Technology Assessment

Constructing Life

The World of Synthetic Biology

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1 Preface

In the summer of 2007 a group of seventeen international top researchers hailed synthetic biology as a ‘new technology revolution’ which could provide solutions to major problems. Synthetic biologists don't just want to create new biological systems, they want to improve them. Clean bio fuels and cheap malaria drugs are just some of the visions synthetic biologists cherish. But social and ethical questions about the impact on health and the environment and abuse through biological warfare, arise. And what of the commercial implications? Can you patent life itself?

The construction of a completely artificial cell is still many years away. Yet with the current knowledge of hereditary information (genomics) and the developments in nanotechnology and IT, synthetic biology is a discipline that is developing extremely fast. Molecular biologists, physicists, chemists and technicians are working together, and influencing each other.

In 2006 the Rathenau Institute published the book Constructing Life, the world's first review of the societal aspects of synthetic biology. Recently the Dutch edition, Leven Maken appeared. In September 2007 the Rathenau Institute informed the Dutch Parliament with a Letter to Parliament called: ‘Synthetic Biology: New Life in the Bio Debate.’ The Dutch Labour Party (Partij van den Arbeid) responded by demanding answers from seven departments of state. This document is the English translation of the Letter to Parliament.

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2 Synthetic biology: constructing life

If we view life as a machine, then we can also make it: this is the revolutionary nature of synthetic biology. Until recently, biotechnologists focused on modifying the DNA of existing organisms (genetic modification). Synthetic biologists go one step further. They want to design new life and construct this from scratch.
Craig Venter, famed for his contribution to unravelling the human genome, sees it as the step everyone has always talked about: “Now that we have learned how to read the genome, we are also in a position to write it”.

The transition from reading to writing DNA, entails a paradigm shift whereby the process of construction takes centre stage. Synthetic biologists view things through the eyes of engineers and regard a cell as a collection of cooperating nano machines. According to Drew Endy of the Massachusetts Institute of Technology (MIT) biology has, until now, always been ‘nature at work’. “Yet”, he says, ”if you consider nature to be a machine, you can see that it is not perfect and that it can be revised and improved.”

