www.biologiedesynthese.fr website content

1) Introduction

We are entering a new world, the world of synthetic biology. It could provide more effective therapies, cheaper medicines, easily recyclable new materials, biofuels, bacteria able to degrade toxic substances from the environment.

Synthetic biology is a fast moving field. It is defined as the rational engineering of biology, aiming to design new biological systems. Synthetic biology will advance our knowledge of living organisms and will develop many industrial applications in the area of health, energy, materials, environment and agriculture.

The current achievements of synthetic biology include a diagnosis system able to monitor annually some 400 000 AIDS or hepatitis patients and the synthesis of artemisinin, a highly effective anti-malarial drug.

1bis) News (on the same webpage)

Synthia project

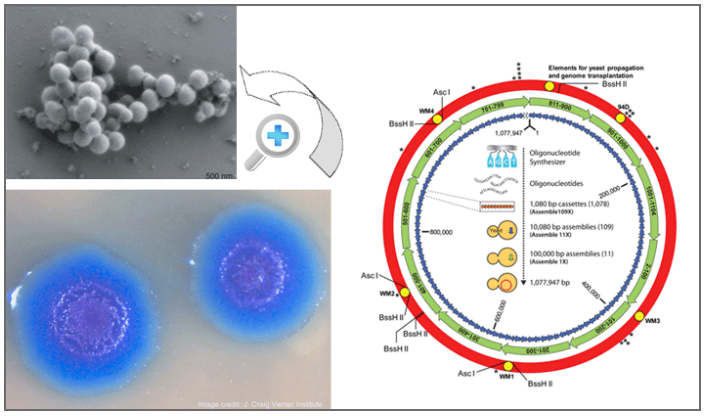
On May 20, 2010, after 15 years of work and $40 million investment, a 20-person team from the J. Craig Venter Institute created the first artificially controlled bacterial chromosome.

The team replaced the natural genome of Mycoplasma capricolum, a bacterium that can produce pneumonia in goats, by a nearly identical genome but synthesized in the laboratory. This genome is a single chromosome of about 1.155 million base pairs, which had previously been decrypted and the information stored in databases.

From this information, containing the base pair sequence, the artificial chromosome has been synthesized. This was only slightly modified by a "filigrame", which allows to be distinguished from the natural chromosome.

First, more than 1000 sequences of about 1000 base pairs were produced by chemical synthesis. Then, the fragments were assembled in several stages, some of them by biotechnological methods involving the bacterium Escherichia coli or yeast.

After removing the restriction enzymes (proteins that cut DNA) in a natural bacterium Mycoplasma capricolum, the scientists transferred the artificial chromosome into it. It took many attempts to make the synthetic DNA replicate and the natural DNA disappears - probably destroyed by the restriction enzymes of the synthetic DNA. Moreover, these modified cells called "Synthia", have replicated and expanded. They were also able to transcribe their genes into RNA and translate them into proteins. Their structure and behavior are identical to those of natural bacteria.



Synthia cell colonies (bottom), seen by electron microscopy (top) and their genome map (right).

However, this is not a synthetic bacterium but only a bacterium controlled by a synthetic genome assembled from fragments of synthesized DNA. The cytoplasm is part of the original host cell. This is equivalent to changing the hard drive of a computer and put in a new operating system.

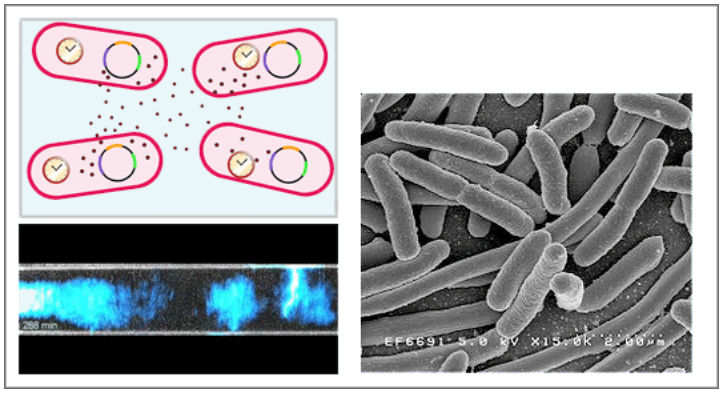
The next step is to design bacteria controlled by a genome of 2 million base pairs, which allows applications in biotechnology: cells able to synthesize medicines, clean the soil or produce biofuel from non-food biomass.

