# Synthetic Biology

Position Paper

Permanent Senate Commission
on Genetic Research
of the German Research Foundation

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# Contents

# 1 Foreword

The possibilities opened up by technology present both opportunities and risks. This is as true in science as it is in all other aspects of life. It is always necessary to weigh the benefits and drawbacks of a new technology and discuss assessments of the content with other parties. Processes such as this, involving the opinions of society, the scientific community, and those responsible for science policy, depend on factual information. Through this position paper on synthetic biology, the DFG aims to contribute to these processes. This document presents an overview of scientific developments since the publication of the first statement on this topic in 2009 and highlights public discussion and areas where action may be needed.

One particular challenge in relation to synthetic biology is the lack of a clear delineation of the underlying subject areas and the application perspectives emanating from their results.

The technological developments arising from synthetic biology are diverse and offer considerable potential with many associated opportunities but also potential risks. It is therefore essential to place the debate on a factual footing to allow critical reflection and discursive rationality.

Both scientific and policy decisions are always dependent on science-based judgements. Before decisions can be made, however, the basis for decision making must be carefully prepared. This position paper, which is supported by the German National Academy of Sciences Leopoldina, is intended to contribute to just such a process.

The authors hope that it will be of interest to the reader and of practical use to policymakers.

September 2018

**Professor Dr. Katja Becker**
Vice President
Deutsche Forschungsgemeinschaft
(German Research Foundation)
Chair of the Permanent Senate Commission on Genetic Research

# 2 Summary and Recommendations

A number of new and ongoing methodologies have advanced the field of synthetic biology since the DFG, acatech (National Academy of Science and Engineering), and the German National Academy of Sciences Leopoldina first addressed the topic in 2009. In this document, the essential scientific advancements achieved so far are enumerated and placed in context within the current public debate.

The core statements of this document may be summarised as follows:

- Synthetic biology is regarded by researchers as an approach or a concept. It is not a clearly defined or demarcated field of research.

- It is necessary to draw a clear distinction between this concept and the underlying methods and techniques. The confusion of terms and concepts often seen in public debate, especially the assumed equivalence of certain methodological approaches and synthetic biology, is unhelpful from a scientific perspective.

- The new possibilities in genome synthesis and genome editing have yielded significant results as key tools and technologies for implementing the concept of synthetic biology. The expansion and development of the principles and approaches of synthetic biology also offer considerable potential for innovation for the future.

- This potential for benefit must be balanced against possible risks—in relation to biosafety and potential misuse (biosecurity and dual use)—and must also be considered in the light of ethical issues. This requires a specific case-by-case examination of any planned work.

- With respect to biosafety, the work currently known does not present any new potential hazards. It is adequately covered by existing regulations, particularly the German Genetic Engineering Act and the Cartagena Protocol.

- The ethical questions arising from the research approaches of synthetic biology are not new. They fall within the existing spectrum of ethical questions relating to genetic engineering and stem cell research. This does not, however, imply that these questions will not require re-examination at some point in the future. The risk of violating boundaries occurs when people lose control over a technology, either because the technology itself has spiralled out of control and can no longer be managed or because of irreversible destruction of the environment and the conditions or resources essential to human life. Proactive ethical monitoring of scientific progress is therefore essential.

- The Central Committee on Biological Safety (ZKBS) should also continue to closely monitor developments. They should pay particular attention to novel concepts, especially ideas for the development of autonomously replicating systems generated without a natural blueprint (‘artificial

life’). At the present time, such ideas are still far from being realised, but it is essential to monitor developments attentively and proactively and discuss possible regulatory and ethical issues in advance, so as to be able to make the necessary adjustments in good time. For example, it is necessary to establish what regulations systems of this kind—which would not necessarily have to be classified as genetically modified organisms—would be subject to and what criteria would apply for establishing adequate risk assessment and, where necessary, safety measures. A proactive approach to ethical monitoring in which opportunities and risk are weighed against each other is also required.

- In recent years, questions relating to synthetic biology have frequently been the subject of public and political debate. Due to the difficulty of clearly defining this area of research, the term ‘synthetic biology’ has become associated with a very diverse and often very broad range of meanings, sometimes including new methods of genetic engineering or indeed genetic technology as a whole. From a scientific perspective, this approach is unhelpful. A distinction must be made between research that is adequately regulated by existing laws and agreements and that which gives rise to new questions.

- With regard to the safety assessment of organisms produced through synthetic biology, discussions relating to the Convention on Biological Diversity (CBD) should concentrate in particular on their potential new properties and on organisms that are neither genetically modified organisms (GMOs) in the sense used by the Genetic Engineering Act nor living modified organisms (LMOs) according to the Cartagena Protocol.

# 3 Introduction

In 2009, the DFG, acatech, and the German National Academy of Sciences Leopoldina examined the opportunities and challenges of this field of research in the publication “Synthetic Biology – Positions”[1]. The statement, which was prepared on the basis of a scientific workshop, considered a number of selected areas of research and potential scientific, societal, and political opportunities and challenges.

Synthetic biology is still a very young branch of science at the intersection of biology and engineering. The aim of the synthetic biology approach is to design and manufacture biological systems with new functionalities or a new combination of functionalities for which there is as yet no known equivalent in nature. Synthetic biology utilises various concepts, ranging from the generation of biological modules to whole networks of biomolecules and the *de novo* synthesis of natural systems (cells).

It was emphasised in the 2009 statement that synthetic biology is not a clearly delineated field of research. It is not possible to strictly demarcate the genetic engineering and biotechnology techniques that have been used for more than 40 years. It is also unhelpful to define synthetic biology simply in terms of a spectrum of methods. It makes more sense to regard it as a further development of the participating disciplines and to understand it in terms of the aims of these disciplines. Within this field, researchers from many different disciplines collaborate to design biological systems with new, defined properties. From a scientific point of view, the idea of viewing synthetic biology as a separate concept is only justified by the conceptual strategy used to achieve a given result.

The main applications of synthetic biology are still in basic research. However, some prominent applications have already emerged in the biotechnology sector (e.g. pharmaceutically active substances, platform chemicals, and bioplastics). In most cases—in line with the approach described above—it is not the product itself but the method of manufacturing that is synthetic or optimised using the tools and methods of synthetic biology.