The paradigm shift of synthetic biology

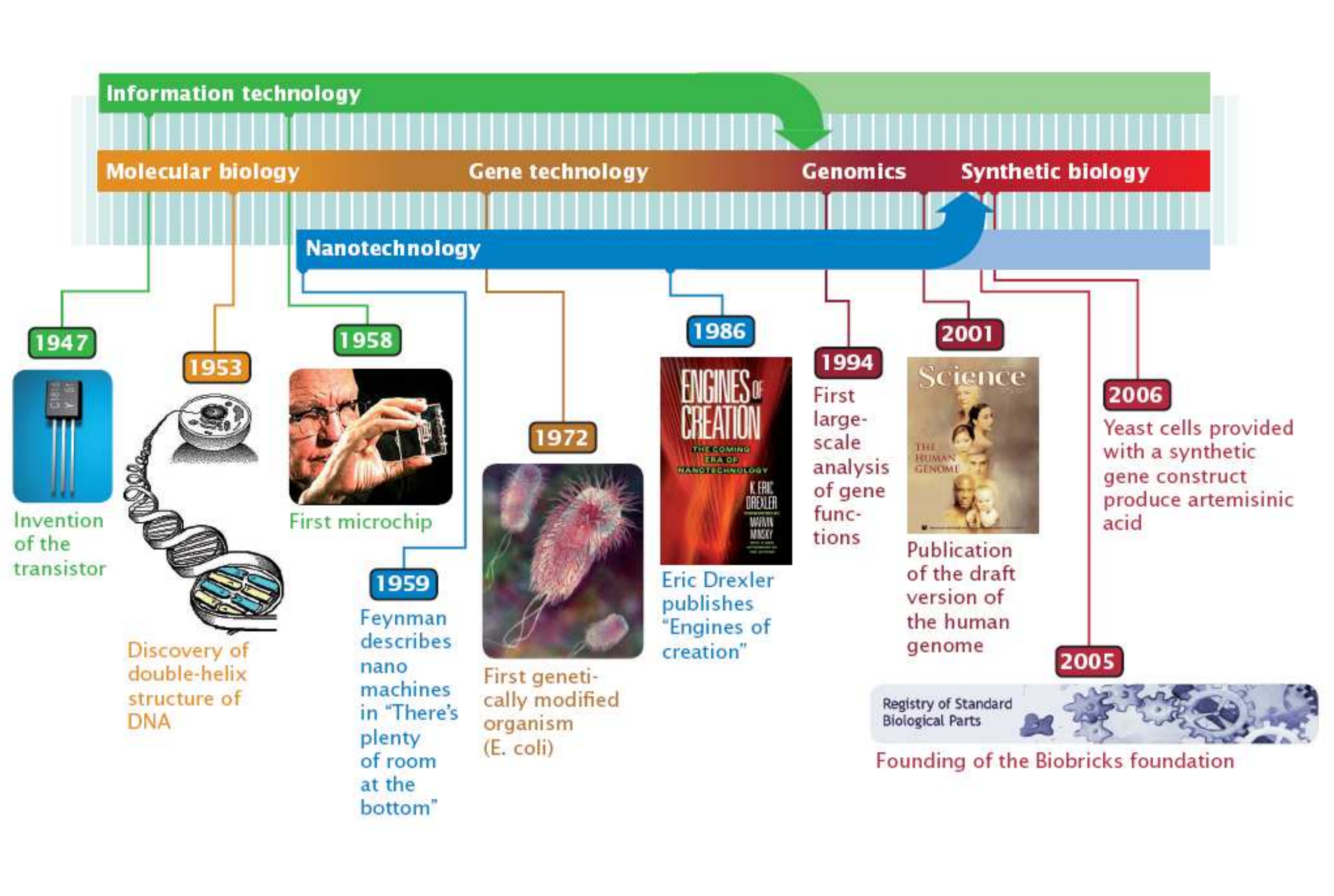
	Genetic modification		Synthetic biology
Technology	Reading / analysing DNA	→	Writing / synthesisis of DNA
	Trial and error		Software programming
Application	Adaption / modification of existing biological systems	→	Design and construction / modulation of new biological systems

The Revolutionary Power of Converging Technologies
Synthetic biology has been hailed as the ‘third technological revolution’ that could eventually provide solutions to climate change, energy - and water shortages, and even our health. In June 2007 seventeen top researchers, including Cees Dekker, a Dutch professor of molecular biophysics, drew a parallel with two other revolutionary technologies that have had fundamental impact: the integrated circuit, the basis for modern electronics, and the discovery of DNA, the basis for molecular biology. In synthetic biology these technologies converge as molecular biologists, physicists, chemists and technologists work together and influence and strengthen each other. [see box 1: Converging Technologies].

Box 1 Synthetic Biology: converging technologies

Three scientific and technological developments converge in synthetic biology:

- **Molecular biology**
- **Modern electronics and information technology**
- **Nanotechnology, the construction of machines and structures at a molecular level**



Molecular biology
Genetically transferable information for biological processes is encoded in the structure of DNA (the letters of the genetic alphabet). By recombining (cutting and pasting) pieces of DNA, the characteristics of natural organisms can be altered artificially, currently a common practice in biotechnology.

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Information technology
Information technology (IT) is a vital tool for reading and interpreting the genetic code. Determining the DNA sequence of viruses, bacteria, plants, animals and humans yields vast quantities of data. Researchers use increasingly powerful computers and specialised software to simulate, design and test biological systems. In 2007, IBM launched BLUE GENE/P, the fastest computer in the world. One second of its processing power is equivalent to that of the processing power of a pile of laptops of two-and-a-half kilometres high.

