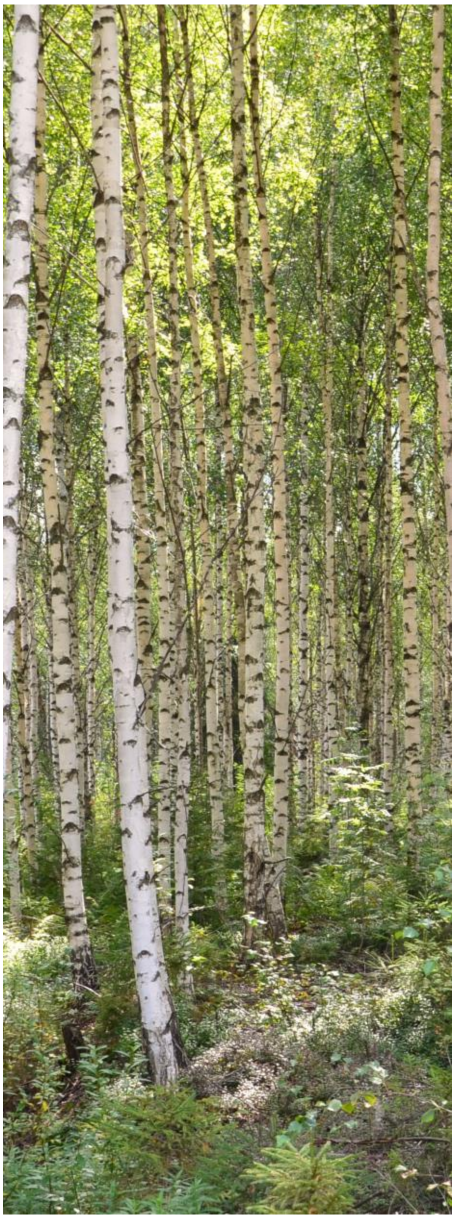
Synthetic biology as an enabler of sustainable bioeconomy - A roadmap for Finland

Living Factories

FOREWORD

This presentation and roadmap for Finland was born from a need to inform the industry, policymakers and the general public of the rapid change in industrial operations made possible by synthetic biology. Finland's bioeconomy strategy emphasises the development of sustainable industrial applications based on renewable raw materials. In these plans, the possibilities of industrial biotechnology are not always sufficiently taken into account. Boosted by synthetic biology, in particular, biotechnology can play a major role as a diversifier and value adder of Finland's bioeconomy.

The work has been done within the Finnish Funding Agency for Innovation (Tekes) funded strategic initiative, "Living factories: Synthetic biology for a sustainable bioeconomy" (LiF). This presentation does not examine the possibilities of plant biotechnology or medical biotechnology, but focuses specifically on the important role of synthetic biology in industrial biotechnology.



We are grateful to Tekes for funding and would like to thank the project's research scientists, management team and the industry representatives who participated in the creation of the roadmap. Their enthusiasm and the support we have received have been invaluable.

15 February 2017

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INTRODUCTION

SYNTHETIC BIOLOGY WILL REVOLUTIONISE BIOECONOMY

Over the last couple of decades, the biosciences have undergone explosive advances in knowledge and the development of new methods, which in turn has opened up new research areas and led to new kinds of commercial operations.

Synthetic biology – a new, but extremely rapidly progressing field of research – is one of the results of this development. Synthetic biology is based on the recently developed quick and affordable methods used to analyse the genomes of organisms, or sequence the nucleotides of DNA, and to manipulate the genome. Of particular value is the vastly cheaper and faster DNA synthesis, which allows the manufacturing of long, synthetic DNA pieces. Biological systems are increasingly designed and constructed using computers. This technological leap brought by biological programming can be compared to the change brought by information technology over the last 40 to 50 years, or industrialisation made possible by mechanical technology 200 years ago.

In particular, synthetic biology will revolutionise industrial biotechnology by utilising living cells or their parts, such as enzymes. Traditional examples of biotechnology are the production of alcohol using yeast and the production of antibiotics using mould. As the methods of genetic technology improved in the 1980s, it became possible to produce, for example, human insulin using yeast and the creation of effective microbe strains producing industrial enzymes. However, the development of biotechnical production strains has been time-consuming and expensive, and the work has largely involved trial and error.

Lego bricks can be used as a simple analogy to synthetic biology. Biological bricks (such as genes) can also be combined to build functional entities of different types

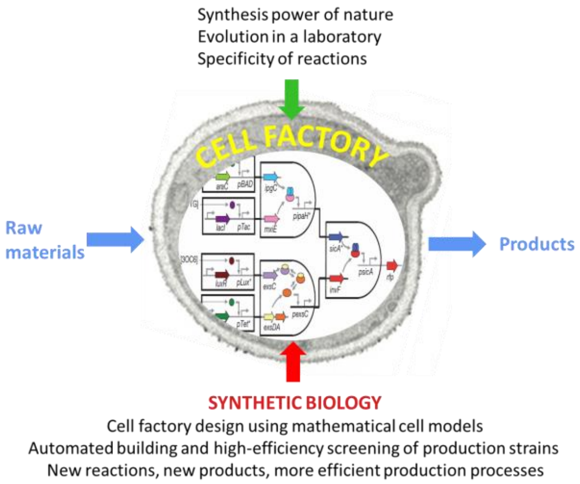
With synthetic biology techniques, development work will become more accurate and an estimated ten times faster by the year 2020. The number of new, biotechnically manufactured industrial products will increase rapidly.

The EU has included biotechnology as one of the six most important technologies for our sustainable future[1]. The approaches made possible by synthetic biology will significantly increase the impact of the field and, in particular, the opportunities brought about by biotechnology. Biotechnology – boosted by synthetic biology – is an enabler technology as its applications are not limited to only a few, specific fields. It is a technological platform that can be utilised in almost all fields of industry. The chemical, energy, food, medical and forestry industries as well as the IT sector can all benefit from synthetic biology.

According to Craig Venter, a leading figure in the field, the greatest breakthroughs in synthetic biology will not take place in the academic world but in industry. For example, many companies in the chemical and energy sectors around the world are already developing processes based on synthetic biology, as they offer new product opportunities and can also save raw materials and energy as well as be cost-effective.

Biotechnology is suitable for both small- and large-scale production. Biofuels are produced in production plants with capacities in the hundreds of millions of litres, while just a couple of hundred litres may be enough for the annual production of valuable medicinal substances. The interest attracted by synthetic biology among young people also raises hopes for the establishment of new start-up companies in the sector.

Biotechnology and synthetic biology are a natural fit with bioeconomy, and their utilisation is a condition for the realisation of the greatest opportunities of the future bioeconomy. Microbial production hosts can use basically any organic materials as raw material, such as wood, fats or straw. Or, just like plants, single-cell microbes can use carbon dioxide as the source of carbon, and sunlight or hydrogen as the source of energy.



[1]http://ec.europa.eu/growth/industry/key-enabling-technologies/index_en.htm

What is synthetic biology?

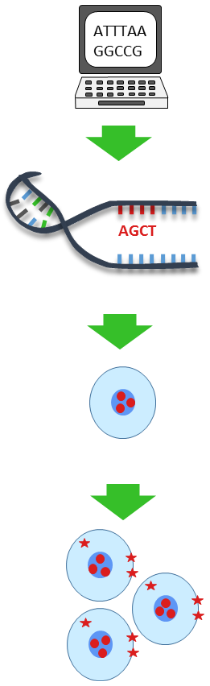
Synthetic biology refers to biological systems designed and built by man; cells, cell parts or organisms not found in nature.

The creation of synthetic systems is made possible by the greatly advanced knowledge of cellular functions defined by the genes and the cheap and quick techniques that can be used to synthesise and modify the DNA code and genome that controls the structure and functioning of the organisms.

Biological knowledge and engineering sciences come together in synthetic biology. Genetic code (DNA) matching the desired biological functions are designed on a computer. These new functions are combined in the manner proposed by mathematical computer models in a living cell. Numerous new kinds of cells can be created rapidly and their functioning tested utilising automation and robotics. Biology becomes programmable and the cell functions can be predicted better.

Richard Feynman, the physicist, said: "What I cannot build, I cannot understand". This is a good description of the new view opened by synthetic biology on biological research and biotechnology. Instead of studying how nature works, we can now start building it based on our own designs.

Synthetic biology will revolutionise biotechnology, and it already has a multitude of foreseeable applications in, for example, medicine, plant biotechnology, nanobiotechnology and industrial biotechnology.



Computer software can be used to design **a genetic code that gives new, desirable characteristics to a production organism**, such as making it produce a new chemical compound.
This genetic code describes the chemical composition of the DNA (the order of the bases A, C, T and G)

The genetic code is synthesised into a chemically equivalent DNA. The synthetic DNA pieces can comprise, for example, a sequence of 10,000 bases and contain 10 genes.

The synthetic DNA is inserted into a cell, where it becomes part of the organism's own genome. Natural DNA can also be replaced by synthetic DNA. Several synthetic DNA pieces can be inserted into a cell either at the same time or consecutively with the help of robotics. The synthetic genes become active in the cell, and the cell expresses the new, desired characteristics.

Once the cell has divided, all of its descendants will express the characteristics defined by the synthetic code. In an industrial-scale production process, there can be billions of synthetic cells (e.g. 10^{10} cells).

Nature is a skillful engineer. Biology offers an astounding number of fascinating mechanisms of action which humans can learn from and utilise for many different purposes. Unlike any other technology, biotechnology naturally offers synthesis power: guided by their genetic DNA code, cells build complex chemical compounds, materials and motorised molecular machines from simple nutrients such as sugar or carbon dioxide. Biotechnology has the added benefit of evolution of the cell properties that humans can speed up and steer in the desired direction. With the help of synthetic biology methods – design and controlled programming – natural functionalities and fundamental biological rules can be utilised better than before. It is very likely that we are on the threshold of a real bio-era.

Synthetic biology is a technology that cannot be disregarded by any know-how and technology based country. The Growth Paths of Industrial Biotechnology for Finland roadmap (2015), commissioned by the Ministry of Employment and the Economy, mentions synthetic biology as one of the most important factors for the future of the field.

This presentation and its roadmap prepared for Finland focuses on the opportunities offered by synthetic biology as a diversifier and value adder of Finland's bioeconomy mostly in the field of industrial biotechnology (as distinct from medicine or plant biotechnology).

SYNTHETIC BIOLOGY AND TECHNOLOGICAL TRANSITION

MINIMALISTIC CELLS AND BIOLOGICAL REGULATORY CIRCUITS

Just like science and technology in general, also synthetic biology builds upon the achievements of previous decades. The border between gene technology and synthetic biology is not always clear. Genes were transferred from one organism to another already in the 1980s, and gene technology laid the foundation for modern biotechnology. Particularly in Europe, production facilities and the industry started developing production strains for the manufacture of chemicals based on modifying the metabolism of microbes. This approach is often called metabolic engineering.

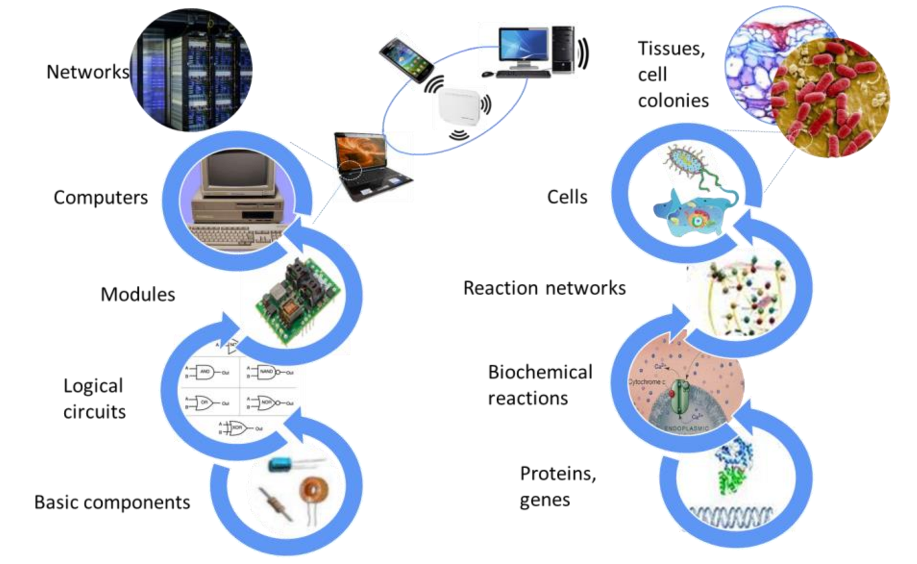
Genetic technologies enabling the modification of proteins were used in the development of new industrial enzymes. One example is so-called directed evolution, where a large number of enzyme variants are created by inducing mutations in the gene that encodes the protein. The desired kinds of enzymes – such as enzymes with improved thermal resistance for the needs of the detergent industry – are screened out of the proteins generated by the mutated genes.

In 2016, President of Finland, Sauli Niinistö awarded Professor Frances Arnold (California Institute of Technology, USA) with the Millennium Technology Prize for her work in the development of directed evolution. Photograph M. Penttilä

At the turn of the millennium, the sequencing of the human genome and other organisms lead to significant technological advances. The first sequencing of the human genome cost USD 2.7 billion and took 13 years of global cooperation[1]. Today, resequencing the human genome costs around USD 1,000 USD[2], and a previously unknown bacterial genome can be sequenced by companies selling these services in a couple of weeks at roughly the same price.

DNA synthesis, building genes in a test tube, is another equally significant technology. Today, long synthetic DNA pieces can be built and transferred into living cells. Unlike in the era of the earlier genetic technologies, it is now possible to design and synthesise entirely new kinds of genes and their combinations for which there are no counterparts in nature. We have transitioned from merely "reading the code of life to writing it".

The early 2000s saw the beginning of vigorous development of the concepts and technologies of synthetic biology, particularly in the USA. The J. Craig Venter Institute announced that it will aim to manufacture a minimalistic, synthetic cell, built using a living bacterium as a model, but with DNA created in a test tube with all genes not needed for the survival of the cell removed. This goal was achieved after years of work and published in March 2016[3]. The new organism, *Mycoplasma mycoides* JCVI-syn3.0, contains 473 protein-encoding genes and reproduces well in laboratory conditions. This kind of a cell can act as a chassis to which genes encoding desired characteristics can be added, for example for the purpose of producing a specific chemical compound. Because the DNA of the organism is thoroughly known, control of the cell's functioning can also be pursued, for example by building genetic regulatory switches inside the cell that work analogously with electronic regulatory circuits.



As in electronics, new functional systems can be built by combining different components in biology[3]

Indeed, analogies from the electronics industry are often used to describe the concepts of synthetic biology.

SYNTHETIC BIOLOGY REVOLUTIONISES RESEARCH AND EDUCATION

Founded in 2006 and funded by the National Science Foundation (NSF), the US research consortium SynBERC (Synthetic Biology Engineering Research Center) played an important role in the global development of synthetic biology concepts, technologies and applications. The consortium members included MIT, Harvard, Stanford, University of California San Francisco and Berkeley. A strong research and innovation ecosystem has grown around SynBERC, in which the steering group comprising nearly 50 international companies plays an important role. The members include major international industrial giants as well as start-up companies founded by students in the SynBERC consortium. The steering group as a whole widely represents different fields of industry. After a ten-year period, the consortium has expanded and continue as the Engineering Biology Research Consortium (EBRC).

Like its predecessor, the new consortium will, in addition to research, be actively involved in public engagement, ethics and safety questions, fostering cooperation in the research industry, and offering strong support to education in the field from high school level all the way to entrepreneurship.

Achievements of synthetic biology

- A new quadruple (instead of triplet) reading system for gene to protein translation
- Proteins with non-natural amino acids
- Synthetic yeast chromosomes forming the basis of synthetic yeast to be completed in 2017 (Yeast 2.0)
- Synthetic living organism with a minimal genome (JCVI-syn3.0)
- Modified stem cells that will enable new forms of treatment for human diseases in the future

[1]https://www.genome.gov/11006943/human-genome-project-completion-frequently-asked-questions/
[2]http://www.popsci.com/cost-full-genome-sequencing-drops-to-1000
[3]Hutchison, C. A. et al. Design and synthesis of a minimal bacterial genome. Science **351,** aad6253 (2016).

Education in synthetic biology has increased worldwide, and synthetic biology institutes have been established, particularly in connection with engineering sciences universities. In the USA, the NSF has channelled over USD 70 million into research in synthetic biology, and it is also heavily funded by the U.S. Department of Energy (DOE) and, in particular, the Defence Advanced Research Projects Agency (DARPA). In 2013 alone, the DOE invested over USD 10 million in the development of methods for the utilisation of biomass in the production of fuels, chemicals and plastics. Research in synthetic biology in the USA is estimated to have received a total of USD 820 million in funding in 2008–2014. China[1] has also started to invest heavily in synthetic biology[2]. The EU has funded research via, for example, the ERASynBio programme (around EUR 17 million).

Of individual EU countries, the UK has made a clear strategic decision to invest in synthetic biology. In the UK, funding for different research organisations in synthetic biology education and research and for commercialisation of the synthetic biology products of companies has to date totalled around GBP 60 million[3], and in 2016 a further GBP 500 million was pledged for the field.

Synthetic biology attracts students around the world. Arranged for the first time ten years ago at MIT in Boston, the International Genetically Engineered Machines (iGEM) competition has grown into an event where in 2015 student teams from 230 different countries competed with their synthetic biology ideas. The design work is based on biological components with standardised functionality (BioBricks) which the students can combine to build new organisms that often possess beneficial characteristics. That said, ever since a student team from India participated in the 2009 competition with a bacteria that generated the scent of a monsoon rain, the number of competition entries that are artistic instead of practical has increased. Finland joined the competition in 2014. Students from Aalto University and the University of Helsinki founded a joint iGEM team, and new Aalto-Helsinki teams have since participated in the competition each year. A unique international and open community of enthusiastic researchers and entrepreneurs will grow from the iGEM participants.

Interest in synthetic biology has also been spurred among researchers in other branches of science, such as physicists, chemists and information processing scientists as well as philosophers and social scientists. Combining different engineering sciences and biology, synthetic biology is a very attractive field for young researchers interested in the natural sciences. The basic idea of synthetic biology – the creative, novel combining of biological modules – makes it conceptually very approachable.

