exchange of views, based on evidence, offers the best hope of creating a context in which the public can realistically assess the fears expressed in more sensationalist accounts. This brief document is a contribution to that dialogue.



Credit: Peter Artymiuk/Wellcome Images

Model of a DNA double helix.

What is synthetic biology?

Synthetic biology is the application of engineering principles to biology. This may involve redesigning a living system so that it does something – manufacture a particular substance, perhaps – that it would not naturally do. Still more ambitious are attempts not merely to re-engineer living systems, but to fashion entirely new ones: to create life itself from non-living materials.

To alter living things – through recombinant DNA technology ("genetic engineering") for example – is not in itself a new undertaking; so synthetic biology has an overlap with several other established scientific disciplines. But the ultimate ambition in this case is greater: to design living things that meet the specific needs and wishes of humans.

Research studies in synthetic biology are still only a decade old. The first department of synthetic biology at a major research institution – the US Lawrence Berkeley National Laboratory – was opened in 2003, and American scientists dominated much of the early research. But several European states too now have active research groups.

Progress has been rapid. The most recent milestone was passed earlier this year when researchers led by the American biologist Craig Venter described how they had transplanted a synthetic genome, a new set of genetic instructions, into a recipient cell. Although hailed as the first successful attempt to create life, this was not strictly the case. The DNA forming the set of genetic instructions used by Venter and colleagues had indeed been derived from non-living material; but the cell into which they were transplanted was actually the shell of an existing bacterium called *Mycoplasma mycoides* from which the original contents had been removed. What the researchers had done was the equivalent of putting a new engine into a car as opposed to building a new car from scratch. That said, the work was an important demonstration of the feasibility of the synthetic biology approach.

Why do it?

For some scientists the technology is an end in itself: a new way of studying living systems to find out how they work. Because synthetic systems can be made far simpler than their natural counterparts they allow researchers to perform experiments that would otherwise be difficult to carry out and perhaps impossible to interpret.

For the wider community the importance of synthetic biology lies in its social and commercial potential. One estimate suggests that the global market for synthetic biology could reach US$2.4 billion by 2013, with applications ranging from medicine to agriculture. Possible uses of synthetic biology include the following:

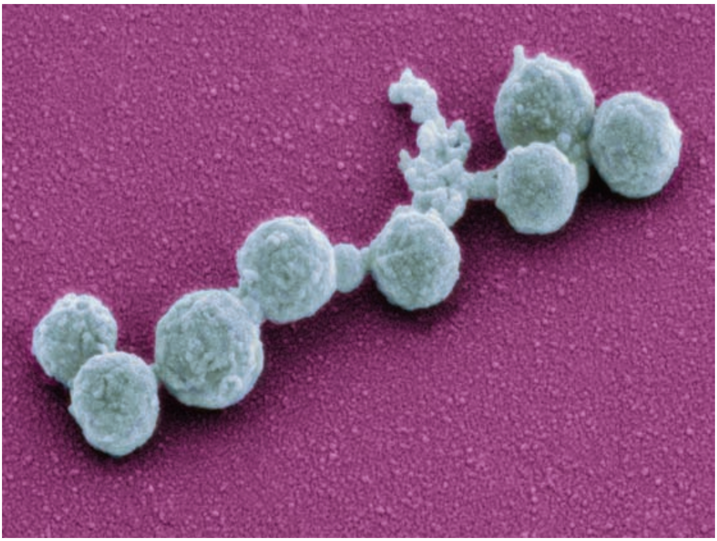
- *Energy*
  Custom-built microbes for generating hydrogen and other fuels, or for performing artificial photosynthesis.
- *Medicine*
  The manufacture of drugs, vaccines and diagnostic agents, and the creation of new tissue.

- *Environment*
  The detection of pollutants, and their breakdown or removal from the environment.

- *Chemical industry*
  The production of fine or bulk chemicals, including proteins to provide an alternative to natural fibres or existing synthetic fibres.

