Mixed signals

Professor Dr Michael Reth, Scientific Director for the BIOSS Centre for Biological Signalling Studies at the University of Freiburg, explores the highs and lows of synthetic biology…

The course of human development, from the stage of hunter-gatherer societies to that of the first civilised cultures, is closely connected to the acquisition of technical innovations. This included not only tools and machines, but also – and above all – the development of agricultural methods. Human curiosity and ingenuity played an important role in the development of the farmer, the technician and the artisan, and knowledge and control of nature went hand-in-hand in this process. From the very beginning, however, it is also possible to observe a distrust of people with special technical abilities. Sometimes they were regarded as highly useful members of society; but more often than not, they were branded as megalomaniacal geniuses or magicians who practised their powers unchecked and without regard for natural and moral laws.

Modern biology is currently struggling with the question of how to manage the enormous complexity of living systems. Several research approaches have been developed to address this question. One of them is modern molecular genetics, which aims to assign a particular cellular function to each known gene. This is often done by switching off or modifying a particular gene and determining the function of the gene product. However, analyses of this kind have their limitations. Oftentimes, organisms will cease to develop at a very early stage following the loss or mutation of a gene, thus preventing researchers from investigating the function of the gene product in detail.

Another strategy for managing this complexity is systems biology. This approach aims at a nearly complete description of the molecular activities of a biological system using modern and fast analytical procedures, and is based on the fact that cellular processes are determined not by individual gene products but by the interaction between a large number of components: proteins, fats and sugars.

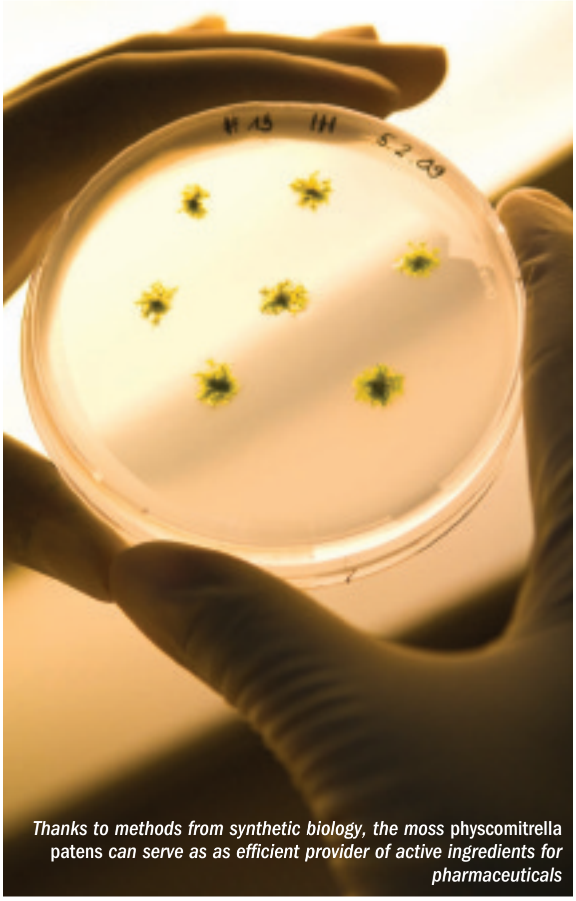
Systems biology thus places more emphasis on quantitative analysis than on qualitative analysis, as the primary goal is to develop mathematical models that can be used to create a life-like simulation of life processes on a computer monitor. Progress in this research area has been hampered by an unanticipated side effect. The biological processes being analysed become increasingly complex as more and more data is collected, and the human brain has a limited capacity to handle such a large mass of data. Thus, the data can only be processed with very fast computers. It is still an open question whether this method has the potential to make not only a quantitative but also a significant qualitative contribution to our understanding of life processes.

Understanding the function of molecules

Synthetic biology developed as an alternative or complementary strategy to deal with this concrete situation. This new branch of research does not initially aim to describe and mathematically model a complete biological system. Rather, it takes a cue from engineering, a field that also works with complex systems, and starts by breaking down a cell into functional subsystems. The keywords here are simplification, decoupling and functional description.