The 2014 iGEM Jamboree in Boston. Finland's Aalto-Helsinki team in their turquoise shirts in the middle row, right of centre. (Photo: Justin Knight, iGEM Foundation)

[1] http://www.synbioproject.org/publications/u.s-trends-in-synthetic-biology-research-funding/

[2] "Front Matter." National Academy of Engineering and National Research Council. 2013. Positioning Synthetic Biology to Meet the Challenges of the 21st Century: Summary Report of a Six Academies Symposium Series. Washington, DC: The National Academies Press

[3] https://www.gov.uk/government/news/over-60-million-for-synthetic-biology

The rapid development of sciences and technologies will open up unprecedented possibilities for the development of new biological systems and production processes. In the opinion of many scientists, we have already moved to the Anthropocene epoch, where the world and nature are moulded by man instead of natural selection. Thus, on one hand, synthetic biology aims to study and break the limits of biology, while on the other hand, it is considered to be essential for the development of sustainable industrial processes and the preservation of our environment[1].

PPP (Public-private partnership) consortiums in biotechnology are increasingly focusing on synthetic biology and the infrastructure supporting it. New consortiums are being established in cooperation between public financiers and the industry. In Europe, these include the French Toulouse White Biotechnology (TWB), the Austrian ACIB, the German CLIB, the Danish Biosustainability Center funded by the Novo Nordisk foundation, and the Dutch BE-Basic that already has an annual budget of EUR 45 million and a cumulative budget exceeding EUR 250 million. In 2014, Scotland established a biotechnology cluster with an initial budget of GBP 10 million, intended to grow to GBP 520 million by 2025. The goal is to increase the number of biotechnology companies to 200. Imperial College London received significant funding from the British Government to establish its Centre for Synthetic Biology and Innovation (CsynBI). The CsynBI is one of the most important global concentrations in synthetic biology.

The USA is continuing its significant investments in synthetic biology. In spring 2016, the SynBio Foundry project[2] received initial funding. Its goal is to combine the resources of ten national laboratories in development work particularly benefiting bioeconomy and the industry. The project involves the construction of new infrastructure and the development of technologies from genome synthesis to production piloting.

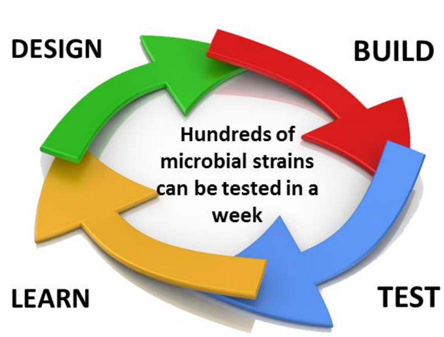
SYNTHETIC BIOLOGY AS AN ENABLER OF SUSTAINABLE DEVELOPMENT

One of the most significant benefits of synthetic biology is considered to be the development of new methods and processes that enable industrial production in accordance with sustainable development and the replacement of fossil fuels. Synthetic biology allows the production of many chemicals, fuels and material components from renewable raw materials such as plant waste or CO_2. By utilising the diverse chemistry of the cell – biochemistry – essentially almost any chemical can be produced, including basic chemicals currently produced using petrochemical processes. In the future, entirely new compounds will be produced that cannot currently be manufactured chemically (or biotechnically).

Today, synthetic biology has already made it possible to modify the metabolism of cells in such a manner that the cell requires less oxygen and carbon for producing the desired product than is possible with the natural metabolism of the microbe. Several examples of excellent polymer structures can also be found in nature (such as cellulose, silk, natural polyesters) that inspire researchers to develop new, strong or electrically conducting materials. We can also learn from nature's energy- or light-generating mechanisms.

It has been said that the economic role of the adoption of synthetic biology could be as great – or even greater – than the birth of synthetic chemistry more than a century ago. In 2016, the World Economic Forum selected the field as one of the ten most significant emerging technologies.

The development work of production organisms is well described by the "Design-Build-Test-Learn" cycle. Instead of the research scientists performing laboratory tests, they are increasingly using computer-aided design (Bio-CAD) to design the characteristics of production microbes, order the synthetic DNA bricks from a store, and build the living production organisms using automation and robotics. New genome editing methods – such as CRISPR – make the building of new microbe strains significantly faster. In just one week, hundreds of new production microbe candidates can be screened and new function-improving changes for the best of them designed. Synthetic biology boosts biotechnology, even if its extreme forms, such as minimal cells, are not yet used.



In industrial biotechnology, synthetic biology enables for example:

- Faster and cheaper development of production strains
- Production of compounds unprecedented in nature but useful to humans
- Design and creation of minimal microbes performing only desired reactions
- Production microbes that need less carbon and energy than natural organisms to generate the product
- Replacement of fossil raw materials with renewables

[1] HS 31.4.2016, p. C6. Kukkamaalareiden uusi aika.
[2] http://syncti.org/research/synthetic-biology-foundry/

MARKET POTENTIAL OF SYNTHETIC BIOLOGY AND NEW ECOSYSTEMS

The global market for synthetic biology has been estimated to grow at around 25 per cent annually, and this growth is expected to accelerate to even above 30 per cent as methods continue to develop. The market is currently dominated mainly by companies selling genome technologies and DNA synthesis, but the share of core products, such as synthetic microbes and integrated production systems, is expected to grow rapidly in the next two to five years.

Amyris and Gingko Bioworks in the US are true pioneer companies in synthetic biology, developing new microbe strains producing fuels and chemicals based on computer-aided design and automation. However, the biotechnology industry is not alone in developing synthetic biology applications; they are also being developed very widely by the chemical, energy, medicine and diagnostics, and food industries. The most significant global companies already utilising synthetic biology include DuPont, Thermo Fisher Scientific, Royal DSM, Novozymes and New England Biolabs.

Examples of industrial applications of synthetic biology:

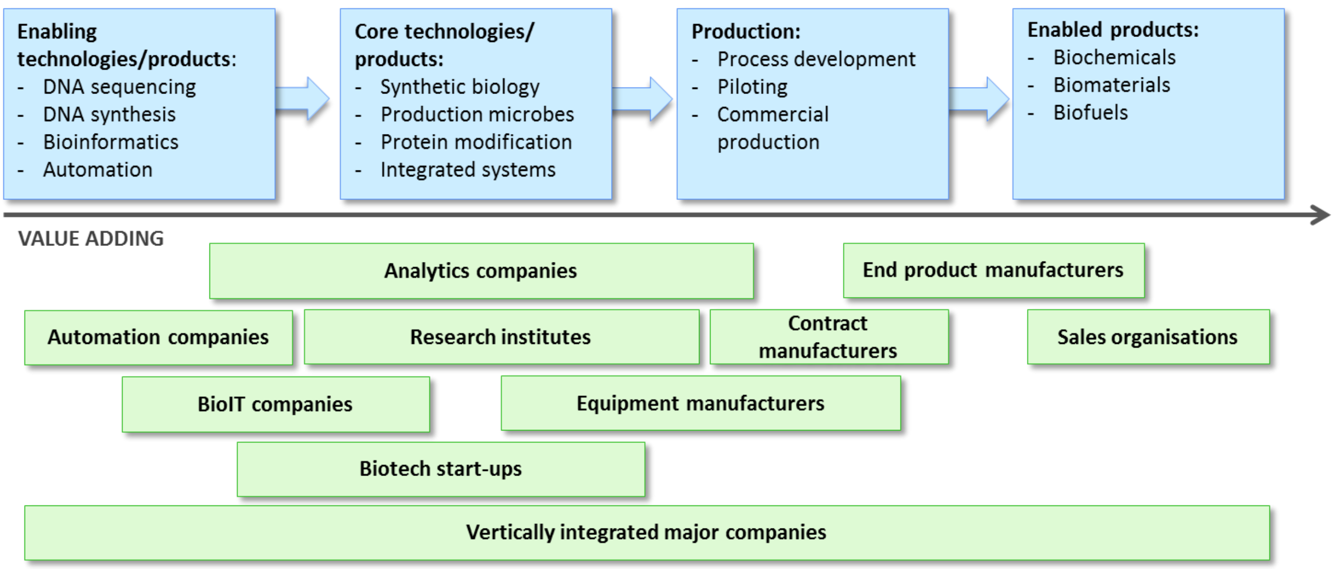
- Biofuel Biofene (Amyris, Total)
- Biofuel isobutanol (Butamax, Gevo)
- Basic chemical acrylic acid (DoW, OPX)
- Malaria medicine artemisinin (Amyris, Sanofi Aventis)
- Cosmetics component alguronic acid (Solazyme)
- Synthetic vanillin (Evolva)

Dedicated business ecosystems are rapidly developing around synthetic biology in different parts of the world. These ecosystems can be described as value chains typical to the biotechnology industry, functioning as a network where the business risk is divided between the different actors of the ecosystem. Ginkgo Bioworks[1] is a good example of this: in 2016, it received USD 100 million from investors for the purchase of synthetic DNA for building new production organisms. Companies specialising in DNA synthesis, Twist Biosciences and Gen9, deliver the DNA.

Global major companies covering several links in the value chain also operate in the value network alongside others; on the one hand, they are customers and partners of virtual companies, on the other hand, they can be seen as prospective exit strategies for financiers.

Large companies, particularly those producing high-volume products such as biofuels, seek to get close to the source of raw materials. The Port of Rotterdam in the Netherlands is an interesting centre for companies refining imported biomass (including wood pellets). Even though the Netherlands is not itself a huge biomass producer, it has invested in large-scale biorefinery infrastructure. Its biorefinery companies are also establishing joint ventures to develop technologies and divide risk. Some of the biorefineries use modified microorganisms as their production organisms. In the future, synthetic biology will play an increasingly important role in these bioeconomy ecosystems.

These ecosystems are still in their early days, and various national and international initiatives, such as the EBRC, SynBioBeta (an international organisation of synthetic biology companies) and the iGEM competition giving birth to start-up companies, continue to play an important role in their establishment and fostering and and boosting their development. Established companies are also interested in these forums bringing different actors and researchers together, as they enable networking and provide a first-row seat for monitoring the latest science and technology advances.



Value chains and actors in synthetic biology

[1]http://techcrunch.com/2016/06/08/ginkgo-bioworks-grabs-100-million-in-financing-to-buy-a-whole-lot-of-synthetic-dna/

GLOBAL MARKET FOR SYNTHETIC BIOLOGY

EXTREMELY HIGH SHORT-TERM GROWTH EXPECTATIONS

Value of the global market in synthetic biology according to Markets and markets (2016):
$5.246 billion in 2015
$14.768 billion in 2020
23% (CAGR) annual growth forecast

Value of the global market in synthetic biology according to BCC Research (2014):
$2.700 billion in 2013
$11.821 billion in 2018
34% (CAGR) annual growth forecast

SYNBIO HAS SIGNIFICANT MARKET POTENTIAL

GLOBAL COMPANIES IN SYNTHETIC BIOLOGY

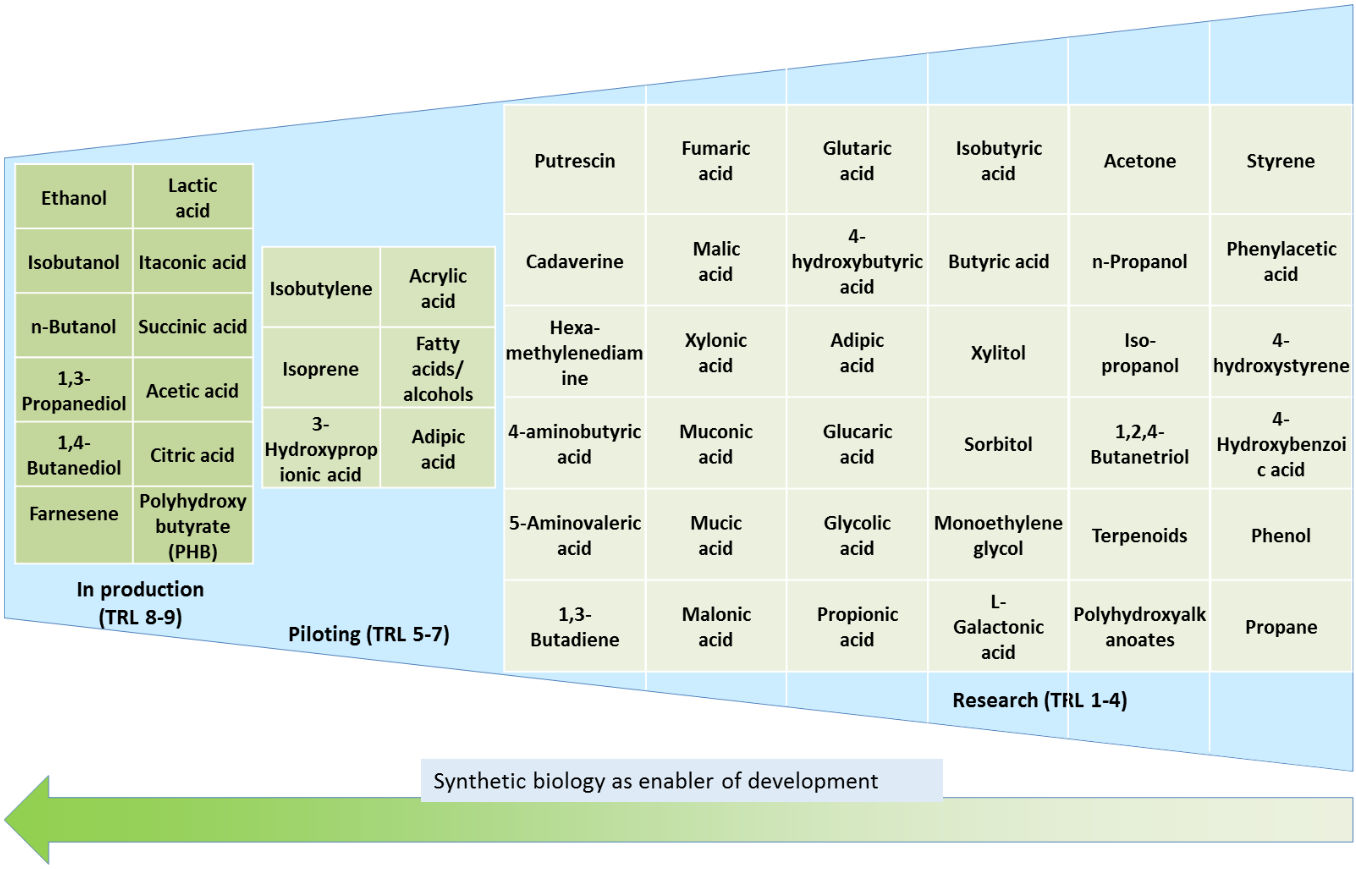
LARGE GLOBAL ENTERPRISES	GLOBAL SMEs	START-UPS AND MICROCOMPANIES
Chemical, IT, agriculture, national defence, medicine, for example: AMYRIS, DUPONT, ROYAL DSM, BRASKEM, NOVOZYMES, THERMO FISHER, AUTODESK, BP, DOW, GSK, MONSANTO, RAYTHEON, LOCKHEED MARTIN	Metabolic engineering, synthetic biology equipment, for example: BIOMAX INFORMATICS, CONAGEN, EVOLVA, INTREXON, GENOMATICA, SYNTHETIC GENOMICS, DNA 2.0, BLUE HERON BIOTECHNOLOGY, GENEART	"Born global companies in their initial phases" that produce synthetic biology equipment and high-risk solutions, for example: BENCHLING, ENEVOLV, GINKGO BIOWORKS, LYGOS, KALION INC, LANZATECH, PIVOT BIO, BENTHIC LABS, REVOLUTION BIOENGINEERING

SYNBIO AFFECTS ALL ACTORS IN THE VALUE CHAIN, FROM SMALL FIRMS TO MAJOR GLOBAL ENTERPRISES

START-UPS IN SYNTHETIC BIOLOGY

FUNDING	ACCELERATING	ENTREPRENEURSHIP
- Crowdfunding, e.g. the Kickstarter-funded Glowing plant - Early-stage seed funding - Capital investment funds	- Accelerator programmes (Synbio Axlr8r / Indie Bio) - Company incubators - Education (iGEM, Lean launch pad)	- From researchers to biohackers

IN ADDITION TO TRADITIONAL SOURCES, GROWTH COMES FROM NEW KINDS OF NETWORKED ENVIRONMENTS, E.G. LABORATORIES SHARED BY MULTIPLE COMPANIES AND WITH THE HELP OF CROWDFUNDING"



Several basic chemicals can be produced with biotech. Research is very strong and the production of many new chemicals has already shown to be possible. Synthetic biology will speed up development work and new chemicals can be taken into production at a quicker pace. The figure does not include fine chemicals or medicines that can also be produced biotechnically.

DO-IT-YOURSELF BIOLOGY AND ART

One fascinating feature of synthetic biology is the hobbyist culture that has arisen from it based on bioediting and resembling the "garage culture" that sprang to life in the 1970s in the IT sector and enriched it. Several of these DIY communities with their own laboratory facilities have been founded, such as BioCurious in San Francisco in 2009, GenSpace in New York in 2011, and La Paillasse in Paris in 2011. In spring 2016, the first "Swedish Bio-Makers Conference" for biohackers was held in Sweden.

The DIYBio movement practising synthetic biology is strongly communal and has a variety of goals, but as a rule, operates under the so-called hacker ethos according to which information is shared freely with a common focus on doing and problem-solving[1].

In addition to scientific curiosity and a desire for experimentation, the DIYBio movement is based on a desire to provide solutions to socially significant problems not tackled by research institutes or companies. DIY biology can play an important role as a breeding ground for new business ideas and SMEs.

These DIY activities are not only highly practical, they create new visions of the future. It is unsurprising, then, that the art community has also discovered synthetic biology – both as a subject and a tool. Art's approach to synthetic biology provides a counterbalance to research, which so often emphasises utility, and may also criticise the role of technology. One of the most famous bioart laboratories is SymbioticA, established in 2000 in Australia (University of Western Australia). Its founding artists Oron Catts and Ionat Zurr were also instrumental in the founding of the Biofilia laboratory at the Aalto University School of Arts, Design and Architecture in Finland. Biofilia and the artists of the Finnish Bioart Society are actively interested in synthetic biology.

Many bioediting-based DIY communities around the world work in a symbiotic relationship with universities. They are more akin to open incubators or workshops, often comprising, in addition to hobbyists, artists, designers, researchers in different fields of natural sciences and engineering, and social scientists. The prospective role of these communities in perceiving and formulating the society of tomorrow is an interesting one.

