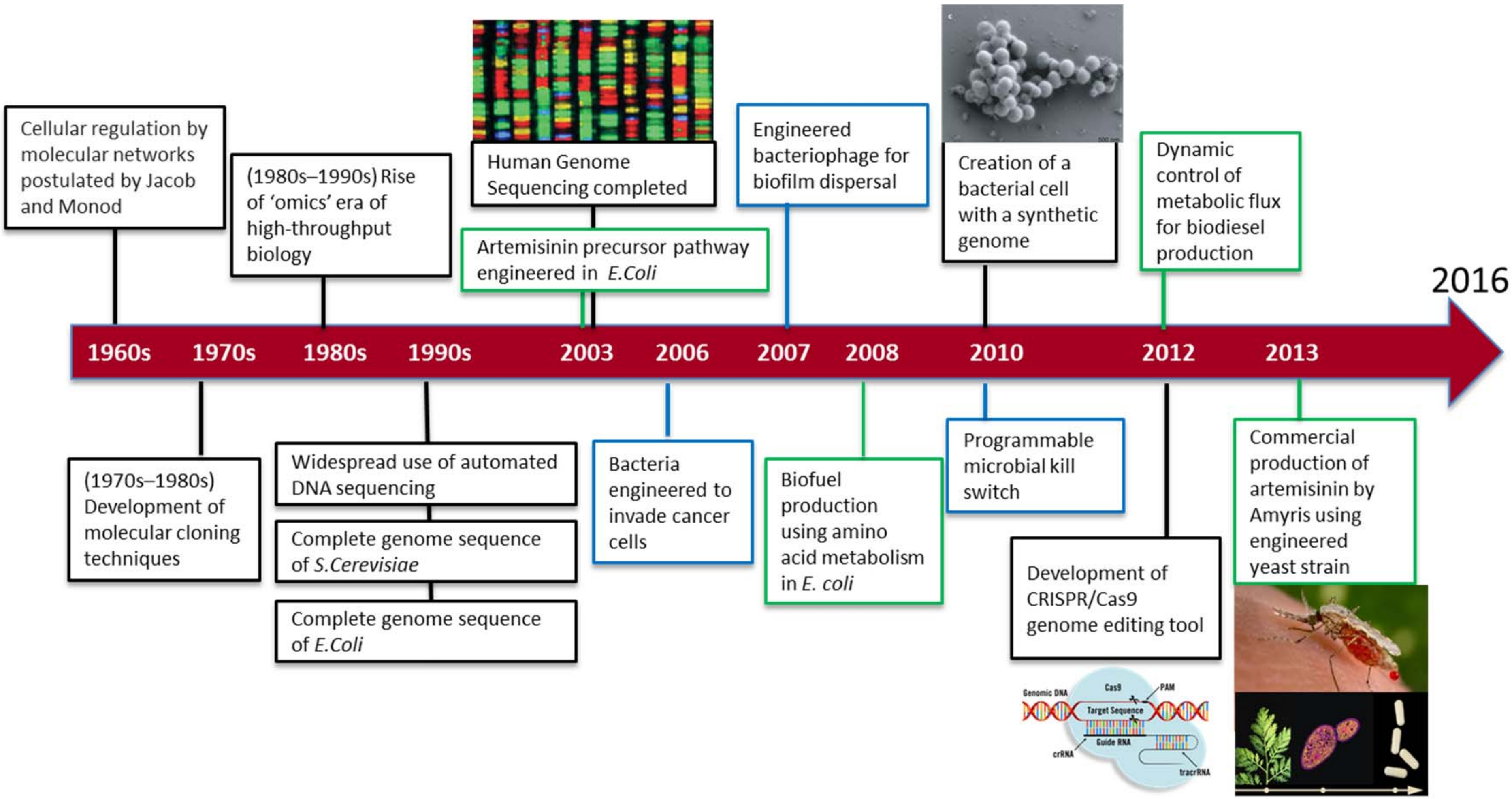
Building a Synthetic Cell – thoughts on a future H2020 FET Flagship initiative



A timeline of synthetic biology

Key to coloured boxes: scientific milestones (black), metabolic engineering (green), therapeutic applications (blue)

Picture adapted from D. E. Cameron, C. J. Bashor and J. J. Collins , *A brief history of synthetic biology* , NATURE REV. **MICROBIOLOGY** , VOL 12 | MAY 2014 p.381 - 390

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BUILDING A SYNTHETIC CELL

The ultimate challenge of Synthetic Biology

The most astonishing scientific breakthroughs and the greatest increase of knowledge within the last decades have arguably occurred within the life sciences, addressing the underlying principles and processes in living systems. Following the genetic revolution, researchers have accumulated an enormous and ever increasing knowledge on the complex set of molecules and their interactions in living cells and organisms. This knowledge has led already to the possibility to modify these interactions, leading to an exciting new area of science and technology called Synthetic Biology.

