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Concept of Law in Biology

Synthetic Biology – Towards an Engineering Science

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The new research field of synthetic biology is emerging from molecular biology, chemistry, biotechnology, information technology and engineering. This paper describes synthetic biology as a 'Science of the Artificial' and identifies structural features of engineering sciences that can be applied to this new kind of biology as opposed to traditional biology. The search for laws already in traditional biology has been difficult. In Synthetic Biology, action and application stand in the foreground and laws increasingly lose ground as a meaningful concept.

Introduction

Historically, biology has been a field based almost entirely on observation and analysis on various levels of description, concentrating on molecules, supramolecular entities, cells or multicellular organisms. But although there are – especially in evolutionary biology – mathematical models such as Mendel's 'laws', Fisher's sex ratio model or the Hardy-Weinberg equilibrium, at each level obstacles to the conclusion that biology has distinctive laws can be found (Ref. 1, p. 62). To date, 'identifying biological laws is not easy', as is stated in an introductory text to the philosophy of biology (Ref. 1, p. 32).

The traditional approach has been to isolate a small number of biological components in order to understand their structure and function. A simple cause and effect relationship of single biochemical events resulting in single effects was the basis for this approach. But today we know that most genes, proteins and other components carry out their functions within a complex network of interactions, with positive and negative feedback loops that regulate their operation. 'Consequently, a single component (such as a gene) rarely specifically controls any particular biological function or disease, and conversely any given component may influence many different functions' (Ref. 2, p. 14). This has to

be taken into consideration as one wants to understand, manipulate and design increasingly complex biological systems. And this makes it even harder to identify distinctive biological laws in the classical sense of eternal truths. Therefore, an instrumentalist reading of biological theory may be advocated: 'the aim of biological theorizing is not, as it is in physical sciences, the identification of natural laws of successive generality, precision and power, but the sharpening of tools for interacting with the biosphere' (Ref. 3, p. 254).

During the last years, new modes of explanation have emerged by the increasingly extensive usage of new machines in biology: computers made possible extensive simulations of complex systems, and sequencing machines and DNA-synthesizers brought about a wealth of data (Ref. 4, p. 7 f.). However, biological laws are not within sight. But the scientific understanding of complex biological systems was improved by systems biology, and at the same time it made possible engineering applications in synthetic biology. '[S]ynthetic biology is not primarily a "discovery science" (that is, concerned with investigating how nature works), but is ultimately about a new way of making things' (Ref. 5, p. 10). Synthetic biology brings about a new age of biological engineering. Biological theorizing, therefore, seems to be better captured by the quote attributed to Richard Feynman: 'What I cannot create, I do not understand' than by reference to laws.

Systems Biology

A report of the Academy of Medical Sciences and the Royal Academy of Engineering describes the approach of Systems Biology and puts at the same time emphasis on the explanatory aspects of this new branch of biology (Ref. 6, pp. 5 ff., emphasis added): 'Systems Biology is a ground-breaking scientific approach that seeks *to understand how all the individual components of a biological system interact in time and space* to determine the functioning of the system. It allows insight into the large amount of data from molecular biology and genomic research, integrated with an understanding of physiology, *to model the complex*function of cells, organs and whole organisms […]. It uses an iterative cycle of computational modelling and laboratory experiment *to understand how the components work together in a system*' (Ref. 6, p. 5). '[U]*nlike much of traditional reductionist biomedical sciences*, Systems Biology investigates the functioning of a biological system as a whole, rather than studying individual components in isolation. It is underpinned by many disciplines including engineering, medicine, biology, physiology, pharmacology and chemistry, computing, mathematics and physics. In addition, it draws upon and often contributes to bioinformatics, mathematical biology and the "omic" sciences' (Ref. 6, p. 8). Then, the relationship between genetic information and systems biology is discussed: '[O]nly very limited information about function can be deduced directly from the genome. Knowledge derived from the genome has already had an enormous impact on biology and medicine but, whereas the individual function of some proteins may be well known, the interactions between the many proteins that constitute a system and how they function together are poorly understood. […] Scientists are now facing the challenge of turning the vast quantities of descriptive information from the revolution in molecular biology into useful knowledge that can aid the understanding of the overall function and behaviour of systems' (Ref. 6, p. 9).