In 2008, bioartists Oron Catts and Ionat Zurr (University of Western Australia) displayed their work "Victimless leather" in the New York Museum of Modern Art. The work was a leather jacket growing from skin cells. Source: I. Zurr

ETHICS AND SAFETY

The foreseeable revolutionary possibilities of synthetic biology in, for example, medicine, plant breeding, environmental technologies and industrial biotechnology, and its spread outside the actual scientific community and industry raise a need for a dialogue on ethical and safety-related concerns. The importance of this dialogue is commonly accepted, and the scientific community remains active in highlighting and addressing these issues. Methods have been developed for preventing genetically modified organisms from spreading into nature. Examples of this are bacteria that require artificial amino acids that are not found in nature in order to grow, or cells that have been forced to repair undesired changes to the genome[1,2]. Guidelines on addressing the possible consequences of synthetic biology have already been drawn up[3-4]. The DIY community has also organised itself, ensuring that its members operate in accordance with good research ethics and informing the general public on synthetic biology, among other things.

Synthetic biology is typically based on gene technology, and its practice has been considered to be subject to gene technology legislation. With regard to new technologies intended for genome editing, the coverage of the current provisions is currently being reviewed both in Finland and throughout the EU. It is important to note that in industrial biotechnology, production takes place in enclosed bioreactors (so-called closed operation), and the modified production organisms are not released into the environment but destroyed after use. It is also important, however, to make sure that legislation and supervision keep a close eye on the rapid technological development. European science academies (EASAC) together with international organisations (IAP) act as advisers to the EU Commission and Parliament on the development of legislation on synthetic biology[5].

[1]Delgado, A. DIYbio: Making things and making futures. Futures **48,** 65–73 (2013).
[2]Mandell, D. J. et al. Biocontainment of genetically modified organisms by synthetic protein design. Nature **518,** 55–60 (2015).
[3]DiCarlo, J. E., Chavez, A., Dietz, S. L., Esvelt, K. M. & Church, G. M. Safeguarding CRISPR-Cas9 gene drives in yeast. Nat. Biotechnol. **33,** 1250–1255 (2015).
[4] Mazerik, J. & Rejeski, D. A Guide for Communicating Synthetic Biology | Wilson Center. (2014).
[5]http://www.interacademies.net/File.aspx?id=23974

INTERNATIONAL ROADMAPS FOR SYNTHETIC BIOLOGY

Several roadmaps and reports on synthetic biology and its role in bioeconomy have been published in recent years. The reports comprehensively describe the opportunities offered by synthetic biology and the measures required to leverage the potential of the technology as efficiently and responsibly as possible.

- The EU's strategic vision on synthetic biology[1]
- USA's bioeconomy plan[2]
- Roadmap on the bioproduction of chemicals[3]
- UK synthetic biology strategic plan 2016[4]
- Joint report on synthetic biology by six science academies[5].

Synthetic biology and its base technologies, such as modern gene technology, DNA sequencing and automated high-efficiency screening of biomolecules, and the industrial biotechnology enabled by these technologies, are seen as playing an important role in, for example, the implementation of the national bioeconomy plan of the United States. As early as in 2012, revenue from industrial biotechnology in the USA alone exceeded USD 105 billion, and the annual growth of the market was around 10%[6].

The reports and roadmaps state that synthetic biology plays a key role in and significantly benefits the development of industrial biotechnology and its impact on the formation of bioeconomy, development of circular economy and our ability to meet current and upcoming challenges, such as climate change, and to transition away from fossil raw materials. The roadmaps highlight the potential of synthetic biology in the creation of commercial applications and the need to create both new commercialisation possibilities and the operating environments that enable them. The reports also emphasise the need to develop education systems to match the multidisciplinary approach required by synthetic biology. Open dialogue between researchers, companies, authorities and the general public should be initiated and maintained.

The European Academies Science Advisory Council (EASAC) prepared its first reports on synthetic biology in 2010 and 2011. It proposes[7] that it is more important to make long-term investments in the research and development infrastructure and culture of synthetic biology than to focus on forecasting short-term results. Long-term investment also lays the groundwork for the birth of applications that are entirely unanticipated and currently difficult to foresee.

The recent Roadmap for European Research Infrastructures proposes that Europe should create centres enabling standardised research and development of bioproducts based on robotics[8]. These centres would allow the distribution of expensive infrastructure costs and the establishment of knowledge centres. Shortening the time required in the development of bioprocesses and reducing costs should be key objectives.

EASAC's report presents a task list to European decision-makers:

1. Establish a competitive research infrastructure;
2. Develop multidisciplinary study programmes required by synthetic biology at universities;
3. Prepare IPR guidelines for matters concerning the protection and open use of inventions;
4. Engage in a public dialogue based on scientific data on the possibilities and risks of synthetic biology;
5. Emphasise the safety issues; and
6. Organise the administration and organs in the field.

INTERESTING READS

George Church and Ed Regis. How Synthetic Biology Will Reinvent Nature and Ourselves. Basic Books 2012.284 pp.

Ginsberg, A.D., Calvert, J., Schyfter, P., Elfick, A. and Endy, D. (Eds.). Synthetic Aesthetics. Investigating Synthetic Biology's Designs on Nature. The MIT Press 2014. 349 pp.

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[1]https://www.erasynbio.eu/lw_resource/datapool/_items/item_58/erasynbiostrategicvision.pdf
[2]https://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf
[3]http://www.nap.edu/catalog/19001/industrialization-of-biology-a-roadmap-to-accelerate-the-advanced-manufacturing
[4]https://connect.innovateuk.org/documents/2826135/31405930/BioDesign+for+the+Bioeconomy+2016+DIGITAL+updated+21_03_2016.pdf/d0409f15-bad3-4f55-be03-430bc7ab4e7e
[5]http://www.nap.edu/catalog/13316/positioning-synthetic-biology-to-meet-the-challenges-of-the-21st-century
[6]Carlson, R. Estimating the biotech sector's contribution to the US economy. Nat. Biotechnol. **34,** 247-55 (2016).
[7]EASAC policy report 13, Dec 2010: Realising European potential in synthetic biology: scientific opportunities and good governance, http://www.easac.eu
[8]http://www.esfri.eu/roadmap-2016

FINLAND – CURRENT SITUATION AND VISION

FINLAND HAS STRONG KNOW-HOW IN INDUSTRIAL BIOTECHNOLOGY

Finland has a strong foundation in industrial biotechnology. Sitra's visionary funding in the 1980s played a major role in the birth of modern biotechnology in Finland and enabled the establishment of new gene technology methods. Industry was also enthusiastically involved, and research conducted by, for example, Alko, Suomen Sokeri (Cultor) and the brewing industry was advanced and modern. The company Finnzymes was founded to produce the restriction enzymes required in gene cloning. Research was done in cooperation with leading international academic and industrial researchers in the field. From these origins, the genetic modification of moulds for enzyme production, for example, has developed into a commercial success story in Finland.

The activities in the 1980s and 1990s laid the groundwork for Finland's leading-edge and impactful know-how today, particularly in the development of sustainable industrial processes and as an enricher of bioeconomy. While the rest of the world focussed on the molecular biology of the model organism, *E.coli* bacteria, Finland had the foresight to invest in the research and industrial production of enzymes breaking down lignocellulose and starch with moulds and bacteria and, in particular, the development of yeast for fermentation processes. Today, these organisms are globally the most desirable production hosts for biorefinery purposes, particularly the production of sugars from plant biomass and their use in the production of fuels and chemicals (so-called sugar platform).

Finland has thus, from the outset, been an important pioneer in industrial biotechnology and related research. Examples include genetically engineered brewery yeasts that were already being developed in the 1980s, the production of efficient enzymes with moulds for the needs of the food, livestock fodder and wood refining industries, and the modification of yeast to enable C5 sugars in lignocellulose, particularly xylose, to be used in the production of bioethanol, or organic acids and sugar alcohols to be manufactured from them. Although not all development work has resulted in industrial production, significant knowledge capital has been established in Finland.

According to an analysis by the Research Institute of the Finnish Economy ETLA, the value added by the Finnish biotechnology industry was over ten times the industry average in the 2000s, even when measured with traditional variables[1]. The value added increased from 20 million to 100 million euros from 2000–2010.

Finnish research institutes and universities, led by VTT, have continuously attempted to adopt new molecular biology technologies and apply them to the needs of the biotechnology industry. These include the structural determination and modelling of proteins, protein editing methods, such as directed evolution, genome methods and bioinformatics, system biology and genome-wide analysis methods (transcriptomics, proteomics, metabolomics), metabolic engineering and the mathematical modelling of cells.

Due to the challenges faced by the Finnish financing markets in the 2000s, parts of the previous Finnish biotechnology business have been lost. The domestic company base has also decreased due to foreign acquisitions. However, deep know-how in industrial biotechnology has been developed with support from the Finnish Funding Agency for Innovation (Tekes) and, for example, at the centres of scientific excellence granted by the Academy of Finland to VTT (Centre of Excellence for Industrial Biotechnology

Examples of research achievements in industrial biotech based on genetic technology in Finland:

1980s

- Improvement of beer filtration characteristics by developing a yeast that produces the endoglucanase enzyme, which breaks down barley glucanes.
- Brewing yeast that does not produce the buttery-flavoured diacetyl, which allows beer manufacturing without secondary fermentation.
- Yeasts producing amylases and cellulases for alcohol production (so-called consolidated process).
- Production of new DNA-cutting restriction enzymes.

1990s

- Biotechnological production of xylitol.
- Baker's yeast using pentose sugars for the production of bioethanol from lignocellulose.
- Efficient enzyme mixtures and production processes.
- Enzyme-assisted bleaching of pulp.
- Production of modified antibodies for diagnostic purposes.
- Production of bioactive compounds with *Streptomyces* bacteria.
- Alkaloid production with plant cells.
- Production of human collagen with yeast.

2000s

- Production of rare sugars with microbes.
- Yeast producing lactic acid, enabling a new, cost-effective process for the production of PLA plastic.
- Moulds and yeasts producing sugar acid derivatives at a low pH from biomass sugars.
- Heat-resistant industrial enzymes.

2010s

- Production of therapeutic antibodies of human origin with mould.
- Production of spider silk with microbes.
- Production of glycolic acid with yeast and its polymerisation into a bioplastic with good insulation properties.
- Many examples of metabolic engineering with regard to the possibility of producing chemicals and fuels with microbes, including photosynthetic organisms.

[1] Kotiranta, A. et al. Raiders of Lost Value | Etla. (2015).

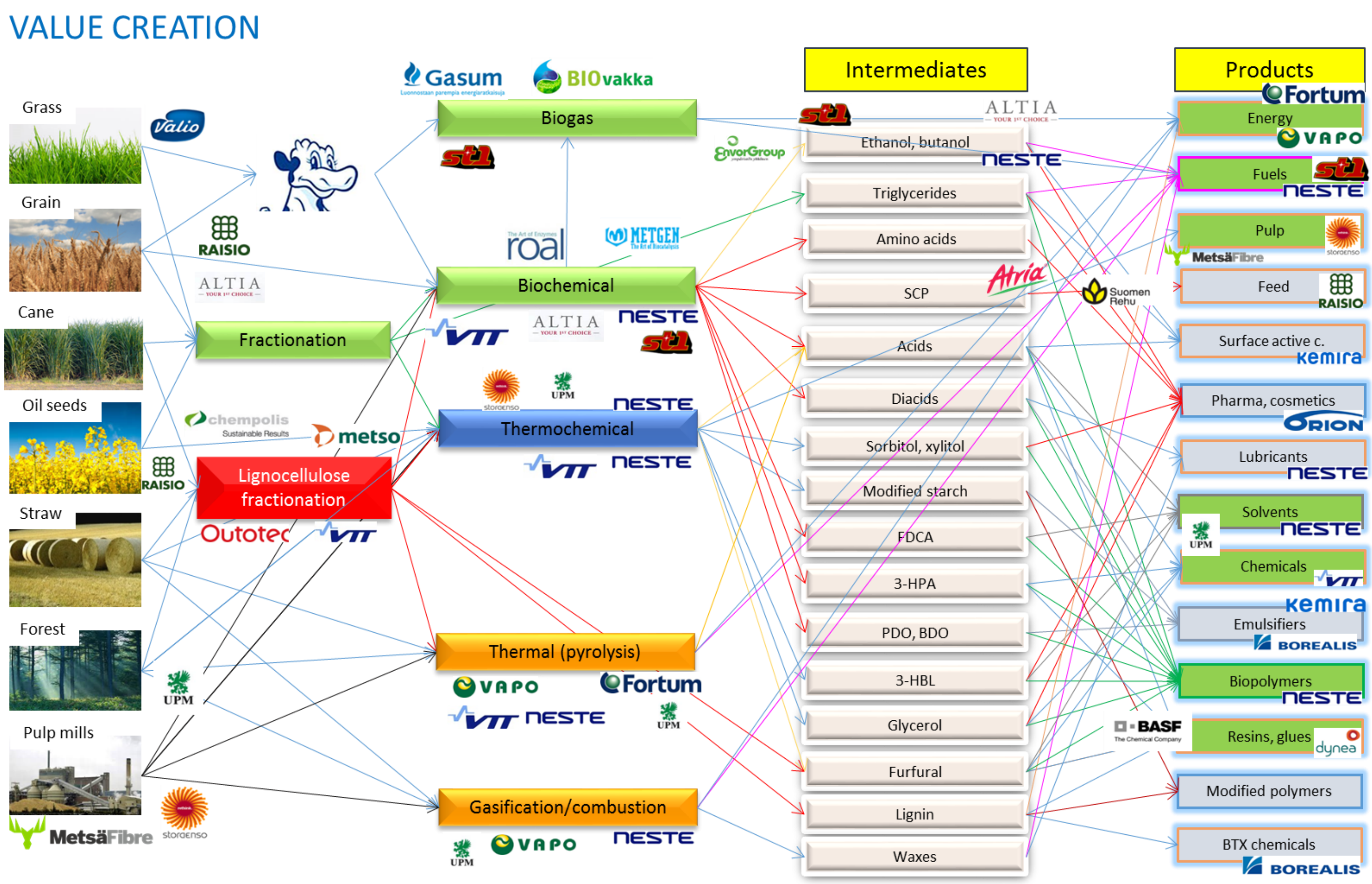
2000–2005, Centre of Excellence for White Biotechnology – Green Chemistry 2008–2013). VTT, in particular, has also maintained its know-how through cooperation with several foreign pioneering companies. Boosted by the SymBio programme of Tekes, the industrial biotechnology cluster IBC Finland established in 2012 transformed cooperation between companies and research institutes, making it agile and capable of rapid experimentation. A need to find faster and more flexible ways of cooperation has already arisen in industrial biotechnology.

SYNTHETIC BIOLOGY IS AN ESSENTIAL TECHNOLOGY FOR THE FULL-SCALE IMPLEMENTATION OF BIOECONOMY IN FINLAND

Climate change is real and it is widely understood that mankind must aim to develop energy-efficient and low-carbon industrial processes based on renewable raw materials instead of oil. This is highlighted by the bioeconomy strategy of Finland, completed in 2014[1]. Significant investments in bioeconomy have been made in Finland in recent years. Both the industry and financiers have started looking for new methods of creating value from biomass-based streams and improving the international competitiveness of the industry through innovations.

In Finland's bioeconomy plans and the operations of the Finnish Bioeconomy Cluster (FIBIC), biotechnology has not received the role it could have and which it does have in many other countries as the renewer of industry. To some extent, this is likely due to shrinking of the biotechnology company base during the 2000s and also to Finland’s focus on forest biomass, instead of primarily considering wood or forestry side streams as raw materials for the production of chemicals or biofuels through fermentation. In the rest of the world, biotechnology plays a major role in the development of lignocelluloses, such as straw, sugar cane waste or energy plants, as fermentation raw material for the production of chemicals.

The situation is changing, however, and Finnish companies that have not previously used biotechnology are hiring experts and starting to develop biotechnical processes. Neste and St1, for example, are interested in the production of biofuels. The member companies of the predecessor of FIBIC, CLIC Innovation Oy, have also announced their interest in the possibilities of synthetic biology in particular. Companies can be found in Finland to cover the entire value chain from biomass to products.



Finnish industry can cover the entire biomass-based value chain all the way to end products. Image: Esa Aittomäki

[1]Bioeconomy strategy 2014, http://www.biotalous.fi

SUSTAINABLE COMPETITIVENESS FROM SYNTHETIC BIOLOGY

The biotechnology roadmap by Pöyry[1] (2015) and the comprehensive report on the role of chemistry and bioeconomy by the National Emergency Supply Organisation[2] (2015) clearly show the opportunities biotechnology offers to Finland's bioeconomy. The raw material base must also be considered in Finland as more than just forest biomass. In the future, also one-carbon (C1) raw materials and the use of light (or hydrogen) as an energy source will become possible through synthetic biology. Synthetic biology could also be an essential part of circular economy utilising waste.

Today, the situation is far removed from times past when gene technology "only" created additional benefits for the biotechnical industry, for example making production more efficient. There is now an acute global need to harness the possibilities of biotechnology and synthetic biology in order to ensure the sustainable development of the Earth. This is also essential to improving Finland's competitiveness.

The global market for renewable chemicals is anticipated to grow to over EUR 80 billion by 2020. This almost double the 2015 figure. Reasons for this growth include increasing environmental concerns, official support measures targeting environmentally friendly processes and raw materials, and technological innovations. Consumers are also beginning to demand non-oil-based products, and their production is already an image benefit for many major companies.

Biotechnology combines the possibility for diverse use of non-fossil raw materials with a unique opportunity to create a more varied product selection.

Due to its high level of biotechnology know-how, VTT has had the opportunity to follow the rapid development of biotechnology and synthetic biology around the world as a member of the industrial steering committee of the SynBERC consortium and a research partner of several foreign companies. This has underscored the need to increase synthetic biology know-how in Finland.

Universities such as Aalto University, the University of Turku and Tampere University of Technology are also active in synthetic biology research and have begun the process of updating their education. The Academy of Finland launched a synthetic biology research programme for 2013–2017 (totalling EUR 12 million).

In January 2014, VTT and IBC Finland conducted a survey on the Finnish industry sector's views regarding the outlook of synthetic biology. The survey respondents represented a broad range of sectors. The majority (80%) of respondents considered the solutions provided by synthetic biology as a rather or very important enabler of renewal. The companies identified the tightening of competition and the need for new innovative technologies as boosters of business renewal; however, they also stated they need more information on how synthetic biology can be used in different business areas.

Over half of the respondents wished for more basic information on the technology and it's developers, two thirds wished for more information on the possibilities opened up by synthetic biology for the operations of the company, and three quarters wished for more case examples from around the world.

Based on the survey, there is clear industrial interest towards synthetic biology in Finland, and a simultaneous need for advice and expertise on how synthetic biology could be utilised in creating a competitive edge for companies.

