synenergene
Responsible Research and Innovation in Synthetic Biology

– PANTHÉON - SORBONNE – UNIVERSITÉ PARIS 1

UNI FREIBURG

Summary Report of the Workshop
Worldviews and Values in Synthetic Biology

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To contribute to Responsible research and innovation (RRI) in synbio, stakeholders should take into account the variety of research agendas gathered under the umbrella of synthetic biology as well as the variety of worldviews held by society. This was the bottom line of the workshop "Worldviews and Values in Synthetic Biology" (WV&Vs) co-organised by Paris 1-CETCOPRA and Freiburg University-EGM under the framework of the 4-year Mobilization and mutual learning action plan (MMLAP) SYNENERGENE supported by the European Commission. The WV&Vs workshop took place at Université Paris 1 Panthéon-Sorbonne on June 6 and 7, 2014.

The organisers have structured the WV&Vs workshop around a questionnaire directed to synbio scientists and addressed to all participants. The answers to the questionnaire provided the organisers with the scheme to select the main topics to be discussed and to frame the sessions accordingly.

Introductory session: Setting the landscape

Session 1: Ways of doing synthetic biology

Session 2: Engineering complexity?

Session 3: Engaging or designing the public?

Session 4: Expanding or blurring the boundaries? Natural/artificial, living/nonliving, nature/society…

Feedback session: What message do participants takes home?

Each session begins with an analysis of these answers by one of the organisers regarding to the topic or broad issue on which the session focuses. Then the participants' interventions are reviewed, followed by a summary of the main points raised during the discussion.

The workshop also featured a student event that has provided a valuable input and opened unexpected perspectives regarding public engagement. Engineering students of ENPC ParisTech (Ecole Nationale des Ponts et Chaussées) were recruited by Sacha Loeve in the framework of the course "Synthetic biology: interactions between science, art and society", during the second 2014 term. Working by groups, they had prepared "synthetic debates" on facebook, role-games to allow someone to put her.him.self at the place of another having different opinions and worldviews, and fictions as ways to display and to explore synbio's repertoire of possibles and imaginaries. A presentation of their works is featured at this page.

[*] Main author. The text of this summmary report is not strictly speaking a verbatim. Word-by-word citations are in quotation marks ("xxx"). Although the text has been reviewed and revised by the workshop participants, it includes some interpretation, gloss and reconstruction. The responsibility for the writing and for the (mis)interpretation of the participants' discourses is Sacha Loeve only. The views and opinions expressed here do not represent those of the institutions involved or mentionned in the workshop .

Introductory session: Setting the landscape

RRI does not just mean assessing and preventing risks. It also calls for *democratic discussion about the goals and potentials of synthetic biology*. In her opening remarks, **Bernadette Bensaude-Vincent** stated three keys preconditions to be met for a fruitful deliberative governance of SynBio.

1) It is necessary to undertake a close examination of the values and meanings embedded in SynBio research and innovation through multi-stakeholder debates about the desirability of the promised futures and about the credibility of a number of claims. Not all European citizens share the enthusiasm of iGEM students for the design of BioBricks. Not everyone is convinced that synbio works for the public good. Some NGOs call for a moratorium on the release of synthetic biology products. Whatever one's position, that designing or re-engineering living organisms is value-sensitive design, and not morally neutral, should constitute a *common ground* for all stakeholders.
2) Not all practitioners of synbio share the same views and methods (as illustrated by the responses we obtained to the questionnaire addressed to synbio researchers in preparation of the workshop). Because SynBio is a multidisciplinary field, "there will probably always be many tribes in SB", stated the editorial of a recent special issue of *Nature*. Avoiding tribalism is currently a priority for synthetic biologists, who want to stand united on issues as vital as intellectual property or regulations. However, in order to avoid the polarization of public debates between pros and cons, it is no less important to *emphasize the distinctive means and goals of the various research agendas* gathered under the umbrella of synthetic biology and to disentangle their related moral issues.
3) The public itself is not to be considered as a global entity that should be feared because it might reject synbio products like GM crops in Europe and threaten all its developments—an attitude which could be referred to as "synbiophobia-phobia": the phobia of public technophobia. Rather, the public is to be viewed as a variety of stakeholders, each one with their own values and interests. Responsible synbio implies much more than anticipation of risks. It requires *care and responsiveness to the multiplicity of views and framings of other stakeholders*.

Benjamin Raimbault provided a scientometric analysis of the institutional dynamics and the researcher's trajectories gathered under the umbrella term of synthetic biology. Since 2004, the field has increased in population, productivity and connectivity; since around 2008, it has entered into a stabilisation phase by forming distinctive groups. These groups coincide with well identifiable techno-epistemic clusters:

- top-down approaches like "minimal genome" and "faster and cheaper synthesis of larger and larger DNA fragments" (all structured around Craig Venter's activities);
- bottom-up approaches like "generating protocells" (from the seminal papers of Jack Szostak in the early 2000s), "stochasticity and cellular noise" (a mathematical as well as biophysical approach that goes back to the 1980s), or "device-oriented programmatic approaches" (structured around the "hard" engineering approach of Drew Endy and the iconic papers on the genetic repressilator and the biological toggle-switch).
- Newer clusters suggest a diversification of the initial engineering approach: "cell/cell interactions", "computer/cell approach", "doing more concrete standardisation", "generating more complex and more applicative devices", and "compound-oriented success stories" (Jay Keasling and artemisinin, and other successful biosynthesis of industry-relevant chemicals).

The result is a rather "tribal" landscape, structured in groups having strong epistemic identities. However, B. Raimbault argues that *this tribal structure is partly due to few star researchers* who bring resource and credibility to synthetic biology. In fact, 8 authors gather more than 60% of the main articles cited since 2004! George Church, Drew Endy, Jay Keasling and other prominent figures of synbio play the

role of "*institutional entrepreneurs*" that goes beyond the scientific community and involves activities related to innovation policy, intellectual property, public relations, and "ethical, legal and social implications".

Synbio is not a solidified body, it is diverse and on the move. Far from hindering its dynamism, the diversity of its disciplinary backgrounds (from astrobiology to virology, from biophysics to microfluidics, etc.) contributes to the structuring of a new techno-scientific field (B. Raimbault) as well as to frame its individual research agendas.

In her presentation, **Margret Engelhardt** emphasised the need to *differentiate the normative evaluation of synthetic biology*. Yet the "continuity argument" (claims such as "we have always done so", e.g. modified organisms, see Sune Holm's presentation below) is often instrumentalized in order to mask the crucial fact that conflicting parties "do not speak of the same synthetic biology". It is thus important to voice this diversity in the public space. Not only synthetic biology is a highly differentiated field, but also the uses and designs of biological systems may have a different significance for different people. The public, she argues, is not a single entity but a set of highly differentiated "landscapes of perception". The concept of life is itself heavily depending on scientific backgrounds (for instance life tends to be seen as a "bag of chemicals" for a chemist and rather as a neguentropic process for a physicist); but also on cultural practices such as gardening, plant breeding or animal farming. Accordingly, new practices like "pharming" and the design of novel forms of "life" may disturb familiar schemes of values in ways that depend on the various means and goals of the type of synthetic biology considered, but also on the cultural context framing its perception.

Discussion

How to find criteria for a nuanced assessment? What should be the level of intervention? At which level of uncertainty? It has been suggested that looking at the disciplinary background is important in order to distinguish the *means* as well as the goals of synthetic biology (B. Bensaude-Vincent). The means—the ways of doing synthetic biology, its modes of intervention—are value-sensitive. For instance, Denis Pompon mentioned the generation of hybrid structures at the interface between "dry" nanoelectronics and "wet" genome engineering. Another issue raised and discussed was: is the level of uncertainty higher when one changes one or two genes or twenty genes? While it does make a difference for technology assessment, for scientists, the matter is not that clear. Changing one gene implies already a great deal of uncertainty. Changing a whole set of genes is often touted as a way to increase predictability, but many researchers actually doubt about that. At the level of means, how are we to define the level of uncertainty? (Geoff Baldwin). On the other hand, if the goals are considered more important, people may accept a higher level of intervention on living organisms, including more animal suffering for instance (M. Engelhardt). To Mark Bedau, while it is certainly important to talk about uncertainty and newness, we also need to rely on analogies with what we already know and understand from past experience. However, when one talks about values and worldviews, and not only about the perception of risk that can always be "educated" to some point, things are more difficult to change (M. Engelhardt). After all, even risk assessment is framed more by worldviews than by sound knowledge. Finally, given the complex ecology that characterises the field, it has been asked if it is relevant to talk of "industrial synthetic biology". Industrial biotech is a huge and well-established field, and arguably industrial synbio is just an extension of it. Contrary to US-researchers, many German researchers involved in the field for funding reasons are still reluctant to define what they do as "synthetic biology" (M. Engelhardt). We should thus be careful to avoid confusing the American situation with the many ones of European countries.

Session 1: Ways of Doing Synthetic Biology

The first session begins with **Sacha Loeve**'s introductory remarks on the answers made by the invited scientists to the WV&Vs questionnaire. Main findings are:

1) again, the high diversity of ways of doing synthetic biology;
2) the remarkable absence of the mainstream BioBricks approach (and nothing, either, resembling Craig Venter's approach on "minimal genome", i.e. the search for the fundamental operating system or "chassis" into which bioengineers would be able to plug all kinds of designed functions). Is it due to cultural differences between European and US synthetic biology? It may also be that the BioBrick approach, despite its high visibility through the iGEM competition, may not be so representative of all the practices of synthetic biology.
3) The answers questioned the popular image of synbio on several points:
   - Contrary to the cliché that synbio is massively *reductionist*, many responses stress the importance of integrated and systemic approaches considering the properties of a living system as a whole. Most of them express a great deal of *scepticism* regarding the analogy between biological pathways and electronic circuits (though not all, see Alfonso Jaramillo's presentation below).
   - A lot of attention seems to be paid to the interaction of synthetic cells with their environment, in contrast to the view of synthetic lifeforms as deprived of access to their environment popularized by the idea of orthogonal life. Although "non mixable" with existing biology, they have to be nevertheless "interfaced", states Denis Pompon. Or else, Sheref Mansy seeks to engineer artificial cells so that they can chemically sense their environment and communicate with other cells.
   - Also noticeable in the responses *there is no antagonism between modularity and complexity* (i.e.: the approach of decoupling and simplifying on the one hand, and the prospect of carefully increasing complexity and generating emergent properties on the other). A question worth to be discussed is: whether simplification is the mean or the goal? Simplifying biology in order to generate new emergent properties, or using emergence in order to generate more simple, manageable and robust modules?
   - Finally, contrary to the popular vision that synthetic biology is "the engineering of biology", for many participants, it seems that synthetic biology is first and foremost *biology*, and only subsidiary, engineering. Engineering is often mentioned as an auxiliary component: A set of methods that *will* (it is often mentioned in the future) *help* improving, optimizing, rationalizing, automating and streamlining synthetic biology.

If engineering is not the major component of synthetic biology, would *synthesis* be a more distinctive feature? S. Loeve ventured the hypothesis of an *epistemological tension between synthesis and engineering*. Could we distinguish between two *ways of learning by doing*?