- *Agriculture*
  Novel food additives.

Which of these applications will be first to make an impact in the marketplace is a matter of speculation, although many commentators foresee biofuel products as a likely frontrunner. Synthetic biology might accelerate the development of "second-generation" biofuels that can be prepared from agricultural waste and plant residues, so avoiding competition with crops grown for food.



Credit: Thomas Deerinck, NCMIR / Science Photo Library

Coloured scanning electron micrograph of synthetic mycoplasma bacteria.

What do we expect of synthetic biology?

A recent survey of public perceptions of synthetic biology commissioned by the UK's Royal Academy of Engineering revealed that awareness of it is limited. But when informed about synthetic biology, members of the general public showed great interest in the prospect of being able to design micro-organisms to manufacture biofuels and medicines. That said they also expressed concerns – for example about deliberately releasing artificial organisms into the environment to tackle pollution. But while they wanted government to regulate synthetic biology they were also mindful that overbearing regulation might stifle its development.

Why has EASAC compiled a report on synthetic biology?

The community of scientists studying synthetic biology within the EU is growing, and several member academies of EASAC have recently organised meetings or published documents on it. But there is a clear need to encourage more research, and to establish a coherent strategy at EU level. It was for these reasons, together with the rate at which synthetic biology is expanding, that prompted EASAC to commission a report bringing together some of its member academies' analyses and perspectives.

The report also sets out to explore several policy issues. These include: the contribution synthetic biology can make to economic growth; the scientific and technical challenges that need to be overcome to realise its potential; the necessary training and investment in research and development; the obstacles that might hinder this aim, including public misunderstanding or hostility; the possible need for new regulations on biosafety, biosecurity and product development; and the prospects for European synthetic biology in the face of global competition.

What sort of research are the scientists aiming to do?

Synthetic biology is an enterprise encompassing many different goals and many ways of working. Some of these goals and methodologies are common to other fields of biology, which is why a neat and tidy definition of synthetic biology is not possible.

The goal of some scientists is to assemble a group of molecules that can work together to achieve a particular purpose such as the production of a novel chemical. Such a module of activity might be inserted into a living organism to alter its activity and encourage it to do or make something outside its normal repertoire. Other scientists, by contrast, are tackling the even greater challenge of creating completely new, self-sustaining and self-replicating artificial organisms.

The EASAC report outlines some examples of the kinds of approach that synthetic biologists are pursuing.

Minimal genomes

The intention here is to define the minimum number of genetic instructions, genes, needed for an organism to survive. Most of the research has been carried out on bacteria in which genes are progressively eliminated, so revealing those which are essential to life and those which are not. Early estimates put the minimum required number at 500–800 genes, but subsequent work has suggested that it may be as low as 300–400. Using this knowledge it becomes possible to design and build cell factories, the output of which will depend on what additional genes are added to the minimal set required simply to sustain the organism's existence. A full knowledge of which genes are essential to do what also helps the bioengineer not only to create new and specialised organisms by eliminating unwanted genes, but to build novel organisms from scratch. In the future one might envisage a kind of core genome available off-the-shelf. Bioengineers could then add to it whatever other elements might be needed to perform a required task. One such task, much discussed, is a bacterium designed to produce hydrogen or some other fuel stuff. But the range of possible applications is vast.

Orthogonal biosystems

The genetic information that all living systems require to function is stored, in coded form, in the sequence of the four types of sub-unit that go to make up the long chains of their DNA molecules. Researchers have been experimenting with various ways of modifying the system so that it can carry the instructions for making types of protein unknown in nature. Even more radical is the notion of synthesising and using alternatives to DNA to create a new type of genetic material. Any such alternative molecule would need properties comparable to those of DNA – information storage, the ability to self-replicate etc – and should be able to act in a similar way. Living systems relying on an alternative of this kind might be unable to interact with conventional (DNA-based) life forms. This could have potential safety benefits.