Based on the survey, the objectives were prepared for the VTT-coordinated research application "Living Factories: Synthetic biology for a sustainable bioeconomy"

According to the survey, Finnish companies consider these possibilities created by synthetic biology to be important, in the following order:

- More efficient and economic biorefinery;
- Production of materials mimicking the functionality of nature;
- Replacement of oil-based chemicals by means of biotechnology;
- New biocatalysts making new reactions possible;
- Specific, intelligent biosensors and systems;
- Speeding up the development work of biological production strains;
- Ability to produce compounds that cannot yet be manufactured biotechnically;
- Ability to produce new kinds of composite materials;
- Use of solar energy as an energy source in bioprocesses;
- Use of C1 compounds (methane, methanol, carbon dioxide) as raw material for bioprocesses; and
- Automated building and testing of genetically modified organisms.

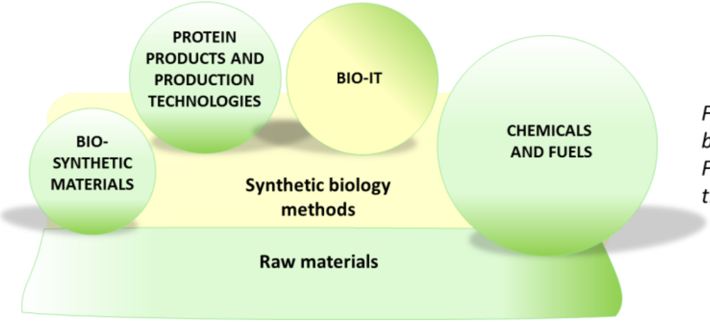
(LiF), which Tekes decided to fund as a large strategic initiative in 2014–2019*. In Finland, the LiF programme funded by Tekes acted as a national initiator and networker of potential ecosystem parties together with different actors such as IBC Finland.

*Due to budget cuts, Tekes discontinued the funding instrument in question in 2016, and the LiF project must acquire further funding from other sources.

[1] Pöyry, 2015. Growth paths of industrial biotechnology for Finland

[2] Pohjakallio, M. Parantaako biotalouden kehittyminen kemian poolin alueen huoltovarmuutta? National Emergency Supply Organisation, 2015.

ROADMAP FOR SYNTHETIC BIOLOGY IN FINLAND



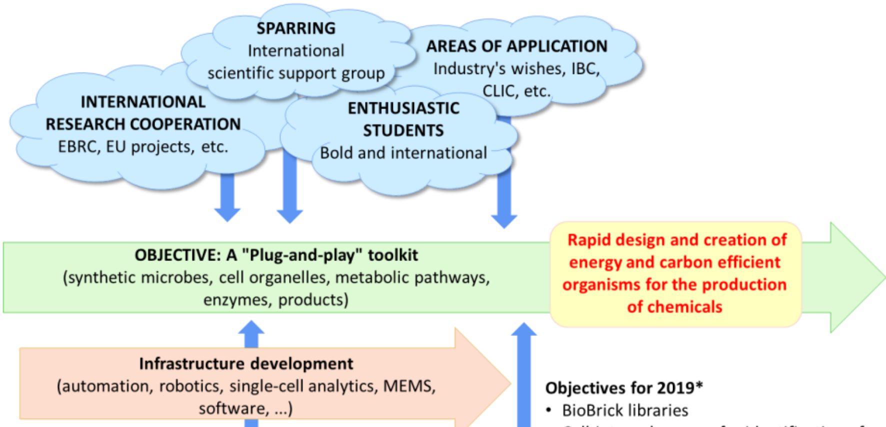
Focus areas of synthetic biology defined for Finland during drafting of the roadmap

Living Factories – Synthetic biology as an enabler of sustainable bioeconomy

The LiF project was a Tekes-funded major strategic initiative for 2014–2019*. LiF is coordinated by VTT, and its other partners are Aalto University and the University of Turku, and Innomedica, which handles administration.

MAIN OBJECTIVES

1. **Develop genome editing and automation techniques that make the design and creation of "living cell factories" quick, predictable and affordable – Utilisation of biotechnology in the industry will increase**
2. **Develop new cellular chemistry allowing one-carbon raw materials to be converted into longer-chained basic chemicals (C1 → Cn) – New products for the chemical and energy industries**
3. **Use synthetic biology to create "living cell factories" that are as energy and carbon efficient as possible – The production process as a whole follows the principles of sustainable development as closely as possible**
4. **Establish a dynamic, international company-research-education environment that is inspired by synthetic biology – A new generation of bold and visionary experts and leaders with new business ideas**



Objectives for 2016

- New genome editing methods
- Genetic regulatory circuits
- Mathematical models describing synthetic systems
- Models depicting the energy and carbon efficiency of cells
- High-efficiency screening at single-cell level
- Screening methods for new biocatalysts
- Plans for the use of C1 raw materials
- New enzymic reactions

Objectives for 2019*

- BioBrick libraries
- Cell-internal sensors for identification of molecules
- *De novo* cell organelles as reactors
- Integrated *in vitro – in vivo* chemistry
- Synthetic cell-internal pathways for carbon-efficient use of CO_2
- Compounds that could not be manufactured before
- Computerised design of synthetic biology
- Computer-aided high-efficiency screening of synthetic cell functions
- Synthetic biology platform for the design and construction of programmable cell factories

* Due to budget cuts, Tekes discontinued the funding instrument in question in 2016, and the LiF project must acquire further funding from other sources.

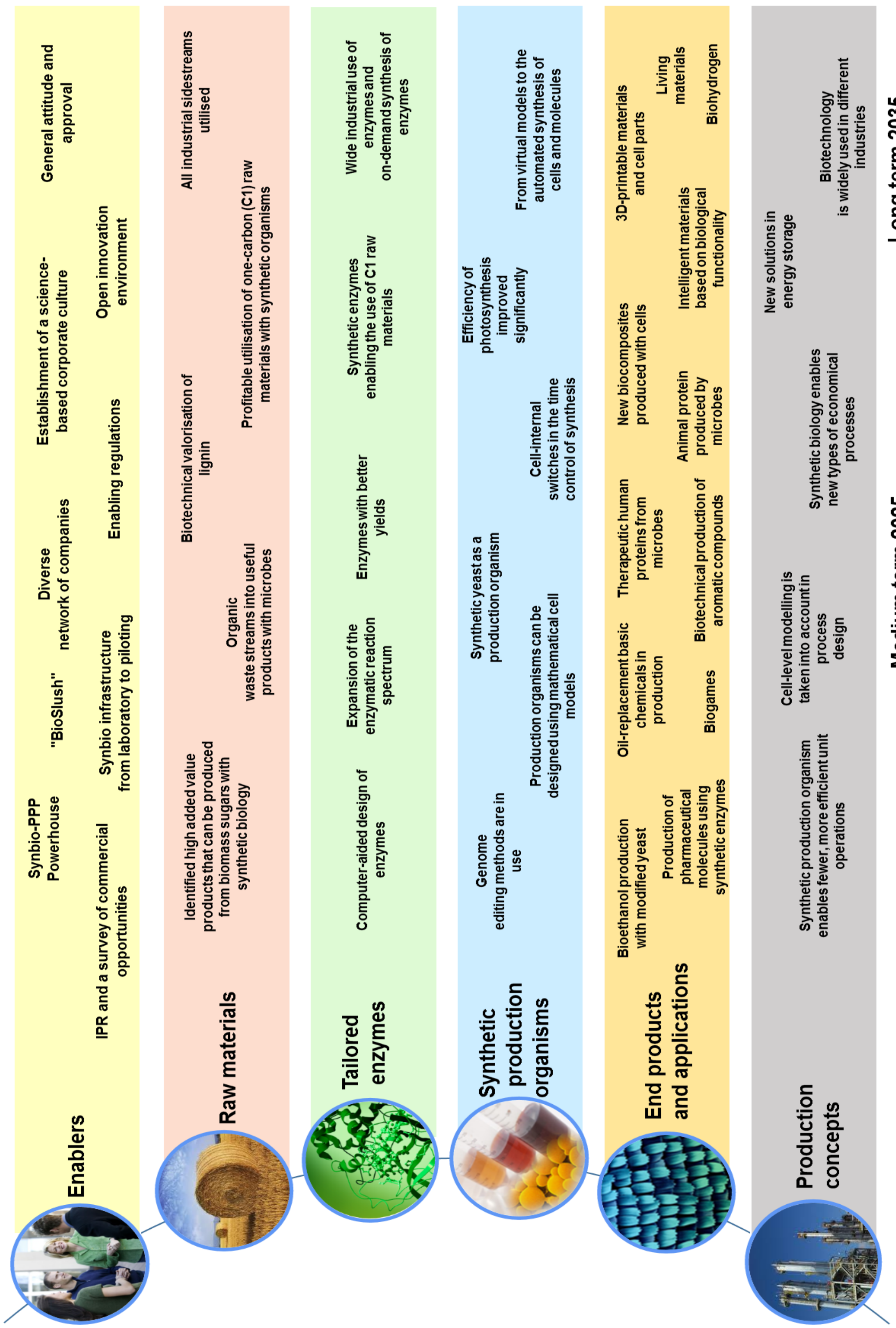
The Tekes-funded Living Factories (LiF) programme initiated roadmap work in cooperation with Finnish industry to create a common mindset and a future path for synthetic biology.

"**Sustainable bioeconomy through synthetic biology**" became the common vision. The issue was examined from the following perspectives: 1. method development for synthetic biology; 2. Finland's strengths; 3. enablers of new product possibilities, raw materials and ecosystems; and 4. development over time.

The roadmap diagram on the next page presents examples of the opportunities synthetic biology could offer Finland over a 3–20 year timespan. It can be assumed that the development could also be faster, but which solutions will become a reality depends on the choices of the research scientists and industry. Some content of the illustrated roadmap is discussed in more detail later in this document (**bolded** in the text).

Four focus areas were defined during the roadmap work: 1. Chemicals and fuels; 2. Protein products and production technologies; 3. Biosynthetic materials; and 4. Bio-IT. Finland has good basic know-how in these areas, which have the potential to grow into significant sources of new business in the future. In addition, new synthetic biology methods must be developed. These activities must be integrated into the ecosystems and sources of raw materials of the Finnish bioeconomy, particularly where products have significant volumes or are part of a biorefinery or circular economy.

VISION
Sustainable bioeconomy through synthetic biology
Biology is the foundation of a large part of industrial production



IMPORTANCE OF THE DEVELOPMENT OF SYNTHETIC BIOLOGY METHODS

Rapid development of synthetic biology methods in Finland is essential in order for Finland to keep pace with technological development. The development of methods is important not only to existing business activities but also to research. Synthetic biology should play a major role particularly in biotechnology education. In principle, the methods are generic and can be used in numerous applications.

Synthetic biology is based on the computer-aided design of biological systems, and the development of cells, cell parts, metabolic pathways and new proteins utilising new, powerful genome editing methods and automation. This Design-Build-Test-Learn (DBTL) cycle greatly speeds up the development of new production strains and increases knowledge of what achievements are possible in the modification of biological organisms. The quicker new genetic variants can be created in greater numbers and their functioning tested, the faster the accumulation of information for the mathematical modelling, which again is necessary for the development of new production strains in a more planned manner.

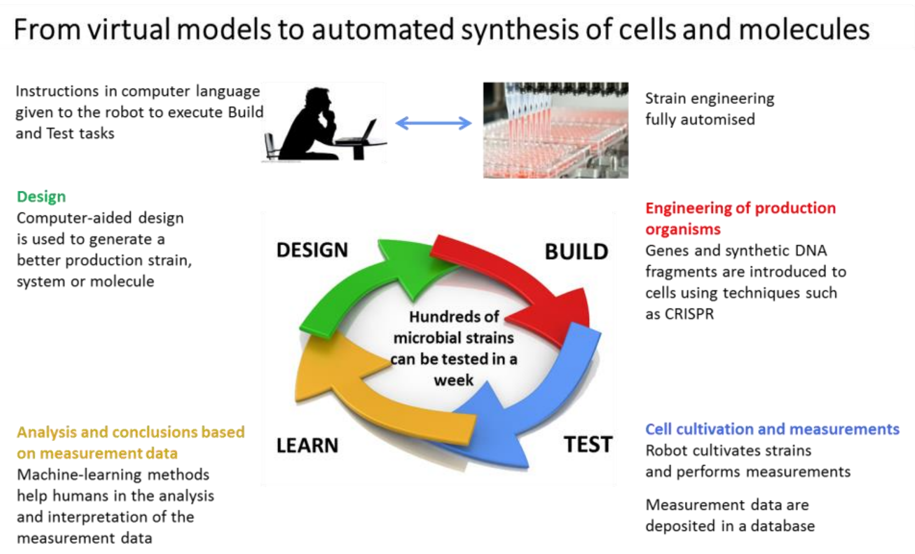
Robotics and automation will be used significantly more in all stages of the DBTL cycle. In addition to new synthetic biology methods, this also enables the more efficient use of mutagenesis and various evolution-enhancing methods. Hundreds of microbes can be bred and screened in a week in order to find the desired kinds. Price is no longer a limiting factor in the sequencing of microbe genomes or in the use of even long synthetic DNA pieces in the development of organisms.

It is clear that every company utilising biotechnology or considering its use must take into consideration the possibilities of synthetic biology methods. For companies that already base their operations on gene technology, the use of synthetic biology methods is a clear competitive advantage, and even essential for maintaining their competitiveness. Those biotechnology companies not using GMOs (genetically modified organisms) must consider how rapidly changes in the world and technologies will have an impact on their own field and force them to also take synthetic biology into account. In addition, companies that do not use biotechnology because the advantages of biotechnical processes have not been clear, or development has been too expensive or slow, will now have an opportunity to consider biotechnical processes in reinventing their business operations.

Great advances can also be achieved in Finland through start-up companies founded on synthetic biology. The ability to carry out biological modifications using the principles of engineering sciences and clear biological functional units (Biobricks) inspires "out-of-the-box" thinking and new ways of coming up with business ideas. There already exist kits designed for young people for practising the basics of synthetic biology, such as the portable "Bento Lab"[1]. This lays the foundation for new thinking about what biology and biotechnology could be.

One important goal of the Living Factories project was to develop the latest synthetic biology methods for application in Finland. **Genome editing methods** such as CRISPR are being developed for the most important production organisms, such as the *Saccharomyces* yeast (and polyploid industrial strains) and other yeast species that have benefits in the production of, for example, organic acids or fats. Methods for the production of industrial enzymes are being developed for the *Trichoderma* mould. Methods enabling rapid strain development are also being developed for photosynthetic cyanobacteria, significantly furthering biotechnological utilisation of these organisms.

Design of production organisms using mathematical cell models is already being carried out, for example as an aid for metabolic engineering in the production of chemicals with microbes. The importance of mathematical cell models will increase further as the rapid development of new strains becomes possible. Modelling helps design genetic modifications that are likeliest to improve biotechnical production, but in the future, it will particularly help design new synthetic metabolic pathways or reactions not based on biochemistry known to nature, or that are difficult to perceive or invent by humans.



[1] Bento Bioworks, http:/www.bento.bio

The more data that is obtained from the "Design-Build-Test-Learn" cycle, the closer we will also be to building synthetic minimal cells (chassis) that only contain known genes required for life or production. Although the organism is not (yet) very minimal, human-designed and built **synthetic yeast as a production organism** could, in principle, be possible within just a few years. Initially, such microbes could be particularly well suited to smaller-scale production that can be controlled better and in which the cells are not subjected to fluctuating and stressful conditions.

Synthetic promoters were developed in the LiF project that can be used to guide the functioning of genes in a controlled manner regardless of external conditions or the cell's own natural regulation. By utilising the principles of synthetic biology, various types of regulation circuits can also be designed and built in cells, allowing the cellular functions to be controlled depending on the signals given. When regulation circuits are designed and built as synthetic, they can be made as independent (orthogonal) as possible from disruptive background stimuli. In this way, controlling the use of nutrients or growth, for example, can be attempted at a single-cell level. **Cell-internal switches in the temporal control of synthesis** are also possible: for example, a certain reaction pathway for product creation can be switched on at a certain stage of the microbe's growth, or when there is a sufficient amount of reaction pathway precursor in the cell.

The final objective is to transition "**from virtual models to the automated synthesis of cells and molecules"**, or automate the design and development of production strains to the greatest extent possible. This requires significant investment in the processing of biological data to guarantee that sufficient understanding for reliable computer-assisted prediction of cell functions can be achieved. To acquire sufficient amounts of data it is essential that robotics and high throughput screening methods are in place.

- Synthetic biology methods (genome editing, metabolic models, design concepts) must be developed and adopted with all industrially important production organisms as quickly as possible.
- Because the new methods can, in principle, be immediately utilised, their use should be made routine by identifying development targets where the methods would be beneficial in current production.
- The development and availability (open access) of the necessary infrastructure (robotics, automation) must be ensured.

BIO-IT AS AN ENABLER OF SYNTHETIC BIOLOGY

Finland has strong know-how in information technology and engineering sciences. The quality of education and research in bioinformatics, i.e. information technology focusing on biological applications, is also at a high level internationally. It would be essential to be able to now leverage this competence potential in biotechnology and synthetic biology as well.

New bioscience methods generate large amounts of data at all functional levels (gene, mRNA, protein, metabolism, regulatory factors, etc.). Building an understanding of this big data is important for modelling the functioning of cells and modifying it to the desired form. Until now, bioinformatics experts in Finland have largely focused on medical applications and human genetics research. Co-operation with information technology experts and medical researchers has already led to the birth of successful growth companies in Finland (such as MediSapiens, Blueprint Genetics, BC Platforms).

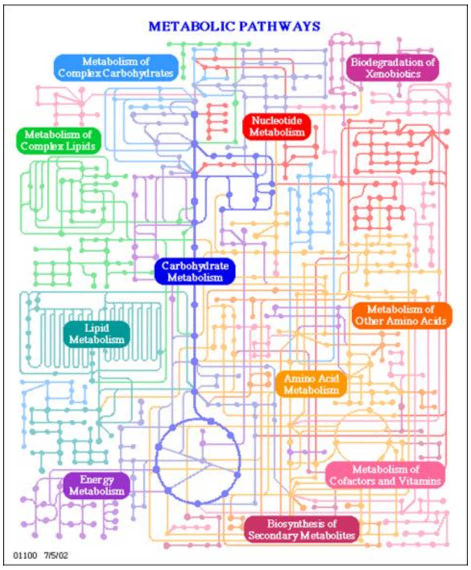
In the synthetic biology laboratories of the future, computers and robots will handle the building of microbe strains and the measurement of their performance. This leaves innovation to humans, if a large part of the design work can also be automated. This will be possible when knowledge of biological systems has been converted into a form understood by computers. There currently exist comprehensive databases for gene and protein sequence data, enzymes and biological reactions. Some synthetic building bricks (BioBricks) are described in their own databases.