In genomics research, bioinformatics is used to further analyse these data, with the result that we know increasingly more about genes. Their role in metabolic processes in cells and their significance for a whole host of biological processes is becoming increasingly clearer.

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Nanotechnology
Synthetic biologists want to use this knowledge to build their own genetic structures, so that plant fibres or sugars, for example, can efficiently be converted into ethanol, raw materials for bio plastics, or drugs. By applying the design and construction principles from nanotechnology, it is possible to write the genetic code (synthesis). Companies have already developed techniques with which the four nucleotides, (from which DNA is constructed, indicated with the letters A, C, T and G), can be attached to each other in any desired order. Using this technology, researchers have successfully reconstructed the poliovirus and, in 2002, the Spanish influenza virus; the genome of both is known. DNA synthesis provides the genetic building blocks with which the design can be realised. Synthetic biologists use these to make standardised biological components. The Biobricks initiative of MIT is an electronic catalogue containing such parts.

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Synthetic biology = construction of biological circuits
“We want to do for biology what Intel does for electronics. We want to design and manufacture complex biological circuits”, says George Church, professor of genetics at Harvard Medical School. IT is no longer just a tool to design and test biological circuits. For synthetic biologists it is also a major source of inspiration. The comparison with micro electronics is particularly apt. A printed circuit board is necessary for the design and construction of micro electronics. Electronic circuits are built on this board, using resistors, transistors and condensers.

In the construction of a biological system, a cell with a minimal genome fulfils the function of a printed circuit board. The electronic components are replaced by DNA sequences whose exact biological functions are known. With this approach, biological circuits with a wide range of functions can be constructed. An example of this is the metabolic pathway that allows a specific protein to be synthesised. Synthetic biologists are therefore focusing on both the development of a suitable cell with a minimal genome and the development of relevant biological building blocks. (see also Box 2)

Box 2 Two approaches: deconstruction and construction

Two research approaches lie at the heart of synthetic biology: deconstruction and construction. These two approaches converge in the development of artificial genetic networks with tightly defined and predictable functions.

Deconstruction

In this approach, existing biological life is unravelled. Functioning living cells are deconstructed step by step until the minimal set of genes a cell needs to live, is determined, - the idea behind the minimal genome. The idea is, that if you can limit the complexity of biological processes by switching off as many genetic characteristics as possiblek, such processes become more predictable and manageable.

These minimal cells can then serve as a living chassis into which standardised biological building blocks can be plugged in. Researchers believe that in this way, they can make viruses, micro organisms and other biological systems that function 'better' than natural life forms, or even fulfil entirely new functions. The Craig Venter Institute is one of the research laboratories that follows this method. In 2005, researchers from this institute established that the minimum required number of genes for Mycoplasma Genitalium is 387.

Construction

Another research line, the constructionist approach, focuses on the creation of new material using bio molecular assembly. Researchers use detailed knowledge of the functioning and structure of DNA and other bio molecules, to artificially reconstruct biological components, such as genes and cell membranes, in the laboratory. An example of this is the reconstruction of the Spanish influenza virus in 2002. To achieve this, the entire genetic material of this virus was synthesised. The Biobricks initiative of MIT is another example. Biobricks is an open source Internet catalogue containing a range of standard genetic building blocks: Lego blocks of DNA.

3 Application areas

Promising potential applications

Many researchers are enthusiastic about the possibilities of synthetic biology. There are three key application areas, and the most important of these is the use of microbial platforms to produce drugs, bio energy and fine chemicals.