Synthetic Biology involves the rational design and synthesis of complex biology-based or bio-inspired systems that display useful functions, even ones that do not exist in nature. Its development signals a new era for humanity where biology has become an engineering discipline. Nature is no longer a static given but a resource enabling mankind with unprecedented opportunities to tackle its huge challenges in health, energy, climate, and more. Despite being a relatively new research field, synthetic biology is exponentially growing, and already leading to unprecedented insights in how living organisms function, which in turn open new ranges of possibilities in technology and applications.

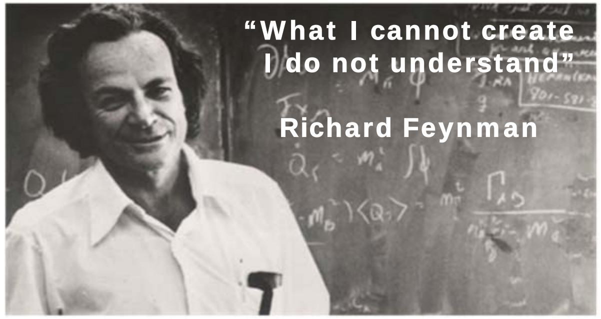
Thanks to synthetic biology is it possible nowadays to engineer genetic circuits, biological modules and synthetic pathways. These can be used to re-program organisms to generate a whole range of products impacting enormously our society in all aspects: from healthcare (cheaper drugs and targeted, non-invasive therapies for e.g. cancer, antimicrobial resistance, malaria), to energy (environmental-friendly fuels); from agriculture and food safety, biological control of pathogens and bio sensing) to new biomaterials with bespoke mechanical or electronic properties produced by bacteria in a sustainable way.

However, while we are getting better in “mixing and matching” biological elements, too often cells remain black boxes of which we still don’t know exactly how they function. This lack of knowledge and control limits our possibilities, and we are confronted with it more and more as we get better in re-engineering organisms. The only way to break through this barrier and really understand molecular processes and interactions in their full complexity, is to construct a synthetic cell from the bottom-up from basic molecular components. This is a flagship worthy challenge. Synthetic cell would present unprecedented control and open up entirely new avenues for drug delivery and many other applications. The challenge to develop synthetic cell technology is truly huge. It requires a concerted effort from biologists, chemists, physicists, engineers, mathematicians and even scholars from the humanities.

We believe that a Synthetic Cell Flagship is the ONLY instrument that will allow to address this formidable scientific challenge and to fully exploit the technological opportunities that it will generate. It will put Europe at the forefront in the race against global threats such as antimicrobial resistance and pandemic risk, aging-related diseases, climate change, energy and food crises.

The scientific challenge: can one build a living cell from individual lifeless components?

One of the grand fundamental challenges of modern science is to reveal the basic operating principles of life. In spite of our increasingly precise understanding of the details of life, its fundamental principles are still to be discovered. While we now have extensive knowledge about the molecular building blocks that form the basis of modern life, we currently *do not understand* how these building blocks collectively operate to define life. Indeed, the origin of life – where first cells emerged out of molecular components on the early earth – is one of science’s greatest remaining enigma’s. We can intuitively distinguish a living from a non-living system, and we can formulate necessary features, such as metabolism and self-replication. But despite a century of research, we still cannot give a satisfactory and unequivocal definition of life, or formulate a predictive theory of how it may spontaneously emerge from its non-living constituents, as would be required for a truly fundamental (i.e., quantitative)



understanding. We believe that the rise of synthetic biology now provides an exciting new route to address these questions, which makes it one of the most outstanding scientific projects thinkable.

Cellular life, which provides the fundament of most organisms, appears to be the result of a collection of highly regulated, energy consuming, dynamic self-assembly and self-organization processes, leading to autonomous entities that can reproduce, transfer information, interact, and evolve. Understanding the physical-chemical principles of these collective processes poses a formidable challenge, which needs to be overcome if we want to be able to understand life itself, and use this knowledge in a rational way for useful applications to our benefit.