1) In engineering, *knowledge-as-control*, learning by *success*, by *successful control*; the knowledge acquired is a set of *design rules* that allow composing subsystems into larger systems to make processes replicable and predictive.
2) In synthesis, *learning from failure*, to realize what we don't know, and thus learning about the *limits of control* (e.g. the failures of Steve Benner and his team to synthesize "better designed" DNA pointed to the crucial but unexplored role of non-syntaxic DNA components—the sugar scaffold and of the phosphate linkers—in nucleobase molecular recognition). As D. Pompon wrote, "The difficulty is not to master what we know but to guess what we do not know".

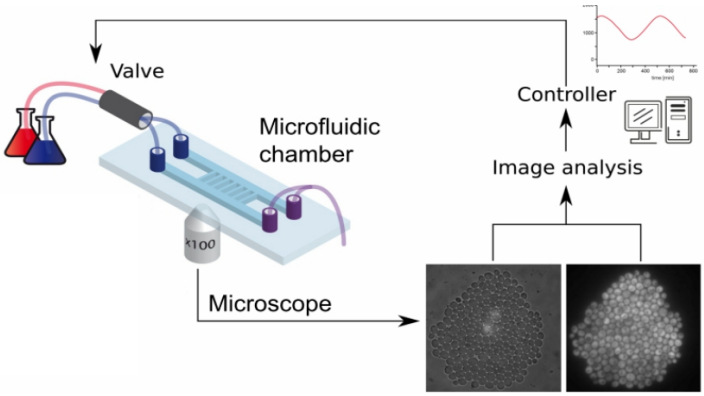
This research strategy is traditionally exemplified by synthetic chemistry. Performing a synthesis is learning to better situate the moving line between control and non-control. The resulting compound is

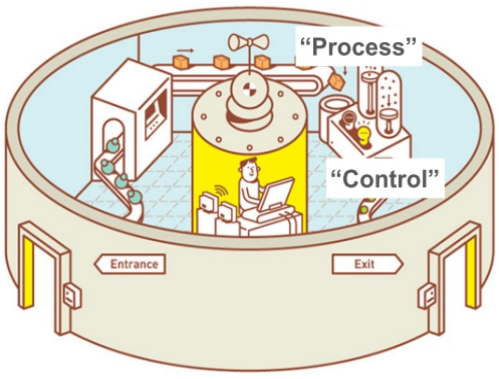
always the result of both control and non-control, and occasionaly something different from the initial aim. Therefore, in chemistry, a synthetic failure can often be turned into success. By contrast, synthetic biology is so dramatically *goal-oriented* that it is less obvious that it can learn from failures and turn them into success the same way synthetic chemistry does. For (academic) chemists who praise the creative work of synthesis, the business of chemical engineering, process optimization and automation is often (dis)qualified as "robot work", good for *applying* knowledge, not for *generating* knowledge. Synthetic *biologists*, it seems, are more industrious and more courageous: They want to do both the creative work of synthesis at the edge of control and non-control *and* the robot-control work of engineering.

Life won't be easy to engineer—but not only because it is complex and unpredictable, and also because synthesis and engineering are rather different research practices, perhaps not incompatible, but at least in tension. Accordingly, the main distinctive feature of synthetic biology at an epistemological level may lie in its attempt to combine this synthesis component with the engineering component in multiple different and unprecedented ways.

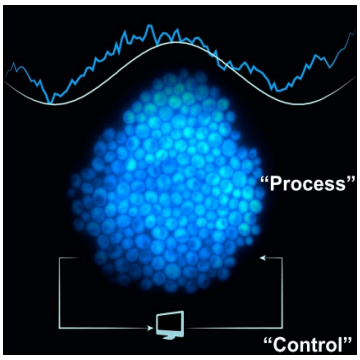
One of these combinations is exemplified in the work presented by **Gregory Batt**, an approach he dubs "cybergenetics": *cells driven by computer*. With his team he is developing a platform for interfacing cells and computer to allow real-time control of gene expression at the level of populations and of single cells. The research has two motivations. 1) From a systems biology perspective: to perturb and observe the complex genetic network of a single cell. 2) From a synthetic biology perspective: to *externalise the control* of biological processes. The goal is thus both to reconstruct the way cells work and to take control of some of its functions.

The cell is seen as a (partial) black box (some processes and interactions are already known). The inputs are additions, silencing, or promotions of specific genes, and changes in the cell's environment induced via a microfluidic device. The outputs are the observation of gene expression rate and levels by an optical microscope integrated to the platform. An original software for imaging quantification and model prediction serves to close the loop between input and output to allow controlling the processes by computer.





The microfluidic device, with its input and output channels plugged into it, resembles a logic gate in an electronic circuit. However, the leading metaphor is the modern factory, conceived as a set of automatic processes externally controlled. Yet contrary to industrial processes, notices G. Batt, in cells the control is internal. For this reason, while it is not difficult to implement new processes (metabolic pathways) into cells, it is much harder to "orchestrate" them, i.e. to control them in a predictive manner. The externalization of control on computer is thus both the mean and the goal of the research, its main challenge.



How far does it work in practice? Batt reports an experiment lasting 15 hours in which his team managed to induce and modulate an oscillatory expression of fluorescent proteins in a population of yeast cells (just as in the repressilator experiment, except that in this case the control is external). On individual cell, however, the performance is limited by the stochastic nature of biological processes that predominates at this level. It should be noticed that in the framework of the experiment, this stochastic character is mostly interpreted as "noise"—something that limits the performance and proper functioning of the device—, whereas for biological systems, "noise" is something that allows them to work at the molecular level.

The potential applications are primarily in research, for optimising the design of experiments in systems biology and quantitative biology: automating and massively parallelizing experiments to gather a high number of data from large wafers of microfluidic devices.

For synthetic biology prospects, the system is presently poorly efficient partly because of the use of a microscope running during long periods of observation, but this latter could be replaced by optogenetic sensors to accelerate and automate the production of outputs. Actually, acceleration is crucial to allow real-time control by diminishing the time-lapse between observation and correction. Progresses are also expected from current advancements in physics concerning control theory in complex stochastic systems, says G. Batt.

Whereas G. Batt's "cybergenetics" is mainly for research purposes, **Marc Delcourt** is an entrepreneur doing *industrial* synthetic biology. M. Delcourt is the CEO of Global Bioenergies, a company dedicated to the conversion of biomass sugars from starch or agricultural waste by biosynthetic microbes into usable hydrocarbons, gaseous olefin.

Currently, olefins are obtained from non-renewable sources (petrol and gas). They are used to produce: fuels (isobutene), plastics (ethylene, propylene), elastomers (butadiene), glue and many other commodities. In order to get bio-sourced rather than fossil-sourced olefins, there are no starting points in nature (no natural metabolic pathways one could improve on). One has to invent new metabolic pathways from first principles in order to force the bugs synthesizing olefins. While this work of metabolic engineering is—or rather was—a challenge, once implemented in the bugs, the industrial process itself is rather simple (2-steps: fermentation and purification), and it's already a continuous process, with two pilot plants in France and Germany. As to the question what is done with waste bacteria and the potential risks associated to them, M. Delcourt's answer is "we follow the rules": they make sure that all used bacterial strains are killed—there are specific processes for that, which involves some extra cost, but there's nothing new in this question, says M. Delcourt.

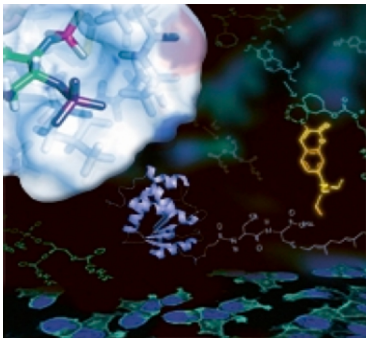
M. Delcourt explains "why we really need industrial synthetic biology": In 2008, when the company's activities started based on Philippe Marlière's ideas ("the inspirer", while M. Delcourt is more the "doer"), the justification was obvious: the imminence of "Peak oil". Yet today Peak oil is receding. New deposits have been discovered and the reserves-to-production ratio (R/P) is presently increasing for oil. However, R/P is decreasing for gas and it is dramatically shrinking for coal. Because of the recent explosion of the Chinese demand, coal consumption increases much faster than reserves. If we merge the 3 main fossil hydrocarbon resources (petrol, gas and coal), the result is a *global* decreasing R/P ratio and a visibility of 35 years with a loss of 1 to 3 years of visibility per year. Adding to this a plausible "energy crash scenario" where China would saturate its coal production system and shift to oil, the conclusion is implacable: At a *global* scale we still dramatically *need* to substitute (a part of) our fossil resources by renewable bio-energies.

M. Delcourt's discourse is framed in terms of ressources, needs and acceptability. The problem with the GMO debate, he says, is that "people have not been really convinced by the need for GMOs". Do we need GMOs for improving crops productivity? Not necessarily: We currently have too much food; the problem is waste, not productivity. Do we need GMOs for fighting pests? Not necessarily: there are other means, and people know that, whereas in the case of *compound-based* synthetic biology, the need is "absolute" claims M. Delcourt. For synthetic biology to be accepted and the market to be deployed, it is thus crucial to make people understand what they "really" need at a *global* scale (hence the name of the company), and accordingly to make them recognize that the "absolute need" of an industry of chemical compounds based on synthetic biology.

In M. Delcourt's vision, synbio aims at replacing some of the chemical processes currently used in industry. For **Ludovic Jullien**, it is rather the contrary: synbio could be a useful auxiliary in "daily" chemical research, and biology-assisted chemistry an attractive paradigm *for chemistry*.

From a chemical point of view, life is nothing but "a chemical experiment at the level of the planet". Throughout astronomical times, nature has explored many chemical possibilities—life on earth being one of them, one that exploits reactions that often occur close to the limits arising from the sole fundamental physical laws. This makes biological reactions very attractive for current chemistry increasingly constrained by economy and sustainability, especially since the main possibility opened by biology-assisted chemistry is, indeed, that of *renewable matter*.

Jullien replaces this new perspective in the history of the relationships between biology and chemistry. In the course of the 19th and 20th centuries, many of the most powerful concepts of chemistry actually came from biology: chirality, polymers, colloids, molecular recognition and macromolecular assemblies or supramolecules. At the same time, chemists have more and more considered biological organizations and phenomena in chemical terms. Meanwhile, biologists have developed powerful tools to analyse and modify living beings, giving access to biomolecular structures, genomes, and transgenic manipulations. From their side, engineers have recently introduced highly sensitive miniaturized devices allowing unprecedented high-throughput investigations. *After decades of analytic reductionism, there is revival of a systemic level of description in biology*, often driven by biophysicists (e.g. 1970s bioenergetics and the chemiosmotic theory), and now there is a trend of "*systems chemistry*" as well. At the beginning of the 21th century, a large body of knowledge, tools, and representations has thus become available to chemists, who can now make one step further by overcoming the sole "passive" attitude towards biological systems.



From the chemist's point of view, the living cell is at first sight a fragile container containing an awful mixture, and in any case a system rather distant from the standard systems encountered in chemistry. It's not a chemical flask or a chemical plant, and chemists like to work pure compounds. On the other hand, it is a chemical system that 1) can autonomously extract reagents and energy from its environment and sustains its internal state; 2) that is submitted to a continuous evolution occurring by generation of molecular diversity. As such, the living cell constitutes a unique platform that definitively offers unprecedented horizons for chemistry: 1) it is a readily available endogenously generated chemical jumble containing sophisticated molecules and materials—the potential of which considerably exceeds what is actually extracted from sources of biological origin. 2) Whereas chemists did not yet devise strategies to positively direct random explorations toward desired functional goals, living cells can be submitted to an evolution targeted to the delivery of desirable chemical functions. This task is being presently addressed in the context of synthetic biology. However, such optimizations have been mostly performed in a context where the cell environment remained close to the natural one.