Production organisms can be designed using mathematical cell models, for example by modelling the changes in the cell's energy level and basic metabolism when a new reaction pathway is introduced for the production of the desired chemical. There already exist numerous calculation tools; the OptGene method, for example, plans which genes should be removed in order to improve the yield of the desired chemical in the selected production organism. More advanced algorithms will be able to design fully synthetic biochemical reactions and find or design enzymes to act as catalysts for these reactions. The BNICE, GEM-Path and Retropath methods are the best in the field in this.

In the short term, it can be seen that cell-level modelling will be routinely taken into consideration in process design in Finnish bioindustry. Because the functioning of the production microbe determines the efficiency of the overall process, **cellular level models** must be included **as part of the modelling of the entire bioprocess** so that the energy efficiency and product yields of the process can be assessed. Thermodynamic models must also be adopted in the examination of cell-level processes.

Automatic design of synthetic DNA circuits will be possible very soon. Today, software specialising in a single organism or certain types of circuits is available, such as the Cello tool intended for the *E. coli* bacterium.

In the future, these kinds of tools will become more common as the functioning of an increasing number of biological bricks becomes standardised and their characteristics described mathematically. AutoBioCAD and other such design software can then use BioBricks libraries as a basis to design practically any regulatory circuit and its behaviour as a function of time. The user needs only to define the system's inputs (e.g. raw material) and outputs (e.g. product chemical, fluorescence). The computer is able to select which BioBricks to use and to output the DNA code that should be ordered from a store to implement the circuit and achieve the desired cell function.



Directing the cell metabolism to synthesise a desired product requires control and modelling of the cell's complex metabolism by the research scientist.

Although many kinds of tools already exist, there are plenty of challenges for Finnish information technology and bioinformatics experts in the application field of synthetic biology. No single tool is able to cover all design needs of synthetic biology. Including all computation steps in a single universal software suite that is also able to control laboratory automation is one of the future challenges. The field of synthetic biology offers many possibilities for new Bio-IT start-ups, such as in the fields of robotics, databases, modelling, analytics, system biology, genomics, data analysis and machine learning.

One way of creating new ideas and possibly even start-up companies is to arrange hackathon events familiar from the software development sector, but now also making an appearance in the field of synthetic biology. In June 2016, the first Bio-Hackathon event was arranged at the University of Cambridge in England. In these events, a large number of information technology experts cooperate to try and solve software development and modelling problems.

Biogames, or games inspired by biology or designing biological systems, are an example of the new kind of business that the synthetic biology community can create. The game industry in Finland is strong, and it could easily be imagined that the industry would also develop games related to biology, synthetic biology or biotechnology. The FoldIt game[1] assisting biological research and product development, developed in the United States (University of Washington, Seattle), already exists. The goal of the game is to solve the three-dimensional structure of a protein. Determining the structure based on just the amino acid sequence is a very difficult computational problem that requires huge amounts of computing capacity. The idea of the FoldIt game is to harness people to the aid of computers. Similar crowdsourcing could also work in the design of synthetic regulation circuits or the optimisation of metabolic networks. The first examples of these already exist: The research team that developed the FoldIt game has also designed the Nanocrafter game[2] for the design of synthetic DNA circuits.

Games intended to support teaching are also a possible area of game development in synthetic biology. While young people are designing their virtual avatars or Tamagotchis, they learn about the functioning of genes and the laws of biology. This idea can also be developed to the level of evolution, process engineering or sustainable development principles, for example.

- Finland's strong IT know-how must be harnessed for the needs of synthetic biology and bioeconomy.
- The field must be supported by arranging events and workshops (e.g. Bio-Hackathon) that attract computer scientists and young people.
- Education must increasingly support the development of multidisciplinary know-how, as computational methods lie at the core of synthetic biology and modern biotechnology.
- Modelling and automation provide an opportunity for significant cost and time savings in the design of bioprocesses, and new computational tools for synthetic biology must be made available to the bioindustry without delay.

CHEMICALS AND FUELS

The production of fuels and chemicals is the most extensive and immediately adoptable application of synthetic biology. An active approach in this application area would bring Finland a much desired boost in one cornerstone area of biotechnology: fermentation (see the sugar platform, p. 25). This would also increase value chain possibilities, from pre-processing of biomass to downstream processing of the product, and the related equipment manufacturing. The production of chemicals, in particular, would generate real possibilities for new, higher-value export products made from biomass raw material. A healthy biorefinery base would be established in Finland where biotechnology would also play a key role. This would encourage new actors and possibly increase smaller-scale production, for example. Because the possibilities of chemicals in particular are numerous and depend on the market potential, the industry must come up with the products. It is difficult for research institutes to start developing specific production strains with public support if no industry needing the strains is known.

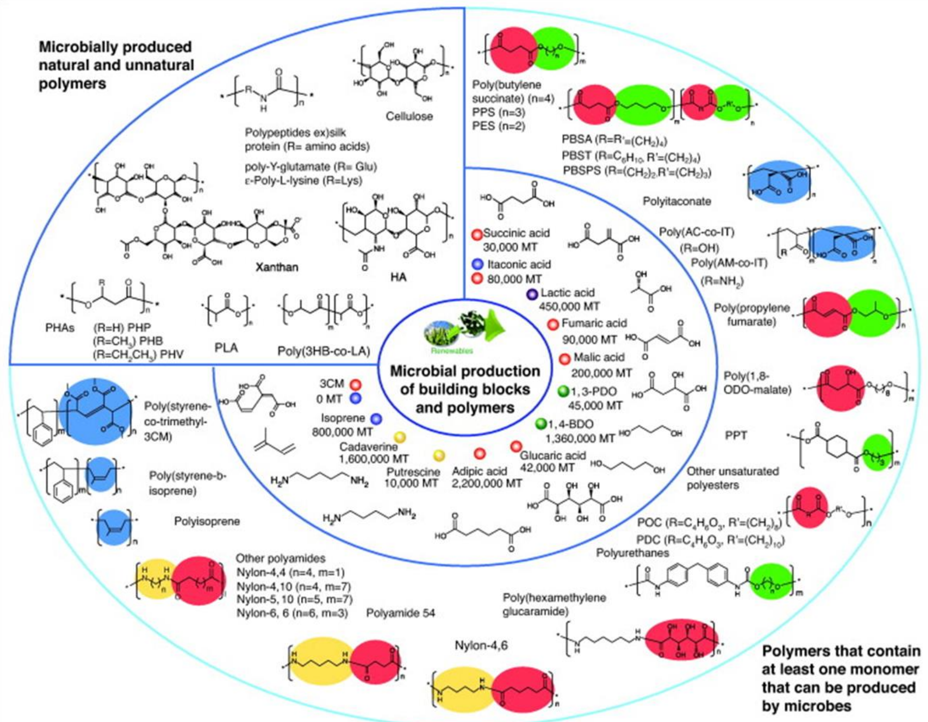
[1]https://fold.it/portal/info/about
[2]http://nanocrafter.org/landing

Bioethanol production with modified yeasts has been among the first subjects for development globally, with the drive to replace fossil fuels with biofuels made from renewable raw materials, particularly lignocellulose. Finnish industry is also increasingly interested in bioethanol production. Strains utilising biomass sugars more efficiently than before or withstanding process conditions can be quickly developed utilising synthetic biology methods and automation.

The efficient production of other biofuels, such as butanol, fats suitable for biodiesel, higher alcohols, etc., requires more modifications in the metabolic pathways of the production organism than ethanol production. Synthetic biology plays an essential role in the development work. Fuels containing carbon will continue to be needed in the future as well, particularly in air traffic and heavy-duty transport.

The industry aims to increasingly use the generic sugar platform technology in the future also in the **production of oil-replacement basic chemicals**. These can be chemically identical, direct replacements of oil-based chemicals (e.g. 1,4-Butanediol), or chemicals from which products with as good characteristics as those made from oil-based chemicals can be manufactured (e.g. succinic acid). In addition to compounds that act as replacements for petrochemicals, biotechnology can be used in the highly efficient production of bioplastic source materials such as lactic acid, which is then polymerised into PLA bioplastic.

Globally, chemical and energy companies are increasingly transitioning to biotechnology in order to manufacture higher-value products and, in the future, also compounds that cannot be chemically manufactured, but are possible using biosynthetic reactions. Page 10 contains examples of interesting chemicals the biotechnical production of which is widely researched.



Lee et al. 2011. Curr. Opinion in Biotechn. 22: 758-767

In particular, the biotechnical production of **aromatic** compounds would be important, because they have applications both as basic chemicals and as medical molecules. The particular benefits of biology are the synthesis of molecules with complex chemical structures and the specificity of stereochemistry. Cheaper and quicker production of **medical molecules** and various additives intended for livestock fodder or food will become possible. Examples include opiates produced with microbes[1], omega fatty acids or vitamins, and the cancer drug produced with plant cells, Paclitaxel.

In principle, **hydrogen** can also be produced biotechnically. Biohydrogen can be produced with cyanobacteria and algae (photosynthesis is modified in such a manner that the absorbed light energy is bound into hydrogen energy) or with bacterial fermentation from various waste streams (wastewaters, agricultural waste).

Transition from petrochemical products to products made from renewable raw materials requires a transition period, because our current society is so heavily based on petrochemistry.

The future vision is that **new functionality of biology will be utilised to a much greater degree in industrial operations** and society.

- The large potential of synthetic biology in the production of oil-replacement chemicals should be utilised in Finland, as well.
- Finland has the know-how for biotechnical production of chemicals and fuels, as well as an increasing number of industrial companies interested in pursuing it (incl. the members of IBC and CLIC). This potential should be reinforced and development work sped up with the help of synthetic biology.
- Industry must define desirable products in order to generate the necessary commercial interest to pursue development work.
- The synergy benefits of biotechnology and chemistry techniques must be taken into account, for example in the use of enzymes as catalysts in synthetic chemistry or in the design of hybrid processes.
- Education should emphasise the interdependence of biotechnology and chemical engineering.

[1] Galanie, S., Thodey, K., Trenchard, I. J., Filsinger Interrante, M. & Smolke, C. D. Complete biosynthesis of opioids in yeast. *Science* **349,** 1095–100 (2015).

PROTEIN PRODUCTS AND PRODUCTION TECHNOLOGIES

Finland has strong know-how in protein production and uses the most efficient production hosts in the world, such as the *Trichoderma* mould. Other microbes are also being researched and used in the production of so-called recombinant proteins. Finland is a globally important producer of industrial enzymes (Roal, DuPont, MetGen). Enzymes are used, for example, by the livestock fodder, food, textile, detergent and wood refining industries. As biorefineries become more common, enzymes modifying lignocellulose will play a key role in the bioeconomy.

Enzymes are increasingly used also in the production of drugs, because they are able to catalyse specific reactions (e.g. different enantiomers) or reactions that are very difficult to achieve chemically. The production of pharmaceutical **molecules with synthetic enzymes** will increase and, particularly, increasing interest in personalised medication will likely increase the need for new, specific, biologically produced drugs. **Therapeutic human proteins** are also produced using **microbes**, which decreases production costs and the price of the drug. Large amounts of authentic antibodies of human origin have been produced in Finland by using mould strains originally developed for the production of industrial enzymes. The genetic engineering of moulds is slower and more difficult than many other microbes, and the work took several years. If new synthetic biology methods, such as the genome editing method CRISPR, had been available at that time, developing the strains would have been much faster.

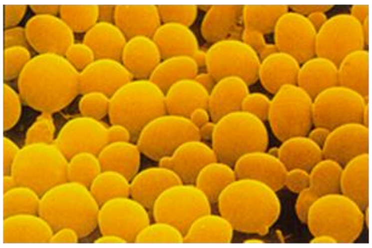
In addition to proteins working as enzymes catalysing (bio)chemical reactions, they can also be useful material components, such as silk from insects or the medically important human collagen. In Finland, these proteins have been produced with microbes. Another interesting product group would be small proteins, antimicrobial peptides that prevent the growth of harmful microbes, thus increasing the shelf life of livestock fodder. There will also be a shortage of new antibiotics in the future.

Synthetic biology makes it possible to modify the amino acid composition of microbe proteins to have optimal nutritional value for humans or animals. In principle, the desired kind of valuable nutritional protein could thus be efficiently produced using cheap organic waste as raw material or, in the future, also carbon dioxide or methane (so-called C1 compounds).

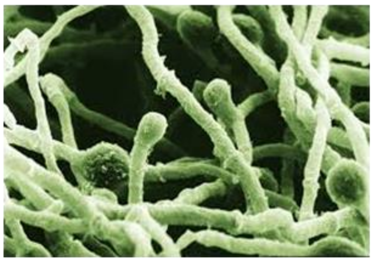
In the same way, **microbe-produced animal protein** could be another product, with microbes used to produce meat-replacement proteins – artificial meat from microbes. It remains to be seen whether GMOs and proteins modified using genetic engineering and synthetic biology will be approved as food.

Computer-aided design of enzymes has already been used for a long time, and the thermal or pH resistance of enzymes, for example, have been improved to better suit detergents or use as industrial process enzymes. A large part of the products of the Finnish enzyme industry contain enzymes with modified characteristics. **Expanding the enzymatic reaction spectrum** will increase in importance, particularly the development of fully synthetic enzymes that catalyse new, non-natural reactions. It should be noted that the modification of microbial metabolism for the production of fuels or chemicals is based on knowledge of dozens of enzymes and other proteins of different types and, in principle, any one of these could be modified to be better or to combine their functions. The DBTL cycle and automation generate a large body of data, which can be used to streamline the design of desired enzymatic reactions.

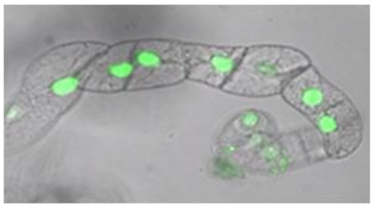
Cell factories important to Finland



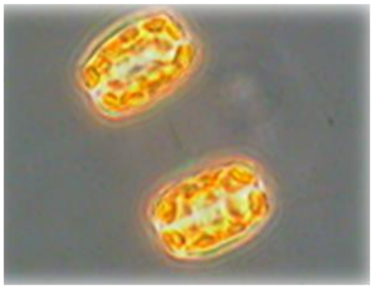
Saccharomyces baker's yeast



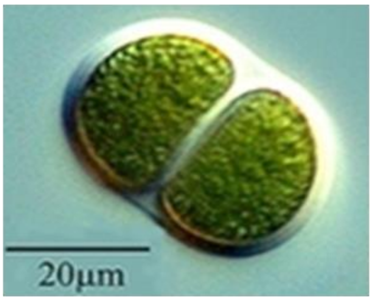
Trichoderma mould



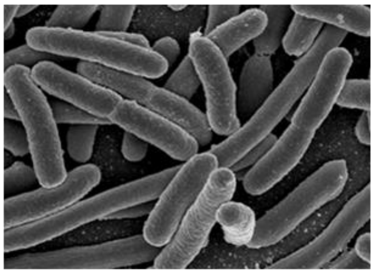
Plant cells



Algae

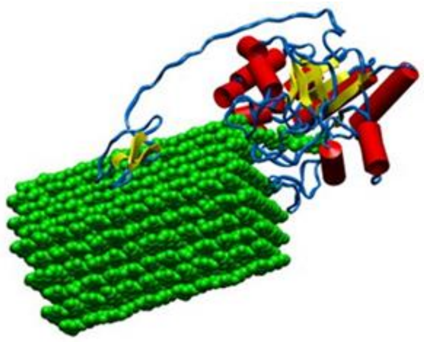


Blue-green alga



E. coli bacteria

Synthetic biology thus plays a role in the design and modification of the functioning of enzymes and proteins, but also in the development of efficient microbe strains producing them. In particular, synthetic biology can enable the development of entirely new types of production strains, tailored to suit each product protein. Such strains do not, for example, produce side products or cause undesired changes to the product itself. If proteins of human origin are produced, the production strains can add correct sugar moyeties to proteins in the same way as takes place in human cells. As is already done for the production of chemicals, cell metabolism can be modified to produce as much of the desired protein as possible. Synthetic **enzymes that are produced better than natural proteins** can also be attempted.



An important enzyme in breaking down crystalline cellulose (highlighted green in the image) is cellobiohydrolase, produced by the Trichoderma mould.

The **wider industrial use of proteins and enzymes and "on-demand" enzymes** could be a longer-term goal for Finland. The production of "on-demand" enzymes is based on in-depth understanding of the structure and functioning of enzymes, and computer software that can be used to predict genetic structures that would produce optimal enzymes if the precursor and the desired end product are known. Automation and wide-scale screening methods using robots are also required in this work.

- The use of synthetic biology methods will significantly speed up the development work of particular, protein production organisms important to Finland and bioeconomy, and the methods should be adopted without delay.
- The synergy benefits of the strong medical research and protein production in Finland must be examined.
- The high quality of protein and enzyme research must be ensured.

BIOSYNTHETIC MATERIALS

Living organisms naturally produce many kinds of interesting materials, and in this application area synthetic biology has almost unlimited possibilities to create new functionality and new products. Biological materials such as cellulose, mother-of-pearl and silk have excellent characteristics. These natural materials have formed the basis for material innovation as research into them has produced an understanding of how new, efficient structures can be achieved through the organisation of material components and the interaction of molecules. Medical applications already exist, but the car industry and chemical industry, for example, are also seeking biotechnical solutions. Application development work is only taking its first steps, but visions can be formed long into the future.

Interesting natural materials can be composed of, for example, proteins (silk, elastane), carbohydrates (cellulose, chitin) or fat derivatives (ricin oil, from which nylon, for example, can be produced), and sometimes inorganic components (such as calcium carbonate in mother-of-pearl). Elastin and silk and their variants have been produced in Finland, too, by means of synthetic biology using bacteria, yeasts and moulds. There are already companies in the USA and Europe aiming at large-scale production of microbial silk.

In material applications, the flagship of Finnish bioeconomy is wood-based cellulose and the textiles and nanocellulose applications, such as medical and film materials, produced from it. In addition to cellulose, another carbohydrate-based natural polymer used in material applications is starch. Chitin present in the shells of shellfish, for example, and the chitosan manufactured from it, also have interesting material technology characteristics.

Due to its abundance and, in particular, the excellent characteristics of cellulose, lignocellulose is certainly an important raw material for bioeconomy. Hemicellulose and lignin with its aromatic units have a much more heterogeneous structure, and the **biotechnical valorisation of lignin** continues to require significant investments. Finland is very strong in the utilisation of lignocellulose and has a high level of know-how of the enzymes used in breaking and modifying it. It is conceivable that synthetic biology could be used to develop, for example, enzymes that modify the glucose structure of cellulose in places where natural enzymes cannot easily do it.