Recent years brought about significant successes in detailed and holistic description of the cellular events, particularly inside bacterial cells. For example, the nucleic acid sequence of a cell can now be compiled very quickly. Bioinformatics methods then allow for the identification of all genes of such a nucleic acid sequence as well as its associated regulatory sequences. The question 'which genes operate when?' can then be answered with an analysis of the transcriptomes. Finally, the protein configuration of a bacterial cell can be determined using proteomics and the metabolic configuration using metabolomics. All these contributed to analysing interactions that give rise to biological function.

Synthetic Biology

Around the beginning of the twentieth-first century, many experts agree that:

> [b]iology has now reached the stage where a sufficient amount of genetic and biochemical data on biological systems has been acquired to enter the synthetic stage. […] [S]ynthetic biology aims to go one step further by building, i.e. synthesizing, novel biological systems from scratch using the design principles observed in nature but with expanded, enhanced and controllable properties. The complexity of such a 'design' goal makes an engineering approach imperative. (Ref. 5, p. 11)

Synthetic biology has emerged on the basis of the findings of molecular biology. It is based on the decoding of complete genomes, the technical advance in chemical and enzymatic synthesis of nucleic acids and the possibility of recording data comprehensively at nearly all levels of cellular information processing. Synthetic biology combines a broad spectrum of natural scientific disciplines and follows engineering principles in order to modify known organisms in a targeted, modular approach, or, in extreme cases, to construct synthetic organisms that do not occur in nature from basic genetic components. Specifically, scientists are promising new pharmaceuticals, bio fuels and materials made from this new technology.

Often, an analogy from Synthetic Biology to synthetic chemistry in the mid-nineteenth century has been drawn:

> Instead of simply analyzing existing molecules, chemists began to synthesize them – including molecules that did not exist in nature. The combination of this new synthetic approach with more traditional analytical approaches revolutionized chemistry, leading to a deep understanding of the fundamental principles of chemical structure and reactivity and to the emergence of modern pharmaceutical and chemical industries. (Ref. 7, p. 521)

Actually, 'the history of chemistry suggests that synthesis will be a necessary complement to analysis in order for biologists to truly understand the mechanisms of complex living systems' (Ref. 7, p. 523).

'Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems' (Ref. 2, p. 6). Therefore, Synthetic Biology can be regarded as a logical advancement of molecular life science and Systems Biology: using systems biology it should be possible in the future to model cellular activities via biocomputing and after altering its genetic information also

to manipulate its functions. This modelling will then show whether the applied genetic modifications are compliant with the life processes in a cell and lead to the desired effects. Should this be the case, Synthetic Biology could use a more or less altered nucleic acid sequence as a blueprint for an in vitro chemical synthesis.

In the following, different approaches pursued by Synthetic Biology are being discussed.

'Craig Venter creates synthetic life form'

One of the most spectacular publications in 2010 was a study by the Craig Venter Group about the in vitro synthesis of a bacterial genome and the proof that such a chemically synthesized genome could be invigorated in a bacterial cell. This paper was accompanied by a press release by the J. Craig Venter Institute entitled: 'First Self-Replicating Synthetic Bacterial Cell', and therefore gained a lot of attention both inside science and in the mass media. The results that were reported under headlines such as 'Craig Venter creates synthetic life form' (*The Guardian*) did not come at low cost. The Craig Venter Group had to develop a number of new technologies to sequence, synthesize and transplant genomes. In 2008 the group described the successful synthesis of the *Mycoplasma genitalium* genome with nearly 0.6 million base pairs. The chemical synthesis of a bacterial genome is intricate because the genome cannot be chemically synthesized at once. Instead it is only possible to synthesize short oligonucleotides that then have to be put together. In the 2010 publication the group reported the synthesis of a larger bacterial genome, namely that of the bacteria *Mycoplasma mycoides* with about one million base pairs. Then, a method has been developed that allows for the transplantation of this bacterial genome into another bacterial cell.