Many desirable chemical functions have not yet been addressed, either because they don't belong to the range of possibilities that have been sampled by biological evolution, or because no appropriate artificial evolution protocol has yet been invented to reach them. Jullien thinks that chemists should take up this challenge and overcome these limitations. It is thus clear that far from threatening synthetic chemistry, synthetic biology revives the chemists' long-standing ambitions.

Oliver Müller reflects on scientific practices from a philosophical point of view. Synbio confronts us with an explosion of "-ing" terms—action terms—that try to capture what synthetic biologists are actually doing: "modelling life", "simulating life", "emulating life", "modifying life", "engineering life", "manufacturing life", "programming life", "designing life", "fabricating life", "constructing life", "creating life", "making life", "tuning life", "tinkering life" and even "kludging life"—not to forget the epistemologically delicate "re"-words, like "remodelling life", "reengineering life", "recreating life", etc. To Müller, this list symptomatic of the "hybridity" of practices that tend to blur the boundaries between scientific practices and other technological, aesthetic or economical practices. The concept of "design" refers not only to a scientific method; It means first "shaping things" according to functional or aesthetics norms, not to mention the social norms of relevant design. The notion of "creation" has similar implications. He raises questions such as: Is designing still science? Could criteria for a "good design" differ from criteria for "good science"? Synbio relies on the hypothesis that making knowledge and making things are one and the same action. This claim, however, deserves critical investigation. It demands a serious enquiry on the conditions of possibility and limits of the assimilation of knowing and making.

Moreover, synbio's modes of action are often associated to goals such as "eliminating the randomness of natural evolutionary advancement" or "making life easier to engineer". Synthetic biologists pursuing such goals envision a utopian future with optimally controlled little organisms that help us to make the world better. The engineering agenda is driven by ideals of control. But is controlling equivalent to knowing in a scientific manner? For sure, control is often based on scientific knowledge, but it has also political implications. The idea that "nature is at our disposal" may be the good old self-understanding of scientists but we know that it is as much about power as it is about advancing knowledge. Extending our control over life goes hand in hand with developing a biolopolitical form of power.

Finally, controlling and designing organisms for investigative purposes raises ethical challenges. Such hybrid practices are considered a "scientific practices". Accordingly they are evaluated in the framework of "free academic research". However, the very practices of synbio blur the frontier between free research and goal-oriented technological or economical activities. As they transcend the laboratory and its usual logical and normative order, the usual standards and ethos of laboratory practices may be no longer applicable.

Discussion

Martin Müller commented on the current prevalence of phrases such as "digital design", which calls to mind ideas of computer screens and interfaces as main features of today's "digitalization of life". For sure, "design" can be understood in many various ways. However, has design anything specific to do with synbio, and in what sense? Gregory Batt admits using the term a lot in the sense of "experimental design". Design is part of the setting of a scientific experiment. Scientists *design* experiments in order to answer their questions. "Design", he says, also expresses the need to idealize scientific experimetal processes: One often starts with a vague question, then designing experiments are ways to clarify research questions. Loeve adds that often, "design" is used in scientific publications to imply "we know how to do that"; it connotes the mastery of mind over matter. But when ones talks about "designing experiments", design takes a rather different meaning: it's about dealing

with our ignorance, refining research questions rather than solving them. Scientific journals push us to overemphasize the "control" aspect of design, argues G. Batt. However, in practice, *experimental* design does not necessarily imply intellectual and practical control. To Ludovic Jullien, "it's a discussion between real world and conceptual world". What chemists want to design is often their own representation of the world. For the very same reason, they are soon facing the limits of their own concepts. Thus design is an obstacle as much as a stimulus in experimental investigations

Marc Bedau returns to Loeve's distinction between synthesis and engineering. This distinction can be maintained as long as one talks about traditional engineering (rational, top-down, etc.). But engineering is no more monolithic than synbio or the public. It is an ever-evolving concept and set of practices. In the discussions, we should be attentive to not restrict engineering to a limited and narrow field. True, admits Loeve, we should not only ask synthetic biologist their definition of life for instance, but also their definition of engineering. In the publications however, what we face is a rather trivial conception if not a caricature of engineering. Are such clichés part of the self-representation of synthetic biologists when they claim doing engineering? Jullien replies that to him, engineering is the integration of established knowledge. Even if engineering changes (it is more multi-scale than before), advances in engineering are still distinct from the growth of knowledge. For him, engineering is knowledge-based but it does not produce knowledge. Batt adds that the progress of engineering follows the consolidation of scientific knowledge. In this respect, synthetic biology doesn't *presently* engineer biology. It seeks to provide tools so that it works. Only when adequate tools are established, it will become engineering. Batt, it seems, makes a distinction between design and engineering: science (experimentally) *designs* (knowledge-based) tools, engineering puts them at work for specific goals.

But aren't these distinctions constantly reworked as synthetic biology communities are at the crossroad of different disciplines and different practices such as science and design (Morgan Meyer)? But aren't these distinctions constantly reworked as synthetic biology communities are at the crossroad of different disciplines and different practices such as science and design (Morgan Meyer)? Jullien still makes a major difference between engineers and academic researchers—the former depend on already established knowledge that they apply to solve parctical problems according to a series of constraints (among which cost-efficiency and economic constraints), whereas academic scientists are free to raise and address their problems—even if, sometimes the chemist has to "play an engineer", i.e. designing an experiment so that it delivers the most cost-efficient results: the less time, money, matter and energy for the most productive, informative and elegant reaction. This is a way to collaborate with engineers while still practicing its own discipline. Even if academics and engineers can well collaborate on a big real-world issue (e.g. CO_2 capture), they won't do the same work. In stark contrast, Gregory Batt, who has a mixed background of computer scientist and biologist, insists that he cannot tell whether he is a scientist or an engineer. In interdisciplinary research, many do both—without making such a great deal of these categories. For sociological reasons, disciplinary partitions are essentially maintained by the universities in their recruitment system, but even this is going to change with research institutes. Design is part of the scientific process. Engineering is different from science, but many researchers actually practice both engineering and science. Batt disagrees with Jullien when he says "I am a chemist, as such I can only propose my own problems, and when I have an engineering problem, then I do interdisciplinary research". Not all scientific questions are disciplinary questions. There are relevant *interdisciplinary* research questions. The point is not to belong to this or that category. It is to make interesting research.

While doing synbio *research*, be it science or engineering, means expanding the range of possibles, the range of possible seems much narrower when it comes to *industry*. Industrial synthetic biology shows the paradox of a breakthrough innovation at the service of rather conservative social goals. Indeed the main finalities are fixing and optimizing our current production and consumption patterns, not changing them. Everything is made to preserve the continuity of existant sectors, if not to maintain the vested interests of the current industrial world. The issue of technological change is addressed only

in terms of resource substitution. However, it is still for producing the same plastics, chemicals, fuels, etc.: all the goods that, allegedly, people "really need". Behind the economic discourse on needs and resources, *a certain image of the public* is presupposed without being questioned. The public is framed as a "responsible consumer", one might say, who should rationally accept to pay the price for a greedy way of life—whose rationality is never questioned either. But what people do "really" need doesn't seem to be a matter of debate or democracy. Industrial synthetic biology seems entirely devoted to a world that would have definitively deployed and generalized our current Western consumption patterns, as if they were doomed to last forever.

Session 2: Engineering complexity?

In the session introduction, **Joachim Boldt** suggests a way to diversify synbio's engineering concepts. Based on the scientists' answers to the WV&Vs questionnaire, he outlines four different ways of dealing with complexity in synthetic biology.

1) *Reducing complexity*: coping with complexity by simplifying living systems as much as possible (e.g. the minimal genome approach, protocell research).
2) *Ignoring complexity*: deliberately ignoring the internal mechanistic details of living systems by designing black boxes with the appropriate inputs and outputs (= "black box design", e.g. BioBricks).
3) *Controlling complexity*: taking control of the system by acquiring a detailed understanding of its internal working (= making "white boxes", e.g. systems biology-based synthetic biology).
4) *Harnessing complexity*: taking advantage of the complexity of organism's evolutionary features, trying to modularize it (= working with complexity, not against it, e.g. evolutionary design, artificial evolution, generators of diversity).

How will synthetic biology evolve? What kind of engineering will it be?

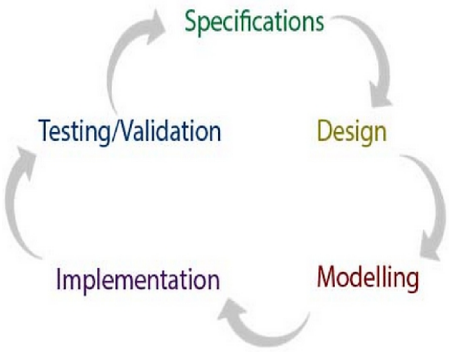
Experimental biologist and agronomist **Thomas Heams** argues that life features fundamentally original dimensions that are—and can only remain—out of reach of engineering. Radically put, life cannot be engineered. Only its mechanistic dimension—i.e. "the tip of the iceberg"—can be engineered. What are the other dimensions of life?

- *Life is messy.* Biological order does exist; 20th century molecular biology and genetic engineering largely relied on it. Though biological order can be tinkered to some extent, it is not deducible from an already pre-established order: Intracellular molecular processes are stochastic, and yet cells work. Individual cells are not driven by program, and yet populations exist, proliferate, and adapt. Whatever the scale, we know thanks to Darwinian dynamics, that predictable macroscopic forms of order always rely on unpredictable microscopic forms of disorder. "You don't engineer disorder", Heams concludes.
- *Life is history.* Any living being is a physical object and a historical object, combining direct physico-chemical reactions with 3.5 billions years of evolution. What makes it alive is precisely this combination. Synthetic biologists can provide new "exoskeletons" for life but they cannot engineer history. Indeed they can *change timelines*, e.g. with experimental (or artificial) evolution, but experimental evolution is not strictly speaking engineering. It is more a kind of management (selecting the "employee of the month" out of the back box at each selection cycle).

- *Life is not only matter*; *it is a dynamic flux of matter*. We are like Theseos's ship, constantly replaced piece by piece, transient creatures who feel like permanent ones. "You can hardly engineer the transient".
- *Life is collective*. No living being can live on its own. No species exists alone. We need our microbiome; we need our ecosystem. Natural selection singles out some individuals among a crowd; "winners" exist thank to "losers". Chance, plurality, is an essential prerequisite for life. Defining the living world as a collection of individual machines in which life would be insufflated is a nonsense. *Life needs life to be life*. It has this tautological dimension that challenges our legitimate need of categories, and drives living forms very far from objects that would have individual properties that you could improve on or modify. "I'm not sure we can engineer plurality".
- *Life is evolutive*. An engineered patented bacteria only stays so until a first mutation occurs, until the first is inserted gene is expelled, until the first function is lost. *Life exists only because it changes*; living beings exists only as non-identical descendants from their lineage, whereas *engineering "is reaching a point"*.