Synthetic biologists are at the same time system engineers and molecular designers. In the former role, they assume that biological molecules behave as parts of a machine, and can thus be characterised according to their functions. In the latter role, they manipulate the biological materials in creative ways, constructing a new system using individual biological components. Once they get this system running like a machine, they can assign each of its components a function and reach a much better understanding of the functioning of the molecules involved. Synthetic biologists are thus fond of a quote made by Nuclear Physicist Richard Feynman: "What I cannot create, I do not understand."

All life processes depend on sending, receiving and processing biological signals. A signalling engineer can develop completely new kinds of signalling molecules by reconstructing a signalling system. Designer molecules like these can function as signalling switches or signalling detectors, and provide new insight into the localisation and regulation of biological signals. These creative experiments can also pave the way for potential applications – for instance in tumour therapy, since many tumour diseases in humans are caused by deregulated signalling processes. By reaching a better understanding of these processes and developing new proteins designed to intervene in the faulty signalling process and correct the deregulated signalling path, scientists can develop completely new therapeutic approaches to combat these diseases.



Thanks to methods from synthetic biology, the moss physcomitrella patens *can serve as as efficient provider of active ingredients for pharmaceuticals*

Experts are of the opinion that the potential for synthetic biology to change or endanger nature is often overestimated. Synthetic biology will certainly play an important role in the further development of biological research, but could it also radically change our living conditions, as the introduction of agriculture or industrial production did? The field would only succeed in this if it were in the position to found an entirely new type of biology and then develop life forms with completely different characteristics. In this case, it would be legitimate to ask whether such biosynthetic creations would still be subject to the rules of evolution as we know it. However, synthetic biology is still far from being able to create life *de novo*, and I do not think that this is the primary goal of the field.

Creating biological components

Synthetic biology is more interested in maintaining life on this planet, helping it to recover from its currently precarious state through a better understanding of life processes – for instance, by developing more environmentally friendly methods for producing medicines or raw materials.

As with any new scientific approach, however, synthetic biology will likely experience setbacks in this endeavour. For example, one of the most important and undoubtedly very useful working hypotheses of the field might prove to be problematical: namely the assumption that it is possible to consider biological components as machines built to serve a specific purpose.

Biological systems were developed over the course of millions of years by evolutionary processes, not by rational design. Biological components may very well be multifunctional by nature, resisting reduction to a single role. Uri Alon has found an apt characterisation of this dilemma: "Cells evolved to survive, not for scientists to understand." Nature takes that which is available and plays with it in the course of evolution. The resulting multifunctionality could prove to be a stumbling block for scientists who wish to construct a biological subsystem with a clear-cut functional description.

In addition, we are still far from being able to describe a cell or a living organism in all of its facets. Every targeted change or *de novo* synthesis of a biological subsystem is conducted against the backdrop of our incomprehension of the overall system. This means that biosynthetic projects are like equations with many unknowns, and there is no safeguard against surprises. However, it should be noted that synthetic biologists are making efforts to decouple their designs from the overall system.

What I find particularly important in the development of this new research area is the dialectical process between synthesis and analysis, the interaction between the new strategy and the established analytical biosciences. Together, they can extend our knowledge significantly.

What synthetic biology will certainly accomplish in the coming years is the creation of an entire range of biological components with new characteristics. I anticipate that signalling research in particular will succeed in developing proteins that function as localised and regulated signalling switches or signalling detectors.

Designing biological molecules is by all means a creative process. The technical knowledge necessary to construct a gene for a new biological molecule out of 10 or more fragments is available today, and can be extended as needed. Moreover, DNA synthesisers are becoming more efficient all the time and many genes can be created new from scratch. A cell can then use these blueprints to build a new molecule. It is very time-consuming work to analyse the functions of these molecules; however, the tragedy of synthetic biology lies in the fact that the creations of its molecular designers remain largely invisible. There is no place where people can admire them, and even the designers themselves have no direct physical access to these infinitesimal works. They are happy just to know that their creations function and influence the behaviour of a cell in the way they intended.

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