The Venter Group synthesized the *M. mycoides* genome and transplanted it into a *Mycoplasma capricolum*. For a short time the *M. capricolum* then had two genomes, the native genome of *M. capricolum* and the chemically synthesized genome of *M. mycoides*. At cell proliferation the two genomes were segregated to daughter cells. After selection, daughter cells with the chemically synthesized genomes were being further proliferated. They were viable and possessed the known properties of *M. mycoides* cells. The chemically synthesized *M. mycoides* genome thus controls the cellular events in the transformed cell.

This 'first synthetic cell' caused a mass media response, which was intentionally induced by the researchers. But other scientists described the result as 'a technical tour de force,' a matter of scale rather than a scientific breakthrough. These differing interpretations of Venter's work just capture the status of research in Synthetic Biology that on the one hand seems dazzling but on the other hand is hard engineering.

Top-down versus Bottom-up: The Minimal Genome

'Minimal cells' contain only those components that are absolutely essential for life. Their 'minimal genome' only contains genes that are required for the survival of the respective organism under defined conditions. Generating minimal cells is an important goal of Synthetic Biology, because with their help it would be possible not only to find out which

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genes of a living cell are essential under which conditions, but also to build a platform ('chassis') for new functions such as the biosynthesis of substances. 'Minimal genomes can be developed using a *top-down* or a *bottom-up* approach. The *top-down* approach uses reduction of the existing genome, whereas *bottom-up* builds the minimal genome from individual DNA fragments.' Constructing minimal cells aims at generating simplified cellular systems. 'This requires the acquisition of transcriptome, proteome and metabolome data, using mathematical modelling within the framework of systems biology. These cellular systems will help scientists to understand the systematic interplay of essential cell modules' (Ref. 8, p. 67).

Genetic components for desired metabolic functions could be inserted into the minimal genome of a cell that is to be used as a 'chassis' and then optimized with respect to efficient production. This engineering approach to biological systems can very efficiently be pursued with so-called 'bio bricks' (see below).

Synthetic Metabolic Pathways

> Metabolic engineering refers to the modification or supplementation of existing biosynthetic capacities either in organisms where some relevant metabolic steps already exist or in those where they are foreign. The targeted metabolic pathway is designed with controlling circuits and integration modules. The necessary DNA sequences are chemically synthesised, recombined and then transferred into a suitable recipient organism. (Ref. 8, p. 70)

Tailored metabolic pathways have long been employed in biotechnology, but within Synthetic Biology they can be utilized for biosynthesis processes that do not occur naturally.

> Although it was previously used for selective modification of individual genes or their regulators in a biosynthetic gene cluster comprising several genes, in 2003 this genetic engineering technique was used in E. coli to construct a complete biosynthetic pathway for producing isoprenoids. The bacterium was programmed so that it synthesised artemisinic acid, the precursor of the anti-malaria drug artemisinin. This procedure involved recombining genes from the plant Artemisia anna and yeast as well as bacterial genes in E. coli together with the necessary bacterial control regions for regulated gene expression. Three years later, yeast was also successfully programmed to produce artemisinic acid. […] The objective of this work is to produce an anti-malaria drug that can be made available at low cost to patients in countries where malaria is endemic. (Ref. 8, p. 71)

Metabolic engineering also becomes important in the field of industrial or 'white' biotechnology, especially for the replacement of petrochemical-derived production processes by sustainable bioprocesses based on renewable resources. All these examples have in common that they are based on a detailed understanding of the biosynthetic pathways, a rational design and further development of the repertoire of experimental genetic engineering methods (Ref. 8, pp.71f.).