Life is all of this combined together. Engineering life relies on the fact that living beings are objects made of interchangeable parts. Yet, biological life is more than an assembly of parts. It is multidimensional: it is also historical, collective, dynamic, unstable, and evolutive. It only exists when all these dimensions are combined. Because of this multidimensional character, Feynman's mantra ("What I cannot create, I don't understand") is misleading. As long as we define life as a collection of genes, a list of functions or group of cells, we can live with the illusion than engineering it is possible. The best synthetic biology could do is to question the boundaries of life, but it would mainly expose its elusive nature. The societal and epistemological consequences of this paradox need to be addressed. They do not rule out the fact that synthetic biology can provide original biotechnological answers to old issues, and generate opportunities and risks. However, they would mainly highlight that synthetic biology is also a *storytelling*, for better or worse, of the way we understand—or rather *want* to understand—the living world.

Geoff Baldwin fully admits that synthetic biologists are indeed taking a mechanistic description of life *because* it serves their purposes. The purpose of such a mechanistic approach is not pure knowledge. It is "interesting and powerful" because it is *action-oriented*. The question is not whether living beings are *really* like machines with interchangeable parts but rather "what we can *do* with that" and "how far it can go". Baldwin agrees that there might be limits to this view and to its efficacy (e.g. evolution pressures). But that's so much the better since he has "no interest, personally, in engineering life in all its dimensions". As a synthetic biologist, he wants to *engineer the mechanistic description of life*; he doesn't want to engineer *sentient beings* for instance, which would raise "strong ethical concerns" (From that, it could be remarked that, as ever since Descartes, the mechanistic view of life is not only a requisite for doing engineering—since there are nonmechanistic forms of engineering too; it is a also requisite for providing ethical compliance and full licence to act). In this respect, synthetic biology is not "the design of life" (of all forms, dimensions, and aspects of life); it is rather the design of those dimensions that are amenable to a mechanistic description of certain organisms (nonsentient microbes) for specific purposes within certain contexts.



More specifically, Baldwin's approach at CSynBI (Center for Synthetic Biology and Innovation) is to "*apply the engineering design cycle to biology*". The "design cycle" is a popular iterative method for creating, tuning and refining an automated expert system until it reaches the desired performance. It

generally incluces steps of analysis/modelling, prototyping/implementation, and then assessment/testing. Any discrepancy between the actual and the desired performance of the prototypical system induces a next iteration, until a sufficient fitting is reach. Yet the biological materials provided by nature have evolved to fit particular ecological niches that do not necessarily correspond with the newly designed contexts we create by making it work for us. We thus need to apply the design cycle to refine the "bioparts" (standardized DNA sequences) so that they can work robustly and on demand within any human-specified system.

The CSynBI centre is thus developing an integrated platform for targeting the mutation of specific genes with aim to harness bacterial growth, in both parallel and combinatorial assembly, combined with genetic switches that will govern the mutation phenotype and prevent further evolution once an end-point activity is reached. With regard to RRI, they are working with social scientists (the CSynBI is co-directed by an engineer, a biologist and a sociologist, Nikolas Rose) to anticipate the potential consequences, with a view to integrate them into the design cycle (e.g. genetic "kill-switches"). The ultimate goal is to come out with a sort of streamlined pipeline for both research and industrial biotechnology purposes. "A mechanistic view of biology, but it works", says Baldwin.

However, there are still challenges to be met:

- To standardise the assembly and the description of DNA-parts so that they can fit with specific functions and work together (assembly: by designing specific DNA-linkers and directed evolution enzymes with modified specificity; description: by using exhaustive datasheets).
- To enhance the accuracy of the mutations induced so that they fully correspond to the desired function.
- To enhance mutation and expression rates, that is, to facilitate and to accelerate the in-vivo work of bioparts, still currently too slow.

This concern with *accelerating biological time* to make it commensurable with the time of human events, desires and actions (also visible in Craig Venter's last book entitled "*Life at the speed of light*") is even more pronounced in **Alfonso Jaramillo**'s presentation on EvoProg, a General-Purpose Programmable Evolution Machine on a Chip (European project supported by the EU 7th Framework Program). Jaramillo works on the development of experimental accelerated evolution technologies integrating *in vivo* and *in silico* evolution. "We want to engineer complexity, but *automatically*", he says. "Complexity is too hard for our miserable brains, so we need algorithms". The aim is to get a faster artificial evolution machine integrated on a microfluidic "droplet device" for the directed evolution of de novo biomolecules. Currently, it is not possible to create biomolecules de novo (e.g. enzymes that never existed) in only a few days. Conventional directed evolution methods are *too slow*: one always has to wait until next evolution steps. Moreover, they allow evolving only a few genes, not entire genomes. Automation of as many steps as possible allows accelerating mutation rates. A. Jaramillo compares the current turbidostats facilities to do massively parallel evolution to the old giant computers of the 1940s like ENIAC. EvoProg would be to these technologies what a MacBook Pro is to ENIAC, several hundreds times smaller, faster and powerful. Like the personal computer, EvoProg is sought to become the "personal evolution machine", allowing "to direct evolution in the same manner as you direct a program on a computer". Instead of using digital codes, the system uses DNA. Instead of using electricity as a medium, the system uses fluids. Instead of microprocessors, the system integrates multiple micro-bioreactors named "CellStat". In order to shorten mutation timelapses, it resorts to a parasite: bacteriophages that infect bacteria in a targeted manner without killing them. Indeed, the replication rate of phages in bacteria is faster than the replication rate of the bacteria that they infect. This faster rate allows phages to take control of the cell's replication machinery. Thanks to phages, bioengineers avoid "wasting their time", i.e. inducing too many

useless mutations in a random way (from this point of view, it is a way to *avoid complexity*). Mutations are then jumping via phage from cell to cell in the circuits of the microfluidic device. In order to get even faster mutations, the system then resorts to a toxin that affects phages, i.e. "a parasite of the parasite".

The ambition to accelerate biological evolution raises a number of issues. To mention only one paradox, humans want to be the masters of evolution, but for developing shortcuts, they need to rely on pre-existing biological "accelerators", bacteria first, then phages, then phages' toxins, and so forth.

In view of the explicit reductionism of synthetic biology, the concepts of complexity and emergence are quite controversial within synbio. According to **Mark Bedau**, a *specific* kind of emergence—"weak emergence"—drives synthetic biology.

The main idea of emergence is that a whole is more than the sum of its parts. More precisely, the whole depends on the parts but it is also autonomous from the parts. Then there are several ways to conceptualise emergence depending on how one conceives the modes of dependence and of autonomy. By "weak emergence", one assumes that the whole *depends on* the parts in the sense that it is *composed* of the parts (the way the whole behave depends on the way the parts are interacting); and that the whole is autonomous in the sense that it is *multi-realizable*. A weak emergent property is a robust characteristic of the behaviour of complex causal webs. A causal web is "complex" in the sense that is so full of context-dependencies, nonlinearities and feedback loops, that its behaviour cannot be derived from complete micro information, except by crawling through all of the gory details of the interactions in the micro-causal web. The causal web is "incompressible": There is no shortcut to predict the behaviour of the whole; one can only crawl though the causal web (which computer models do), let its behaviour deploy and/or rely on past observations of emergent behaviours. The system displays general pattern of behaviour that can be partly predicted by empirically observing it and by studying the causal web in more details, but it can't be predicted from initial rules or scientific laws. Moreover, weak emergence compatible with reductionism (contrary to strong emergence, the kind of emergence philosophers are generally interested in); it even *depends on reduction*, but on a specific kind of reduction, "complex reduction".

Bedau contends that synthetic biology is first and foremost the activity of *engineering synthetic cells to have desired weak emergent properties*. This would explain the prevalence of "Edisonian" trial and error strategies in synthetic biology as well as the importance of *synthesis*: Synthesis is crucial for discovering weak emergent properties. Since the behaviour of the system cannot be analytically predicted, it must be synthesized and observed over and over again—hence also the emphasis on the standardization of parts, and on the reprogramming and the refactoring of genomes. However, many synbio leaders, like Drew Endy, notice this feature of emergence and declare that proper engineering is an effort to get rid of emergent properties (cf. Boldt's "ignoring complexity" approach). This is a natural reaction for coping with complexity. However, looking at the results, they are obviously not getting rid of emergent properties: they are rather constraining or channelling them in order to get partly predictive behavioural patterns. They try to figure out how to live with emergent properties by means of proper standardization for limiting their unwanted effects (e.g. by limiting the number of activable genes or contexts that would give rise to complexity, i.e. the "reducing complexity" approach noticed by Boldt). Finally, it is still a matter of *engineering desirable emergent properties*. It's not getting rid of emergence, but rather "creating emergence of the kind we want".

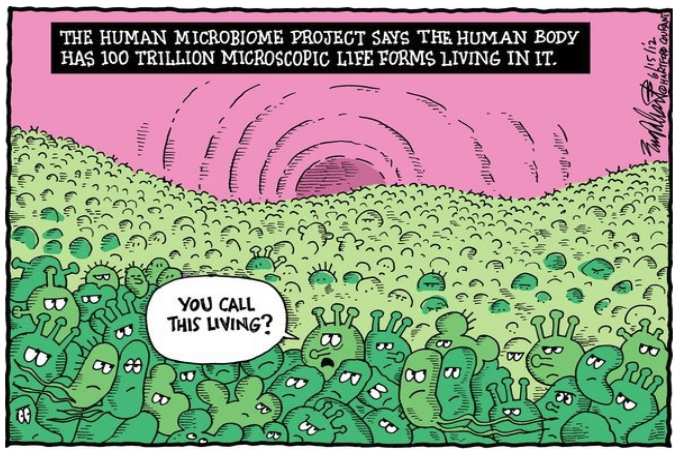
In addition to these epistemic aspects, weak emergence has also

– metaphysical implications: Simple life forms are nothing but complex chemical mechanisms.

– Ethical and social implications: Engaging social responsibility towards synthetic life requires an appreciation of emergent properties. Indeed, if the whole can be more than the sum of its parts, then protocells, for instance, would certainly be chemical machines but not *merely* chemical machines. Dealing with emergent properties requires caution and care (new risk assessment frameworks that

consider these emergent properties, and to rethink the precautionary principle), but emergent properties also require an examination of the values we engage in order to deal with them.

The interrelation between the epistemological and the ethical is also central for **Beatrice de Montera** in her presentation on the human microbiome. Recently, metagenomics have revolutionized the way we think our biological identity in demonstrating the co-evolution of humans and bacteria. The metagenome is not a "second human genome", as the press advertised; it is rather the dominant micro-organism of a complex ecosystem, i.e., a *collective* genome. The metagenome is, moreover, inseparable from the technologies of high-throughput sequencing that came out from the Human Genome Project in the 2000s. These technologies allow profiling genomic diversity and complexity (instead of relying on cultivated clonal cultures as in traditional microbiology and genetic sequencing). The main findings of human metagenomics are a high individual variability (no one common microbe was present in *all* body sites or *all* individuals) and simultaneously the existence of generic types of microbial population correlated with metabolic pathologies (e.g. diabetes, obesity). 3 main human "enterotypes" were identified. They are not dictated by age, gender nor ethnicity, but rather influenced by long-term nutritional cultures.



B. de Montera participates with the Catholic University of Lyon in a metagenomic paltorm for sequencing the human microbiome, MetaGenoPolis. The project aims at delivering microbiome-based diagnostics, prognostics, and nutritional recommendations for health institutions as well as for the industry (e.g. Nestlé, Danone). The idea is to pave the way for a personalized microbiome-based medicine. Accordingly, there are also projects—for now anticipatory—to introduce engineered bacteria ("personalized bacteria") inside the gut and study its adaptative behaviour. Cultivated ex vivo (outside the gut), the engineered bacteria would have to be rendered dominant in order to have a therapeutic effect. The issue is thus very complex, but it is already thinkable.