Drugs

For some time now, genetically modified organisms have been used to produce drugs. With the application of principles from synthetic biology, new possibilities arise. For example, American researchers have developed a synthetic metabolic pathway that causes yeast cells to produce artemisinic acid. This is a raw material for an anti malarial drug that is currently extracted from plants. Thanks to this approach, the drug can now be produced for a tenth of the current cost price. A similar approach can be used for the production of taxol, which is used for the treatment of cancer, and prostratin, which is being clinically tested for the treatment of HIV infections. Various research institutes and companies (including oil company British Petrol) are currently working on the development of micro organisms with optimised, synthetic metabolic pathways for the production of bio fuels and fine chemicals.

Measuring instruments based on biosensors

A second application area is that of advanced measuring instruments based on biosensors. These are cells that respond to specific signals from the environment. They can be deployed to recognise (pathogenic) bacteria such as *Salmonella* or *Legionella*, or to detect pollutants in the soil, air or water, and to measure bio molecules in the human body, such as the sugar level in diabetic patients.

In 2005, students from the University of Texas hit the headlines in the international scientific press with an imaginative experiment: with a smart combination of genetic components from cells (so-called Biobricks, see Box 2) they successfully designed a bacterium that responds to red light. Applied to a dish, these bacteria functioned as a photographic film on which a print could be made if the film was illuminated. They are now refining this system in the laboratory, with a view to developing new biosensors.

Living drugs and stem cells

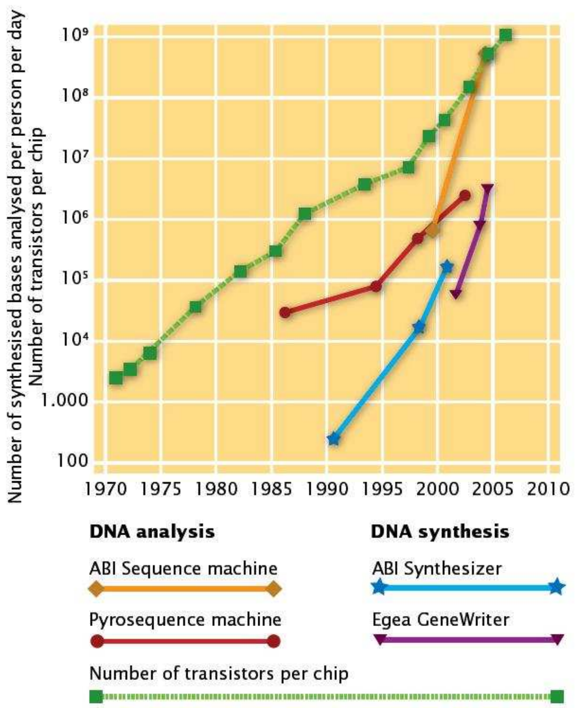
A third promising application area is that of living therapeutics (drugs). With the help of modified bacteria and viruses, researchers think it will eventually be possible to combat cancer cells and inhibit HIV infections. There are also researchers who think that it will be possible to use synthetic biology to guide the differentiation of stem cells in a controlled manner to produce, for example, skin, nerve or muscle cells. This would enable damaged tissues or organs to be replaced.

4 Current Research

At this stage, synthetic biology research is mainly focused on the exploration of fundamental principles of artificial biological systems which might give the impression that all of the promising applications are still a long way off. However, there are reasons to assume that synthetic biology will make considerable advances over the next few years. Major steps in the creation of artificial life are being made by research institutes, the technology of DNA synthesis is developing at a phenomenal rate with parallels to the microelectronics industry, and synthetic biology is attracting significant industrial investment.

The Craig J. Venter Institute recently made world headlines with a successful attempt to equip a bacterium with an entire DNA from another bacterium. This involved introducing a large number of genes at the same time into an organism; it is seen as an essential step towards the creation of artificial life.

In 2007 it is already possible to synthesise the complete genome of a virus, for which the DNA sequence is known, and the use of synthetic genes in molecular biology research is commonplace. Some researchers think that within ten years it will be possible to synthesise entire yeast genomes. Yet in contrast, there are many researchers who believe that living systems are so complex that it is doubtful whether these expectation will be realised.