Synthetic Regulatory Circuits

Genetic circuits are the key for modifying cellular regulation processes and converting them into externally controllable genetic circuits. For example, DNA exerts its biological

function via precise control of gene activity. Viruses, bacteria and eukaryotic cells use a wide range of complex regulatory mechanisms for this control.

> The gene activity can thus be closely harmonised to the metabolic and tissue-specific requirements of the cell at all levels of gene expression – from the formation of the primary transcript to the post-transcriptional modification (found in eukaryotes) and protein biosynthesis. […] There is no clear boundary between classical biotechnology and synthetic biology with respect to the development of artificial circuits. […] If several of these circuits are combined, positive and negative feedback processes can be used to create complex cybernetic systems with differing characteristics. A key role is played by the so-called repressilator, which is an oscillating regulatory system based on the combination of three bacterial repressor proteins. The construction of even more complex genetic circuits will benefit to an increasing extent from the development of functionally defined modules such as 'BioBricks'. But their interplay can only be predicted to a limited extent and must therefore be assessed empirically. (Ref. 8, p. 70)

Actually, electronic engineering can be viewed as a valuable model for the construction of biological systems: 'This combination of technology and methodology for designing and fabrication semiconductor chips – the "chip fab" – constitutes one of the most successful engineering paradigms of all time' (Ref. 9, p. 46) – whereas today's genetic engineers predominantly 'are still hard-wiring every circuit' (Ref. 9, p. 46). One of the methods that contributes to the success of electronic engineering is standardization, i.e. what can be transferred to biotechnology:

> Standardization of technologies allowed chip engineers to specialize in circuit design or fabrication and to thereby manage complex problems at different levels of abstraction. Bio fab engineers can also cope with complexity by using abstraction hierarchies to hide unnecessary information. Thus, a bio fab designer working at the level of whole systems need worry only about which device to include and how to connect them to perform the desired function without having to manufacture each device from scratch. Similarly, a device-level designer should know the functions and compatibility of individual parts within a device, whereas a parts-level engineer should understand how each part works internally but need not be able to synthesize its DNA raw material. (Ref. 9, p. 48)

Code Engineering

The central tenet that underpins much of current molecular biology lies in the relationship between DNA, RNA and proteins. The genetic code (the DNA) instructs cells to produce proteins by transcribing the DNA sequence into an intermediary messenger RNA (mRNA). The mRNA is then translated into a polypeptide chain comprising a defined sequence of the 20 naturally occurring amino acids to produce proteins that carry out most of the cellular functions and activities within organisms.

It is generally accepted that proteins play a key role in practically all biological processes. Long ago, other technological fields, such as medicine or material sciences, recognized their potential as well. But there do not exist natural proteins for every need. However, methods for the production of tailored proteins are still very limited. It is, for example, possible to chemically synthesize long polypeptide chains in vitro and also include amino acids that cannot be found in natural proteins – but this synthesis is very intricate and its products are still far from the purity and complexity of biological proteins. Genetic engineering on the

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other hand allows for the easy production of complex and pure proteins, but all natural organisms can only use 20 amino acids to construct their protein molecules because of the genetic code's limitation. Therefore, a promising perspective for the synthesis of new proteins is to expand the genetic code. This is not as absurd as it might seem: on the one hand the genetic code of all modern creatures is basically universal, hinting at its establishment billions of years ago. But, on the other hand, there are also variations in natural creatures. We know, for example, of chromosomally coded genes, where the codons UGA, respectively UAG, can be replaced with the specific amino acids selenocystein and pyrrolysin, even though these codons normally are stop signs and thus not assigned to any amino acid. Furthermore, the amino acid formylmethionine is being installed in bacteria as the first amino acid of all newly synthesized proteins. To do that, the ribosome uses the codon AUG that originally stands for Methionin. Many creatures use this code alteration to equip a (usually very small) part of their proteins with additional chemical groups for the control of biological processes.