Within MetaGenoPolis, B. de Montera is involved in an ethical research that focuses on the metaphors scientists use to name their biotechnological entities (e.g. "macrofactory", "living machines"). The research addresses key issues such as the vision of ethics held by researchers, their communication with the public (to which point should it be "controlled"), but also the ontological status of the microbiome (i.e. what kind of entity it is) and of the future engineered bacteria with regard interacting with and within the microbiome.

The ontological status of the microbiome is very controversial. Some scientists view it as an organ, others as an ecosystem, and the human individual plus the microbiome is sometimes called a "superindividual". The main features associated with the microbiome are: vulnerability, uncertainty, unpredictability, and ecological equilibrium. The microbiome has thus often a strong ethical significance for scientists, some saying for instance "there's something inside me that prevents me to do extreme things". The different microbiome metaphors reveal as well as promote different levels of ethical awareness and responsibility: while the phrase "macrofactory" suggests the controllability of the microbiome, the term "living machines" re-introduces the idea of life as a feature of the microbiome that can't be fully controlled. Concerning the status of the possible future engineered microbiome, researchers admit that their research strategy will strongly depend on their underlying values.

To B. de Montera, the microbiome calls for a relationist ontology inspired by philosophers such as Gilbert Simondon, for whom the process of individuation of the individual occurs in relation with other beings constituting a milieu that co-evolves with the individual at multiple scales. Strictly speaking, "there are no individuals, only processes of individuation", and in this process we need our bacteria.

Discussion

What is the role of the philosopher in biotechnological research settings? To B. de Montera, ethics is transdisciplinary research. The aim is not to revolutionize the philosophical concept of life. It rather to help scientists to focus with their own methods on issues that can only become salient through the transdisciplinary crossing of multiple perspectives. Ethics is not science either, but it is research, and a kind of research that is complementary to science.

The same goes for engineering, as the discussion came back on the ideas of "evolutionary engineering" and the engineering of desirable emerging properties. Engineering is a way of doing research that complements science in many respects. There is not one single concept of engineering to be opposed to a "purely scientific" approach. Why thus, couldn't we engineer disorder, by resorting to noise, for instance? Or else, engineering history, or at least historical timelines, by outsourcing the results of simulations performing in silico evolution? True, admits Heams. However, he remarks, isn't it ironic that all that the "first wave" of synbio wanted to avoid—Darwinian evolution, emergent properties, stochasticity, etc.—is now promoted as the core of a "second wave"—and supposedly wiser—synthetic biology? But since the effect of Darwinian evolution is to increase modularity, Jaramillo adds, it's not opposed to engineering ideals of "rational design". The problem is practical (rather than ontological): One does not build cathedrals by throwing stones randomly: one needs blueprints, planning, concrete, and well standardised bricks. And that's were the human designer enters the scene. Finally, the point might not be whether or not life can be engineered, Heams concludes. It is rather to acknowledge that, by using evolutionary methods such as chance/selection dynamics, we are not the *only* engineer: we co-produce the outcome with a plethora of other entities that are helping us to solve the problem. The question is not "engineering life" or "engineering *versus* life", but "*co-engineering with life*".

Session 3: Engaging or designing the public?

Introducing the session, **Tobias Eichinger** indicates—according to the consensus response to the questionnaire—that the public knowledge and understanding of synbio seems to be at a very low level. That means that in the course of informing and involving the public, the possibility and the potential to influence and to govern the public opinion is still given. The strategy of shaping is the intention of some who want to avoid a negative public reaction as it has emerged in the field of genetic engineering—here it is to be discussed the common motive of "synbiophobia-phobia".

In principle most people in the field attach importance to public engagement, and many argue for more balanced forms than a top-down-approach, such as forms of open dialogue or mutual learning. That adresses the tension between an approach of *information or education of the lay public* on the one hand and an approach which is more *shaping the public opinion in a normative way* on the other hand—be it by emphasising the continuity of synthetic biology to previous human interventions in nature (Sune Holm) or by promising the design of a radically new future (Martin Müller).

- Should public engagement be a duty for its own sake or a useful strategy to communicate scientific and/or commercial enterprises?
- But how useful is referring to "one" public, and how could diversity be conceived within the public sphere—what about "the diversity in synbio and its publics" (Sacha Loeve)?

– And finally: what about the role of art, artists and artistic approaches in the context of the relationship of synbio and the public (Jane Calvert)? Could and should that way of dealing with synbio seek to make it more suitable for common audiences, as a "beautiful science"?

As each of the questions raised during the discussion was specifically addressed to one of the speakers, they are reported hereafter immediately after each talk.

It is often argued that synbio or GM is nothing essentially different from long standing practices using living beings for our own purposes (breeding plants, animals, making vaccines, or using microbes for making cheese or brewing beer…). "We've been doing this for millenniums". This "continuity argument" is used to create public acceptance or to stress that no new regulations are needed. **Sune Holm** is interested in the structure of the continuity argument as something that should be disentangled in order to clarify public debates. He thus assesses its validity and questions its presuppositions from a formal point of view.

The continuity argument can be presented in the following form:

"If *P* (e.g. synbio) is ethically problematic, then *R* (e.g. breeding) is also ethically problematic;

since R is an established practice, then there is nothing ethically problematic in P".

In other terms, if one does not find the established practice problematic, then one has no reason to find the new one problematic. Or else, if we think that the new practice is problematic, then we should also find the older one problematic (e.g. breeding, agriculture…).

To sum up, the continuity argument is based on two assumptions:

(1) That the new practice is similar to the older practice regarding its ethical acceptability;

(2) That there is nothing ethically problematic in the older practice since it is well-established.

On what grounds do these two argument stand? It is easy to see that the validity of (1) relies on (2). However (2) is not a self-evident matter of fact: the claim that the established practice is unproblematic should be supported (generally it is *not* supported and it is presented as self-vindicating); otherwise, it relies on nothing but (1), or rather on the intention to claim the validity of (1). It is thus a circular argument.

During the discussion, Bensaude-Vincent pointed out the metaphysical assumptions on which the continuity argument is based. In particular, the continuity argument relies on the *assimilation of technological development and the artificialization of nature*. The purpose of the continuity argument is to show that such artificialization is normal or that it is "natural" to humans… A key assumption akin to what she calls "the chemical paradigm of the 20th century": the purer it is, the more human-controlled it is, the better it is. But B. Bensaude-Vincent stresses that this paradigm is collapsing today because of environmental crisis, pollution, and other questionings of this conventional view of progress. Today, progress and artificialization of nature do not walk hand by hand anymore. For this reason, the continuity argument is probably no longer going to create public acceptance.

Finally, the continuity argument orients the debate in ways that exclude other legitimate matters of concern: public worries are not limited to continuity or newness; they also care about social justice, labelling, uncertainties, values, etc.

Offering only few compelling realizations, synbio is mainly future-oriented. But what kind of future does it offer? **Martin Müller** focuses on synbio's "biopolitical" agenda—i.e. how prominent synthetic biologists like George Church or Craig Venter position themselves as *engineers of future societies*. Synthetic biology, claims G. Church, "will reinvent nature and ourselves". Indeed, if "life" and "nature" could be programmed and controlled by "biological design", also the "future", one might claim, could be programmed and controlled by science and engineering. Such an ambition to control society and the public is also part of the promise of synthetic biology, argues Müller.

Crucial for these narratives are code-centered bio-cybernetic figures of thought and the topic of "digital design". In this context, it is *the computer* that becomes the main instrument of control and of colonization of the future through the tools of the present. Control is mainly viewed as digital control. The future that synthetic biology pretends to offer is thus nothing but an extension of the present: digital life, digital society.

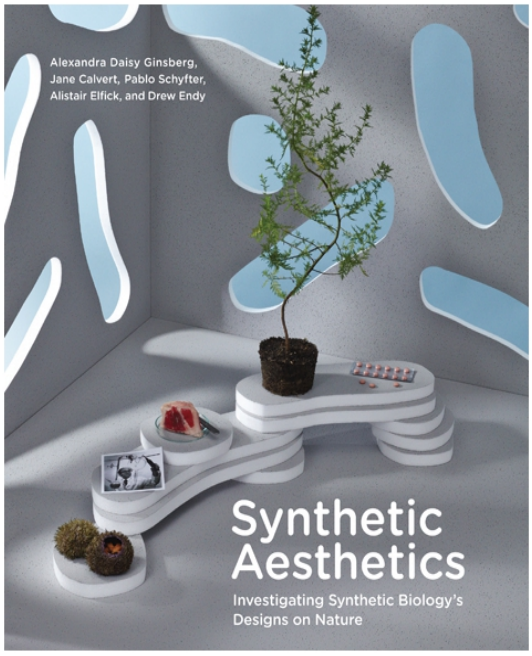
What about the hidden political rationalities that biopolitics convey? Beyond attempts to control life there are also issues of authority, stressed Pascal Ducourneau: *Who* is granted the legitimacy to control life as well as to define *how* life should be controlled? Thus, the discussion should not only focus on the technological side of control; it should be more explicitly political too. In his response, M. Müller argues that the new technoscientific descriptions of life call for new conceptions of "biopolitics", after Michel Foucault and his heirs (Nikolas Rose, Paul Rabinow).

In her presentation, **Jane Calvert** discusses the Synthetic Aesthetics project, which brought together synthetic biologists, social scientists, and artists and designers. Six artists/designers were paired with six scientists/engineers. Together they produced a diverse range of work that addressed issues such as: the specific challenges of designing with things that evolve; the limitations of engineering metaphors in synthetic biology; the multiplicity of timescales exhibited by bacteria; the things humans and bacteria share (through a project of making human bacteria cheese!), and the value-laden character of design.

"Engaging the public" was not the aim of Synthetic Aesthetics. Participants were not placed in the role of the "members of the public", if such a thing means anything. The project was more about expertise than about engagement, about *alternative expertise*, however—i.e. About how different ways of seeing each other's work that transform the sciences, as well as the arts and the relationships between them.

It was not "designing the public" either. Indeed, art-science projects are often criticized as becoming a tacit means of facilitating public acceptance. The involvement of designers in synthetic biology programs is even sometimes seen as a way to "design the society" that goes with the technoscience. But the project was not about beautifying or better communicating the science. The tone was neither utopian nor dystopian, but rather messy and ambiguous. It was an attempt to explore the intersection of different practices in a way that allowed for dialogue and dissent, by "thinking through things", critically envisioning the future while expressing this in a tangible form.

The material objects produced by artists and designers often have an immediacy and an ability to travel that opens up new types of discussion and can help us find new languages and metaphors. Involving artists and designers in synthetic biology can bring out new relations between things, knowledge, people, visions, etc. that did not exist before. It is in this respect that such work provokes reflection about the social, political and economic complexity of the technology, and can help articulate a wider range of objectives, pathways and outcomes than would be envisaged otherwise. In conclusion, the project was about neither engaging nor designing the public, but rather co-constructing science and art as new ways of initiating divergent discourse on synbio.



Tobbias Eichinger commented on the status of the artist. S.he is often seen as a mediator between science and society, and not as a researcher, why? It's like the idea of social scientists being part of the public, it's a misconception. Today, an artist or a designer is not a scientist, but s.he is a researcher.