Synchronization of transcriptional regulators of E. Coli

In January 2010 a team of scientists from the University of California at San Diego was able to synchronize the molecular clocks of a colony of bacteria.

Ten years ago, using techniques of synthetic biology, researchers created artificial clocks in individual Escherichia coli bacteria. This time the clocks were not only built but also synchronized in a colony of bacteria.

Bacteria can synchronize the expression of some of their genes by a mechanism called quorum sensing: they communicate with each other by chemical messengers that provide information on the population density of their species or other species, which sometimes allows them to have symbiotic behavior. One of the chemical messengers is acyl-homoserine lactone (AHL), a small molecule that easily diffuses across cell membranes.



Escherichia coli bacteria (right) were modified to get artificial clocks synchronized (top left) and to highlight their oscillations (bottom left).

Using components of Vibrio fischeri, a luminescent bacterium of seawater, and Bacillus thuringiensis, that lives in the soil or water, scientists designed a system where the AHL molecule is involved in the expression of two genes: one produces an enzyme that catalyzes the synthesis of AHL, the other another enzyme that degrades the AHL. These loop actions are antagonists, therefore they generate oscillations of the AHL concentration. A third gene expressing a green-fluorescent protein was coupled to this mechanism in order to view these oscillations.

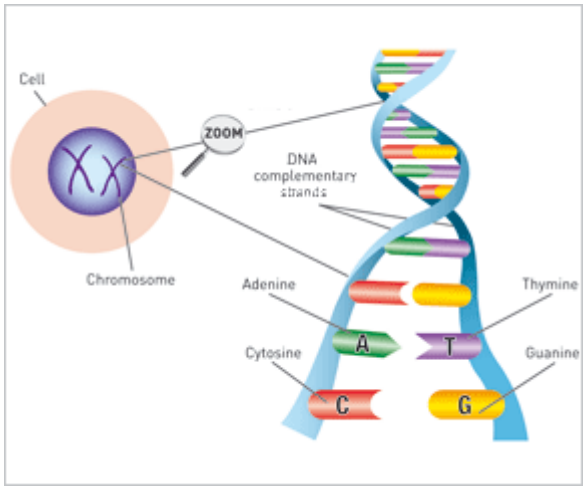
The dual role of the AHL - activation of genes producing the oscillations and messenger between cells - allows clock synchronization in a colony of bacteria, so that all its members "flash" in unison.

This research could help the understanding of sleep-wake cycles and diffusion rates of hormones in the body and find applications for the treatment of sleep disorders and seizures.

Another possibility is to develop cellular implants that can produce specific and precise doses of hormones like insulin or other therapeutic proteins. The patients will no longer have to remember that they must take medication at set times.

2) Basics

The DNA molecule forms the base of all life. Thanks to it cells multiply, organisms grow and genetic traits are passed from parents to children. The DNA molecule consists of two strands coiled into a helix. On each of two strands successive bases bind; there are four types of bases, complementary pairs: adenine (A) binds with thymine (T), cytosine (C) with guanine (G). Thus, if a strand fragment contains the sequence CTAAAGG, the complementary sequence on the other strand is GATTTCC.

