THE CHALLENGES OF SYNTHETIC BIOLOGY

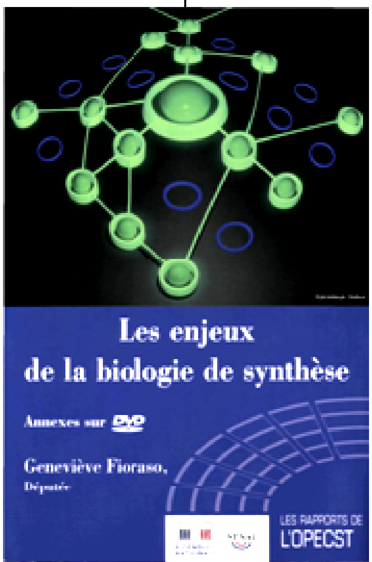
Summary of the report by Mrs Geneviève Fioraso, deputy.

Based on some 160 hearings in France and abroad (Switzerland, United Kingdom, Canada, Germany and Italy), report no. 4354 drawn up by Mrs Geneviève Fioraso, a deputy, sets out to analyse the challenges of synthetic biology (SB), the developments of which are considerable. SB is a component of the bioeconomy, the weight of which represents 12% of the GDP of the United States, a rate which could reach 25% in 2030.
The report therefore takes stock, in the most comprehensive and precise manner possible, of the state of the art of knowledge and research in SB, and the questions it raises with regard to its technological potential, sometimes presented as nothing short of an industrial revolution.

SB, AN EMERGING SCIENTIFIC AND TECHNOLOGICAL FIELD

Although the idea of SB was expressed in France in 1912 in doctor Stéphane Leduc's book, the first world congress on SB was organised in 2004 at the Massachusetts Institute of Technology (MIT) in Boston.

Interdisciplinary per se, this new field owes its emergence to the progress achieved in the last decades in different disciplines, especially molecular biology and systems biology.



SB uses DNA sequencing

Sequencing consists in defining the number, type and order of nucleotides, in other words the fundamental components of DNA. By defining these nucleotides, the genes present can be determined, which forms a prerequisite before DNA synthesis.

Today, synthesis biologists sequence in a week entire genomes, thanks to high speed technologies, whereas, at its beginnings in the 1970s, sequencing was limited to a few hundred nucleotides and required a year.

SB is based to a large extent on the artificial synthesis of DNA

The information derived from sequencing, stored in computerised databases and accessible on the internet, allow synthesis biologists to produce basic units called biobricks. This way, in 2002, researchers from the University of New York replicated for the first time the poliovirus genome using digitised sequences and not by basing themselves on living organisms.

In 2010, the American researcher, Craig Venter, announced he had synthesised the entire genome of the bacterium *Mycoplasma mycoides* and had transplanted it in the bacterium *M.genitalium*. Craig Venter *et al.* thus created a bacterial strain autoreplicating with DNA built in its entirety.

SB is a global approach to living organisms made possible by systems biology

Genome sequencing, the development of high speed technologies and mathematical and computer modelling have led systems biologists to take an interest in identifying and modelling networks, thanks to which genes and proteins interreact to fulfil cell functions.

Systems biology therefore allows SB to use intracellular networks or create new ones.

THE NOVEL APPROACHES OF SB

SB aims at producing systems that may be living or not, depending on the methods it uses and the potential application to which it leads.

Methods employed

Among the most currently quoted approaches, four are distinguished:

- A first method – called the bottom up method – is based on the assembly, as in a Lego game, of a series of parts having identified and predictable functions that can be used in various platforms. This is the reason behind the MIT Registry, which contains 12,000 biobricks. These code precise biological functions and are easily combined and exchanged between different laboratories. The bottom up method and the MIT Registry were developed by trainee engineers. For them, SB is defined by the application of engineering rules to biology, in order to make the latter more predictable.
- A second method – called top down – aims at transforming living organisms, by removing, replacing or adding specific parts, for instance by transplanting or suppressing metabolic pathways (set of biochemical reactions). Among the most famous experiments appears the previously mentioned genome transplantation by C. Venter.
- A third method seeks to build a standard cellular environment (chassis) with the cytoplasm surrounding DNA (protocells). However, this work is still at its beginnings and is considered as science fiction by some scientists.
- A fourth method aims at *rewriting the genetic code*, in other words the entire set of correspondence rules (code) allowing the genetic message to be translated into proteins.