Jane Calvert adds that one of the outcomes of the Synthetic Aesthetics project was to blur the identities. For instance, from the perspective of the artist, the scientist was also a member of the public. Having artists doing science experiments or having works of art co-produced with scientists renders the science/public divide uncertain.

How has the interaction of these different fields having different ways of doing design changed the concept of design, asks Oliver Müller? Not by abstract discussions, J. Calvert answers: by reciprocal borrowings, extensions of one's own way of doing design, and excursion into the other's domain.

Sacha Loeve's presentation starts with comments on the May Special Issue of *Nature*, entitled "Beyond divisions: The future of synthetic biology". In the editorial, strong concerns are expressed about synbio's lack of unity (of common definition, standard method, and shared goal): "the discipline suffers from its divisions". All the special issue is then devoted to the search of solutions to overcome these divisions…

But why is such lack of unity so problematic? By contrast, Loeve recalls that the first issue of *Nature Nanotechnology* (2006) started with an editorial featuring 13 interviews of researchers expressing 13 different opinions of what nanotechnology means to them. Interestingly, it was not seen as problematic, since it was no question for nanotech to become a *discipline.* Most part of these researchers did not present themselves as "nano-researchers". They did rather say: "I am a biophysicist…a solid-state physicist…a synthetic chemist…etc." and "I *do* nanotech". Although synbio presents in many respects the same kind of multidisciplinary profile than nanotech, it seems much more concerned for its *unity as a discipline*, and to a point that epistemic and cultural diversity is seen as a threat, the threat of "tribalism". Why is that problematic? Why a unique identity matters? Loeve identifies 4 reasons:

1) *Funding*: calls for investment require that synthetic biology appears as something unique, qualitatively different from current biotechnology. Otherwise, it will be supported by the same funding avenues, and there will not be a tsunami of investments like in nanotech, brain science or bioeconomy, all supported by large national, federal or European initiatives. It is a "discontinuity argument".
2) *Industrialization* requires standardization as well as critical mass. The newness (or the prospective unity) of the multidisciplinary field of synbio is voiced in terms of engineering: How diverse synbio might be, it must agree on unified, generic standards in order to become real engineering and reach

an industrial-level critical mass. Industrial systems need networks where information and interchangeable elements can constantly circulate and be exchanged. Without standardisation, the engineering approach will not stand because it will lack general rules to specify which parts should be used for which function. Biobricks, for instance, would remain conventional molecular biology—hence the repeated claim that in order to make biology engineering, the field must seek unity around unified standards.

3) *Market norms*: the *Nature* issue speaks of a "cultural divide" between the supporters of open access and those of intellectual property. But it's more a "market divide": agreeing on common norms is necessary for organizing, stabilizing and optimizing the market. In order to bridge the gap between these two visions, a way forward is often suggested: It consists in that bioparts are freely available whereas built-up devices made from these bioparts are eligible for patenting. In capitalistic terms, this scheme is a convenient way to boost innovation by dropping the production costs of bio-devices. It is a market-based approach to the unification of the field.
4) *Fear of public backlash*: synthetic biologists would have to stand united in order to *win* the public acceptance. Using a very agonistic vocabulary, it is explained that if synthetic biologists do not "present a united front", then not everyone will agree that SB is "a force for good". Here, the public is seen as a force of dissolution that echoes the issue of the lack of internal cohesion of synbio research. "If synthetic biologists cannot agree on common standards and regulations, how will the public ever agree with them?". We have thus a kind of mirror image between the controversies that could burst within the field and the controversies that would come from outside the field, from the public side. The public is depicted as *the* major source of risk—that of a mass refusal of the technology—and this caricatural image of the public serves in turn to compel synthetic biologists to unity.

The dream of unity might be a poisoned dream. Instead of unifying the field, it might be more relevant to highlight and to value the *divergences* between the multiplicity of epistemic cultures of synbio in order to let the technology open to social shaping. For this, it is important to avoiding constructing a standard model of "the" public defined by its disposition to confidence, to acceptance or to refusal.

Synthetic biology applies a principle of epistemic opportunism that takes "whatever works" in a broad exploration of the possible. However, one may doubt that all forms of possibilities are possible together, at the same time and in the same common world. In other terms, the question is not only that of the possible. It is also that of the *compossible:* What is possible together? Thus, instead of unifying the field behind the flagship of "making life easier to engineer" and applying the principle of "whatever works", it might be more relevant to allow people to *contrast and compare* different approaches of synbio in order to better identify where choices of society should be made. Instead of packaging synbio into a big standardised black-box, why not engaging people to participate in the elaboration of different standards suited for different technological as well as societal goals? Why not opening the standards to social shaping? Why not working on the embodiment of a diversity of values into these standards?

Standards are very technical, remarks Geoff Baldwin in the discussion. It's really the most painstaking and industrial part of the design process. It's technical considerations, and that's why standards are useful. They are a huge part of what industry is. How could people be engaged in the process of defining standards? That would seem too involving. Sacha Loeve answers with a comparison. Think about the internet: the standards and communication protocols (TCP-IP, HTTP, HTML…) that allows it to technically work are also and simultaneously issues of power and empowerment: they define what is interoperable with what; they delineate the perimeter and the degrees of liberty of what people can or can't do. Issues of power and politics are also embodied in the most technical questions. Insetad of setting "social" and "technical" questions apart, we should work on the implementation of a diversity of values in synbio's technical standards.

Session 4: Expanding or blurring the boundaries? Natural/artificial, living/nonliving, nature/society…

In her review of the responses to the WV&Vs questionnaire, **Bernadette Bensaude-Vincent** stresses that the distinction between the natural and the artificial seems totally irrelevant for scientists designing living cells or mimicking biology. This is not unexpected. For instance, Ludovic Jullien argues that nature is a chemical experiment at the scale of the planet. For most of the participants, nature is view as a kind of engineer providing clues, materials or letters, that is, the alphabet to start with for reprogramming life. There is no ontological boundary between the natural and the artificial. Could synthetic biology could be viewed as a paradigmatic exemplar of the so-called "post-modern" era which undermines all the divides established by modernity? Quite interestingly, synbio even undermines the commonly established equation between living and natural. For the first time, living and natural are no longer synonymous.

However, it doesn't mean that synbio is simply erasing all distinctions. On the contrary, the answers offer a variety of options for refining the role of nature in its relation to humans. George Church, for instance, argues that we have to replace the divide "natural vs. artificial" with "beneficial vs. harmful", as it is more relevant that for ethics and policy. He expresses an anthropocentric view of nature which blurs the boundary between nature and society. Sheref Mansy says that we should better make a distinction between "intentional" and "non-intentional" instead of natural vs. artificial. He also suggests that synthetic biology is a methodology to probe the divide between living and nonliving. Mimicking life doesn't mean replicating life, but understanding what it is by better circumscribing what it is not. Denis Pompon proposes a more subtle distinction between making artificial organisms that break up with the rules of biology (fully "orthogonal" organisms), and making artefacts that nature could have been generated and selected – life as it could be or as it could have been (one might call them "diverging" organisms). This implies making a distinction between different kind of possibles.

Denis Pompon presents the recent evolutions of metabolic engineering. Classical metabolic engineering starts from pre-existing organisms (yeast, bacteria…) in order to produce already-known substances of interest (drugs, biofuels, polymer precursors, and other of fine chemicals). It uses biodiversity and the repertoire of existing enzymes to induce and catalyze non-natural boisynthesis pathways with artificial evolution methods. To D. Pompon, the beginnings of metabolic engineering was "reductionist" in the sense where, starting from available known biodiversity, it proceeded by reducing the diversity of metabolic processes to constrain them to produce the compounds of interest—thus the classical approach consisted in *reducing the range of possibles*. It was a convergent, funnel-approach.

Now the new approach follows an opposite trend: it increases the diversity of both the substances of interests (compounds synthesized into plants or animals, e.g. artemisinin in yeast; or even non already existant enzymes) and the metabolic processes of the organisms that produce these substances (i.e. orthogonal strategy designing species based on alternative biochemistries). The new approach thus *expands the range of possibles*, as well as the disparity between these possibles. It is a diverging, open-ended approach.

This was allowed by new biodevices and processes such as large-scale automated genome construction and the production of expanded biological repertoire, not only at the level of DNA (new bases), but also at the expression level (new amino acids, new proteins). Protein design has recently focused on the production of hybrid enzymes combining synthetic chemistry, nanotechnology and biochemistry (half organic/inorganic catalysts, artificially scaffolded or compartmented enzymes). Or else, Pompon mentions a genetic plug to provide eukaryote cells with chemoautotrophy (a mode of growth with no other source of carbon than CO_2).

Metabolic engineering is thus no longer just a matter of adding or replacing genes; it is also working on the interrelations and regulation of multiple synthetic pathways (tunable synthetic promoters); or on pathway-interactions between different cells (population-level sensors), and their integration in system-biology based approaches (in silico cells). Thus, a new challenge in metabolic engineering is *synthetic regulation*.

Finally, synthetic regulation implies an understanding of the relationships between preexisting and synthetic processes so that everything works well (D. Pompon mentions a case where they had to find a solution to the problem that the biosynthesis of vanillin killed the bacteria that were sought to produce it). Artificialization is thus not the unique way forward: one must devise the adequate interfaces to make these diverging systems compatible with each other, and find balanced ways and trade-offs to combine artificial and natural processes. In synthetic biology, Pompon concludes, "the design is rational, but the product that you get in the end is the fruit of chance, of necessity, and of complexity".

The latest trends of metabolic engineering thus testify for the ambivalence of the natural/artificial issue: On the one hand, rather than just blurring the divide, these practices seem to *expand* it. Indeed synthetic metabolic processes are driven farther and farther away from their natural predecessors. Moreover, as synthetic biology designs new genome editing tools for synthetic biology, it even acquires "an autocatalytic behaviour" by which this process of artificialization reinforces itself. On the other hand, with the focus of recent metabolic engineering on hybrids and on synthetic regulation, nature and technology seem interfaced in new ways. One might say that if "the natural" is thought in *metaphysical terms* as referring to the *origin of production*, then yes, synthetic biology is a definitive leap forward in the artificialization of life, an attempt to set organisms apart from their "given" nature. However, if "the natural" is thought in genuinely *metabolic terms*, as a regulation-relationship between inner organic processes and their external environment (etymologically *metabolè* means both "change" and "exchange"), then one should conclude that, paradoxically, artificial life needs nature.

In a half-decade years, there have been a shift in the paradigmatic picture of synthetic biology from "God to Geek", claims **Franck Delaplace**. "So God, please leave this room, let's talk about the geek science of synthetic biology". Hos talk about "the use of computer for programming biological functions" addresses the issue of designing a domain-specific computer language dedicated to synthetic biology. In this perspective, bioinformatics seeks to become a tool for the design of safe and well-characterized biodevices showing properties of modularity, standardisation, interoperability, predictability and efficient tunability. The bio-geek's challenge is to built schemes allowing to program biodevices as we usually program software. High-level computer programming language is ultimately based on low-level binary machine-language; biological high-level function is (supposedly) based on low-level DNA coding. "The dream" says Delaplace, it to render them mutually translatable. From this, he raises two questions:

1) the notion of "language": how to design a language to specify biological functions? For designing a language, a semantics is needed, based on the abstract description of biological properties. It requires modelling the way the medium operates.
2) the notion of "compiler": how to automatically translate high-level biological function into DNA sequence? Bioinformatics also have to set some compilation principles: rules translating high-level specifications into low-level specification.