An extended genetic code allows for the inclusion of novel amino acids into proteins that thereby receive new properties that can be used as new catalysts or medical agents that do not yet exist in nature. Of course, special strategies are needed for the manipulated organisms to remain functional in spite of the code alteration. The molecular centre for the code and its alterations is the transfer-RNAs (tRNAs). They have an anti-codon complementary to the respective triplet and transport the amino acid that is to be installed. There is at least one tRNA for every amino acid. Special enzymes, so-called aminoacyl-tRNA-syntheases (AARS), ensure the right amino acids get loaded onto the tRNA. The AARS carry out the matching of the amino acids with the DNA triplets (that is the genetic code) and guarantee the correct translation. There are different approaches to influence the function of the AARS. So-called suppression-based methods alter the AARS (and therefore also its particularity) via mutation and selection. Simultaneously, the original meaning of a stop-codon is being suppressed. Finally, the suppressor tRNAs recognize a stop-codon and insert an amino acid at this place.[10]

With regard to biological laws, it bears some irony that the genetic code – implemented in organisms for billions of years and therefore a true candidate for an 'eternal biological law' – has now been engineered and extended. Of course, the genetic code never had the status of a law in Galileo's or Newton's sense, but is only a correlation table; in an evolutionary sense, it is a frozen accident.

Other 'Sciences of the Artificial'

The above examples taken from Synthetic Biology shall not obscure that many other 'Sciences of the Artificial' (Herbert A. Simon) have been established and illustrate how engineering complex systems not only build upon analysis but also can contribute to an understanding of complex systems. Whereas Synthetic Biology still is based upon the principles known from biology, these 'Sciences of the Artificial' may exhibit new principles.

Both the predecessor and analogy for Synthetic Biology, 'Artificial Life' emerged at the interface of biology and computer science 25 years ago: 'Artificial Life is the study of

man-made systems that exhibit behaviors characteristics of natural living systems' (Ref. 11, p. 1). Biology has long been faced with the fact that we know of only *one* type of life (i.e. based on carbon-chain chemistry), and, consequently, we have difficulties in deriving general principles of life from this single example. Artificial Life tried to generate alternative life-forms – 'life as it could be', as Chris Langton described it (Ref. 11, p. 2) – by simulation or synthesis. This is done in order to improve and to broaden our understanding of what life is and to understand the organizational principles underlying the dynamics of living systems. Life is seen as a property that emerges from the interaction of a great number of simple non-living parts. 'It is this … local determination of behavior that AL employs in its primary methodological approach to the generation of life-like behaviors' (Ref. 11, p. 3).

The typical experiment carried out by an Artificial Life researcher occurs in a computer. Simple-structured entities react to local situations in their environment, including encounters with other entities. The *global* behaviour that emerges within a population of entities is studied. An early example of Artificial Life research is the 'Game of Life' – a formal system that very clearly demonstrates how global patterns arise as the result of simple local interactions: on a large square lattice each square 'cell' may be either ON or OFF. The state of each cell in the following time step is determined as a function of its own state and the state of its eight neighbours. Depending on the starting configuration, there can arise global patterns such as 'gliders' moving across the lattice as a result of the local interactions. The patterns are usually visualized by indicating ON (OFF) cells as black (white). 'Life' can very easily be implemented on digital computers and serves to emphasize the importance of choosing the right level of analysis in looking for patterns in complex systems.[12]

Although computer simulations are especially well suited to analysing complex systems, because every single parameter can be controlled and measured with absolute precision, a logical consequence of Artificial Life research is to go beyond computer simulations, and experiment in vitro and in vivo. This opened the door to bio-engineering.

Synthetic Biology as an Engineering Science

Synthetic Biology utilizes techniques that are also used in engineering design and development. 'The essence of this approach is to define the specification of the part, device or system that is required and to develop a design which meets these specifications' (Ref. 2, pp. 18–19). In engineering, systems are normally built from standard devices, which in turn are built from standard parts. The standard parts and devices are all fully characterized and may be used in the design of multiple systems.