Metabolic engineering

Another application of synthetic biology is in the creation of new biosynthetic pathways to produce useful materials that living organisms do not naturally create. One frequently quoted example is the use of modified yeast cells or the bacterium *Escherichia coli* to produce artemisinic acid, a precursor of artemisinin, an anti-malarial drug traditionally obtained (but in inadequate amounts) from the plant *Artemisia annua*. Deriving artemisinin from yeast could cut production costs by 90 per cent, according to one prediction.

Other examples of metabolic engineering include: the production of the anti-cancer drug taxol in the yeast *Saccharomyces cerevisiae*; the creation of a precursor of spider silk using the bacterium *Salmonella typhimurium*; the manufacturing of second-generation biofuels in yeast; and the synthesis of hydrocortisone from glucose, again in yeast.

Regulatory circuits

The natural activity of cells is controlled by circuits of genes analogous to electronic circuits. So another approach to making cells do new things relies on creating novel internal circuitry to alter their pattern of activity. Using well-understood genetic components that act as molecular switches it should be possible to devise artificial gene networks. Linked together and implanted into natural systems such networks could be used to control what those systems do, when, and how frequently. Integrated into suitable cells an artificial network might be used to sense and correct metabolic disturbances of the kind found in diabetes.

Protocells

As already pointed out, the most dramatic endeavours in synthetic biology are attempts to create manmade cells that are capable of self-assembly and self-repair and able to reproduce. Many hurdles will have to be overcome before this goal is achieved; but it is a realistic one, and several research groups are pursuing it. One such is the European Union funded PACE project: Programmable Artificial Cell Evolution.

Bionanoscience

Nanotechnology, the engineering of systems at the molecular scale, though longer established than synthetic biology, is also one of the newer disciplines within science. The molecular-scale motors and other machines that it creates (or can envisage) have a self-evident relevance to any scientist in the business of synthesizing whole cells or other living systems. Such is the overlap between nanoscience and synthetic biology that attempts to define their respective boundaries are as difficult as they are futile.

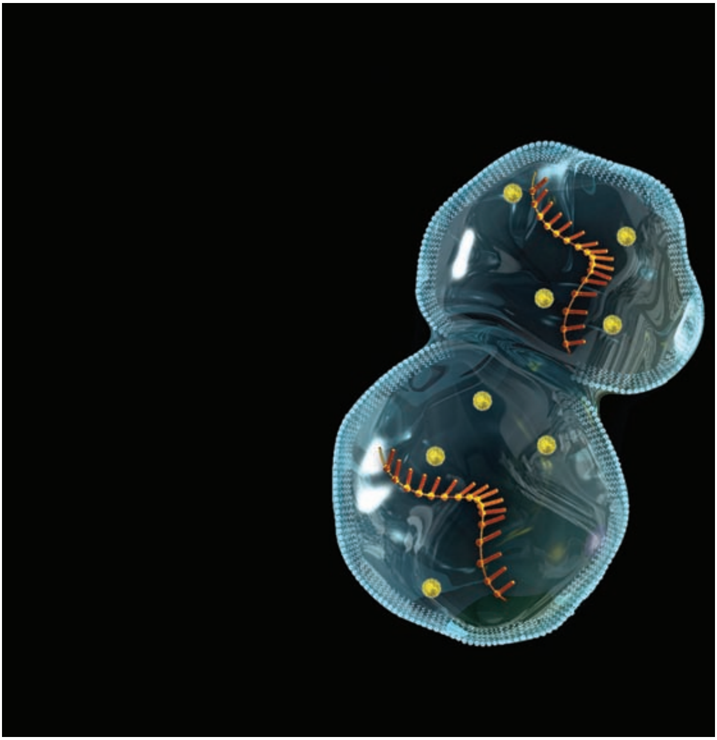
What are the risks posed by synthetic biology?

The risks created by the development of synthetic biology are of two types: biosafety, in which adverse consequences are the result of accidental or unforeseen events; and biosecurity in which the insights of synthetic biology are used with malign intent – in weapons, for example.