Given the difficulty of clearly defining the field, public debate often centres on a very broadly defined term that may encompass large areas or indeed all of genetic technology and molecular biology. This definition determines the way in which discussion proceeds and can lead to discussions and recommendations for handling synthetic biology that are redundant with respect to existing rules or even contradict them.

In recent years there has been a series of new scientific developments in the field of synthetic biology, some of which have been prominently discussed in the media. In this document, the key

[1] DFG, acatech, Leopoldina. Synthetische Biologie. Standpunkte. 2009, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

scientific advancements of the last few years will be outlined, and then the public and political debate on synthetic biology will be examined and possible new areas of action analysed.

# 4 Scientific Developments

The general understanding that has developed in the scientific community is that synthetic biology refers to the rational, knowledge-based, and modular design of biological systems. Specific approaches have emerged as key examples of this branch of research: the targeted configuration and modification of existing biological systems or systems based on biological principles in order to create functionalities or combinations of functionalities which have not yet been described in nature. Greater emphasis is given to design concepts from the technical engineering sciences such as standardisation, modularity and orthogonality, which—ideally—permit the extensive design of novel yet functional systems on the drawing board.

**Modularity:** Step-by-step breakdown of a complex system into clearly defined functional subunits and components. For example, a gene, a protein, or an entire metabolic pathway may represent a module.

**Orthogonality:** Drawing on an engineering principle, this refers to the targeted replacement of system components with external, largely autonomously acting parts. In a sense, a 'biological parallel world' is created with non-naturally-occurring biomolecules.

This should be distinguished from the method used to achieve particular functionalities, which often combines a variety of technologies drawn from genetic engineering, biotechnology, engineering, or chemistry.

First, the technological developments (tools and technologies) are examined in more detail below, and then the higher-level principles are considered.

## 4.1 Key Tools and Technologies for Implementing the Concept of Synthetic Biology

As with life science research as a whole, developments in synthetic biology have benefited enormously from the very rapid developments of new technologies and the enhancement of existing ones in recent years. At the same time, the demands and approaches of synthetic biology have served as drivers of technological progress. Inspired by the concept of synthetic biology, researchers have already taken existing technologies to the next level or invented new tools where specific ones were lacking. These methods are applied across the full spectrum of the life sciences; they are not limited to the field of synthetic biology, nor should they be equated with synthetic biology.

For example, the production of synthetic DNA and its use—a development that made many aspects of synthetic biology possible in the first place—has become a routine application across all areas of life science research. New technological developments such as the miniaturisation of synthesis with the aid of microfluidic systems, light-controlled synthetic chemistry combined with lithography techniques, DNA laser printing, and synthesis via nanopores may be expected to

deliver more efficient forms of synthesis with the associated further reductions in cost.[2,3,4,5] This in turn will allow new applications to emerge, for instance the synthesis of large sections of the genome.

DNA assembly is still a rapidly growing field of technological development. In recent years an array of increasingly reliable and efficient methods has been developed for the configuration and combination of DNA molecules. This has made it possible to generate DNA on a scale of megabases (1 megabase = 1 million base pairs), or on the scale of magnitude of bacterial genomes. These developments have significantly aided research into synthetically manufactured genomes and extensive genome modification. Examples include the synthesis and partial modularisation (physical sorting of genes into functional groups) of a *Mycoplasma* minimal genome[6,7] (see also Principles, below) and the Synthetic Yeast 2.0 project[8]. Although it may seem currently out of reach, plans to synthesise the complete human genome are already being discussed.[9]

The availability of technologies for the targeted modification of naturally occurring genetic information in living organisms has also increased dramatically over the last few years. Some of these technologies are collectively referred to as genome editing or genome surgery. Many rational technologies in synthetic biology have successfully made the transition from basic research to practical application.

Thanks to multiplex techniques with directed evolution (multiplex automated genome engineering, MAGE)[10], researchers have successfully modified and expanded the genetic code. This technology makes it possible to automate and accelerate the natural principles of evolution in order to systematically optimise microorganisms and their genomes. A development that had a substantial

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[2] Chow BY, Emig CJ, Jacobson JM. Photoelectrochemical synthesis of DNA microarrays. Proc Natl Acad Sci USA, 2009, 106:15219–15224.

[3] Lee CC, Snyder TM, Quake SR. A microfluidic oligonucleotide synthesizer. Nucleic Acids Res, 2010, 38:2514–2521.

[4] Olasagasti F, Lieberman KR, Benner S, Cherf GM, Dahl JM, Deamer DW, Akeson M. Replication of individual DNA molecules under electronic control using a protein nanopore. Nat Nanotechnol, 2010, 5:798–806.

[5] Stoloff DH, Wanunu M. Recent trends in nanopores for biotechnology. Curr Opin Biotechnol, 2013, 24:699–704.

[6] Gibson DG, Glass JI, Lartigue C, Noskov VN, Chuang RY, Algire MA, Benders GA, Montague MG, Ma L, Moodie MM, Merryman C, Vashee S, Krishnakumar R, Assad-Garcia N, Andrews-Pfannkoch C, Denisova EA, Young L, Qi ZQ, Segall-Shapiro TH, Calvey CH, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC. Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome. Science, 2010, 329:52–56.

[7] Hutchison CA 3rd, Chuang RY, Noskov VN, Assad-Garcia N, Deerinck TJ, Ellisman MH, Gill J, Kannan K, Karas BJ, Ma L, Pelletier JF, Qi ZQ, Richter RA, Strychalski EA, Sun L, Suzuki Y, Tsvetanova B, Wise KS, Smith HO, Glass JI, Merryman C, Gibson DG, Venter JC. Design and synthesis of a minimal bacterial genome. Science, 2016, 351:aad6253.

[8] http://syntheticyeast.org

[9] Boeke JD, Church G, Hessel A, Kelley NJ, Arkin A, Cai Y, Carlson R, Chakravarti A, Cornish VW, Holt L, Isaacs FJ, Kuiken T, Lajoie M, Lessor T, Lunshof J, Maurano MT, Mitchell LA, Rine J, Rosser S, Sanjana NE, Silver PA, Valle D, Wang H, Way JC, Yang L. The Genome Project-Write. Science, 2016, 353:126–127.