Moore's law (exponential increase in the speed) also applies to the analysis and synthesis of DNA

The speed of the development of DNA synthesis, exhibits strong similarities with the dynamics in micro electronics, where the calculating capacity has increased exponentially for many years (Moore's law, see below). Parallel to this, it is expected that the speed and accuracy with which DNA can be synthesised will exponentially increase in the coming years. Specialised DNA synthesis companies will produce more genes for ever-lower prices and this will provide an important impulse for research.

Synthetic biology is attracting considerable interest from industry. In 2006, the American firm Amyris Biotechnologies acquired twenty million dollars of venture capital for the development of synthetic biology applications in drugs and bio energy. In the spring of 2007, the oil company BP invested five hundred million dollars in a program for developing efficient production systems for bio fuels. During the last seven years, the German gene synthesis company Geneart has become one of the fastest growing companies in Bavaria with over a hundred employees.

For synthetic biology developments in the Netherlands, see Box 3.

Box 3 Synthetic biology in the Netherlands

Thanks to companies such as Genencor-Danisco, DSM and the Kluyver Centre for Genomics of Industrial Fermentation in Delft, the Netherlands has a strong position with regards to applications in the production of fine chemicals. The University of Groningen envisages possibilities for the synthesis of large numbers of new proteins that will subsequently be tested for their (biomedical) functionality. The use of biosensors can be interesting for companies such as Philips, who are focusing on the development of equipment for medical diagnostics. The Kavli Institute for Nanosciences in Delft plans to initiate a large research program on bio-nano-synthetic biology in the future.
The developments in synthetic biology have caught the attention of several advisory bodies and institutes. In 2006 the Netherlands Commission on Genetic Modification (COGEM) published a monitoring report discussing the significance of synthetic biology for the analysis of bio safety risks and current legislation.

At the end of 2006, the Rathenau Institute published the world's first detailed study of societal implications of synthetic biology: Constructing Life, followed by the Dutch edition Leven maken. In the same year, the Minister of Education, Culture and Science approached the Royal Netherlands Academy of Arts and Sciences (KNAW) to investigate, together with the Health Council of the Netherlands and the Advisory Council on Health Research (RGO), whether a scientific foresight study in this area was worthwhile. These advisory bodies have appointed a work group to ascertain what else needs to happen following the monitoring report from COGEM and the publications from the Rathenau Institute.

5 New life in the biodebate

For the past thirty years, developments in biotechnology have led to public debate and disquiet; the marketing of genetically modified maize, for example, and Dolly the sheep, and Herman, the bull. Synthetic biology raises important ethical and social questions about the possible impact on human health and the environment and possible abuses for biological warfare or terrorist attacks. A number of themes need to be reconsidered.

Theme	Genetic modification	Synthetic biology	Significance for the biodebate
Biosafety	Original host organism as reference	No more natural reference	New questions and uncertainties about risk analysis
Misuse / bioterrorism	Known, risky viruses and bacteria	Difficult to establish what short DNA fragments will be used for	Monitoring misuse of potentially risky organisms and research becomes more difficult
Intellectual property	Limited number of genes	Number of genes virtually unlimited	Research & innovation impeded
Ethics	The alteration of existing organisms	The creation of (partially) artificial life	Boundary between life and machine blurs

Bio safety

In August 2007, British livestock was infected with the viral Foot and Mouth disease (FMD), which was traced to a research laboratory in nearby Pirbright, raising again the issue of bio safety. Synthetic organisms can also escape. At present, experiments with synthetic biology follow the safety principles of genetic modification to which existing legislation applies. There are three types of risk in genetic modification:

- Infection of laboratory staff. Despite all precautionary measures, laboratory staff can become infected with synthetic viruses or micro organisms from the lab with pathogenic characteristics.
- Synthetic viruses or micro organisms can escape via clothing, instruments or laboratory animals and thereby cause harm to the environment or contribute to the spread of new diseases for humans and animals. In the worst scenario, an infection of laboratory personnel is discovered too late, leading to an epidemic.
- A disruption of the ecological balance. If synthetic biological systems are used outside of the laboratory for a specific task and time period under specific circumstances, for example to clean up an environmental contamination, such organisms might have a disruptive effect on the ecological balance. In the worst possible scenario, the situation gets out of control and there is a presence of ‘Green goo’ (unidentifiable material), comparable with the ‘Grey goo’ from nanotechnology. Also new organisms, which have escaped or have been deliberately introduced to the environment, can lead to a contamination

of natural genetic sources. The exchange of genetic material between synthetic and natural biological systems leads, in principle, to the contamination of the natural genetic pool.

The question is whether the current risk assessment system for genetically modified organisms is prepared for the future developments in synthetic biology. The Netherlands Commission on Genetic Modification (COGEM) published its first monitoring report concerning this in 2006. This report made it clear that there are many outstanding uncertainties and questions at policy level.

- Can the current risk assessment system be adjusted if it proves to be unsatisfactory? And if so, how?
- What needs to be known about the characteristics of an organism for a good risk assessment?
- Does a distinction need to be drawn between completely synthetic organisms and existing organisms with new synthetic parts?
- How can the risks of synthetic genes and organisms be assessed if there is no longer a natural reference?

Some researchers state that synthetic life will be so weak that it will never survive outside of the lab. Others propose constructing artificial biological systems in such a manner that they can only survive and reproduce under strictly controlled conditions (in the laboratory or a fermentation vessel). For both propositions there is insufficient scientific evidence and further research is needed.

Misuse and bioterrorism: monitoring is becoming more complex

The five deaths from Anthrax through letters sent shortly after the attack on the World Trade Centre in New York in 2001, placed bioterrorism high on the agenda. The international treaty on biological weapons (Biological and Toxin Weapons Convention – BTWC), signed in 1972, is focused on combating the misuse of natural pathogenic viruses, bacteria and toxins. It lists many different pathogenic organisms that can be used to develop biological weapons. On the blacklist are Anthrax, the smallpox virus, and the BSE virus; other examples include the Asian flu virus and the Ebola virus. Strict controls on the trade and use of these viruses and bacteria can limit, but does not completely exclude, misuse.

Supervision is more difficult
With the emergence of synthetic biology, supervision will be more complex still. The reconstruction of the polio virus and the Spanish Influenza virus make it clear that it is technologically possible (although still highly complex) to reconstruct pathogens on the basis of existing DNA building blocks . A number of American and European gene synthesis companies screen orders for potential misuse. This is already difficult for long DNA chains at a gene or genome level, but for short DNA fragments, it is virtually impossible and therefore scarcely effective.

Dual use research
In the United States in particular, the authorities fear misuse through ‘dual use’ research. This is research into pathogenic organisms for medical, biological or agricultural applications which can also be used for biological weapons. In 2004 the American National Scientific Advisory Board for Biosafety (NSABB) was founded, whose task is to improve the safety measures involving research into the life sciences. Synthetic biology is one of their priorities.

Bio security code of conduct

The awareness among biologists about bioterrorism is low. That is apparent from the reaction of the sixteen hundred biologists who recently participated in bio security workshops organised by the universities of Exeter and Bradford. Efforts are, however, being made to change this, as, for example, various countries are working on ethical codes of conduct. The Interacademy Panel (IAP), a worldwide network of scientific academies, drew up the IAP Statement on Biosecurity at the end of 2005.
This document can serve as a guideline for the compilation of such a code of conduct. Five items are crucial: making researchers aware, following safety requirements, education and information, the responsibility of researchers to signal abuse, and supervision. In the Netherlands, the Ministry of Education, Culture and Science asked the Royal Netherlands Academy of Arts and Sciences to make a contribution to the national Biosafety Code of Conduct. This code has now been compiled and will be presented to the Minister of Education, Culture and Science in the autumn of 2007.