A French geneticist - Philippe Marlière – and Belgian and German researchers have thus managed to force a bacterial strain of Escherichia coli to develop by using another molecule than thymine to synthesise its own DNA. Thymine is one of the 4 nitrogen bases in DNA (adenine, guanine, cytosine, thymine). In this experiment, thymine is replaced by a normally toxic synthetic molecule, 5-chloro-uracil-E.coli, the genome of which comprises 5-chloro-uracil which does not exist naturally.

THE CONSIDERABLE POTENTIAL APPLICATIONS OF SB

SB finds applications in many fields as different as health, energy, the environment, agriculture or industrial processes. Scientists have therefore seen in SB the revolution of this century and a means of providing solutions to the key challenges facing mankind: cancer, energy crisis, climate change, etc... - even if major debates are taking place on the feasibility of these applications.

The production of *artemisinin* and of *isobutene* are two examples illustrating how SB reuses living organisms or can transform biological systems that do not exist naturally.

Artemisinin is a molecule extracted from an herbaceous plant, *Artemisia annua,* known and used – mainly in Asia – to treat malaria. Jay Kesling, a professor at the University of Berkeley, has developed an SB-derived synthesis process for artemisinin. He modified some genes of baker's yeast, *Saccharomyces cerevisiae*, to make it produce a chemical precursor of the drug, by transferring the genes necessary for its production from the plant to the yeast. The marketing of artemisinin could be authorised as of 2012 in the United States.

The bioproduction of isobutene, which is a gas extracted from petroleum, has been developed by the French company Global Energies, located in Evry (Essonne). This process is based on an artificial metabolic pathway. Once assembled in micro-organisms, the latter converts sugar to isobutene, which can then be used to produce fuel (diesel, kerosene), PET (plastic bottles) or butyl rubber (air chamber).

SOCIETAL CHALLENGES OF SB

Apart from on the economy, SB has many repercussions on society in four fields: risk assessment and management; intellectual property challenges; research and training; the dialogue between science and society.

SB-related risk assessment and management

Owing to the capacity of SB to transform and create living organisms from scratch, and to propose production methods accessible to garage biologists, in other words amateurs capable of engaging in SB outside public or private laboratories, the Canadian non-governmental organisation ETC feels that SB can heighten the risk of bacteriological warfare or such an attack. According to ETC, this risk is exacerbated on account of the uncertainties surrounding the techniques used by SB. For all these reasons, ETC advocates, in the name of the precautionary principle, a moratorium until broad debate in society is taking place and strong governance is set in place taking fully account of SB-related risks.

Conversely, without denying the risks of environmental dissemination of transformed or produced bacterial strains, the U.S. presidential advisory commission on bioethics recommends 'prudent vigilance'. This implies continuous monitoring of the adequacy of regulations for SB developments. The European Group of Ethics, while referring to the precautionary principle regarding the risks of environmental dissemination of micro-organisms, has drawn closer to the position of its American counterpart. Referring to garage biologists, the US presidential commission and the FBI recommend, rather than a regulation, the dissemination of a culture of responsibility among the members of this community.

Like the ethics commissions, States do not wish to introduce regulations or a moratorium, especially as they emphasise the strategic dimension of SB applications.

SB challenges in terms of patents and intellectual property

These challenges are all the more important as SB combines computing and biotechnology and can therefore come under different intellectual property regimes.

In this context, the question arises of the adequacy of the present legal framework resulting from the TRIPs Agreement of 1994 (Agreement on Trade-Related aspects of Intellectual Property Rights) and from American and European patents laws. In effect, - owing in particular to the extensive conditions of patentability they lay down – these mechanisms have promoted abuses such as the broad spectrum patents filed by C. Venter, or else the grant in the United States of patents on algorithms.

Law professors and NGOs have therefore proposed alternatives to patents, such as open access biology – inspired by the open-source model applied in computing – of which the MIT biobricks registry is an application. Another alternative is copyleft, which consists in authorising any copy or modification, provided no limitation is entailed.

While abuses exist, which should be prevented, a balanced legal framework should however be promoted, allowing patents to protect job-creating inventions and guaranteeing access to data necessary for the advancement of research.