[10] Wang HH, Isaacs FJ, Carr PA, Sun ZZ, Xu G, Forest CR, Church GM. Programming cells by multiplex genome engineering and accelerated evolution. Nature, 2009, 460:894–898.

impact on molecular and cell biology, and thus the field of synthetic biology, was the introduction of CRISPR/Cas technology[11] in 2012. This has significantly simplified and accelerated the process of achieving targeted genetic modifications (the removal, insertion or swapping around of DNA sequences), from bacteria to higher multicellular organisms (fungi, plants, animals and humans). CRISPR/Cas-based technologies have now become widely used in many areas of basic and applied life science research. However, in the public perception they are often increasingly equated with synthetic biology, or synthetic biology is reduced to these technologies alone. CRISPR/Cas was first discovered through knowledge-driven basic research in microbiology. The concept of synthetic biology contributed to the development of CRISPR/Cas into a usable tool and now utilises this technology, as do many other life science disciplines including medicine.

The growing combination of rational molecular design with experimental (Darwinian) evolution at the level of proteins and functional RNA, as well as the level of organisms or viruses (Adaptive Laboratory Evolution), may also be regarded as a new development. Experimental evolution is being used increasingly often in combination with synthetic biology approaches for optimisation purposes, for example, to further improve a rationally designed and implemented starting system (such as a synthetic metabolic pathway). Alternatively, a rational, synthetic system can create selective pressure in a specific direction to stimulate directed evolution. This complements the original strong emphasis on the design/engineering principle of synthetic biology.[12]

## 4.2 Principles and Approaches of Synthetic Biology

In this section, examples of important basic principles or trends are outlined to illustrate concepts in synthetic biology. This is not intended to be a complete list. The principles can be combined and are thus not completely distinct from one another. It is important to note again at this point that a clear distinction must be made between molecular genetics methods on the one hand and the concepts of synthetic biology on the other.

*Top-down approach*

This includes techniques such as the reduction of an existing (usually microbial) genome.[13] Among other things this approach is used to identify the minimal genetic equipment of an organism (the 'minimal genome') required, for example, for survival under particular conditions. This information may then be relevant to the production of so-called 'protocells' (see below). For example, an existing minimal genome can be used as the starting point for further establishing more complex cell functionalities. The assembly of the *Mycoplasma* minimal genome mentioned above is certainly an outstanding achievement in synthetic chemistry, but attempts to re-sort the genes

[11] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science, 2012, 337:816–821.

[12] Mans R, Daran JG, Pronk JT. Under pressure: evolutionary engineering of yeast strains for improved performance in fuels and chemicals production. Curr Opin Biotechnol, 2018, 50, 47–56.

[13] Choe D, Cho S, Kim SC, Cho BK. Minimal genome: Worthwhile or worthless efforts toward being smaller? Biotechnol J, 2016, 11:199–211.

demonstrate that we are still scientifically far from the genuine drawing board design of functional genomes.

*Bottom-up design of self-replicating systems*

The bottom-up design of a synthetic cell from individual molecular components (a 'protocell') is currently regarded as one of the greatest scientific challenges. The ability to manufacture a self-replicating system constructed from biological components requires a complete rational understanding of the fundamental principles of biological life at the molecular level. These approaches seek to answer fundamental biological questions about life and offer the possibility of pioneering new technologies.[14] Based on the developments and successes of recent years, there is discussion of the possibility of launching an international, interdisciplinary initiative with a time horizon of 10 to 20 years to address and resolve this challenge. Several initiatives have been set up (MaxSynBio[15] [Max Planck Society, DE] + BaSyC[16] [NL] + BrisSynBio[17] [UK]) and have established networks to study the fundamental principles required for the construction of synthetic cell-like structures.

Liposomes play a crucial role in efforts to construct synthetic systems capable of self-replication.[18] These are spheres or bubbles encased in a lipid membrane that resemble the casing of a cell and act as a compartment for biological reactions. By joining specific liposomes with the aid of a 3D printer, scientists have been able to generate light-controlled artificial tissue-like structures, opening up the possibility of further interesting findings in the field of 'tissue engineering'.[19] So far, however, no one has succeeded in creating autonomously replicating systems *de novo*. Researchers have already produced autonomously oscillating systems that simply require an energy input in order to sustain a continually repeating sequence of biochemical reactions independently of additional external factors. This is regarded as one of the necessary prerequisites for the production of synthetic cells.[20]

[14] Jia H, Heymann M, Bernhard F, Schwille P, Kai L. Cell-free protein synthesis in micro compartments: building a minimal cell from biobricks. N Biotechnol, 2017, S1871-6784(16)32503-1.

[15] www.maxsynbio.mpg.de

[16] www.tudelft.nl/en/2017/tu-delft/dutch-researchers-join-forces-to-build-synthetic-cell

[17] www.bristol.ac.uk/brissynbio

[18] de Souza TP, Fahr A, Luisi PL, Stano P. Spontaneous encapsulation and concentration of biological macromolecules in liposomes: an intriguing phenomenon and its relevance in origins of life. J Mol Evol, 2014, 79:179–192.

[19] Villar G, Graham AD, Bayley H. A Tissue-Like Printed Material, Science, 2013, 340:48–52.

[20] Loose M, Fischer-Friedrich E, Ries J, Kruse K, Schwille P. Spatial regulators for bacterial cell division self-organize into surface waves in vitro. Science, 2008, 320:789–92.

*Further developments*

Work aimed at producing functional but not autonomously replicating synthetic systems is further advanced than efforts to create a protocell. Models of this type, both *in vitro* (in the test tube) and to some extent *in vivo* (the modules and systems may be or become part of autonomously replicating systems) may be regarded as further design approaches within synthetic biology. The *in vitro* combination of individual 'modules' to form complex 'systems' not previously described in nature is particularly promising of new functionalities, especially for the production of new metabolic pathways. One example is the recently published $CO_2$ fixation pathway, not found in this combination in nature, which uses 17 enzymes from nine different organisms including three technically modified enzymes.[21] However, the functional establishment of the new metabolic pathway, which was initially designed on the drawing board, required several subsequent optimisations and modifications of the enzymes to make sure they functioned under the same reaction conditions.