We intend to address the challenge of truly understanding the mechanism of life by building a synthetic cell from the bottom up (which contrasts sharply with efforts using a top down approach – see box. **We aim at putting together basic molecular components and have them interact into a functioning synthetic cell. Building a cell from the bottom up, will allow us to answer fundamental question of ‘how life works’.**
More profound bottom-up understanding of life will bring huge intellectual, scientific, and technological rewards. At the same time it will raise fascinating philosophical and ethical questions as it impacts on our fundamental understanding of ‘what life is’. Such questions intrigue the general public and scientists alike, opening up fascinating prospects for viable humanities-science dialogues.

State-of-the-art in science
The prospect of creating synthetic life has inspired scientists for many years. Recent progress by for example Craig Venter’s group has demonstrated that synthesized genomes containing several hundreds of genes can lead to viable cells [1][2]. However, while this top-down approach of creating a minimal cell by selectively removing components from wild-type genomes has been highly successful, it does not reveal how the remaining gene products act together to create life. For example, the function of 30% of the genes in Venter’s most recent minimal cell is entirely unknown, leaving open many essential questions on how these cells work. As a result, it has not yet been possible to rationally design and construct, bottom-up, a simple form of life based on a limited number of building blocks (see e.g. [3]). While our fundamental understanding of the individual building blocks of life is rapidly growing, putting a minimal set of components together such that life-like properties emerge remains a formidable, yet exciting challenge.
Importantly, in recent years, tremendous progress has been made in the bottom-up reconstitution of basic cellular machinery. Following a strong push for quantitative studies of individual building blocks driven by the fields of biophysics and biochemistry, there has been rapid progress in the reconstitution and quantitative understanding of complex biological systems and processes (such as complex membranes and transport systems, sophisticated DNA processing machineries, complex cytoskeletal systems, self-organized spatial protein patterns, cell-free gene expression etc.). In parallel, the possibilities for genome engineering have exploded with the development of tools such as CRISPR technology [4]. All these rapid advances in biophysics, biochemistry and genome engineering, together make it possible to take on the challenge of integrating basic individual systems into biologically functional entities, and to embark on the ultimate quest of building a synthetic cell.

<u>Relevance, future and emerging products and markets.</u>
Knowledge of life processes offers unprecedented opportunities for a healthy and sustainable world in many areas of Health, Agrifood, Materials and Energy. Better understanding of the molecular underpinnings of cell behaviour will allow us to develop <u>targeted drugs</u> to specific locations and tissues in the body, and <u>patient-tailored treatments in personal medicine,</u> for example for cancer. Similarly, it leads to new methods and tools that will pave the way to new applications in <u>drug delivery systems</u>, <u>novel screening methods for antibiotics and drugs, biosensors</u> and against <u>antimicrobial resistance</u>. Design of synthetic cell systems will allow mankind to produce new, smart and <u>environment-friendlier materials</u> in high-tech industry, new <u>biofuels and biodegradable polymers</u>. It will also facilitate sustainable production of safe and healthy food: potential applications include the development of new materials for food biotechnology, fast and reliable <u>analysis and control of contaminations</u>, and new methods for <u>pathogen control</u> and for the prevention of <u>animal and plant diseases</u>.

These are merely a few examples. Unanticipated applications will surface once such a synthetic cell is realized and next-generation synthetic cells will emerge or evolve from the initial prototypes. Designer synthetic cell systems undoubtedly will find their use as mini-reactors in biotechnology (fine chemicals, bioactive compounds, complex chirality, platform chemicals), nanotechnology (devices, sensors), bio refinery (materials, platform chemicals, polymers), environmental remediation (water, soil, mineral recovery), and health (e.g. drug delivery, biosensors).
A recent survey by industry researchers in metabolic engineering [5], noted the following: *"To date, scientists succeeded in chemically copying natural blueprints and modelling of a near-minimal genome organism – milestones of synthetic and systems biology. However, a microbial cell designed and synthesized independent of blueprints will be the ultimate test for our insight into those principles. Joint efforts by systems and synthetic biologists might decipher those principles in the future."*

A challenge for Europe

Strengthening scientific leadership

Establishing synthetic cells from the bottom-up is one of the major challenges of the 21st century. We foresee that first realizations will be achieved within 10-20 years. It requires a large-scale effort that unites the highest expertise and experimental research activities of various disciplines: physics, chemistry, engineering, and obviously synthetic biology (and brings in additional expertise from engineering and modelling). Worldwide there are several initiatives based on complementary approaches to minimal life. Notably in the US a number of research groups is active in the field, besides Craig Venter, Jay Keasling (Berkeley), Jack Szostak (Harvard). Also Japan hosts a number of minimal cell groups like Ueda (Tokyo Univ), Kondo (RIKEN) and Yomo (Osaka Univ.)