Natural materials are not necessarily suitable for all desired purposes. With the help of synthetic biology, material characteristics can be tailored by modifying the genes controlling their synthesis. However, modification of the main components of plants, such as lignocellulose, may hinder the growth of the plant. There is currently another problem, the EU's heavy restrictions on growing GMO plants in the open.

It is notable that biomaterial components can be produced in closed bioreactors, as can other industrial biotechnology products, which also enables the use of GMOs. Like with other biomaterial components, the synthesis of lignocellulose is determined at the single-cell level. The synthesis can thus be adjusted through genetic engineering, and materials can be produced using only the cells without growing the entire plant.

Some bacteria naturally produce cellulose with different characteristics to that of trees or grasses. Genes responsible for the synthesis of cellulose can be transplanted between species. Microbes also produce other interesting materials. These include the polyester PHB (PHA) produced by bacteria from butyric acid, suitable for use as a packaging material. Cyanophycin is an example of a microbe-produced polyamide.

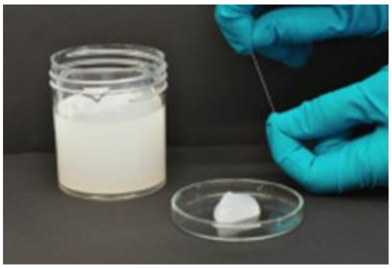
The design principles and methods of synthetic biology can be put to maximal use in the manufacture of biological materials in particular. Unlike conventional use of trees and plants, in industrial biotechnology cells can be modified to rapidly produce exactly the desired material component as the sole product. Sugars from biomass or organic waste can be used as raw material in biotechnological production. In the long term, closed production in bioreactors with photosynthetic organisms using carbon dioxide will also become possible.

Synthetic biology can be used to create variants of cellulose or PHB, for example, with different material characteristics. We discussed above (p. 21) the use of microbes for the production of small compounds as source materials for chemical polymerisation. Long-chain polylactic acid (PLA) can be produced from the lactic acid molecule, and polyglycolic acid (PGA) from glycol acid. Synthetic biology enables polymerisation to take place inside the cell by using enzymes suitable or modified for the purpose. Additionally, mixtures of precursors can be produced, such as polyglycolic lactic acid. In the future, the synthesis of cellulose and PLA, for example, can be combined in the same cell. This approaches the long-term vision of the production of **new biocomposites directly by cells**.

Intelligent materials based on biological functionality can be, for example, electrically conductive or water-resistant, or can contain components of natural origin such as antimicrobial compounds or sensors detecting toxic chemicals. Due to their structure, they can refract light and retain brilliant colours for a long time. They might even be able to detect changing environmental conditions such as temperature, humidity and pH and change their state accordingly.

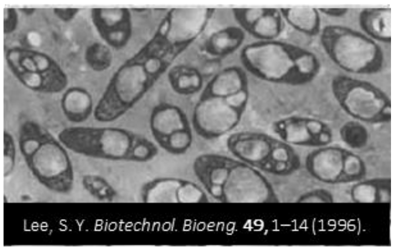
Biosynthetic materials are a source of inspiration for artists and designers, whose visionary ideas can provide the basis for new small enterprises. The implementation of some reasonably simple ideas could already be begun today. One example is a Dutch company that adds microbes to cement; the microbes seek cracks and repair damage by producing calcium carbonate. An example of **living material** akin to science fiction is the idea of using skin as a a cover for a building, that would sweat out excess heat in warm weather. The **3D printing of biosynthetic materials, cells and cell components** is already being experimented.

The above-mentioned ideas are possible in Finland, and some are already at the research stage. Finland has a high level of know-how in the industrial application of bio-based natural materials. In the future, this know-how can be complemented with biotechnical solutions and by learning from how nature works. The "Molecular Engineering of Biosynthetic Hybrid Materials" centre of excellence of the Aalto University (coordinator) and VTT studies new biological materials[1].



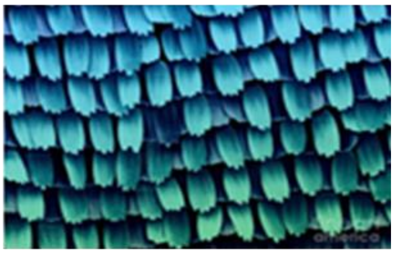
Nanocellulose

Mother-of-pearl



PHA-producing bacteria

Chair grown from mould



Refractive wing structure of a butterfly

Spider silk

[1]http://hyber.aalto.fi/en

- Finland has an excellent opportunity to be a pioneer in the development of new, biosynthetic materials and the goal-orientation of this field of research should be reinforced.
- Production of special products with a higher value should be developed in parallel with bulk applications of biomaterials.
- New investments are required in basic knowledge of material sciences and the modelling of material characteristics.
- The ideas of young research scientists should be actively worked into business ideas, and Finland's excellent design know-how must be utilised.

BIOECONOMY RAW MATERIALS AND BIOPROCESSES

In principle, any organic matter or side or waste streams containing it can be used as raw material for biotechnological processes. Organic raw materials were originally created biologically, and in natural ecosystems, organisms can also break them down and use them as nutrition. The so-called C1 compounds, or one-carbon compounds, carbon dioxide (CO_2), carbon monoxide (CO), methane (CH_4) and methanol (CH_3OH) can serve as raw materials for biological processes. In the future, synthetic biology and, in particular, the evolution of enzymes will likely make it possible to also use fossil waste (e.g. oil-based plastics) in the production of new bioproducts.

The benefit of biotechnology compared to many other techniques is the ability to use an often highly heterogeneous "impure" renewable raw material and synthesise from it – from simple sugars or carbon dioxide – highly diverse products. Genes responsible for the ability to use different raw materials can be transplanted from one organism to another. For example, the genes responsible for the ability to use xylose (birch sugar originating from the hemicellulose of lignocellulose) have been inserted into *Saccharomyces* yeast, allowing the utilisation of all sugars in the raw material in the production of fuels or chemicals.

One benefit of biotechnology is that many complex chemical reactions can be performed in a single unit operation (with microbial cells in a bioreactor) once the production organism has first been genetically engineered to produce the product. **Synthetic production organisms enable the reduction of unit operations and enhance efficiency** also in many other ways; for example, by facilitating product purification by consuming impurities in the raw material, thus eliminating the need to separate them from the end product at the end of the process. In an optimal situation, the raw material is converted into the end product as directly and efficiently as possible. This may be possible, if easily decomposing waste materials, for example, are used as raw material. Unit operations are thus reduced in number and made more efficient, consumption of energy and water is decreased, and the use of waste promotes circular economy.

The organisms used in biotechnical processes are often not efficient enough naturally to compete with highly developed petrochemical processes based on fossil oil. It is possible that the production microbe does not initially produce the desired product at all, or only very small amounts. However, as stated above, the significant improvement of microbes and processes is possible. The metabolism of the production organism can be modified in such a manner that the chosen raw material can be converted into only the desired product with the highest possible yield. For example, the production capacity of the organisms already in industrial production of bioplastics, yeast producing lactic acid, and bacteria producing 1,3-Propanediol, was increased 100–1000-fold. However, the development of these processes to a commercial level took 10 to 15 years at a cost of over 100–150 million dollars using traditional genetic engineering methods.

The slowness of this development work has been partly due to a lack of biological knowledge and partly to a lack of a real need and pressure to replace oil with renewable raw materials. Another significant reason hindering development has been the slowness of production strains development, which can now be significantly improved by synthetic biology.

In the future, the role of biorefineries and biotechnology in bioeconomy will be significant. Future innovations remain for the large part impossible to predict. The future vision is for **biotechnology to be widely used in different industries** and in Finland also in the production of export products with a high added value.

Today, only around 8% of crude oil is used in the production of chemicals, the rest is used for energy. However, the monetary value of chemicals is around 40% of all oil-based products. The share of biobased chemicals is expected to grow to 30% from the current 15% by 2025. Indeed, instead of merely incinerating them for energy, biomass reserves should primarily be used for products where carbon is essential, such as liquid transport fuels, basic chemicals and material products. This is also a prerequisite for the sustainable development of our planet.

BIOMASS SUGARS (THE SUGAR PLATFORM)

The use of sugars of plant biomass origin for the production of biofuels and chemicals by microbial fermentation is one of the most important biorefinery technologies worldwide. Bioethanol production is the first example of this, the development of which has been boosted by renewable fuel directives. The so-called first-generation technology is based on the use of starch as well as cane and beet sugar as raw material. The production facilities are large-scale plants, tens of thousands of cubic metres in size. These processes can use traditional biotechnology and non-GMO yeast that ferments the sugar into ethanol. Enzymes produced by yeasts are used to release glucose from polymeric starch, produced since the 1980s with efficient GMO strains.

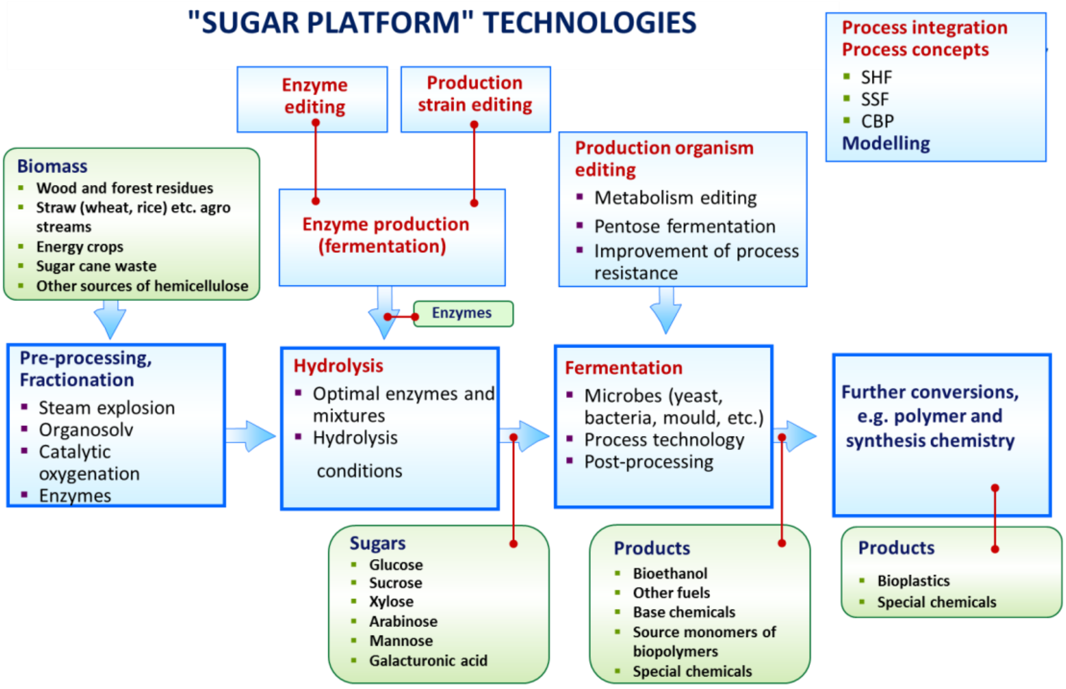
Research into the breakdown of the so-called second-generation raw material lignocellulose with the enzymes cellulase and hemicellulase has been carried out in Finland since the 1980s. The need to find cheap raw materials not suitable for consumption for biofuel production and the needs of biorefineries has made the use of lignocellulose one of the most important areas of development in the last two decades. VTT in particular has researched the pre-processing of straw, wood chips, sugar cane waste and energy plants, and their enzymatic hydrolysis into sugars. Yeast strains that can use all sugars present in biomass (glucose, xylose, arabinose) - have also been developed, and metabolic modification has been used to make the yeast produce biofuels and chemicals. Some of the research results have been patented and carried out in cooperation with Finnish or foreign industry.

Lignocellulose-based bioethanol has proven to have significantly lower CO_2 emissions than petrol and to be sustainable. Several companies, such as DSM-POET, Dupont and Chemtex, and the Finnish St1, have begun bioethanol production from second-generation raw materials.

For example Butamax (joint venture of Dupont and BP) and Gevo are developing biobutanol production, and Amyris together with Total are developing the production of fuels suitable for air traffic. Neste has studied the production of microbial oil suitable as raw material for renewable diesel. Today, the development of the most efficient production strains is largely based on synthetic biology, and in the future, the role of new biotechnologies will grow significantly.

Despite advances in technology, biomass-based biotechnical production of fuels is not yet economically competitive enough. In addition to mass products (such as transport fuels), biorefineries should also produce products with high added value, such as further processed lignin products, in order to have a positive overall economy. The mass products should also produce at least a moderate margin. In particular, **products must be identified that have high added value and can be produced from biomass sugars with synthetic biology** and that benefit from the chemistry of the organic raw material, such as the oxygen it contains. This would make the possibilities of synthetic biology attractive to the industry and improve the profitability of bioeconomy.

It must be noted that the bottleneck of the sugar platform technologies is not necessarily the biotechnical part of the production chain; the pre-processing of biomass, for example, still needs development, as does the often expensive separation of the product from the fermentation solution. Because the production microbe plays the main role



Fermentation of biomass sugars into different fuels and chemicals using genetically engineered microbes is one of the most important production concepts of bioeconomy. The most significant biotechnical parts of the process are highlighted in the picture with red titles. Synthetic biology plays a large role in making them more efficient. Synthetic biology solutions can also contribute to the integration and efficiency of the overall process. SHF (Separate hydrolysis and fermentation), SSF (Simultaneous saccharification and fermentation), CBP (Consolidated bioprocessing) in producing the actual product chemical from the raw material, attempts should be made to achieve the highest possible production rate, yield and titre (RYT); this is possible by modifying the strain by means of synthetic biology. Production strains can also be developed to better tolerate the product itself, low pH, or toxic compounds generated during pre-processing of the raw material.

Added benefit can be achieved if the production organism also produces enzymes that break down plant biomass and convert lignocellulose into sugars. This kind of a consolidated bioprocess (CBP) has been developed for the production of bioethanol, for example. The same microbe can then be used to carry out several unit operations at the same time, avoiding the traditional multi-stage production process.

Finland's bioeconomy is based largely on wood biomass, which the country has most per capita in the EU, and fourth most in the world. The annual growth of wood biomass in Finland is around 100 million m^3, of which the sustainable harvesting volume is currently estimated at around 70 million m^3. In total, around 50 million m^3 of domestic wood and 10 million m^3 of imported wood is consumed annually. In addition, the new bioproduct plants that are planned or are under construction in Äänekoski, Kuopio and Kemijärvi will need a total of around 13 million m^3 of pulpwood[1]. Bioethanol production from wood chips, for example, is planned for some of these plants.

It is important to identify high added value products that are profitable to produce. In this way, more high added value export products could be produced from the limited biomass reserves in Finland as well, and the biomass reserves would be utilised better. On average, 70% of lignocellulose is sugar, from which almost any product can be produced, particularly with the help of synthetic biology. Biomass sources that are unsuited to the production of fibre products should be identified. These could include fractions from existing processes, waste with lignocellulose content, and non-wood biomass. Straw and energy plants, for example, can be more easily hydrolysed into sugars than wood.

Different pre-processing methods are available, some of which, in principle, would enable the separation of all biomass components (cellulose, hemicellulose, lignin) for utilisation in high added value products in the new biorefineries. An example is the Organosolv biomass pre-processing method of the Finnish company Chempolis. This raises the importance of being also able to utilise, for example, the fraction containing pentose sugars of hemicellulose origin. It has been proven in Finland that xylitol and xylonic acid can be biotechnically produced from the pentose sugar xylose with high yields.

Some earlier estimates of the suitability of sugar platform technologies for Finland have highlighted the high price of biomass, the still-in-development status of sugaring technologies and, in particular, the large transport costs of raw materials other than wood. The situation must, however, be reassessed because the climate objectives are becoming stricter, regulations and the operating environment of the industry may change, and technologies advance. If investing in cheap bulk products such as bioethanol from Finnish biomass is considered profitable, there is cause also to invest in the fermentation of biomass sugars into products with higher added value.

The EU's removal of country-specific sugar quotas in 2017 will open interesting new opportunities and it will be possible to consider the development of biorefineries based on sugar beet also in Finland.

It is important to involve industry in assessment and development work so that in Finland, too, it would be possible to identify the relevant value chains and utilise biotechnologies that play a major role in the rest of the world in the currently ongoing transition from oil-based production to renewables.

- The industry (and researchers) must identify cost-effective and sustainable sources of raw materials and process concepts that would enable the more diverse use of Finnish biomass reserves and biotechnical production.
- The industry must identify interesting products that could be produced from biomass sugars.
- Because fermentation-based production from biomass is largely a generic technology, know-how must be developed in order to guarantee a strong foundation for the production of many different kinds of products.
- The bottlenecks and development targets of the overall processes must be identified, and, for example, biotechnical solutions proposed for them.
- Finland's globally high-level biotechnological know-how in sugar platform technologies should be utilised maximally.
- Synthetic biology should form an essential part of development work, and the industry should be aware of the opportunities it offers.

WASTE AND THE CIRCULAR ECONOMY

Discussions on circular economy, where community and industrial waste is reused where possible, mention too seldom the possibilities of biotechnology in using waste as raw material in the production of new products. It should be noted that most large-scale biotechnical processes have traditionally been based on the use of cheap side and waste streams rich in carbohydrates as raw materials. Examples of the utilisation of waste include the production of industrial enzymes with moulds by using lactose-sugar-containing whey from the dairy industry as raw material, St1's ethanol production from bakery waste, and the use of mash from beer brewing as a nutrient source in microbe fermentation.

[1]Pohjakallio, M. Parantaako biotalouden kehittyminen kemian poolin alueen huoltovarmuutta? National Emergency Supply Organisation, 2015.

Many streams currently explored as raw materials for fermentation are highly impure, such as pre-processed lignocellulose mentioned previously, which closely resembles pine tar. Microbes can adapt to using these waste and side streams surprisingly well. This often requires the modification or mutagenesis of the strains; they can also be made more efficient through synthetic biology.

Many organic wastes could be easier raw materials for microbial production than, for example, straw or wood chips. Cellulose-based packaging materials are "pre-processed" and easily hydrolysed into sugars with enzymes. Some food waste and sugar beet waste should also be utilised. The pectin in sugar beet waste, for example, can be used in the production of dicarboxylic acids with modified moulds; these acids are suitable for replacing fossil precursors of PET plastic.

Microbes are currently used in environmental biotechnology to break down organic waste released to the soil into harmless substances. The same characteristics can be utilised in breaking down plastic and rubber waste back into their monomers and further into new products. The French company Carbios, for example, is developing enzymes and microbes for breaking down waste plastics. Organisms modified using synthetic biology will thus enable the use of substances other than sugar-based waste materials as raw material.