In view of the complexity of the biological systems and the new functionalities to be realised, design methods from the system sciences can in particular be used for conceptualisation on the drawing board.[22] The systematic nature of these methods not only enables the rapid design of the individual modules and systems, but also allows deduction of diverse *a priori* predictions, i.e. before implementation in the laboratory.[23] These include, for example, the influence of disturbance variables on the desired function of a module (robustness) or also the dynamic behaviour of the overall system (stability) and can thus help estimate and minimise the probability of a loss of control.

Special mention should be made of efforts to use DNA or XNA (see below) for digital *in vitro* and *in vivo* information storage.[24,25] The important potential benefits include the potentially enormous storage density ($10^{18}$ bytes per $mm^3$) and the particular longevity of these polymers.[26,27,28,29] Re-

[21] Schwander T, Schada von Borzyskowski L, Burgener S, Cortina NS, Erb TJ. A synthetic pathway for fixation of carbon dioxide in vitro. Science, 2016, 354, 900–904.

[22] Halter W, Tuza ZA, Allgöwer F. Signal differentiation with genetic networks. Proceedings of the 20th IFAC World Congress, Toulouse, France, 2017.

[23] Steel H, Papachristodoulou A. Design Constraints for Biological Systems That Achieve Adaptation and Disturbance Rejection. IEEE Transactions on Control of Network Systems, 2018, 5:807–817.

[24] Church GM, Gao Y, Kosuri S. Next-generation digital information storage in DNA. Science, 2012, 337:1628.

[25] Shipman SL, Nivala J, Macklis JD, Church GM. CRISPR-Cas encoding of a digital movie into the genomes of a population of living bacteria. Nature, 2017, 547:345–349.

[26] Grass RN, Heckel R, Puddu M, Paunescu D, Stark WJ. Robust chemical preservation of digital information on DNA in silica with error-correcting codes. Angw Chem Int Ed, 2015, 54:2552–2555.

[27] Zhirnov V, Zadegan RM, Sandhu GS, Church GM, Hughes WL. Nucleic acid memory. Nature Mater, 2016, 15:366–367.

[28] www.technologyreview.com/s/607880/microsoft-has-a-plan-to-add-dna-data-storage-to-its-cloud

[29] www.sciencealert.com/microsoft-could-be-storing-data-on-dna-within-the-next-three-years

writing digital information into a DNA sequence as well as synthesizing and reading out the information is still, however, a time-consuming process. But as with DNA sequencing over the last few years, it is anticipated that DNA synthesis will become cheaper as time goes on. DNA may therefore offer an alternative to long-term data storage based on both *in vitro* and *in vivo* systems.[30,31]

In addition to the possible use of DNA for information storage, DNA and RNA polymers are already being used as structuring components in nanotechnology applications. The shape of the components can be influenced and programmed through their coding sequence.[32] The term DNA or RNA origami refers to *in vivo* and *in vitro* applications that, in addition to their passive function as a structuring component, also include complex constructs with specific functions, such as DNA scaffolding for optimising biosynthetic metabolic pathways[33], or programmable nanorobots[34]. The limitations inherent to the synthesis and provision of sufficient quantities of sequence-specific (and therefore structure-specific) DNA for *in vitro* applications have already been overcome on a laboratory scale, with the result that the DNA origami concept is, in principle, scalable for production purposes.[35]

Significant progress has also been made in the field of xenobiology.[36] Researchers working in this field are seeking to replace natural nucleic acid molecules (RNA, DNA) with synthetic nucleic acid analogues (XNA) to achieve higher chemical stability, enlarge the genetic code, and enable the production of modified proteins.[37] The *in vitro* replication of XNA has already been achieved.[38,39] However, XNA components cannot currently be synthesised using natural or modified organisms.

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[30] Blawat M, Gaedke K, Hütter I, Chen XM, Turczyk B, Inverso S, Pruitt BW, Church GM. Forward Error Correction for DNA Data Storage. Procedia Comput Sci, 2016, 80:1011–1022.

[31] Erlich Y, Zielinski D. DNA Fountain enables a robust and efficient storage architecture. Science, 2017, 355:950–954.

[32] http://cadnano.org

[33] Castellana M, Wilson MZ, Xu Y, Joshi P, Cristea IM, Rabinowitz JD, Gitai Z, Wingreen NS. Enzyme clustering accelerates processing of intermediates through metabolic channeling. Nat Biotechnol, 2014, 32:1011–1018.

[34] Douglas SM, Bachelet I, Church GM. A logic-gated nanorobot for targeted transport of molecular payloads. Science, 2012, 335:831–834.

[35] Elbaz J, Yin P, Voigt CA. Genetic encoding of DNA nanostructures and their self-assembly in living bacteria. Nat Commun, 2016, 7:11179.

[36] Schmidt M, Pei L, Budisa N. Xenobiology: State-of-the-Art, Ethics, and Philosophy of New-to-Nature Organisms. Adv Biochem Eng Biotechnol, 2018, 162:301–315.

[37] Malyshev DA, Dhami K, Lavergne T, Chen T, Dai N, Foster JM, Corrêa IR Jr, Romesberg FE. A semi-synthetic organism with an expanded genetic alphabet. Nature, 2014, 509:385–388.

[38] Pinheiro VB, Holliger P. The XNA world: progress towards replication and evolution of synthetic genetic polymers. Curr Opin Chem Biol, 2012, 16:245–252.

[39] Pinheiro VB, Arangundy-Franklin S, Holliger P. Compartmentalized Self-Tagging for In Vitro-Directed Evolution of XNA Polymerases. Curr Protoc Nucleic Acid Chem, 2014, 57:9.9.1–18.

Clinical research is increasingly emerging as another field of application for synthetic biology. In some cases, complex systems are used to treat disease, often in combination with electrical engineering and chemical modules. The biological component is most commonly a genetically modified eukaryotic cell stimulated to produce a specific response via chemical or optical signals. Although the modified cells are not capable of self-replication, they do in principle possess this potential if fundamental problems surrounding the controlled replication of foreign cells in existing tissues (e.g. the human body) can be resolved. Prominent examples include thought-induced gene expression[40] and the improvement of disease symptoms in mice with diabetes or psoriasis by means of programmed genetic circuits.[41,42]

## 4.3 Applications of Synthetic Biology

Research and development in an academic environment has produced a variety of examples of the successful implementation of synthetic biology in usually prototypical applications. The iGEM (international Genetically Engineered Machine) competition that emerged from a course at the Massachusetts Institute of Technology (MIT) in 2003 is an impressive example of the creative potential available. Scientific journals concentrating on synthetic biology have already been established, for example ACS Synthetic Biology.