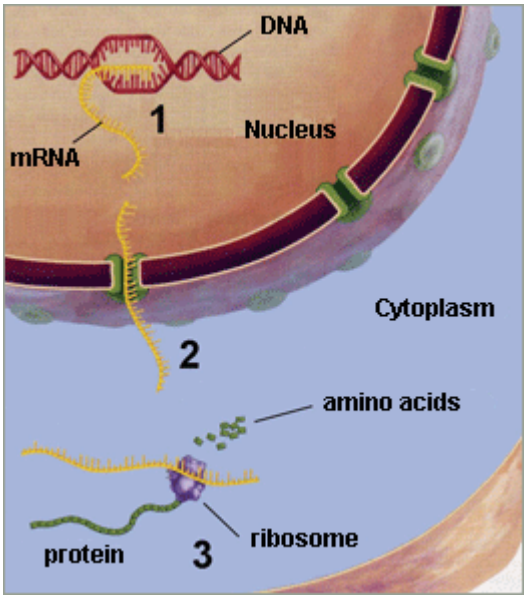


The DNA molecule consists of two strands coiled in a helix on which there are four types of complementary bases linked in pairs. Adenine (A) binds with thymine (T), cytosine (C) with guanine (G).

An inherited trait like hair color is encoded by a gene, which is a segment of DNA. The set of genes form the genetic code, for humans it has some 30 000 genes spread over 3 billion base pairs.

The genetic code plays an important role in protein synthesis. The gene is copied by an intermediate messenger, called messenger RNA, a process known as transcription. RNA migrates to specific units called ribosomes, where it is translated into a chain of amino acids, thus forming the corresponding protein. For example, the gene that encodes the hair color of a person determines the production of melanin, the pigment responsible for this color.

The ribosome reads the messenger RNA by sequences of three base pairs, each sequence is translated into an amino acid (there are twenty of them in living organisms). This is attached to the amino acid chain already translated the same way, just as an additional pearl is attached to a necklace. The sequence of base pairs in a gene determines the sequence of amino acids, therefore the structure of proteins. An average-sized protein contains about 300 amino acids, which means we can get 20^{300} different types of proteins, which is a huge number. This explains why proteins, the building blocks of the living organisms, have such varied functions: oxygen transport, muscle contraction, chemical messengers, tissue structure. Besides water, proteins represent 40% of the human body weight.



Protein synthesis: the DNA gene sequence is copied into messenger RNA (1). The messenger RNA leaves the nucleus and migrates into the cytoplasm where it encounters a ribosome (2). The ribosome reads the messenger RNA in the order of its sequence and links the amino acids to form the protein (3).

Living organisms have key components (cells, genes, proteins) that enable growth and reproduction. One of the goals of biological research in recent decades is to understand how these components interact, one main area being the relationship between DNA, RNA and proteins.

The traditional approach of biology research has been to isolate a small number of biological components to understand their structure and function. But this reductionist approach is limited since biological systems are multi-scale and multi-level: most genes, proteins and other components perform their functions within a complex network of interactions with positive and negative feedback loops. In general, a given biological function or a specific disease is not completely controlled by a single gene and conversely, a gene can determine several biological functions.

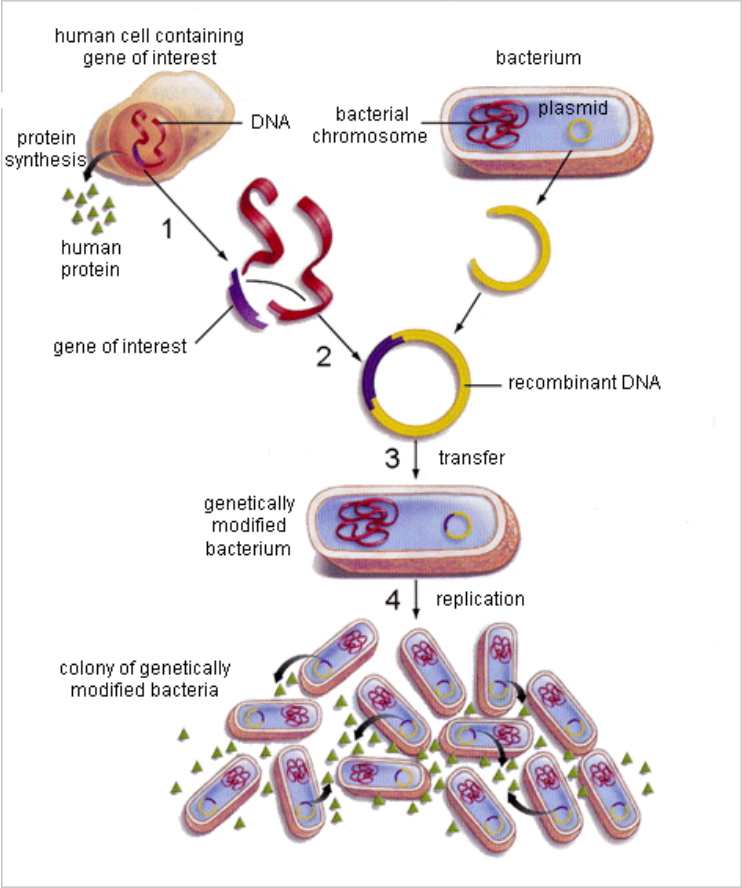
It is to understand increasingly complex biological systems as a whole that a new discipline called systems biology has emerged. It benefits from advances in investigative techniques of molecular biology but also mathematical modeling and computer simulation.