In 2014, around 93 million tonnes of waste was generated in Finland, of which almost 80 million tonnes was soil and mining industry waste. Household waste amounted to around 1.09 million tonnes, of which 0.43 million went to landfill and 0.64 million to incineration. Since 2016, placement of biodegradable waste in landfills has been prohibited, so the amount of household waste going to incineration or sorting is believed to increase. The largest individual waste fraction that could be reasonably directly utilised biotechnically would be incinerated wood waste, of which 2.95 million tonnes were generated in Finland in 2014[1].

Instead of attempting to fractionate useful components out of difficult, heterogeneous waste or incinerate it, some of the waste could be used as raw material for microbes in the production of fuels, basic chemicals and, for example, livestock fodder proteins. Biotechnology would thus play an important role in **having all industrial waste streams utilised** in the future.

- Finland must examine the (near) future possibilities of waste collection and sorting, and identify the waste streams that are most suitable for use as raw materials in biotechnical production.
- The functionality of some process systems using waste streams must be studied without delay and any bottlenecks must be identified.

CARBON DIOXIDE AND OTHER ONE-CARBON (C1) COMPOUNDS

In the long term, even Finland's bioeconomy cannot be based on just forest biomass. The use of various waste materials and also of carbon dioxide and other one-carbon (C1) raw materials will be inevitable in the future.

Industrial carbon dioxide emissions are not only a major contributor of greenhouse gas, but a significant raw material loss. If the CO_2 emissions of the 25 largest individual plants generating combustion gases in Finland, totalling 20 million tonnes in 2012[2], were converted into transport fuel, it would be enough to replace all fossil oil used in Finnish transport (5.09 million tonnes in 2012[3]). CO_2 emissions to the atmosphere would be halved if the CO_2 generated by factories – whether originating from fossil or biomass-based raw materials – would first be reduced to fuel and used in transport, and only then released to the atmosphere.

The decisions taken to reduce CO_2 emissions made in 2015, the year of the Paris climate conference, and afterwards, will increase the price per tonne of CO_2 released. Technology using carbon dioxide as a raw material will therefore be needed soon. Finnish industry is also interested in using CO_2 as raw material.

In principle, there are several alternative biotechnical routes for the use of carbon dioxide in the production of various products; some of these routes are presented in the figure on next page. In practice, the profitability of each alternate route depends on the selected product, the price of energy and the available carbon-based raw material. The process alternatives are at different stages of development, and they all have their own practical yields and energy efficiencies. As a rule, the development work still needs significantly more effort than biotechnical processes based on sugars in plant biomass. In order to be economical, the product must have a value of at least EUR 2 per kg so that the energy costs of CO_2 reduction can be covered. Synthetic biology offers significantly more possibilities, because it allows the selection of a market and a product with sufficient value, and the development of a microbe strain precisely for the production of this product.

Life on Earth is based on the natural ability of biological organisms to bind atmospheric CO_2 and build long-carbon cell components and functional molecules, chemical compounds and structural components from it. Just as plants, also single-cell algae and cyanobacteria bind CO_2 by photosynthesis using sunlight as the energy source. Some bacteria are able to bind CO_2 by using hydrogen as the energy source. It has been proposed recently that bacteria could have the ability to also use electrons as a direct source of energy through so-called microbial electrosynthesis (MES), but this hypothesis has yet to be proven.

[1] Official Statistics of Finland (SVT): Waste statistics (online publication), Appendix table 1. Waste processing 2014, Helsinki

[2] www.energiavirasto.fi

[3] www.oil.fi

Three main lines based on biotechnology are beginning to stand out in the utilisation of C1 compounds with the help of microbes:

- Microbes photosynthesising CO_2 using sunlight;
- Microbes using CO_2 and hydrogen; and
- Microbes using "pre-reduced" C1 compounds (carbon monoxide, methane, methanol).

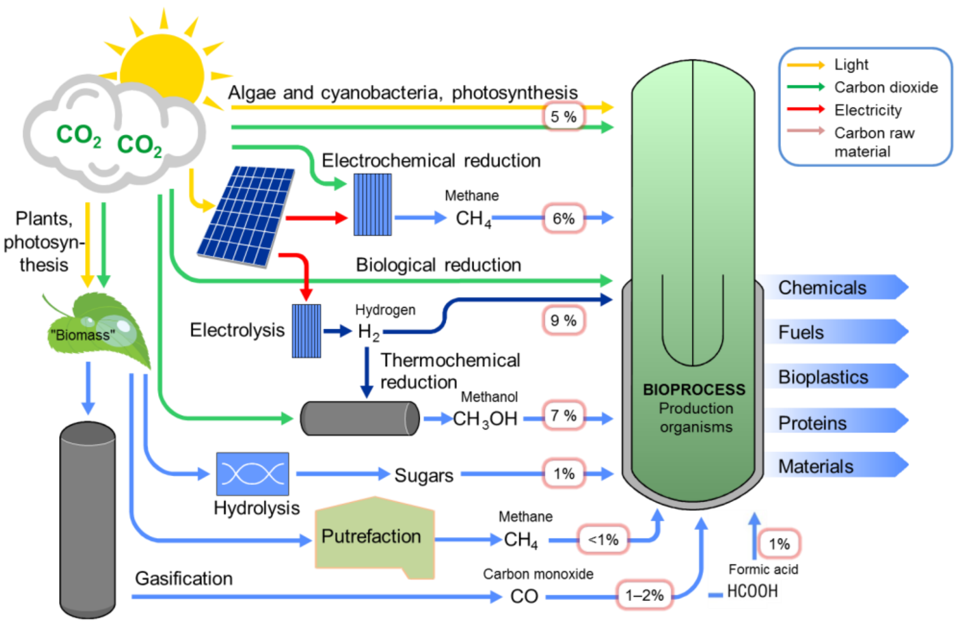
Much research has been conducted globally on the use of photosynthesising microorganisms, photosynthetic cyanobacteria and, in particular, algae for the production of biofuels and useful chemicals directly from CO_2. Algae are able, for example, to produce large amounts of fats suitable for biodiesel raw material. Research has also been carried out on growing algae in open pools to be used as a renewable raw material instead of plant biomass in further processes such as fermentation ("sugar platform"). Thus far, the insufficient light intake of microbes is a factor limiting the profitability of photosynthetic processes. Current industrial processes are based on the small-scale production of high-value products, such as the omega-3 fatty acids naturally produced by algae. However, the development of bioreactors enabling efficient light transfer is strong in the Netherlands, for example, which will likely enable cost-effective production in the future, and also the use of photosynthetic organisms improved by synthetic biology for the production of numerous compounds from CO_2 in the atmosphere or generated by industry. Research in the field is very active.

Bacteria using hydrogen instead of light as the energy source in binding CO_2 are older than photosynthetic organisms. They include the Knallgas bacteria developed by Newlight Technologies in the US for the production of PHA (polyhydroxyalkanoates) from CO_2 and hydrogen for the manufacture of plastics. The French EnobraQ has launched a particularly challenging synthetic biology development project attempting to develop a yeast that uses hydrogen as its energy source and CO_2 as its source of carbon. When successful, this would make yeast, which is a good industrial organism, to have the production pathways for a target product and also the ability to use sources of carbon and energy that are entirely new to the organism.

Carbon monoxide (CO) contains sources of both carbon and energy that microbes can utilise; with synthetic biology, they can be harnessed to produce transport fuel, polymers or enzymes from it. Lanzatech, originally founded in New Zealand but currently based in the United States, has been a pioneer in the utilisation of carbon monoxide generated as a side product by steel mills. Lanzatech's process can also use synthesis gas generated during the gasification of biomass or waste as the raw material. This offers one additional possibility for utilising waste materials in a way other than incineration. Development of the technologies necessary for the utilisation of industrial side stream gases or synthesis gas, which have a high energy content, could also be initiated in Finland.

Like carbon monoxide, methane (CH_4) is a one-carbon gas with a high energy content. Around 89 million tonnes of methane are generated globally each year from the anaerobic decomposition of biological materials in landfills, wastewater treatment plants and farms. Today, waste methane is being utilised by further refining it into biogas, produced and distributed by Gasum Oy in Finland, for example. Refining methane into biogas usable as fuel is currently profitable only at the largest locations generating waste methane, leaving smaller methane sources, for example at farms, unutilised and contributing to greenhouse gas emissions. In Finland, livestock production generates around 13–17 million tonnes of manure[1] with a biogas potential of around 0.06–0.25 million tonnes of methane. Additionally, around 90 million tonnes of natural gas generated during oil production is burned as waste each year because the technology available for its collection and storage is usually not implemented.

Methanotrophic bacteria that naturally use methane are able to utilise it mainly in aerobic conditions as a source of carbon and energy. The US companies Calysta and NatureWorks are developing a bacterial strain for the production of lactic acid from methane. This enables the manufacture of biodegradable polymers from, for example, shale gas in the United States.



Proposal on the possible routes for carbon dioxide (CO_2) conversion into carbon sources suitable for bioprocesses. The percentages indicate the energy efficiency of the conversion in accordance with the first law of thermodynamics (light, electricity and chemical energy were treated equally). The photosynthesis of algae and cyanobacteria produces biomass that may also already contain the desired product. Image: Juha-Pekka Pitkänen & Peter Blomberg

[1]Pohjakallio, M. Parantaako biotalouden kehittyminen kemian poolin alueen huoltovarmuutta? National Emergency Supply Organisation, 2015.

CO_2 can also be reduced thermochemically using hydrogen to methanol (CH_3OH) or electrochemically using electricity to, for example, formic acid (HCOOH). Methanol and formic acid are liquid C1 compounds, so they dissolve into water more efficiently than gaseous compounds, which also increases the efficiency of the fermentation process. The solubility of oxygen, carbon monoxide, hydrogen and methane in water is over one thousand times poorer than that of, for example, glucose (900 g/l). The mass transfer of gases is one of the biggest financial challenges of the bioprocessing industry, as the gas supply and mixing of the reactors require significant amounts of energy.

The conversion of methanol by the metabolism of a cell is cheaper energy-wise than that of C1 gases. The usage concentration of methanol is limited only by the toxicity of methanol to each organism, but it can be assumed that their tolerances can be improved. Methanol, generated as a side stream of the wood processing industry, has been previously used in Finland for the production of single-cell protein by yeast. Methanol is also used as the raw material in the production of recombinant proteins with the *Pichia pastoris* yeast. The first examples of transferring the ability to use methanol to the *E.coli* bacterium, which does not naturally have this ability, have already been published[1]. Methanol is a cheap and noteworthy source of carbon for biotechnical production, but is not currently available in Finland in large amounts.

Global annual production of methanol amounts to around 100 million tonnes[2]. Around 2 million tonnes of methanol per year is made from CO_2. The Icelandic company Carbon Recycling International produces 5 million litres of methanol per year from hydrogen and carbon dioxide via a thermochemical process using cheap geothermal and renewable electricity, allowing the production of hydrogen at a competitive price[3]. Methanol is itself already a fuel and a precursor for many basic chemicals, and is thus a noteworthy key compound that can be produced from CO_2. It has also been proposed that a large proportion of industrial production could be based on methanol in a so-called methanol economy (cf. hydrogen economy)[4]. Synthetic biology can be used to expand the spectrum of host organisms and products and to produce higher-value products that cannot be produced from methanol using chemistry techniques.

Today, the hydrogen required as the energy source in the utilisation of CO_2 in particular is mainly derived from natural gas. In the future, the price of renewable electricity such as bioelectricity, solar and wind, will be more competitive and hydrogen will be manufactured by breaking down water into hydrogen and oxygen by electrolysis.

The Tekes-funded strategic initiative, the Neo-Carbon Energy project[5], is developing technologies for the utilisation of CO_2 using renewable sources of energy. VTT, Lappeenranta University of Technology and the University of Turku are involved in the project, which supports biotechnical development work.

For over ten years, now, the University of Turku has performed research on photosynthesis reactions and developed molecular biology methods for use with photosynthesising microorganisms, cyanobacteria, for example in centres of excellence funded by the Academy of Finland (System biology of photosynthesising organisms, Molecular biology of primary producers; University of Helsinki has been involved in this project), and is currently also developing synthetic biology concepts and tools. The extensive use of C1 raw materials is also a focus area of VTT. The Tekes-funded Living Factories project used synthetic biology to develop microbes that use C1 compounds to produce chemicals.

Interest in the biotechnical utilisation of C1 raw materials has greatly increased. It is clear that raw materials other than plant biomass are also needed in Finland, and that C1 waste streams must also be utilised instead of releasing them into the atmosphere. Compared to plant biomass, large amounts of C1 waste is generated. For example, the largest individual solid biomass waste is currently wood waste to be incinerated; around 2.9 million tonnes of which is generated annually in Finland alone. Roughly the same amount of CO_2 is generated by Neste's Porvoo oil refinery. Wood waste is located over large areas and is heterogeneous (contains energy), whereas CO_2 is generated locally and is a homogeneous raw material, but its utilisation requires an additional source of energy.

- The use of C1 carbon sources and the ample C1 waste streams as raw material are essential for sustainable development, and investments must be made in the development of these processes in Finland, too.
- The sources of C1 raw materials in Finland and the possible value chains for their utilisation must be investigated.
- The natural ability of biological organisms to use C1 carbon sources and synthesise practically any chemical compounds from them must be utilised (bio-CCU, biological carbon capture and utilisation).
- The theoretical energy and carbon balances of the different bio-CCU concepts must be calculated and the possibilities for practical implementation of the concepts evaluated.
- The possibilities of synthetic biology in the efficient utilisation of C1 carbon sources for the production of chemicals must be immediately adopted in bio-CCU projects.
- The efficiency of photosynthesis can be improved with synthetic biology, and research must be leveraged in the development of production microbes.
- Sufficient education in biophysics and bioenergetics must be ensured.
- The use of C1 carbon sources and bio-CCU are at the first stages of their development, and their research must be invested in the long term.

[1] Müller, J. E. N. *et al.* Engineering *Escherichia coli* for methanol conversion. *Metab. Eng.* **28,** 190–201 (2015)
[2] www.methanol.org
[3] www.carbonrecycling.is
[4] Olah, G. A. Beyond oil and gas: the methanol economy. Angew. Chem. Int. Ed. Engl. **44,** 2636-9 (2005)
[5] www.neocarbonenergy.fi

LIVING FACTORIES – THE PROJECT'S VISION FOR FINLAND

VISION 2025: RESEARCH & TECHNOLOGY

- A production process based on synthetic biology has been developed in Finland
- The production efficiency and product spectrum of biotech has been proven to be competitive with petrochemistry
- Significantly improved energy efficiency of processes and reduced CO_2 emissions
- Strong investment in synthetic biology when developing sustainable solutions and processes utilising biomass
- Close R&D cooperation between companies, research institutes and universities
- Finland is one of the leading countries utilising synthetic biology

VISION 2025: INNOVATION ENVIRONMENT

- Synthetic biology is a natural, integrated part of engineering sciences
- Next-generation visionary experts and leaders
- Latest biotechnical methods are used by companies
- New SMEs with new products and business ideas
- Strong, international biotech ecosystem with a shared vision and mission
- Active cooperation with foreign companies and investors
- Dynamic, interactive and sustainable bioeconomy

VISION 2025+: BUSINESS OPPORTUNITIES

- Plants producing biochemicals and fuels using lignocellulose as raw material
- Use of CO_2 as raw material in biotechnical production
- Wide product spectrum of industrial enzymes that have been specifically tailored for the desired processes
- Sugar side streams from the P&P industry used in the production of polymer precursors using synthetic biology
- Software company that develops system-level integration tools for automated strain development
- An SME using microbes to produce biomaterials

COMMON MINDSET REQUIRED

A common mindset is now required in Finland. If we really aim to develop a bioeconomy that is not based solely on forest biomass and that opens possibilities for added value products of a new era, all key actors must have an understanding of biology and the potential of biotechnology. The development and adoption of new competencies requires goal-orientation and investment.

The market growth to which bioeconomy aspires requires new, more efficient production processes. By developing and adopting new technology, Finnish industry can secure its place in this growing market.

For the development of synthetic biology, the companies in key positions are the traditional Finnish actors: forestry companies managing biomass streams, companies developing bio-based fuels and chemicals, industrial enzyme producers, and SMEs developing technologies and processes for the industry. Establishing new companies to serve the value chain or attracting foreign actors to Finland to fill essential parts of the chain is a task for both existing companies and financiers.

It must particularly be noted that biotechnology and synthetic biology offer significantly more new business opportunities than merely business utilising biomass and wastes. In the future, biotechnologies can create companies of an entirely new type in Finland – expanding the horizon beyond the current IT and gaming sectors. As it is a new, disruptive technology, predicting biotechnical innovations is difficult.

The Tekes-funded Living Factories programme has crystallised its own view of the target state made possible by synthetic biology and its vision for Finland (see above). The guiding idea is that synthetic biology is the key to sustainable bioeconomy, and that **biology is the foundation of a large part of industrial production**. The modernisation and expansion of biotechnology has also an important role beyond bioeconomy for the development of a competence-based, dynamic Finnish society.

ENABLERS

It has been estimated in connection with Finland's bioeconomy strategy that investments made in bioeconomy resources today will, realistically, produce returns in 2030. If no investments are made, the resource base will not be sustainable. A similar idea applies to investments related to synthetic biology know-how and development.

In order for it to be possible to make the vision of this roadmap a reality in Finland and ensure the conversion of the possibilities of synthetic biology into competitive business operations in domestic companies, enabling measures are needed; these are presented in the following sections.

IPR AND A SURVEY OF COMMERCIAL OPPORTUNITIES

In biotechnology, the aim is to patent new genes and gene combinations as quickly as possible for the production of a specific product or the development of better production strains. Companies around the world are keeping a very close eye on the development of biotechnology and analysing the usefulness of new information with regard to their own production technologies. Although the number of restrictions on granting patents is increasing, the patents are often very broad and cover almost all genes from any organism controlling a specific reaction, even if only a few of them have been shown to work. In principle, important patents covering many products could be obtained, for example related to the use of specific raw materials (e.g. xylose, C1 compounds). Companies, universities and research institutes have been patenting biotechnical ideas related to bioeconomy for years, and the patents cover the field to a large extent.

Because an invention is the first observation of a potentially useful cellular function caused by a specific genetic modification, it must be patented immediately for competition reasons even if development of the process may take years.

Without education in molecular biology or familiarity with international actors in the field, understanding of the world of patents and the means to achieve operating leeway will be lacking. This may restrict and repulse newcomers to the field. Understanding the market value of new bio-based products also requires special know-how. The most obvious biofuels and biochemicals replacing petrochemical products are already under intensive industrial development around the world. Companies form joint ventures or attempt to find their own development target, perhaps aiming further into the future.