Why so many efforts worldwide? Because this is a grand scientific challenge, of Nobel prize relevance, that will undoubtedly lead to fundamental breakthroughs in chemistry, physics and biology, and at the same time will open up entire new areas for applications, from bioengineering to nanomedicine.
Europe has a large number of world-top researchers from various countries and disciplines, currently working on different aspects of minimal life rather independently. Many of them have received awards and funding (e.g. ERC grants) for seminal work in this field. There are currently several initiatives at national and European level to coordinate the efforts[1]. Recently a group of European top researchers from the physics and chemistry communities have started a dedicated European community with a common ambition to engineer synthetic life using a bottom-up approach. This initiative for the moment includes researchers from a multi-disciplinary consortium in the Netherlands, researchers supported by the MaxSynBio programme on synthetic biology that was initiated in Germany by the Max Planck Gesellschaft in 2013, as well as researchers from other European countries (most notably the UK). This is only the beginning: Scandinavia, Italy, France and Switzerland are also very active in this challenge and will surely join the initiative. It is clear that Europe harbours ambitious top scientists that are leaders in their respective fields. Together they would be in a fantastic position to lead a synthetic cell project worldwide. A Synthetic Cell Flagship is a unique opportunity to combine the efforts of the diversity of networks already operating in Europe in life sciences, physics and chemistry and take on the challenge for Europe as world leader in synthetic biology.

From science to industry to society: the synthetic cell revolution

Building a synthetic cell will not only answer one of the fundamental questions in science, "how life works". It will simultaneously lead to a new technological and societal revolution, with considerable impact. In a way, this can be compared with the invention of computers where pioneering scientific discoveries in the mid-20th century paved the way to personal computers and internet. The path towards a synthetic cell itself will similarly allow the development of unprecedented new application areas such as

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[1] *Existing synthetic biology initiatives (not-exhaustive) in Europe relevant to this initiative*:
National: BaSyC Consortium in the Netherlands, MaxSynBio program started in 2013 by the MPG in Germany, BriSynBio research centre in UK, OLIM in Munchen
European: the ERASynBio initiative, https://www.erasynbio.eu, the COST action Emergence and Evolution of Complex Chemical Systems, http://www.systemschemistry.com/cm1304/

medicine, food, biomaterials and sustainable fuel production and use. These areas are currently subject to global threats such as climate change, food and energy crisis, pandemic and chronic diseases affecting Europe's citizens and people further afield.

Businesses recognize the potential of synthetic biology in terms of applications, and have demonstrated interest in this research field. Many research groups are actively collaborating on the different research threads in synthetic biology with companies such as DSM, Friesland Campina, Codexis and Corbion, Unilever and Fibriant. Another recent example of emerging innovation is the YES!Delft 2nd incubator with biotech facilities, officially opened to assist starter companies and supported by European funds itself. Application fields of such existing and starting companies cover sectors from regenerative medicine, pharmaceuticals, to food and nutrition, animal health to self-healing materials, bioplastics and sustainable fuels.

Building a synthetic cell is an interdisciplinary challenge involving not only physics, chemistry and biology, but also ICT, social sciences, humanities and law. It is clear that unravelling fundamentals of the basis and origin of life, by answering to one of humanity fundamental questions, raises by itself again a number of new, fundamental questions of profound ethical and philosophical significance.

The perspectives opened up by a synthetic cell are fascinating: a plethora of potential benefits for society comes into view. At the same time, various risks may be involved. This calls for responsible research and innovation. **We feel that to this purpose a leading and united common approach for Europe is needed and should be an essential part of the Flagship Synthetic Cell.** Besides addressing the impact and implications of synthetic biology, a flagship would be also an ideal platform for scientists, policy makers and industry to reflect on the issues involved, to generate common standards and regulations and to engage into well informed dialogue to address any public concern.

Similarly, a common European policy will be needed to regulate the intellectual property of the technology that will be made possible by synthetic biology. Synthetic biology has already captivated the interest of industry. While science proceeds along the path to a synthetic cell, a clear and transparent framework building process is necessary to define ownership, coordination and terms of use of results and products at European level.

Building a synthetic cell to better understand life is an attainable and realistic objective. Scientific progress in the coming 5 to 20 years – provided it is sufficiently funded will enable Europe to become a leader in facing many of the global challenges to life on earth in all its appearances. Really understanding life will enable Europe to protect life itself better. We are convinced that now is the right time to launch a Synthetic Cell Flagship.

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