3) Biotechnology

In recent decades researchers have developed a set of techniques known as biotechnology, able to manipulate and rearrange genes of various organisms (bacteria, plants, animals), mainly used for synthesis of drugs.

For example, growth hormone secreted by the pituitary gland plays a crucial role in the growth and development of the child; its deficiency causes dwarfism. Originally the disease was treated by injections of hormones extracted from dead bodies, which made the treatment very expensive and could spread disease.

Through biotechnology, the gene encoding the growth hormone has been identified, isolated and inserted into the genetic code of the bacterium Escherichia coli. The bacteria can multiply rapidly and produce the hormone in large quantities and without any risk.



Biotechnology: the gene of interest is isolated from the human genome (1) and inserted into a bacterium plasmid (2). The plasmid is then transferred back into the bacterium (3), which multiplies rapidly in colonies and produce large quantities of human protein (4).

By similar techniques biologists have produced insulin, necessary for the treatment of diabetes, the drug called Leukine, used in the treatment of cancer and viral infections, the vaccine against hepatitis B and other drugs.

4) Synthetic biology

The methods of biotechnology are somewhat standardized: the specific gene is extracted from the DNA of a natural organism and transferred into another organism, which can produce with higher speed and efficiency the protein associated with the gene.

Synthetic biology has emerged by combining the concepts of systems biology, whose goal is the understanding of complex biological systems as a whole, with biotechnology, which has technological objectives. Synthetic biology aims not only to achieve the direct synthesis of a gene by chemistry, genetic engineering or nanotechnology, but also the use of engineering approaches (as in computer science or robotics) for a rational design of new biological systems.

There are several strategies:

The so-called "top-down" approach is to change a natural biological system to obtain a simpler system, easier to understand and handle. For example, one can remove many of its genes from a bacterium, keeping only the minimum necessary for survival under laboratory conditions, as the "Mycoplasma laboratorium" of the J.C. Venter Institute. Another example is the "Synthia" project, carried out by the same laboratory, where natural DNA of the bacterium was completely replaced with a synthetic DNA.

The opposite approach, called "bottom-up", is to define basic building blocks with well defined functions and assemble them to make biological systems, much like a Lego set. This strategy is used in the iGEM competition on synthetic biology, hosted every year by MIT and involving a thousand students.

We can go even further and create "proto-cells", vesicles with walls similar to membranes of living cells, which can selectively absorb small molecules and transform them inside using simple cellular machinery. These proto-cells can perform various functions such as detection and reporting of health disorders before symptoms of disease occur. In particular, proto-cells launched in the digestive system and naturally eliminated can be used as a non-invasive diagnostic system.

These approaches are complementary and aim to advance our knowledge in biology and evolutionary science. They have also many industrial applications. Today, the status of synthetic biology is similar to that of synthetic chemistry in the nineteenth century. Synthetic chemistry allowed the synthesis of quinine, aspirin and paints, and in the twentieth century, drugs, synthetic fibers and plastics. Synthetic biology seeks the use of natural diversity and biological systems to produce drugs, biofuels and materials of tomorrow.