One characteristic of design today is the ability to undertake detailed computer modelling. This means that the expected behaviour of the part, device or system under development can be simulated in detail. Implementation of systems in Synthetic Biology normally means modifying synthetic DNA and inserting it into an *E. coli* cell or some other chassis. Finally, 'testing and validation is particularly important in synthetic biology because it is the response to the insertion of modified bacterial DNA which determines whether or not the specification and the design have been properly realized' (Ref. 2, p. 19).

Developers in automobile or aviation construction also use computer models for intensive simulations and tests in this way. If the models finally meet the requirements, a prototype and finally a newly developed car or airplane can go into construction. In the field of life sciences, synthetic biology therefore represents the last step towards technical engineering. Development of a part, device or system can involve a number of iterations, with each iteration refining the design and its implementation.

Synthetic biological systems use artificial means to obtain new biological components and novel living organisms that do not occur naturally in that form. By rational design, the assembly of synthetic and biological units can lead to new substances and systems, for example, novel polymeric molecules and tissues as well as entire cells and organisms. Technological innovation, e.g. the synthesis of nucleic acids and DNA sequencing, have pushed the field of Synthetic Biology, but it has to be noted that 'there is no clear line between synthetic biology and genetic engineering processes, which have been in use for over 30 years: for example in the synthesis of recombinant gene products' (Ref. 8, p. 62).

A report by the SATW reminds us of the 'complexity of biological systems, which makes it difficult to reliably engineer them and essentially converts every industrial development project into a research project that needs to cope with unexpected fundamental hurdles or completely new insights into the biological system' (Ref. 13, p. 4). It is commonplace to state that biological organisms are much more complicated than any machine designed by man. Nevertheless, Synthetic Biology aims at 'designing processes' in biotechnology. Of course, design processes in more mature fields, such as classical engineering disciplines (e.g. mechanical engineering or electrical engineering) today are more elaborated, and their 'success rate of design efforts is by orders of magnitude better than in biotechnology' (Ref. 13, p. 5). Five Points are central to engineering science and to Synthetic Biology – and have yet to be implemented in biotechnology (Ref. 13, p. 6f.):

- *Comprehensiveness of available relevant knowledge*. Currently, for example, the function of a quarter of the genome of the bacteria *E. coli* (an organism biologists have been studying extensively until today) is unknown – given such deficits, we can hardly claim to know how life works.
- *Orthogonality*. The combined parts of biological systems (e.g. the molecular components of cells) should be independent so that a modular composition is possible and no unexpected side effects do occur. In natural cells however molecular components influence each other in manifold ways.
- *Hierarchy of abstraction*. Whereas in synthetic biology subsystems should be analysed on different levels of abstraction, biotechnology focuses on the molecular level. In engineering sciences such as electronics, however, abstraction on different hierarchical levels allows for an effective division of labour (different experts are responsible for different levels with their respective details; in biology these could be metabolic paths or genetic circuits).
- *Standardization*. Biological systems are complex and multifaceted. The path to tailored components of synthetic biology is still long.

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- *Separation of design and manufacturing*. Unlike, for example, in the automobile industry, in biotechnology this division is still far from being common practice. The unification of bio sciences and engineering sciences, which is now on the horizon for synthetic biology, is a precondition for the division of these tasks.

Conclusion

The goal of engineering and technological sciences is to generate knowledge about laws, structure and rules for technology. All this is pursued with a regard to using this knowledge in technological applications. A diverse but targeted array of methodologies is employed ranging from the rational and systematic to the intuitive and heuristic. Technological knowledge is often about single facts, events and cases. 'The particular case or the particular event is both prerequisite for gaining law-like propositions by induction and starting point as well as dominant criterion for action' (Ref. 14, p. 27; translated). Whereas the search for laws already in traditional biology has been difficult, in Synthetic Biology, action and application stand in the foreground and laws increasingly lose ground as a meaningful concept.

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