Regarding the first challenge—language—, one of the main characteristics of the biological medium is its openness: organisms present a high variability; they are sensible to environmental variations; they

have a systemic and multi-scale organisation that can't be analysed following a reductionist approach listing all the components in a non-ambiguous manner; some parts are not-reducible to a limited set of properties. These ontological properties of the medium demands a reflection on the design choices of the programming language: Shall we consider this openness or shall we adapt the context in order to close the system? (In other terms the question is to choose how much we need to reflect or to "betray" the ontological properties of the medium in the programming language). Shall we address the behaviour (the organism seen as black-box with inputs and outputs) or the structure of the system (the molecular stuff it is made of)? Shall we base the semantics on the observation of the biological stuff or on the model that summarizes our understanding of it? In summary, the question is how to formalize the biological since there is *no a priori formalizer in the medium* (contrary to a computer which follows formal rules)? How to *formalize the aformal*?

Then, Delaplace explains one possible "solution" that he and his group explores at the Genopole, while insisting that this is only one possible solution among other (since, again, there is no unique solution dictated by the medium). This solution includes an abstract description of the context; biological processes are abstracted into a set of causal relations; these causal relations are composed into compartments; 2 kinds of objects or "agents" are considered: either constants (that specifically address particular genes for instance) or variables, that express a general process (e.g. inhibition, activation) specifying only "abstract" genes (gene 1, gene 2, etc.). The description is kept as short as possible. The language is compact.

Regarding the second challenge—compiler—, the compilation principles are based on the observation rather than on the model only: the biodevice is said functional if the observed behaviour fits the modelled expectation. A purely model-based set of compilation principles will always face the contestation of some biologists, says Delaplace. Biology is not physics. In biology, one will always find someone telling you that "your model is wrong". So the task is not to find a unique true model; it is to define robust relationships between the abstract behaviour and the observed behaviour. The notion of behaviour is central: "we do not translate the structure, we compute the behaviour". Finally, the realization of the compiler is based *not on translation but on matching*. Each sequence is matched with a set of behaviours. The validity of the compilation is constantly re-assessed and refined by observing the system until the programmed function corresponds with the observed behaviour. It is once again, an application of the "design cycle" (see G. Baldwin's presentation above). This implies aslo the acknowledgment that *the reliable device can be more than the sum of its programmed functions*, and the *integration of this fact in the programmation scheme*.

Their "solution" regarding the compilation goes as follows: a database of components is constituted, together with a set of functions to program; the task is then to cover the behaviour of the programmed functions with the components. The core of the software is a selection of the behavioural matchings, assisted by directed evolution algorithms. Finally, This software architecture is part of a larger project, which will associate the later with another software which is in charge to check the safety and the security of the components.

Regarding the natural/artificial issue raised in this session, it is useful to contrast this approach with mid-20th Century cybernetics. At first sight, the two would seem rather similar, reflecting a unique trend of "digitalization of life" (see M. Müller presentation above). However, it is clear from the presentation of Franck Delaplace that contrary to the old cybernetic paradigm, based on the recognition of "natural" analogies between organisms and artificial automata, current bioinformatics first aknowledges that there are irreducible differences between the two "mediums". Then, it is a mind-boggling effort to artificially design ways to get them work analogously. The analogy between natural and artificial functions is not the starting point but rather the end-point. In other terms, biology seems interesting for computer scientists precisely because it is a medium *recalcitrant to formalization*.

Pascal Ducournau and his two students (**Simon Desbois** and **Florentin Berger**) address the issue of the boundary between science and society. They present the results of collective sociological fieldwork study conducted by students in the master "*Gestion sociale de l'environnement*" (social management of environment) under the supervision of P. Ducournau and F. Blot at the University of Albi. The students are trained to cross-disciplinary approaches combining sociology, geography and ecology. Based on qualitative interviews with practitioners in a lab developing new ways of factoring biofuels and bioprocesses for the industry based on synthetic micro-organisms, the study focuses on the way synthetic biologists address *the question of risk*. Indeed, there is a collective recognition for the necessity of an assessment of risk issues within synthetic biology. Should this assessment be internal or external to the synbio community? Should it be expert-based or citizen-based, or mixed? In other terms: is synbio able to tackle by itself the question of risk?

First, it is necessary to question risk perception by synthetic biology: do they identify risks? What kind of risks? And what kind of rationality shapes this perception?

Main results are:

- A recurrent discourse according to which "there is no risk": these organisms are strictly confined; and even if they would escape, the fact that they are over-adapted for their tasks gives them no chance to survive into the environment.
- Another discourse is: "there are risks, but they are under control". Intervening on life is always risky and uncertain. But with synthetic biology these modifications are no longer random, thus by definition synbio provides humans with more control on biological modificationds. After all, we will never be able to control everything, but controlling a little is more risky than controlling more. Thus synthetic biology reduces uncertainty and lowers the probability of risk.
- Another line of argument puts that "risks are less important than expected benefits". "All technologies are risky"… "I wouldn't say that synthetic biology have no risks", but "we have to put the risks in relation to the benefits". The benefits are always identified with *production*: molecules of interest, fuel for instance. With biofuels, the main rationale is always the same: we have to find technical solutions to maintain our current standard of living (see M. Delcourt's presentation above).
- Or else, risks are unanticipated events per essence, referred to as "unlucky events". "In Japan, they were unlucky [with Fukushima]", confronted with "things that should never happen". Zero risk doesn't exist but risk is essentially "bad luck".

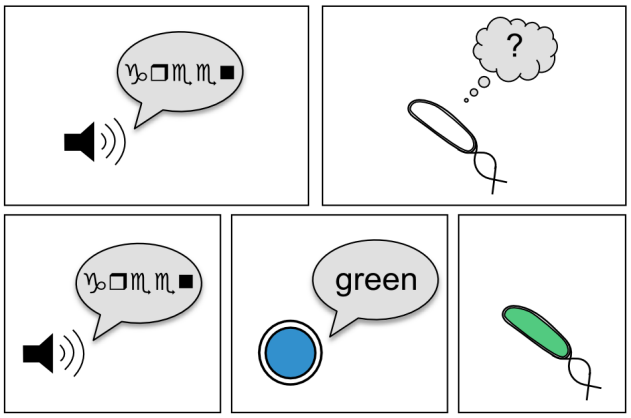
In summary, risk is perceived through a dominant *productivity-oriented* rationality. Synthetic biology is first regarded as a set of tools for increasing productivity. It is always the benefits in terms of production that are assessed first, while the question of risk is secondary or external to the main framework. Risks are side-products. In this perspective, it is only if the risks are quantitatively greater than the expected production benefits in terms that they will have a chance to be carefully examined.

The results of this survey raised doubts among those who conducted it about the ability of synthetic biologists to address the question of risk. Risk have either no existence, or a low-probability existence. In any case, they are rendered unthinkable since they are not measurable in the dominant production-oriented framework. To conclude, self-regulation is a dead-end. Risk assessment should not be let to the synthetic biology community alone, it should involve other components of society as well.

Sheref Mansy seeks to build "artificial cells to deceive natural cells". He first recalls how immediate and intuitive our recognition of life is. In front of a chick and a stone, everyone can tell which one is alive and which is not. There's no PhD needed for that. Things get worse when one asks about the *criteria* for making the distinction between living and nonliving. One frequent answer is that living beings *reproduce*, and thus evolve. Good answer: without reproduction, no evolution; without evolution, we won't be here to admire the wonders of life on earth. However, there are stuff we consider nonliving that do also

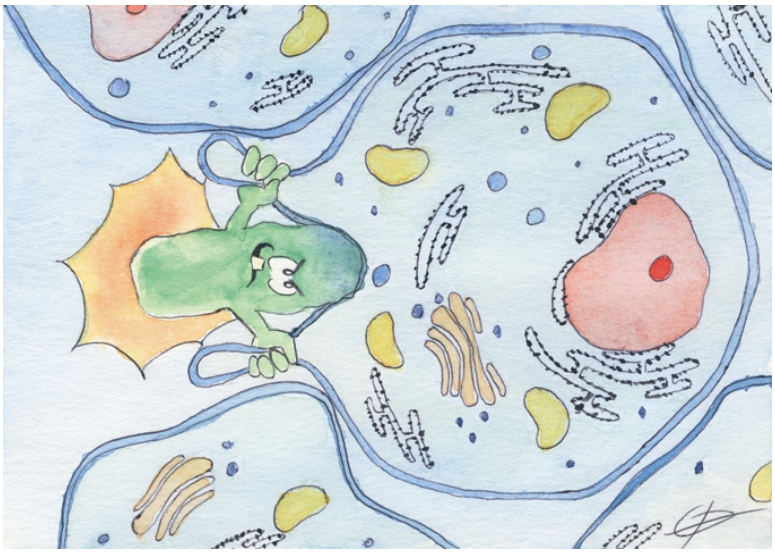
reproduce: crystals, computer programs. Moreover, some living beings are not able to have kids, and yet we do not say they are no longer alive. It's the same with other definitions of life: Every time someone came up with a definition of life based on a unique property (such as autonomous growth, self-organisation, adaptation, etc.), one can always play the same little game and find living things that do not fit the definition, or nonliving things that do fit the definition. That's very frustrating, especially for a scientist working on artificial cells in a lab: How do you know if you succeed? You have built something, but how can you tell it's alive? There is no unique definition of life.

Generally, scientists work with a conventional definition such as the one of the NASA, coined by Gerald Joyce: "life is a self-sustained chemical system capable of undergoing Darwinian evolution". Such a definition is not bad, but it is still unsatisfying since it does not connects with the intuitive manner by which people feel what is alive and what is not. It is not that scientists do not see that such a definition is unsatisfying. They need to rely on a well-establish definition, and they use this working definition because they don't have a better one (and S. Mansy confesses using it himself). Why not acknowledging once for all that *there is a subjective component* in our recognition of life? We recognize life because we are living stuffs! Then an alternative way of addressing the problem is offered: *letting things we recognize as being alive—e.g. cells—deciding whether something we have built is, or not, alive*.



Such an approach is similar to the procedure imagined by Allan Turing for evaluating artificial intelligence in the absence of an agreed upon definition of intelligence. A modern (and simplified) interpretation of the Turing test stages someone chatting with a friend, who is then substituted by a program. The program passes the test as long as one still believes that s.he is chatting with h.er.is. friend. In other terms, the Turing test is an *imitation game*: it addresses intelligence as the capacity to make itself recognizable as such by another being that we commonly consider as "intelligent". Intelligence is no longer a set of properties enclosed in someone's head. It's a certain behavior. It's the same with life in the cellular Turing test that Mansy's group is attempting to devise. The artificial cells will have to be "cellular mimics", endowed not only with gene expression and replication capabilities, but, most important, with abilities to chemically communicate, sense the environment and respond to it. Will *E-coli* feel like communicating with another *E-coli*, or will it behave in a manner showing the human experimentalists that it's not the case?

Probing life through chemical communication is really the main goal of Mansy's group. Life is thus apprehended as an activity and as an interaction and rather than as a set of substantial properties. While their approach does not presuppose a clear boundary between living and nonliving, it does not negate the intuitive, commonsensical and almost esthetical dimension of life that everyone recognizes. Quite the contrary: it tries to integrate this mundane dimension of life at the core of the experimental procedures of synthetic biology. I this respect, the approach embodies a different of relation of science with society: the search for a common rationality rather than a superior, "extramundane" rationality.