Meanwhile several applications have already emerged:

5) Achievements

Artemisinin is an effective drug against advanced stages of malaria. It is extracted from a plant used in traditional Chinese medicine known as sweet wormwood, but with low efficiency therefore it is expensive. It can be produced by chemical synthesis, but the process is very laborious and difficult to industrialize, in part due to the asymmetric geometry of the molecule.

A yeast strain has been made by synthetic biology, which produces artemisinin acid, precursor of the artemisinin drug. The cost has been divided by two; the product purity and availability have been significantly improved.

Patients with AIDS or hepatitis are monitored by an effective diagnostic tool that can highlight with great sensitivity the ribonucleic acid (RNA) specific to certain viruses. The tool is able to detect very low levels of RNA in a sample solution, up to eight molecules.

The RNA is first attached to a substrate, then has attached to it a network of labeled molecules, visible in ultraviolet light and acting as a detector. Key components of these links are capture probes made of two parts: a sequence of natural nucleotides (adenine, thymine, cytosine, guanine) complementary to an RNA fragment and a sequence of artificial nucleotides expanding the genetic code, and another sequence of artificial nucleotides located on the substrate and detector.

Natural nucleotides can only pair with natural nucleotides and artificial nucleotides only with artificial nucleotides, making the system very sensitive.

Blue-green algae produce small quantities of hydrocarbons. The genes involved in this process have been identified and introduced into the genome of the Escherichia coli bacterium. Using synthetic biology, the bacteria metabolism has been modified to produce hydrocarbons that can be used as biofuels.

Isoprene, used in rubber production, is naturally produced in small quantities by almost all living creatures (including humans, plants and bacteria). The gene encoding the enzyme of isoprene synthesis has been identified only in plants like the rubber tree, capable of synthesizing natural rubber, a scarce resource. Synthetic biology has allowed the design of a new gene encoding this enzyme that, moreover, is optimized to operate in a specific microorganism. The objective is to develop biochemical production of synthetic rubber, currently only produced from petroleum.

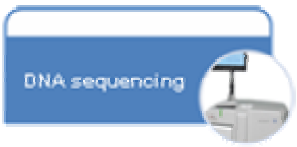
Bacteria such as and Rhodococcus sp. or Pseudomonas putida can absorb small amounts of petroleum and degrade it into less toxic substances. However, they prefer to feed on traditional sources of carbon such as glucose. Using synthetic biology, some non-essential genes can be switched off to change the bacteria's metabolism. By blocking sugar absorption, the bacteria are forced to consume and degrade toxins.

Millions of people worldwide are affected by arsenic poisoning of drinking water. Conventional detection techniques, based on fluorescence, are expensive, tedious and require sending water samples to laboratories.

Bacteria Escherichia coli have been modified by synthetic biology and turned into an arsenic detector. The bacterium has a detoxification system activated by arsenic, as well as the ability to degrade lactose into lactic acid. The gene of the detoxification system has been isolated and coupled to the gene of lactose degradation. Thus, in the presence of arsenic, lactic acid is produced by the modified bacterium, the acidity increases in the medium and can be detected by a simple pH test carried out with litmus paper.

Synthetic biology needs powerful tools to succeed in these applications.

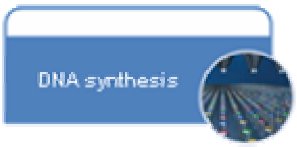
6) Tools



This is the reading of the position of the four base pairs - adenine (A), cytosine (C), guanine (G) and thymine (T) - in DNA to identify the positions and functions of genes.

The DNA molecule is too large to be sequenced in a single step. Using ultrasound or other mechanical means, the DNA is cut randomly into smaller fragments that are easier to read. As initially there are many DNA molecules, a multitude of fragments of different size are obtained, some of them having common sequences. Each fragment is read, the information is stored in a computer and powerful algorithms are used to reconstruct the complete DNA sequence.