It should be quickly determined what understanding of the field of IPR and the market is needed by Finnish companies. What factors could possibly limit the enthusiasm of, in particular, new companies interested in the field to adopt biotechnology? Do several companies and actors in the potential value chain have any common needs or even common development and product targets that could be jointly advanced by means of synthetic biology, and create a possible patenting strategy to achieve them?

SCIENCE-ORIENTED CORPORATE CULTURE AS BASIS FOR NEW INNOVATIONS

The utilisation of synthetic biology is dependent on the latest achievements of science and technology. New scientific findings or technical solutions may have great significance for how efficient production organisms can be made or how quickly new findings can be patented or strains brought into production. Biotechnical development is only in its early stages and has immense potential change current assumptions regarding the possibilities of bioeconomy.

In Europe and Finland, bioeconomy is observed from the perspective of biomass-based raw material, while in the USA, for example, the focus is on new products made possible by bioeconomy that create actual added value. For this reason, the US national bioeconomy strategy[1] heavily emphasises biotechnology, which enables a wide product selection. The marriage of biotechnology and information technology in the US, giving birth to a unique scientific and innovation community embedded with world-class companies in the San Francisco area, has made it natural for the USA to believe and invest in synthetic biology and the automatic data processing supporting it.

The SynBERC consortium in the USA is a good example of how the modernisation of biotechnological corporate culture can be sped up with a heavy emphasis on science. Around twenty entirely new viable companies were founded by the professors and students of the consortium, several of which have grown into engines running a new business ecosystem. Another example is Flagship Ventures, also from the USA. It is a Boston-based private capital investment company that operates as a business accelerator: it picks out development-worthy results from research and builds companies based on them. In 2016, Flagship Ventures announced the first listed synthetic biology company founded in this way.

In addition to science-based companies, **a diverse company network** must have financiers, service providers and facility providers. In addition to these, in order to make synthetic biology a sustainable competitive edge for Finnish industry, we must ensure a high level of academic education. Without an understanding of the possibilities brought by new technologies, Finnish entrepreneurs, policymakers and decision-makers will be unable to make informed choises. Education should aim at bold and visionary actors who also have a clear idea of the principles of sustainable development and the realities of successful business operations. Business teachers should understand the special characteristics of the biotechnical industry.

Finland has a good foundation and evidence of the strength of a **science-based corporate culture**. Biotechnology and the IT required by synthetic biology are among the strengths of Finland. We also have excellent know-how in materials sciences and design, which enables the utilisation of biotechnology in the design of new, visionary high-tech products. We must endeavour to better integrate biotechnology with the competence networks that are important to it. A high-quality Finnish research company education environment possessing a critical mass is a powerful and important source of support for the Finnish business world.

HIGH-QUALITY OPEN ACCESS INFRASTRUCTURE

Computer-aided design and automation are cornerstones of synthetic biology. It must be ensured that, in addition to more traditional biotechnical equipment, the needs of synthetic biology will also be taken into consideration, and Finland can have a **synbio infrastructure from the laboratory to piloting.** This is essential for the rapid development of production strains and processes, reduction in labour expenses, and faster launch of products in the market. Agile experimentation must also be possible.

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[1]https://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf

The Finnish Research Infrastructure (FIRI), a joint venture of Aalto University and VTT partially funded by the Academy of Finland, supports bioeconomy and also includes synthetic biology equipment. The new construction plans for the Otaniemi campus may make internationally high-quality facilities possible: there, competence, software and equipment could be made available to different actors as flexibly as possible. The Finnish research infrastructure has a natural connection with VTT's Bioruukki, which houses, for example, pilot equipment intended for the pre-processing, fractionation and gasification of biomass. It must also be assessed whether the equipment intended for the fermentation of gases and the growing of photosynthetic organisms is sufficient for the future needs of Finland. The infrastructure should be integrated with other EU-level actors to enable expensive equipment to be used across borders, thus increasing the networking that is important to Finnish research and industry.

A change in mindset is also required. Synthetic biology particularly inspires students and small-scale entrepreneurs. A **BioGarage** should be established for workshop activities and the building of new prototypes, and it should be connected to a party well versed in GMO regulations and ethical responsibilities. The BioGarage could serve as a common, multidisciplinary workspace for iGEM students, designers and "one-man companies". It would have a natural connection to a university, and Aalto University, for example, could offer many kinds of synergy benefits across scientific and art sectors. It is important to spread information on the "open access" synbio infrastructure.

INSPIRATION FROM "SYNBIO-SLUSH"

The competence of the Slush events that have been a great success in Finland could be utilised in organising an international **"Bio-Slush"** event. A Slush emphasising biotechnology and synthetic biology would probably have a different character than the more traditional bioeconomy business events. The first event could be in the form of an "event fair" as there are no actual start-ups competing for investor funding yet. The event could also include other topics made possible by synthetic biology in addition to industrial biotechnology, such as the medical and IT sectors (including the Bio-Hackathon). This idea is supported by VTT's plans to promote, for example, the digitalisation of bioeconomy and the organisation of science pitching sessions.

"SynBio-Slush" would thus not mean just an event for a narrow field, but the overall idea of **Finland becoming one of the innovative forerunners in synthetic biology.** In addition to top-level research, being a forerunner also requires vital domestic companies and extensive networks both in Finland and abroad so that international entrepreneurs and financiers can be persuaded to attend.

A lack of Finnish investors who understand the biosciences is a key problem. This understanding should be increased particularly now, as biotechnology and synthetic biology are increasing their role also in bioeconomy and the food sector (in addition to medical biotechnology). The question is not only how research scientists and new entrepreneurs can make their message clear, but also whether financiers understand the possibilities of biotechnology. The best foreign investors have strong bio-know-how, which enables risk-taking and the founding of new companies even on the basis of the investors' own ideas.

In June 2016, the Living Factories programme arranged a seminar discussing business opportunities in biotechnology. One of the speakers was Doug Cameron from First Green Partners, USA. His message describes the dimensions of investing in biotechnology: "I am open to anything, which does not violate the laws of thermodynamics". This statement must not be understood as a joke but a knowledge-based statement which is factual particularly when making investments in the production of oil-replacement fuels or basic chemicals.

The idea of activating the industry and other potential parties to create a new fund investing in biotechnology was proposed during the seminar.

PUBLIC APPROVAL AND ENABLING LEGISLATION

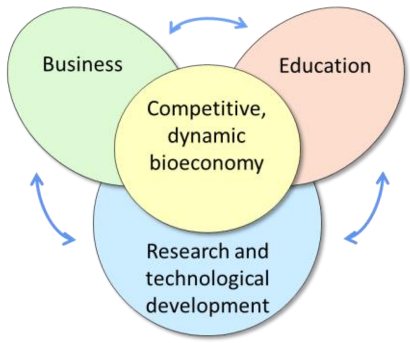
Public discussion on the ethics and ethical methods of synthetic biology is of a primary importance. The utilisation of new, science-based technologies will not progress if the general public is categorically opposed to them, as has happened with the utilisation of GMOs in farming and the food industry. A sufficient amount of information and opportunities for discussion must be offered from the start – this must be taken into consideration already today. Good cooperation between media outlets enlightening the general public and research scientists is important.

Enabling regulation goes hand-in-hand with public discussion on ethics. What can be done and what cannot? In Finland, the Board for Gene Technology is the competent authority on matters involving the application of gene technology legislation. The Board processes permit applications and deals with problem cases and is very aware of the challenges of synthetic biology. Finland is heavily involved, for example through science academies, in the provision of advisory duties based on research data for the EU Commission and Parliament towards the development of synthetic biology legislation. Companies must also have active dialogue with authorities in order for Finland to be able to develop as a user of synthetic biology. The difference between closed and open operation must be made clear to the general public.

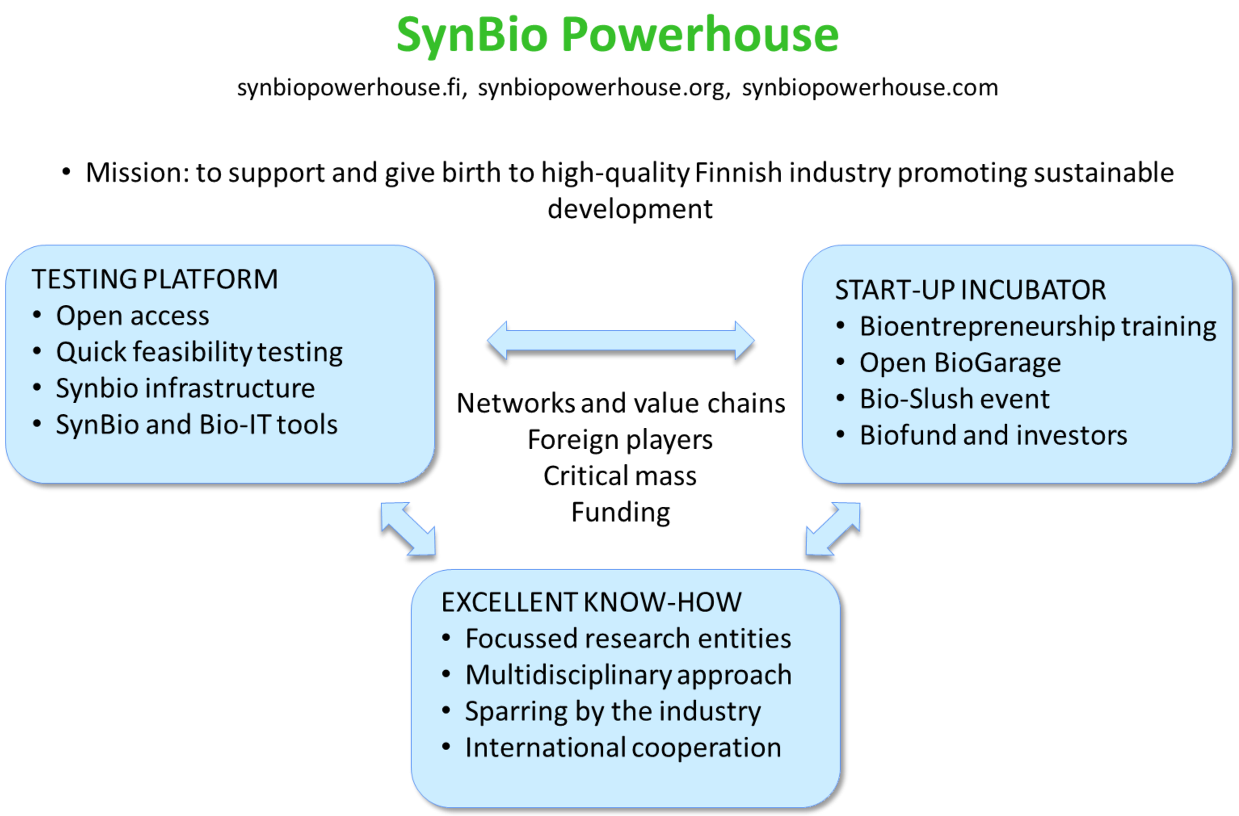
SYNBIO POWERHOUSE AS THE MINDSET INITIATOR

In many EU countries, academia and the business world work in close cooperation in biotechnology and synthetic biology clusters. A similar way of acting is also needed in Finland. During the roadmap work, the idea was raised of establishing a **Synbio Powerhouse** group in Finland as a public-private partnership. Leading figures in the business world and research should come together in the group to generate ideas for and coordinate cooperation between synthetic biology researchers and the industry, the establishment and boosting of a start-up culture for synthetic biology, and the production of advice and expertise in the field for different stakeholders.

The Synbio Powerhouse also requires financiers with a vision for bringing about a new industrial revolution in Finland. Its task is to ensure that bold and visionary ideas stemming from synthetic biology can also be implemented by Finnish start-ups, because they are an essential part of the transformation of industry. The assembly of the Synbio Powerhouse group and its detailed action plan are recommended to be done as part of the continuation period of the Tekes-funded Living Factories project.



Based on the strength of the above factors, an **open innovation environment** can be established.



REALISATION OF THE COMMERCIAL POTENTIAL OF SYNTHETIC BIOLOGY REQUIRES COOPERATION AND COMMITMENT

Industry

Industry is required to commit to cooperation with Finnish research scientists. Research cooperation in Finland is a long-term opportunity – as the cooperation progresses and develops, it will be easier for research scientists and industry to set common goals that are also supported by the development of basic research in a direction supporting Finnish industry.

Industry partners are invited to be involved in the creation of a biotechnology-oriented fund. SMEs are required to develop commercial industrial biotechnology applications from promising technologies. Without an informed, biotechnology-focussed fund, it is difficult to establish new companies in Finland. The lack of biotechnology expertise among existing funds presents a bigger problem than lack of finance itself. This expertise can be found in Finnish industry.

Financiers

Converting a promising technology into a commercial success requires informed financiers. Financiers are invited to the biotechnology-oriented fund together with industry partners. With the participation of industry, expertise in the market and biotechnology is ensured. The hope is that Tekes would participate in establishing activities such as a biotechnology accelerator in order to ensure the sufficient maturity and commercial requirements of the fund's potential investment targets. The financiers (Tekes, Academy of Finland, etc.) are also responsible for enabling long-term research.

Ministries, decision-makers

Finnish industry needs spearheads. During the extended recession Finnish industry cut back on investment in early-stage research and product development. The process industry in Finland – the energy, forestry and chemical industries – are cornerstones of Finland's export and economy and also large employers. An SME ecosystem established around these industries will also create opportunities for growth and success stories. We hope that Finnish decision-makers will take a long-term view and make the bold decision to choose synthetic biology as a national technological focus area. Synthetic biology will revolutionise industrial production.

Start-up community

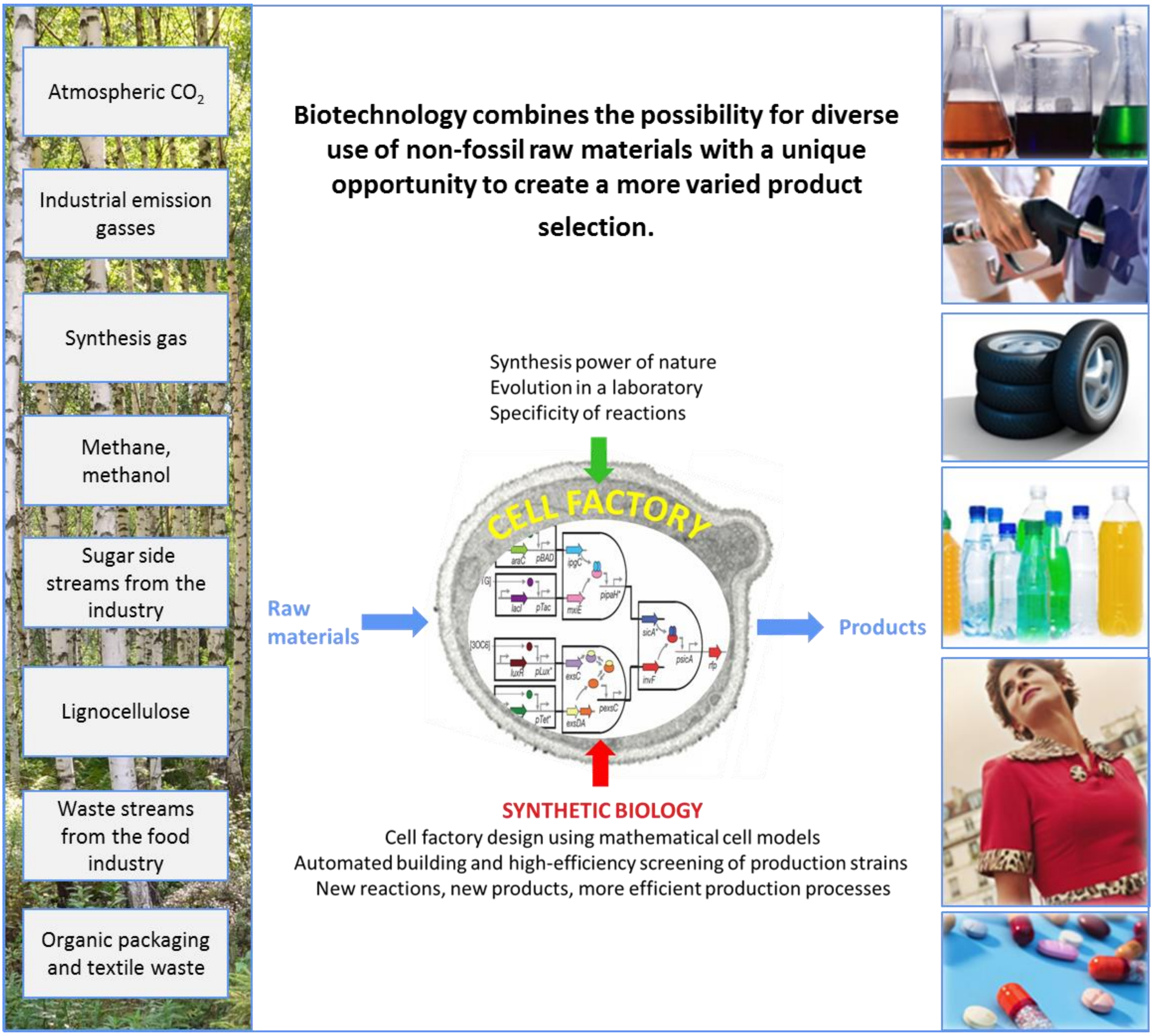
The start-up community is invited to improve the prerequisites for the birth of synthetic biology companies. These prerequisites include garage laboratories and an informed mentor network. The Finnish manufacturing industry, among others, has key knowledge of the needs of the market and commercialisation possibilities.

Research institutes and universities

Research institutes and universities bear the responsibility for developing synthetic biology technologies and maintaining internationally high-level research. They are encouraged to work in closer cooperation with Finnish industry in such a manner that the common goal of increasing Finland's competitiveness is achieved. Universities bear the responsibility for arranging multidisciplinary education supporting biotechnology and synthetic biology that also encourages entrepreneurship.

We invite all the above-mentioned parties to the Synbio Powerhouse

The first step on the Roadmap for Synthetic Biology in Finland is to establish the Synbio Powerhouse. The Synbio Powerhouse will be initially established as a group in which key parties agree on the steps to be taken to develop a synthetic biology ecosystem in Finland. In the longer term, the Synbio Powerhouse is seen as a public-private-partnership actor that helps accelerate the creation and commercialisation of innovations through cooperation between industry, start-ups and research institutes.



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The document (PDF) can be downloaded from: http://www.vtt.fi/inf/julkaisut/muut/2017/syntheticbiologyroadmap_eng.pdf