By comparison, the implementation of the concept of synthetic biology in technical industries is not very advanced, at least in terms of the criterion of a functionality that has not yet been described, or not yet been produced in this specific combination. The production of 1,4-butanediol, isobutene, and isoprene may be regarded as flagship projects involving a combination of genetic engineering and elements of synthetic biology that have made an important contribution to the establishment of a production process. The biotechnological production of 1,4-butanediol from sustainable resources was also very economically successful. A biotechnological process has been developed for this basic compound of the chemical industry, of which millions of tonnes are used worldwide and which could previously only be produced petrochemically. No naturally occurring microbial synthesis pathway for 1,4-butanediol has so far been discovered.[43]

Another flagship project is the artificial synthesis of the anti-malarial substance artemisinin. Over a period of ten years, in a public-private partnership, a partially artificial synthesis pathway has been designed and developed to production scale. The aim was to make the substance, tradi-

[40] Folcher M, Oesterle S, Zwicky K, Thekkottil T, Heymoz J, Hohmann M, Christen M, Daoud El-Baba M, Buchmann P, Fussenegger M. Mind-controlled transgene expression by a wireless-powered optogenetic designer cell implant. Nat Commun, 2014, 5:5392.

[41] Ye H, Xie M, Xue S, Charpin-El Hamri G, Yin J, Zulewski H, Fussenegger M. Self-adjusting synthetic gene circuit for correcting insulin resistance. Nat Biomed Eng, 2017, 1:0005.

[42] Schukur L, Geering B, Charpin-El Hamri G, Fussenegger M. Implantable synthetic cytokine converter cells with AND-gate logic treat experimental psoriasis. Sci Transl Med. 2015, 7, 318ra201.

[43] Yim H, Haselbeck R, Niu W, Pujol-Baxley C, Burgard A, Boldt J, Khandurina J, Trawick JD, Osterhout RE, Stephen R, Estadilla J, Teisan S, Schreyer HB, Andrae S, Yang TH, Lee SY, Burk MJ, Van Dien S. Metabolic engineering of Escherichia coli for direct production of 1,4-butanediol. Nat Chem Biol, 2011, 7, 445–452.

tionally extracted from the plant (*Artemisia annua*, sweet wormwood), available in sufficient quantities and at lower costs even when harvests fail. Baker's yeast, the biological host organism, was genetically modified, and plant genes were inserted. This gave rise to a precursor molecule that would be chemically difficult to achieve, which was then converted via chemical catalysis outside the yeast into the active substance. This metabolic pathway has now also been successfully implemented in a crop plant (tobacco) with high biomass production.[44]

Tools developed from the concepts of synthetic biology are used in many different kinds of application-oriented research and as key technologies by commercial companies. Particular mention should be made of biosensors, which are used for environmental monitoring, identifying active substance candidates, and optimising biosynthesis pathways.[45,46,47]

[44] Fuentes P, Zhou F, Erban A, Karcher D, Kopka J, Bock R. A new synthetic biology approach allows transfer of an entire metabolic pathway from a medicinal plant to a biomass crop. eLife, 2016, 5. pii: e13664.

[45] Bereza-Malcolm L, Aracic S, Mann G, Franks AE. The development and analyses of several Gram-negative arsenic biosensors using a synthetic biology approach. Sensors and Actuators B: Chemical, 2018, 256, 117–125.

[46] Li N, Huang X, Zou J, Chen G, Liu G, Li M, Dong J, Du F, Cui X, Tang Z. Evolution of microbial bio-sensor based on functional RNA through fluorescence-activated cell sorting. Sensors and Actuators B: Chemical, 2018, 258, 550–557.

[47] Schulte J, Baumgart M, Bott M. Development of a single-cell GlxR-based cAMP biosensor for Corynebacterium glutamicum. J Biotechnol, 2017, 258, 33–40.

# 5 Synthetic Biology in Public Debate

In recent years, there has been frequent discussion of various issues relating to synthetic biology such as legal regulation and the ethical evaluation of new methods and products. Synthetic biology has also been the subject of international political discussion, for example, in the negotiations surrounding the Convention on Biological Diversity (CBD). These topics of discussion are examined below with reference to the current state of scientific knowledge.

## 5.1 Assessment of Biosafety

The 2009 statement noted that most of the molecular biology methods used in the various areas of synthetic biology research fall into the category of genetic engineering. From the standpoint at that time, there were no special risks associated with this technology; the existing legal provisions—particularly Germany's Genetic Engineering Act, based on the relevant EU directives—were regarded as adequate. At the same time, given the rapid development of this field of research, it was suggested that future scientific development should be closely monitored and that the Central Committee on Biological Safety (ZKBS), the central body for the safety assessment of genetic engineering, should be tasked with monitoring synthetic biology. The Federal Ministry of Food and Agriculture (BMEL) followed this suggestion. The ZKBS has yet to be legally appointed as the assessing body for the biosafety of synthetic biology research.

In November 2012, the ZKBS presented its first monitoring report (ref. no.: 46012)[48]. This report describes scientific advancements and analyses them in terms of whether there are any developments requiring additional regulation. No additional need for action was identified as a result of this report. This appraisal was supported by the statements of other organisations.[49]

The scientific developments achieved since then, outlined previously, also provide no grounds for revising this view. The modules referred to above for the design of 'viable' systems each have a reference in nature.