SB requirements in terms of training and research

Presented as a 'disruptive technology' and an 'industrial revolution', SB requires States to implement a decompartmentalised training and research strategy based foremost on interdisciplinarity – as confirmed by the iGEM contest. Such goals suppose sizeable, long term investments.

In this respect, the following can be seen:

- A clear lead of the United States - except in systems biology and biochemistry – fields where Europe – and especially France – is on the cutting edge;
- China's pronounced interest for SB, as proven by the higher participation of Chinese teams in the iGEM (Internationally Genetically Modified Machines) contest and various international symposia organised in China during 2011;
- Germany also has a lead: the Länder and the ministry of research fund sizeable programmes;
- A similar approach in German-speaking Switzerland in Basel, Zürich and at the Federal Polytechnic School of Lausanne;
- Real commitment in the United Kingdom, hampered in the present economic climate by the reduction of public spending;
- As for France, strong abilities, but scattered too broadly, with disciplines still too compartmentalised both in training and research, for want of a sufficiently proactive policy. In addition, research exploitation and the optimisation of industrial partnerships are insufficient. France, as neurologist Hervé Chneiweiss warns, could 'miss the bioeconomy train';
- A few excellence research niches in Italy (especially on protocells), without any global strategy at the national or regional level;
- The roll-out of a European Community network –ERA-NET – in systems biology with a facet devoted to SB. In 2011 a working group gave rise to an ERA-NET devoted to SB, based on workshops on standardisation, intellectual property, and security and safety, which have not yet been the subject of European Community harmonisation.

The need for serene dialogue between science and society

A good understanding of SB and its challenges by citizens is essential in a context marked by the failure of the public debate on nanotechnologies held by the National Commission for Public Debate (CNDP), and a climate of mistrust of scientists as regards research at the dividing line between sciences and technologies. Further, the introduction of serene dialogue represents application of the principle highlighted by the US presidential commission on bioethics according to which *'science is a shared resource belonging to all citizens and concerning them all'.*

Consensus exists among the researchers met by the rapporteur on the need for upstream, transparent dialogue to avoid attitudinal and overly binary debates.

A few divergences appear on the agenda for such dialogue, some fearing they will frighten public opinion by a debate far too upstream from industrial applications.

Given the practices observed in Europe and the United States, the consultative approach initiated in the United Kingdom from 2007 to 2010 is exemplary. This approach, which resulted from long analysis by the BBSRC (Biotechnology and Biological Sciences Research Council), has allowed decentralised dialogue to be organised in the best conditions. Citizens, researchers in hard sciences and human sciences, NGOs and regulatory bodies have thus taken part in it.

Five key ideas are expressed by the report as a preamble to the recommendations:

- SB's contribution to fundamental research;
- The constant link between fundamental and applied research;
- The interdisciplinarity requirement;
- A new ambition for science-society dialogue;
- National expertise to be developed on pain of being left behind by other countries.

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The report is available at the following address: http://www.assemblee-nationale.fr/13/pdf/rap-off/i4354.pdf

RECOMMENDATIONS

For controlled, entirely transparent, development of synthetic biology

1. Promote a public environment favourable to synthetic biology

- Identify biotechnologies and, especially, synthetic biology, as strategic for science – fundamental and applied research – training, technology, industrial applications and services;

- Provide for public funding for training and research in the synthetic biology sector, in conjunction with systems biology, by designating it expressly in the future investments programme and in ANR (French national research agency) programmes, of universities and research bodies;

- Focus resources and organise networked research cooperation from a few pacesetting platforms ranging from fundamental research to applied research, in an integrated approach: Paris-Ile-de-France (Evry Genopole in particular), Toulouse, Bordeaux, Grenoble, Strasbourg;

- Decompartmentalise the initial training necessary for the development of systems and synthetic biology and promote interdisciplinary training. Connect these training courses to the platforms: biology, chemistry, biochemistry, mathematics, computing, but also human and social sciences for issues related to governance, ethics, industrial property, the economic model, and the health, environmental and societal impact;

- Promote, in the European Commission 'Horizon 2020' initiative, European networking, by explicitly integrating synthetic biology in it, and by developing Era-Net programmes;

- Set up an annual international synthetic biology congress in France to promote exchanges and good practices, especially regarding the various aspects where ethical questions arise.