Biosafety

Many areas of biological research create concerns about safety, but synthetic biology does pose some particular threats. It takes little imagination to appreciate that an entirely novel self-replicating organism that escaped the laboratory and entered the environment could cause all sorts of harm, depending on the properties and activities with which its designers had endowed it.

One method of minimising the likelihood of unforeseen consequences would be to create organisms that could survive only by relying on nutrients or other essential materials that are not found in nature. However, even this is not a foolproof recipe because many microbes have the capacity to transfer genes "horizontally": to swap bits of genetic information with others of their own kind, and even with the members of other species. Moreover, a novel self-replicating microbe would presumably have the capacity to evolve, and might develop dangerous properties. Any synthetic organism would need to be handled with the highest safety standards – adapted, perhaps, from those already devised for handling genetically manipulated organisms – and subject to close regulation at national and European level.



Credit: Henning Dalhoff / Bonnier Publications / Science Photo Library

Artwork showing a protocell (artificial cell) dividing to produce two daughter cells.

A further complication is that the release of a synthetic organism would not necessarily be accidental. To perform its task, a novel microbe engineered to clean up some form of environmental pollution would have to be released freely into that environment. Scientists contemplating any such action would have to set an exceptionally high threshold of certainty that the organism would be unlikely to trigger events which had not been contemplated.

Biosecurity

Good regulation, though essential, can offer only limited protection against would-be bioterrorists who might be interested in synthetic biology as a weapon. The true extent of this threat is disputed. Some scientists point out that it would be easier to misuse natural pathogens rather than wholly novel ones. But, as suggested in a report published ten years ago by the CIA, synthetic biology could produce engineered microbes capable of creating diseases worse than any yet known to man. So it follows that improving biosecurity is, to say the least, prudent. The groundwork has already been undertaken by an interacademy panel; this has listed the principles that need to be taken into account when formulating codes of conduct to minimise research misuse by those working in the biological sciences. These principles include: an awareness of the potential consequences of research and a refusal to undertake work that can have only harmful consequences; an adherence to good laboratory working practices; knowledge of and support for national and international laws and policies to prevent the misuse of research; and an acceptance of the duty to report any activity that violates codes such as the Biological and Toxins Weapons Convention.

Increasingly easy access to DNA sequences – in effect to sets of genetic instructions – will see the techniques of molecular biology being adopted by disciplines such as engineering which have little experience of biological agents. If standards of biosecurity (and also of biosafety) are to be maintained, it will be important to ensure that all newcomers to the bioscience community understand the risks involved.

In parallel with these developments there is a continuing debate on the right balance between scientific self-governance and statutory regulation. One survey has revealed that synthetic biology researchers recognise the importance of avoiding a public backlash of the kind that undermined work on genetically manipulated organisms in agriculture. Most, it seems, favour a mix of international guidelines, national laws and self-regulation, accompanied by initiatives in public education and awareness-raising.

Who owns the intellectual property rights in synthetic biology?

Some commentators continue to argue that synthetic biology, like other developments such as the sequencing of genes, should not be patentable. The knowledge, they insist, should be freely available to all. However, the patentability of biotechnology inventions in general is now well established under a European Commission directive and governed by the European Patent Convention. That said, patenting issues in this field continue to be debated.

Two problems in particular have emerged: the creation of overly broad patents that may foster monopolies, hamper collaboration, and stifle innovation by other researchers; and, conversely, the creation of unduly narrow patents that can impede subsequent applications because of the complexity of licensing arrangements required to deal with multiple holders. The multidisciplinary nature of synthetic biology, which requires that patent expertise be drawn from several different fields, may serve to exacerbate these problems. Or it may not; an alternative view holds that the discrete and separate entities that go to make up synthetic biology are relatively well suited to commodification. Either way, EASAC advises patent offices to take care when asked to grant broad patents.