In a recent commentary on a report by the CDB Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology (see below for more details), the ZKBS noted that no organisms have yet been developed using the methods of synthetic biology that cannot be regarded as genetically modified organisms (GMOs) or living modified organisms (LMOs) in the usual sense as defined by the

[48] www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/ZKBS/01_Allgemeine_Stellungnahmen_deutsch/01_allgemeine_Themen/Synthetische_Biologie.html

[49] A publication by Dechema (2011; http://dechema.de/2011+Thesenpapier+zum+Status+der+Synthetischen+Biologie+in+Deutschland.html) comments on the current state of synthetic biology in eight thematic areas. In particular, this paper also shows that the currently applicable legal provisions for the assessment of the potential risks of research are sufficient. The research report (2012; www.gentechnologiebericht.de/publikationen/synthetische-biologie-2012) by the interdisciplinary working group "Genetic Technology Report" of the Berlin-Brandenburg Academy of Sciences and Humanities focuses on the prospects and implications of synthetic biology. The report also points out that "current research in synthetic biology (...) falls within the legal framework for genetic technology research". This view is shared by the scientific committees of the European Commission (2014; https://ec.europa.eu/health/sites/health/files/scientific_committees/emerging/docs/scenihr_o_044.pdf), although with the reminder that some specific areas or products of synthetic biology could fall outside the applicable legal framework for genetic engineering.

Cartagena Protocol on Biosafety.[50,51] In this context, they also recommend that the safety assessment of organisms manufactured with the aid of synthetic biology should concentrate on new properties and novel organisms that are not GMOs or LMOs in the sense used by the Cartagena Protocol. This appraisal was reinforced in the second ZKBS monitoring report on synthetic biology published in June 2018.[52] Following analysis of the international state of research, the report concludes that—apart from technologies such as DNA synthesis—systems produced so far are subject to the German Genetic Engineering Act and that biosafety can be assessed by means of established methods.

Nonetheless, developments must continue to be carefully monitored. Special attention must be given to completely novel concepts such as xenobiological approaches and new possibilities in genome editing, which make it increasingly difficult to draw a clear distinction between 'natural' and 'non-natural' genetic modifications—currently still a decisive criterion with regard to the legal necessity to assess potential hazards in genetic engineering. It should be emphasised that risk assessment cannot be carried out on an 'across-the-board' basis, e.g., on the basis of the technologies used; rather, individual research undertakings must be examined and evaluated.

At the present time, it would seem that the development of autonomously replicating systems generated without a natural blueprint ('artificial life') is unlikely to be achieved in the near future. But in this context in particular, an array of regulatory and ethical questions would need to be discussed, especially as such artificially produced organisms could not necessarily be classified as GMOs. It therefore appears necessary to proactively monitor and diligently discuss developments in this field of research so that any necessary legal adjustments can be implemented promptly. This assessment is also supported by the most recent ZKBS monitoring report published in June 2018.[53] The report notes that protocells without an equivalent in nature would not automatically be subject to the Genetic Engineering Act and that such systems would make it necessary to develop separate assessment criteria and, where necessary, safety measures. At the present time, according to the report, only individual elements of artificial cells have been researched, but the production of autonomously replicating protocells that cannot be compared to natural organisms has not yet been achieved. However, it also notes that current research work in connection with protocells does not involve any biological risks. In the view of the ZKBS, it is also likely that the reduced genome of autonomously replicating, artificial minimal cells would give them reduced fitness, with the result that they would be scarcely viable outside the lab. In addition to the aspects described in the ZKBS report, the use of system-theoretical methods can be applied to construct synthetic organisms with greater reliability or to protect against loss of control by means of redundant safety mechanisms.

The Genetic Engineering Act regulates both the contained use and deliberate release of genetically modified organisms. For the contained use of the systems produced so far, there are clear regulations that may be considered adequate on the basis of the current state of research. In the case of the deliberate release of novel organisms, their impacts on the environment, which the

[50] http://bch.cbd.int/protocol

[51] https://bch.cbd.int/database/record.shtml?documentid=113221

[52] www.zkbs-online.de/ZKBS/SharedDocs/Downloads/01_Allgemeine Stellungnahmen/01_Allgemeine Themen/2. Bericht der ZKBS zur Synthetischen Biologie (2018).pdf

[53] Op. cit., p. 26.

Act regards as an asset deserving protection, must also be taken into consideration. This requires the extensive examination of potential consequences of the release of genetically modified organisms in terms of changes to the ecosystem as a whole. Although in the eyes of the public there are often fears about loss of control and the unpredictability of potential consequences, all scientific research so far indicates that, due to their extremely specialised metabolism, the systems produced do not possess any recognisable potential for uncontrolled dispersal in nature. Their fitness is substantially more restricted than natural organisms that have arisen through natural selection over millions of years. Xenobiology is regarded as another important biological safety component in this respect, particularly with a view to reducing the potential hazards associated with artificial autonomously replicating systems, as these require components that are not available in nature.[54] Concepts in xenobiology are therefore being discussed as a safety measure to prevent the uncontrolled exchange of genetic information or the uncontrolled spread of biological systems.

In summary, recent advancements in synthetic biology do not give rise to any fundamentally new problems for risk assessment. The technologies *per se*—which, as explained above, are not specific to synthetic biology and should certainly not be equated with synthetic biology—do not present any specific hazards. However, their applications must be assessed on a case-by-case basis. Developments in the field of synthetic biology should therefore continue to be closely monitored by the ZKBS, which has the expertise needed to assess the biological risk of both genetic engineering research and genetically modified organisms. The monitoring process should cover the questions of whether entities might arise that are no longer covered by existing regulations, whether it is necessary to develop new criteria for an adequate risk assessment of new organisms developed through synthetic biology research, and what form these criteria and their methodological application should take.

## 5.2 Ethical Debate

As with any new scientific concept, the question must be asked as to whether the technologies or products of synthetic biology give rise to new ethical issues. Are current ethical standards, for example those that apply to genetic engineering research, adequate or does synthetic biology introduce something fundamentally new? Does it demand a fresh assessment of the risk to humans and the environment compared to conventional research?

As a general rule, the technological procedures used in synthetic biology do not exceed the scope of the procedures used in conventional, genetic engineering and biotechnology research. No new ethical problems arise compared to familiar areas of research in genetic engineering, cell biology, or developmental biology, all part of the wider environment of synthetic biology, be it the production of transgenic plants and animals, cloning, the creation of chimeras, cell reprogramming, assisted reproduction, or genetic enhancement[55]. As with genetic engineering research, it is neces-

[54] Schmidt M. Xenobiology: A new form of life as the ultimate biosafety tool. Bioessays, 2010, 32:322–331.