DNA sequencing is also used to check whether the synthesis of a DNA molecule was carried out properly.

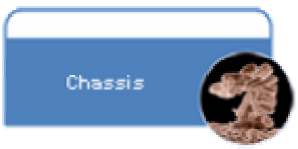


This is the "custom" manufacturing of DNA molecules in any order of base pairs, regardless if they belong to living organisms or are sequences with no equivalent in nature. The difficulty of the synthesis increases with the size of the DNA.

The first step is chemical synthesis of short sequences of hundreds or thousands of base pairs. Then, larger sequences of thousands of base pairs are assembled by specific enzymes. The final assembly of the synthetic DNA is achieved using molecular biology techniques involving bacteria. The rate of DNA synthesis is limited by this final step and significant research effort has been devoted to automating it.

Producing large amounts of DNA fragments quickly and at low cost, building and handling proto-cells makes microfluidics a valuable tool for synthetic biology._At micron scale liquids like water have a different behavior than at the everyday macroscopic scale: as their inertia is low one can accurately monitor their mixing and movement to handle DNA sequences or proto-cells. In addition, working with small amounts of liquid reduces reagent consumption and makes handling cheaper.

Particularly useful is the "lab on a chip", a plate of glass or plastic with microchannels where fluids move and perform several complex operations (transport, mixing, heating, results reading). In other words, it is a device that "shrinks" the laboratory to a few cm^2 chip and allows the integration of multiple operations of the DNA or proto-cell synthesis.



Once synthesized, the DNA must be "inserted" in a biological frame, a favorable environment for its operation and translation of genes into proteins. By analogy with

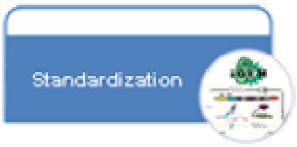
computers, the synthetic DNA is the software and the chassis is the hardware.

Many natural chassis are used today. They are living organisms whose initial DNA has been extracted: the bacterium Escherichia coli, host of our intestines, yeast, which makes beer and bread, or the harmless Bacillus subtilis, abundant in the soil. To function successfully the inoculated DNA should not be too different from the original DNA of the chassis, which severely limits the versatility of these solutions.

That is why there are attempts to use artificial systems called minimal cells. They have only a minimum of chemicals that enable them to function as a biological system. Minimal cells are easier to control but their construction is a big challenge.

Mathematical modeling and computer science are necessary to process the large amounts of data produced by DNA sequencing (the human genome has 3 billion base pairs), model and simulate complex interactions between components of living organisms and, design and predict the behavior of biological systems before building them.

A feature of synthetic biology is the use of engineering methods: beginning by defining the specifications (system characteristics), then designing the system by assembling standardized components listed in computer databases. This is followed by modeling (checking the system as a whole), implementation (system building) and validation testing (checking that specifications are met). These five steps can be repeated several times and it may be necessary to redefine the specifications, modify existing components or create new ones. Design and simulation require significant computational resources.



Standardization is specific to synthetic biology. In electronics, a radio is manufactured by assembling various functional units (tuning circuit, amplifiers, oscillators, modulators) with well defined functions. Each of them is build from standardized components such as transistors, resistors and capacitors. Standardization allows different manufacturers to produce compatible components. In addition, a functional unit that has been tested and validated also becomes a standard component and can be used thereafter. Similarly, in synthetic biology one can design standardized and modular devices and biological systems: DNA sequences are basic components, protein pathways are functional blocks and so on.

To avoid contamination of natural organisms with genetic material from synthetic biology organisms, the latter are physically isolated in confinement structures. Nevertheless, there are two other methods. Trophic confinement consists in making synthetic organisms dependant on nutrients that only the laboratory can provide. Semantic confinement is the design of synthetic organisms whose genetic code or carrier of genetic information is different from

natural organisms, thereby preventing interference. Trophic and semantic confinements are now fields of intense research.

With these powerful tools, synthetic biology will pave the way for unprecedented medical and industrial applications, the same way that nanotechnology has led to numerous applications in electronics and materials engineering.