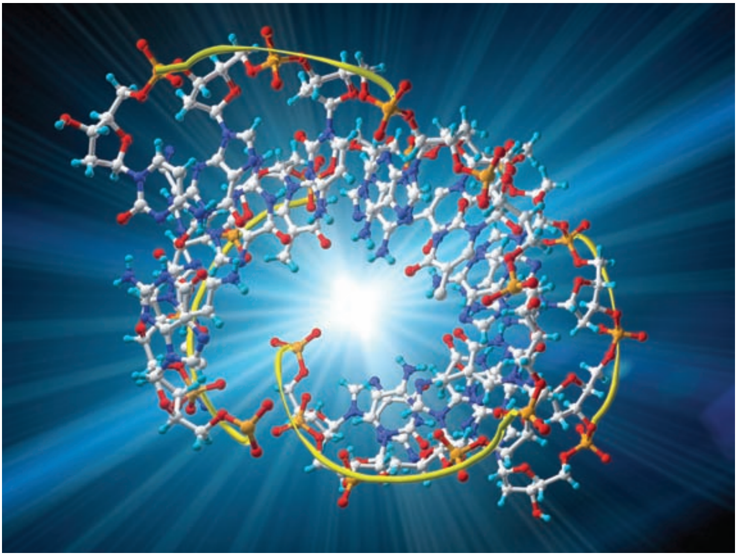
As elsewhere in bioscience there may be scope for alternatives to conventional patenting arrangements. The sharing of information in patent pools, for example, is already being used by the pharmaceutical industry. EASAC hopes its member academies will help to build an open and cooperative research environment in synthetic biology, while at the same time encouraging investment and avoiding the infringement of existing rights. Synthetic biology has lessons to learn from the variety of public-private research partnerships already in operation in bioscience, many of which already include a commitment to open innovation.

What is EASAC is recommending?

Addressing itself to EU policy makers, the report poses a number of questions that need to be answered if Europe is to make its full contribution to the development of synthetic biology, and to get the most out of it. The issues covered by these questions – many of them referred to within this summary of the report – include research capacity and higher education within Europe, the protection of innovation, public engagement, biosafety, biosecurity and regulation. The report also makes many recommendations in these areas. Too numerous to list in this document they range from the specific (e.g. that EU control of the approval of novel products emanating from synthetic biology should generally be subject to the same regulatory framework as exists for those from other sources) to the general (eg the importance of continuing discussion of ethical issues in synthetic biology).

The EASAC report finishes by recognising that the infancy of synthetic biology, its rapid progress, and its overlap with other technologies make it a challenging topic for policy-makers. As yet there is still no consensus on whether it will actually prove to be a transformational technology and, if so, whether it can be fitted into the current frameworks regulating science.

Synthetic biology, besides helping us to understand natural biological systems, could make a big contribution to innovation within EU countries, and so also to their global competitiveness. If living systems are ever to be engineered by humankind, Europe should be playing a full part in their development and use.



Credit: Pasieka / Science Photo Library

Computer artwork of threose nucleic acid (TNA), a synthetic molecule structurally similar to DNA and RNA.

We thank the members of the EASAC working group who have helped compile the full report on Synthetic Biology: Volker ter Meulen (Würzburg), Bärbel Friedrich (Berlin), Adam Kraszewski (Poznan), Ulf Landgren (Uppsala), Peter Leadlay (Cambridge), Gennaro Marino (Naples), Václav Paces (Prague), Bert Poolman (Groningen), György Pósfai (Szeged), Rudolf Thauer (Marburg), George Thireos (Athens), Jean Weissenbach (Evry).

We also thank Geoff Watts (London) for his support in writing this summary of the full report.

EASAC – the European Academies Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

The EASAC Council has 25 individual members and is supported by a professional secretariat based at the Leopoldina, the German Academy of Sciences, in Halle (Saale). EASAC also has an office in Brussels, at the Royal Belgian Academies for Science and the Arts.

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