Some researchers are concerned that under the banner of national security, restrictions will be imposed on the publication of research results. To date, there would seem to be little basis for this concern. Science academies in particular, are well aware of the importance of an undisturbed progress of science.

Intellectual property: the patent mountain

At the end of May 2007, the American patent Office announced that Craig Venter had requested a patent for the minimal genome of a synthetic bacterium called Mycoplasma Genitalium. British magazine The Economist commented: ”This time he is proposing not just the patenting of a few genes, but of life itself”. The awarding of intellectual property rights is thought to facilitate innovation. In exchange for publishing his invention, the inventor receives a temporary monopoly on its commercial exploitation. Recombinant DNA technologies and the results of this, are considered to be inventions under patent law and therefore patentable.

DNA Patents

Genes that have been isolated from an organism, even if they are almost identical in terms of structure (base sequence) as genes from nature (or the human body) are considered patentable. These types of patents can be compared with substance patents for new chemical products. Such a substance patent covers all – including future – use of the new compound so also those that are unknown at the time of the patent application. What applies for isolated genes, also applies for synthesised DNA sequences and cells with a minimal genome, and these are also, in principle, patentable.

Researchers, particularly in the United States, fear that the large number of patents on biological building blocks will hinder the progress of their research. For new applications in particular, where many different gene patents play a role, the bringing together of widely spread and fragmentary rights can cause problems. This is already playing a role in drug research into complex diseases such as Alzheimer's and cancer that involve a large number of genes. Synthetic biology could exacerbate these problems. What sort of bureaucratic nightmare will a company end up in when it tries to construct a complete chromosome on the basis of these genes?

Research exemption

In Europe, researchers make use of patented discoveries without patent infringement, thanks to the right of research exemption, arranged at the national and European level. Yet this research exemption applies to 'research of the patented', and is invalid as soon as the research is focused on a commercial innovation. For public-private research in particular, the boundary between academic and commercial research is often not clear. When it comes to innovation programmes, such as the Dutch National Genomics Programme, there is a strong emphasis on validating the research results via patents. Patents can therefore have an inhibitory effect. In the Netherlands, this discussion about this, is scarcely getting off the ground.

Emerging open source movement

In the United States the situation is more dire. There, research exemption does not even exist since university research is considered to be a commercial activity. Researchers therefore fear that the growing mountain of patents will increasingly impede them. Alternatives are being sought to safeguard freer access to technological knowledge. For example, the geneticist Richard Jefferson has set up the Biological Innovation for Open Society (BIOS). This organisation promotes the free use of patents in the area of agro biotechnology. In cooperation with the International Rice Institute, researchers in Korea, China and Kenya have started to set up a freely accessible database of rice-related patents. The American synthetic biology research community recognises the importance of freely accessible knowledge in the public domain for sustainable research. That is why the Biobricks initiative was developed in 2004 , which is an open source system in which everyone has free access to well-defined DNA sequences.

The need for ethical reflection and societal involvement

Should the patenting of genes be possible at all? We attribute different values to living than to non-living material. We mostly regard life as being worth protecting, with the level of protection being dependent on the life form concerned. In similar discussions, such as therapeutic cloning and stem cell research, human gene therapy and the permissibility of genetically modifying animals, it is the moral questions that colour the debate.

The discussion about the patenting of genes and genetically modified organisms clearly has an ethical aspect. The breast cancer related gene BRCA-1,was largely mapped with public funding yet the company Myriad Genetics has obtained three European patents on this. In 2002 this led to Dutch MPs asking whether such patents would lead to a monopoly of Myriad Genetics on the diagnosis and treatment of that type of breast cancer.