7) Applications

Several drugs currently used are extracted from plants or act according to therapeutic principles of medicinal plants. They could be manufactured by synthesis or improved to reduce side effects. This may involve modifying the plant genome to improve therapeutic properties and integrating it into a process of chemical synthesis. Synthetic biology could also enable the development of personalized therapies: drugs could be tailor made depending on the patient's genome or adjusted to the patient's organism.

Infections are better treated if detected quickly and early, before disease symptoms appear. Infection detectors could by built using synthetic biology: when a pathogen enters the body, it triggers a chain of biochemical reactions producing a fluorescent protein, visible in ultraviolet light. They could be used to detect bacteria that cause urinary tract infections or Staphylococcus aureus, known to have developed resistance to antibiotics.

Damaged tissue can be repaired by tissue engineering. Burn victims receive skin transplants produced by techniques of artificial growth. Severe fractures are repaired by inserting scaffold materials for bone reconstruction: bone cells adhere to the scaffold, attach, grow and gradually replace the scaffold material. Cartilage can also be reconstituted by these methods. However, current techniques can not properly control the growth form. Synthetic biology could produce intelligent scaffolds with a better guidance of tissue growth and even extend the tissue engineering techniques to organ reconstruction.

Bioethanol is used as fuel for vehicles or as an additive to gasoline to reduce harmful emissions. It is an alcohol produced by fermentation of sugars contained in plants. This process is performed by natural bacteria, but its effectiveness is limited. Synthetic biology could improve fermentation and enable the use, as raw material, of genetically modified plants able to grow throughout the year.

Another way is to grow bacteria or fungi capable of synthesizing heavier, more energetic alcohols such as butanol. These new microorganisms, produced by synthetic biology, could survive in butanol unlike natural bacteria such as Escherichia coli or fungi as yeast. The same techniques could be used to produce biodiesel from vegetable oil, a cleaner fuel than conventional diesel.

At the same time, synthetic biology will seek to improve microorganisms capable of direct synthesis of hydrogen by photosynthesis, thus avoiding the use of sugars or cellulose as raw materials and preserving food crops.

Spider silk, a material very light and resistant, can already be synthesized. Using traditional biotechnology techniques, the gene for spider silk has been isolated and introduced into the

genome of a goat. Its milk-secreting cells also produce silk, we simply collect the milk and extract the silk. Synthetic biology could produce DNA sequences that do not exist in nature, paving the way for the development of new materials, more efficient, cheaper and environmentally friendly.

The mollusk's shell is a composite material: small plates of minerals such as limestone are trapped in an elastic protein mesh, which gives the shell exceptional hardness and strength. By synthesizing the genes involved in the shell structure, we hope to produce this type of composite materials with larger size and on a larger scale.

Polymers and plastics are increasingly important among the materials used today. They are produced from petroleum and, in general, are not biodegradable. Synthetic biology will enable the manufacture of new plastics from plants, which could also be biodegradable.

Based on the biosensor developed for detecting arsenic in drinking water, other devices could be developed. They could detect toxic substances (dioxins, chlorinated derivatives), heavy metals (cadmium, mercury) or explosives (TNT) in the environment. In the next step, the biosensor could be coupled with genetically modified bacteria able to assimilate or degrade these toxins and clean the soil.

Emissions of carbon dioxide are the main contributors to global warming. Synthetic biology could develop artificial photosynthetic systems, able to assimilate with high efficiency carbon dioxide and convert it into plants.

The development of new genetic technologies in agriculture is closely linked to the development of new environmentally friendly energy sources. Synthetic biology could produce new plants for use as raw materials in biofuel production. These plants would have a higher crop yield and could be processed more efficiently into fuel.

These plant crops could be optimized for harsh and complex environments, in view of climate change, and particularly for highly populated developing countries.

Finally, conventional chemical pesticides could be replaced by better targeted biological substances that degrade in the soil after having finished their action.

As with any new technology, synthetic biology raises optimism and enthusiasm, but also concern and distrust.