[55] See also: DFG, acatech, Leopoldina. Synthetische Biologie. Standpunkte. 2009, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (p. 39–42, here p. 40).

sary to achieve legal clarity on issues of justice (property rights, patents, rights of use). Established rules for risk assessment and for monitoring research and its applications should therefore be applied consistently in the form of internationally recognised principles so that the consideration of ethical issues is covered by regulations for conventional research, genetic engineering, and biotechnology.

Even if no fundamentally new ethical questions arise, it must be taken into account that the extent and scale of research exceeds what has been previously done—as a result of the increase in uncertainty associated with the development of new synthetic organisms, non-natural reference systems, and the highly complex nature of research. This in turn increases the risks in connection with safety (biosafety) and potential misuse (biosecurity and dual use). This is discussed, for example, in the most recent Consensus Study Report published by the National Academies of Sciences, Engineering, and Medicine, USA, under the title “Biodefense in the Age of Synthetic Biology”[56]. Consequently—and experts are unanimous on this—new standards are needed for risk assessment in order to adequately assess the potential consequences, including unintended harm to people, landscapes, and the environment.[57] Ethical questions affect the assessment of the consequences of technology and the likelihood and potential for harm of possible errors, whether, for example, rapid and effective countermeasures could be taken following the unintentional release of synthetic products (the biosafety problem). The greater a non-calculable or non-manageable residual risk, the greater the additional risk in the event of misuse (the biosecurity and dual use problem). In view of the accelerated pace of progress in research, it is therefore important to discuss an enhanced culture of safety.

An important instrument for further research, particularly given the high levels of uncertainty, is the precautionary principle. By “intensively monitoring the consequences,” this principle enables us to flexibly adapt empirical practice to possible scenarios and also develop scenarios that take into account unintended harm to people and the environment and responses to it. Applying the precautionary principle can exploit error-minimising possibilities and reduce risks arising from specific mechanisms of synthetic biology—for example the unintended release of organisms—by ensuring “that the manufactured entities are unlikely to be viable or to undergo evolution outside the laboratory”.[58] The precautionary principle therefore provides an ethical method of proactive safety measures instead of simply seeking to respond reactively after damage has occurred, if such a response is still possible.

It will be crucial to work towards international regulatory standards facilitating self-regulation within the research community. It would also be desirable to encourage more ethical debate and involve the general public, for example, through interdisciplinary discussion platforms. This is indeed an

[56] www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24890&_ga=2.71343568.2133597207.1529479193-2077026416.1529479193

[57] See op. cit., p. 39.

[58] Op. cit., p. 39.

ethical imperative, given that decisions for or against particular technologies affect not just science, but global society and the environment as a whole.

However, in addition to reflecting on safety issues in basic and applied research, there are also fundamental ethical questions relating to technical procedures. As with genetic technologies in general, it is necessary in relation to synthetic biology in particular to establish whether it violates fundamental ethical boundaries. Some regard in the aim of creating novel forms of life, or manufacturing life by technical means, a violation of such boundaries.

Although no new questions arise in terms of the technological and legal safeguarding of safety and justice, nonetheless the potential blurring of the line between technology and life in the field of synthetic biology could represent a fundamentally new ethical challenge. Should it become possible to manufacture life artificially, would this definitively violate an ethical boundary? Does synthetic biology represent something fundamentally new to our understanding of humanity and human capabilities?

To answer these questions, two points must be clarified: 1. What is an ethical boundary? 2. What constitutes a violation of this boundary?

Ethics sees freedom as the scope for human action, and its fundamental criterion is therefore to protect, and if appropriate enlarge, this freedom, but not to endanger it. This freedom comprises two aspects:

1. The ability to develop technology
2. The responsible use of technology

In other words, an ethical boundary can be violated in two ways: first, when the use of technology is removed and second, when the possibilities of the responsible use of technology are hampered or even prevented. From an ethical perspective, both aspects must be protected, or in other words violation of the respective boundaries must be prevented. For the purposes of technology, however, this means that an ethical boundary is not—as is so frequently claimed—determined by nature or by biological life. This boundary has been continually moved by technological advancements. It is human nature to regard nature not as something set in stone but as something that can be manipulated, including with technology. Although there are limits to this manipulation, they do not lie in a blurring of the line between nature and technology, nor in a blending of technology and life. Rather, they lie where human freedom as a prerequisite and object of ethics is jeopardised.

In the case of synthetic biology, this means that the emergence of new biological–technical characteristics does not itself violate the limits of what is ethical. The accusation of people ‘playing God’ also does not stand, even if they were to develop the ability to manufacture life via technical means.

However, the risk of violating boundaries does occur when humanity loses control over its own technical capabilities, either because the technology itself gets out of control and can no longer

be managed, or because of irreversible destruction of the environment and the conditions or resources essential to human life. In this case, even the benefits of technology, the medical and economic advantages that it makes possible, would no longer constitute an argument, as this would call into question both human freedom and dignity.

Even weighing harm against benefit would reach its limit here, as there is a degree of harm that outweighs anything else. For all harm/benefit comparisons, the precautionary principle advocated above is the method of choice, since it enables us to prevent pernicious harm to the conditions for human life and the environment we live in. If the risks cannot be averted by means of the precautionary principle, it is necessary to diagnose whether a general ethical boundary has been violated, i.e. whether synthetic biology gives rise to potential harm to humanity in its structure of ethical determination. This cannot, however, lie solely in the blurring of the line between natural and artificial, because this blurring is not in and of itself ethically questionable. The cultural modification of natural life already blurs the distinction between the natural and the artificial, technology being simply a particularly distinctive form of the artificial. The technical modification of life becomes ethically problematic only when a risk arises that the artificial begins to perpetuate itself in such a way that the technology can no longer be managed and controlled. If the ability to manage and control the technology is jeopardised, then its use would have to be halted and, if necessary, research would have to be adapted to the problem.

This would however alter the measure of ethical evaluation. The issue would no longer be specific hazards to humanity and damage to the environment but further-reaching irreversible risks to human existence. This then concerns the core issue of ethics, that of the loss or maintenance of human freedom. From this follow all the criteria for weighing the benefit and harm of a particular area of research. These must be measured in terms of the preservation of humanity and the conditions of life upon which it depends.