2. Set up a comprehensive and integrated sector

- Accompany the setting up of a genuine sector, ranging from fundamental research to industrial applications, without forgetting training, the search for partners, research exploitation, startup incubators, and also pilot line production in industry;

- Anticipate and define the application sectors to be supported as a matter of priority for health, the environment, energy, green chemistry, in terms of French specific expertises;

- Ensure there is a balanced legal framework preserving public access to knowledge on living organisms while allowing the patentability of job-creating inventions, while making sure of its harmonisation at the European and international levels; promote in this framework the cooperative initiatives of researchers and/or companies sharing data on living organisms and forming a public registry open to all;

- Re-examine, in this spirit, the TRIPs Agreement (Agreement on Trade Related Aspects of Intellectual Property Rights), to reflect on the possibility of a specific regime adapted to the inventions of the biotechnologies sector;

- Remedy the incoherences of Directive 98/44 of 6 July 1998 on the legal protection of biotechnological inventions, to prevent abuses stemming from an abusive practice of patentability and clarify the open access biology regime adapted from the open-source model;

- Promote European technology monitoring and impel the scientific callings of youths, with a European registry of living organism bricks and a European 'iGEM'; add to it systems biology competence so that the complexity of living organisms is better perceived and so that organisms are not considered simply as a mere construction game.

3. Analyse and control the risks related to synthetic biology

- Introduce, in applied and partner-based research on SB, research and training activities on biotoxicity, ecotoxicity, biosecurity and the societal impact by involving human and social sciences;

- Ensure the existing regulations (GMOs, nanotechnologies, chemistry...) are applied to fundamental and applied research and check they match the advances of synthetic biology.

In this spirit, integrate natural risks in the scope of the European Commission 'Horizon 2020' initiative;

- Guarantee the transparency of this analysis of risks and the result of monitoring, by placing them on line, and by planning, for example, for the publication of the DGA (State directorate responsible for armament programmes) report on biosecurity options;

- Promote the creation of an international framework for the assessment and regulation of identified risks, justified by the cross-border nature of SB and adapted to its specific characteristics as a disruptive and highly evolutive emerging field ;

- Work towards the setting in place of a standing body worldwide, along the lines of the IPCC, to analyse issues of standardisation, biosafety and biosecurity, prior to any marketing of synthetic biology products;

- Proceed, every three years, as part of an OPECST (Parliamentary Office for Scientific and Technological Assessment) assessment mission, to examine these mechanisms analysing and controlling risks, with a view possibly to recommending adaptations of regulations. This recurrent OPECST assessment mission should be laid down in law to guarantee its regularity.

4. Promote serene public discussion on the challenges of synthetic biology

- Organise public debates in cooperation with all parties concerned (SB scientists and human and social sciences scientists, politicians, research institutes, Europe, NGOs, companies, trade unions...), as well as regularly held conferences of citizens, to take account of the evolutions of SB;

- Encourage and develop, from the earliest age, interest for science and technology, prior to serene exchanges on subjects as complicated as synthetic biology, by setting in place attractive educational methods and by ceasing to consider sciences only as a channel for selection;

- Revive curiosity for and the credibility of the scientific approach by using, as a basis, the expertise of CCSTI (Centres of scientific, technical and industrial culture) and of Universcience, by generalising outreach initiatives;

- Ensure scientific education from the earliest age, by reinstating the hours of mathematics and sciences education, which have been cut in primary and secondary schools;

- Involve the media in this approach by following the example of the Royal Society in the United Kingdom in providing for regular training on the state of the art of research and the challenges raised by the development of synthetic biology and providing for the creation of pluralistic TV programmes on emerging sciences like SB;

- Define, by taking account of the result of these consultations and debates, a 5, 10 and 15 year entirely transparent development plan, by entrusting to OPECST, as part of its afore-mentioned assessment mission, the task of appreciating the manner of its implementation and possibly recommending certain changes;

- Generalise this process to all emerging scientific and technological disciplines where public concern is starting to be seen, so that it is taken into account in a transparent manner and so that citizens choices are respected;

- Carry out, as part of the afore-mentioned OPECST assessment mission, as well as on the occasion of interim public hearings, follow-up of the progress in raising public awareness on the challenges of SB.