8) Responsible innovation

One of the goals of synthetic biology is to create new forms of life, which naturally raises ethical questions about mankind's responsibility to make life artificially. The possibility to act on its own species or alter the natural evolution of life increases this responsibility.

Synthetic organisms such as viruses or other pathogens could be made with malicious intent, which raises new challenges in biosafety. This situation is even more worrying as technologies of molecular biology have become available for a growing number of people: information on techniques of molecular biology and structure of viruses can be found on the Internet, some companies can synthesize custom DNA sequences at more affordable prices, and even non-academic amateur groups of synthetic biology called "biohackers" have arisen.

Beyond the deliberate release of synthetic organisms into the environment, there is a risk of accidental release, which could have negative effects on the environment and health. Because of the versatility of synthetic biology, synthetic organisms could be radically different from natural organisms and therefore have unusual and unpredictable behavior. However, synthetic biology can design, model and characterize a synthetic organism before it is built. This prior knowledge, even if not perfect, can anticipate a possible misbehavior.

As a multidisciplinary field (biotechnology, electronics, software), synthetic biology raises difficult questions about intellectual property protection, particularly the patenting of genes or software. In addition, protecting by patents of bio-standardized components could hamper future research in the area.

Finally, another sensitive issue, not specific to synthetic biology, is the control of technology by a few big companies. Invoking law of intellectual property they could override regulations.

These perspectives are of great concern and society must weigh the benefits and risks to decide how to develop the field of synthetic biology. Meanwhile, several steps can be taken: screening of sensitive DNA sequences, protection systems for people working in the laboratory, regulations for product traceability, transparent information to the general public, ethics committees to examine the opportunity to develop this area of science and technology.

These problems, which are political and social decisions rather than scientific and technological choices, are not specific to synthetic biology. To make technological choices and implement them citizens must have a scientific culture. Accordingly, it is important that citizens can access information, have appropriate training and participate in public debates on the subject.

9) Resources

Chronology:

- 1953: J. Watson and F. Crick discover the double helix structure of DNA, the genetic information of all living beings;

- 1972: H. Khorana and his collaborators carry out the first synthesis of a gene, a transfer RNA of yeast (77 base pairs);

- 1975: "Asilomar Conference", where biologists, doctors and lawyers first discussed the potential hazards of recombinant DNA and made recommendations for the regulation of this technology;

- 1977: development of DNA sequencing: chemical degradation (A. Maxam and W. Gilbert) and enzymatic synthesis (F. Sanger);

- 1978: first genome sequenced, the virus PhiX174;

- 1995: first bacterial genome sequenced, Haemophilus influenzae;

- 2000: human genome sequenced;

- 2003: synthesis in 14 days of the virus phiX174 (5386 base pairs) at the J. Craig Venter Institute;

- 2004: "Synthetic Biology", first international conference on synthetic biology, MIT;

- 2005: L. Y. Chan, S. Kosuri and D. Endy redesign the bacteriophage T7;

- 2005: first international competition on synthetic biology, iGEM.

Websites on synthetic biology:

http://syntheticbiology.org

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http://igem.org

Educational websites on molecular biology:

www.snv.jussieu.fr/bmedia/sommaires/gbm.html

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www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html

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www.bioclips.com

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http://publications.nigms.nih.gov/insidethecell/index.html

Reports on synthetic biology:

Synthetic Biology: Applying Engineering to Biology, Report of a NEST High-Level Expert Group, European Commission, 2005 (http://www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf)

Synthetic Biology: scope, applications and implications, The Royal Academy of Engineering, Royaume-Unis, 2009 (www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf)

Extreme Genetic Engineering - An Introduction to Synthetic Biology, ETC Group, Canada, 2007 (www.etcgroup.org/upload/publication/602/01/synbioreportweb.pdf)

Les Enjeux de la Biologie de Synthèse, Geneviève Fioraso, OPECST, France, 2012, (in French) (www.assemblee-nationale.fr/13/pdf/rap-off/i4354.pdf)

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10) Credits

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