The following steps should therefore be considered in relation to synthetic biology from an ethical standpoint:

1. The ethical questions arising from synthetic biology are not new. They fall within the existing spectrum of ethical questions relating to genetic engineering and cell/developmental biology. Ethical issues are also already taken into consideration by means of existing laws and researchers' obligations.
2. This does not, however, imply that ethical questions have been resolved once and for all. They may require re-examination at any time if the gap between technical manipulation and ethical management can no longer be bridged, i.e. if the technical manipulation can no longer be controlled.
3. Preventing this requires methodically proactive measures and safety precautions. This means that it is an ethical imperative in itself not to regard ethics as merely a response to potentially harmful developments. The ethics of research require proactive ethical monitoring, which, given the rapid pace of development in research, not only reactively combats harm but also retains the ability to evolve and adapt to changed needs.

4. This proactive monitoring is not solely the responsibility of researchers. Not only scientists, but society as a whole should be involved in deciding on ethical issues. However, researchers do have a duty to make the facts of their research as transparent as possible and to communicate their work in a clear, balanced way. In this manner, informed dialogue can support the self-regulation of science without dictating to it.
5. To make this dialogue as informed and fact based as possible, it is appropriate to establish a platform for discussion. Such a platform would serve to promote an objective public perception of the opportunities and risks associated with research, as well as its critical monitoring. Ethical questions no longer concern researchers and research users alone, but everyone. In this sense, ethically monitoring research becomes a matter of no less than preserving the human heritage. For this, individual members of society must be able to discuss the issues together as fellow citizens.
6. Such public debates also serve to build trust in science and prevent the spread of irrational fears with respect to biological research (compare green genetic engineering). Promoting this trust also requires that researchers and research institutions can demonstrate that they place value on the safety of people and the environment. This includes being able to respond appropriately to crises, anticipate hazards, and develop an exit scenario. However, building trust in science is made more difficult when economic and political interests are tied to research, behind which safety interests may be relegated to second place. Here too, it helps disclose possible links of research with business and politics.
7. As long as it is possible to conduct proactive ethical monitoring of synthetic biology, it will be possible to balance opportunities and risks against one another. But if this possibility of proactive supplementary ethical research should diminish, there would be a real risk that ethical considerations would be taxed beyond merely weighing harm and benefit. In a scenario like this, the ethics of science itself would be called into question, which translates into the orientation of research development towards humanity and human freedom. To maintain not only the ethical but also the technical scope for action, it is however essential to preserve this and prevent it from being jeopardised by technological developments. Future research in synthetic biology must pay due attention to this.

In the past several years, the German Ethics Council has addressed the topic of synthetic biology on multiple occasions, organising a number of events and producing relevant publications. In February 2010, a Bioethics Forum was organised on issues relating to synthetic biology, and in November 2011, the German Ethics Council held a public conference on ‘The Workshop of Life – The Importance of Synthetic Biology to Science and Society’. The German Ethics Council decided at the first of these events that it was not necessary for the time being to issue a special statement but that future developments in synthetic biology should continue to be appropriately monitored. The discussion begun there was continued at the second event.

Questions relating to the responsible handling of developments in synthetic biology are also discussed at scientific conferences. At its next conference, the German Association for Synthetic Biology (GASB), a learned society established in 2017, has chosen to address societal and ethical questions in addition to scientific ones.

## 5.3 Political Debate

Synthetic biology has cropped up repeatedly in political debate in recent years. In 2016, a report was published by the Bundestag's Office of Technology Assessment and was subsequently discussed in the Bundestag Committee on Education, Research and Technology Assessment.[59] This report considered "synthetic biology in a narrower sense" and "synthetic biology in a wider sense." This 'wider sense' is understood to include the use of the full range of genetic engineering methods (e.g. CRISPR/Cas technology + gene drives). The report describes the current state of research, development, and application and, based on this, presents recommendations for future regulation that do not distinguish between the established methods of genetic engineering and the new questions likely to be presented by synthetic biology research. However, such a distinction is regarded as absolutely necessary. It is essential to differentiate between tried-and-tested work that existing legislation already sufficiently regulates and that which gives rise to new questions as to its regulation. In the latter case, assessment is needed on a case-by-case basis.

**Gene drive:** A method for propagating genetic elements or gene constructs within a population of sexually reproducing organisms, with the genes being inherited by significantly more than 50% of offspring.

The debate over synthetic biology also found its way into negotiations on the Convention on Biological Diversity (CBD), with initial 'draft decisions' being discussed in Cancun in December 2016. A first report by an Ad Hoc Technical Expert Group (AHTEG) is already available, which is intended to lay the foundation for discussions at the next conference of signatories. This discussion also rests on a very broad concept of synthetic biology that makes no distinctions between different types of research. The considerations are therefore in no way specific to synthetic biology, which is also not the actual reason for the CBD discussion. The practice of unduly equating synthetic biology with new molecular biology methods, which is seen frequently and is not scientifically justifiable, is also covered in the most recent statement by the European Plant Science Organisation (EPSO) on the relationship between plant breeding methods and synthetic biology.[60]

In the context of the CBD negotiations a very general discussion is taking place that may nonetheless have far-reaching impacts on synthetic biology and other scientific disciplines. As stated above, the ZKBS has made a statement on the AHTEG report. This statement specifically points out that all known work so far in synthetic biology is subject to the regulations of the German Genetic Engineering Act and the Cartagena Protocol on Biosafety. This also applies explicitly to any organisms bred through gene drives that have raised serious concerns over the potential impacts of their release on the ecological balance (see the general statement issued by the ZKBS, ref. no. 45310.0111, February 2016)[61].

[59] www.bundestag.de/blob/421086/aeff5fe36dcb75d9e9d3bff73d114b7c/synthetische-biologie-data.pdf

[60] www.epsoweb.org/webfm_send/2329

[61] www.bvl.bund.de/ZKBS/SharedDocs/Downloads/02_Allgemeine_Stellungnahmen_englisch/01_general_subjects/Recombinant gene drive systems (2016).pdf

# 6 Annex

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