In the discussions about gene technology, key values such as autonomy, justice and naturalness play an increasingly important role. There was strong reaction by the Canadian ETC Group due to the awarding of a patent on a synthetic organism with a minimal genome to Craig Venter. "Will Craig Venter's company become the 'MicrobeSoft' of synthetic biology?" There is considerable concern that patenting the building blocks of life will favour rich countries and hinder free access to knowledge and technology.

What is life?

Since synthetic biology is no longer based on existing life forms, but is focused on the creation of biological systems that are entirely or partially synthesised, other ethical questions also arise. May we intervene in life? What is our definition of life? To what extent do we still view artificial biological systems as 'living material'? How does a completely artificial cell differ from a machine? What criteria do we use to determine to designate life? Do we restrict the principle of 'worthy of protection' to natural organisms, to (evolved) creation, or do we consider artificial forms of life also worthy of protection?

Public involvement and the government

In May 2006, a group of 35 societal organisations sent a letter to the organisers of the second International Synthetic Biology Conference in Berkeley. In this letter they stated that synthetic biology is not just an issue for scientists: this development requires a broader public involvement and dialogue.

Including all interested parties at an early stage in important policy questions regarding potentially significant and controversial technologies is wise, but engaging public involvement in a worthwhile and effective manner is far from easy, however. On the one hand governments must take regulatory responsibility with respect to biosafety, bioterrorism and intellectual property. But it is also important that an open discussion can take place in society about the ethical questions associated with synthetic biology. The debate about synthetic biology demands a facilitating, rather than an organisational role from the government.

6 Recommendations

Synthetic biology can challenge existing concepts and the resulting policy in various ways. The challenge demands immediate action from the government. The Rathenau Institute makes six reccomendations:

Biosafety

1. Initiate research
It is expected that synthetic biology will develop rapidly over the coming years. As legislative changes are usually a lengthy process, we advise the Ministry of Housing, Spatial Planning and the Environment, to develop a strategy in the short term. Research into new biosafety-related uncertainties, associated with synthetic biology must be quickly deployed. Here, the questions from the COGEM monitoring report form a good starting point.

2. Feature on the European Agenda
Biosafety is regulated at European Union level. That is why the Ministry of Housing, Spatial Planning and the Environment must place the question on the EU agenda as to whether synthetic biology demands amendments to the European protocols and directives for the introduction of genetically modified organisms into the environment (2001/18/EC) or their contained use (98/81/EC).

Misuse and bioterrorism

3. Arrange national and international harmonisation
The current package of measures to counteract bioterrorism is focused on the products (what), in this case the DNA sequences, those who place the order (who) and the location from where the order is made (where). Developments in the area of synthetic biology demand an expansion of the current approach. To counteract bioterrorism where results of synthetic biology research are used, international harmonisation is needed between safety experts, the universities and companies involved, and the biosafety officers from research institutes. The Dutch National Coordinator for Counterterrorism should take the initiative towards this.

4. Increase awareness of researchers
Researchers must report the misuse of biological agents and their possible unintentional wrong use. Therefore the Ministry of Education, Culture and Science should increase the safety awareness of researchers. One way of doing this is actively disseminating (for example via information campaigns and workshops) the Biosecurity Code of Conduct compiled by the Royal Netherlands Academy of Arts and Sciences. Feedback from the research community must be arranged to increase the feasibility of this code of conduct.

Patenting

5. Reconsider valorisation strategy
The patenting of genes does not always facilitate innovation. Particularly with new applications, where a large number of patents play a role, the current patenting system reaches its limits. The Ministry of Economic Affairs and the Ministry of Education, Culture and Science should therefore consider using the options of open source approaches in the case of publicly funded gene technology research.

Ethics and society

6. Encourage ethical reflection and societal involvement
Synthetic biology will fuel the public and ethical debate about biotechnology. The government must create space for public involvement and reflection on fundamental ethical questions about biosafety, bioterrorism, patenting and the definition of 'life'. This requires facilitation as opposed to regulation. This could mean informing citizens to enable them to form their own opinion.

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