Winfried Römer says that he doesn't feel like belonging to a discipline called "synthetic biology": as he started training in chemistry, did a PhD in biochemistry, a postdoc in cell biology and biophysics, and now works with his team in Freiburg on medical projects, he considers himself as an interdisciplinary scientist working at the interface of many research fields. Not surprisingly, his object of study is also a complex interface of its own: the interaction between pathogens and the human cells at the level of the plasma-membrane, with its intricate mesh of molecular signalling receptors and processes. The aim is to understand the mechanisms by which viruses "manipulate" the hosts' biochemical signalling pathways to make their way inside cells, and eventually to find inhibitors to protect cells from this intrusion. The hypothesis is that behind the complexity of the mechanisms, a generic concept of lipid-mediated endocytosis applies. As W. Römer explains, the top-down approach (i.e. doing Silencing RNA screening, blocking one molecule…) does not allow reducing the complexity to find a limited set of molecular candidates. So the team chose to probe these processes in much simpler and controllable *in vitro* systems, e.g. with a giant unilamellar vesicle that mimics a minimal plasma membrane, as starting point. That's where the synthetic biology aspect is involved: they reconstruct membranes bottum-up to understand the physics of phagocytosis.

For now, they have reconstructed the first steps of the mechanism by which a toxin is penetrating the cell by triggering signals that induce microtubule-invaginations carrying the toxin into the plasma membrane. They want to show that the same lipid-mediated endocytosis mechanism is at play with other pathogens more complex than toxins, i.e. viruses and bacteria. For this, they try, step by step, to build up a more and more complex synthetic system (integrating receptor molecules, ligands, actin tubules, etc. into the synthetic membrane) that will eventually resemble the native cellular process. In a decade, they expect having succeeded in building completely functional cellular mimics that are migrating, dividing and communicating.

Discussion

Is it really possible to settle the question of the difference between living and nonliving with a laboratory experiment, asks Morgan Meyer? For "natural and artificial", the thing is not obvious, says Sheref Mansy: These terms are more convenient ways to communicate than distinctions testable by scientific methods. With "living and nonliving", the cellular Turing test is at least a way to address the problem.

Sacha Loeve stresses that the Turing test in the original 1950 article is far more subtle than the popular and politically correct version that the artificial intelligence community retained. It's not just "can you be cheated by the computer by believing that you are chatting with a human" but "can the computer be faking that he is a man simulating a women and thus cheating the interlocutor in the same way that a human is able to blur the sexual difference". It's really strange. There are 3 characters and their respective identities are voluntarily blurred by Turing, not only the computer/human identity, but the man/female identity as well. It's a protocolar definition of intelligence, and of intelligence as simulation, hence why the ultimate test for simulation seem to consist for Turing in the ability to blur the

sexual identity. So Turing is not only the inventor of the abstract concept of the computer, he is also the inventor of gender studies! More seriously, following the real Turing test would mean having not 2, but 3 bacteria: one interrogating (natural) cell, a hidden artificial cell, and a hidden natural cell. So how would it work? Yes, admits Mansy, the approach is just an adaptation of the Turing test that he thought could be useful for addressing a lot of problems that can't be addressed otherwise. About the gender point, Vic Norris once suggested that the best way to see if an artificial cell is truly accepted as natural is to see if natural cells try to mate with it.

Marc Bedau remarks that after decades of research in the field of founded by Turing, artificial intelligence, we don't really now more about what intelligence is, perhaps because we took the wrong direction in trying to answer a question that Turing said initially we should discard. Finally we went back to Turing in the sense that we made this question go away while finding usable, doable ways to address and to make artificial intelligence (which are today common and unimpressive components of our computers and mobile phones architectures…). So after some years doing these experiments on artificial cells, will we be able to know more on what life is? Or will the question "what life actually is" go away? Will it help dissolve the question or answer the question in the long run?

S. Mansy: "I do not have the answer". These experiments may or may not teach us more about what life is, but the reasonable hope is that these answers will serve as foundation for other exciting experiments… Perhaps "life" is a term for poets, as Andy Ellington says. Beatrice de Montera even reports that in order to create synthetic species, some claim that one must "eliminate the logic of life". That we must get rid of the question of life was true for the biology of the last 25 years, remarks Bernadette Bensaude-Vincent, but now the question seems to make sense again. The NASA definition, for instance, is meant to provide criterions to recognize life if by chance we find something approaching on another planet. That was also the story told in the first chapter of Jacques Monod's *Le hasard et la nécessité*: A fiction about a spatial program where some sort of robotic expert system is programmed to automatically detect life, reminds Loeve. And his conclusion was that it's mostly impossible. However, Loeve adds, isn't it already very valuable to tell what life is *not*? Self-organisation? Interesting, but not enough! Replication? Interesting, but not enough! And so forth. The heuristic value of technological models of life since Aristotle may lie in the fact that, in the end, they help us to tell what life is not rather than what it is.

The discussion also focuses on control and risks: does the prevalence of the notion of control in synbio lead to an underestimation of the question of risk, which is about the limits of control? Control is indeed liked with the production-oriented rationality that Pascal Ducournau and his students have pointed out: controlling cells is seen as a means to transform micro-organisms into micro-plants able to produce all the things that we want. Since the main assumption is that, technically, we are able to control, risks seem under control as well. The idea is that "controlling life will create a more secure situation for human beings". M. Engelhardt stressed that, having conducted similar interviews, she has observed that directly framing the questions in terms of risks create such sterile answers. It seem thus better to interrogate scientists on concrete problems like "do you think such organisms should be contained or not, how, and why?". Then one can get very open talks from scientists. Otherwise, many of them coming from molecular biology are just sick of the discussion about GMO, because they had bad experience in the past in trying to be open. But if you go to concrete cases, then you also find high openness and sensibility. This kind of experience should be mentioned to complete the picture. One of the students replies that they did not ask "what do you think about risks?", but "what are you doing?", and they get this discourses about risks mentioned during open talks as well. G. Baldwin adds that risk is also a question of design after all; he evokes the "safety by design" approach. It may reduce risks to have biodevices as unnatural as possible, but this may also create new and rather unknown risks.

Bedau stresses that the disagreement of scientists about synbio's risks (some saying that there are risk, some disagreeing) will not disappear if one gets other components of society involved. Thus it is not

clear whether public engagement offers an alternative to this particular problem. The problem, answers Ducournau, is to know wether *society* is able to tackle the question of risk. Yet this problem has not be addressed so far. Thus, it remains an open question that should not be discarded. And it could provide the risk issue with other rationalities at play. On the rationality through which risk is perceived, Loeve remarks that if you think in terms of production or *poiesis*, the bacteria is always a means to an end which is the product; and then, risk is always a by-product. If you try to think in terms of action, modes of action, *praxis*, you do not disregard the product, the utility of it, but it's a different question, because then, you also have to consider the value of the technical act in itself, whatever it will bring. In the case of vanilla evoked by D. Pompon, what it means to engineer a bacteria so that it produce something that kills it? What's the value embodied in the technical action? From the point of view of production, no problem: vanilla is good for us; from the point of view of action, the question of the intrinsic value of the technology is raised. D. Pompon specifies: it was not about engineering bacteria so that it poisons itself with vanilla, but on the contrary to engineer bacteria so as to *prevent* such poisoning. The success of the process was to find some turnaround to avoid it. So it would seem legitimate from the point of view of action after all.

Feedback session: What message do participants take home?

Social scientist: The way synbio scientists address the notion of life; and questions related to the way the methodology of interviews can influence the results.

Synbio scientist: Takes home the concept of emergent properties.

Synbio scientist: That the natural and the living aren't exactly the same thing is something he haven't really thought about before. "Engineering with Darwin": a really cool expression!

Social scientist: Caught a terrible cold in Paris and wonder if it's synthetic biologists' fault (joke). Appreciated the openness of discussion and received a lit of inputs to think about.

Synbio scientist: The necessity to adapt to a general audience was a valuable exercise. Was shocked about the outcome of the survey telling that synthetic biologists were unable to assess risk, because that's half of the job to do that since we do not want to expose our colleagues to risks.

Social scientist: The outcome was not an inability but a perplexity. The workshop was rich but the political dimension of synthetic biology was not enough addressed.

Synbio scientist: The social, ethical and political collective discussion that took place is full of emergent properties. We can't exactly tell what the outcome will be and we must be aware of that. The goal is not to find the unique proper way of doing this; it's to try many different things, such as engaging with artistic or fictional work, doing theatre, etc. and to look at the effects; It is to experiment and to observe. It's an ongoing iterative process in which we are engaged in.

Social scientist: We need to create collective risk assessment involving various forms of rationalities, economic, ethical, social rationalities.

Social scientist: It's great to have so many different perspectives; realized that scientists care for a definition of life in a philosophic way. On the other hand, there were so much topics to discuss that sometimes the discussion lacked a bit of focus and deepening.

Synbio scientist: Struck by the diversity of views and questions; could not imagine that synbio raises so much questions; remarks that synthetic biology is not in line with cybernetics. To program biological devices, one needs to comply with the rules of the computer. It is the computer which monitor the rules; they are not dictated by the medium. Thus bioinformatics is about finding some tricks in order to adapt the rules to the medium.

Theater maker: Takes home the focus on metaphors and the language of synthetic biology. For instance the "re-" words: It would be interesting to make a philosophical analysis of what is meant in this little "re-".

Laypublic person: It was interesting to see how risk is touchy as a subject. How can we talk risks in a productive sense? Do we need new cultures of talking risks?

Biologist: Need to rework the notion of "engineering": co-engineering things with living beings would be a useful notion. Since cells are more than machines, just like we are talking about "biopolitics", we could talk about "cell sociology": send questionnaire to cells and asks them about their life. It's not a joke: experimental biologists should think more about methodologies sociologists have for humans. They could find ways to implement something like this in experimental science.

Student in history and philosophy of science: Working on artificial life for master's degree, couldn't get what synbio is because of its diversity. Here had another glimpse on its diversity, but in a much more pleasant and comprehensible way. Struck by the fact that diversity was not considered as an obstacle to overcome but accepted as something to investigate and to work with. Was also struck by the fact that nothing is value-neutral in synthetic biology. A question worth asking: what is the identity of a synthetic organism? If you change the whole chromosome, will you still keep the scientific gender and species name or change it? Likes the idea of controlling cells by acting on their environment, rather than on the cell itself. The idea of function is everywhere in synbio. It should be

further conceptualized. Wonder if emergence is not a way to bring back vitalism in an acceptable way.

Social scientist: diversity, diversity, diversity! "Life" as a term for poets? Perhaps scientists as poets!

Social scientist: to go from synbio debate 1.0 to synbio debate 2.0, we have to ask other questions than risks. Discussion about arts seem to be important part of this debate 2.0. Some questions might be better asked on the theatre place than on the lab.

Social scientist: We should get rid of power-point presentations in the design of the debate!

Social scientist: The workshop was a way to bring in many perspectives into the discussion. Takes home bits and pieces, not one big message. Happy that the debate develops in ways that avoid the dead ends of the GMO debate. The discussion is maturing.

Social scientist: The discussion was full of ethnographic moments that invite understanding the relationships between synbio scientists and social scientists in interesting, telling, ways.

Synbio scientist: Was comforted to see how the discussion between science and humanities was active and reactive. We succeeded in reaching some common language. It's really important. Was however frustrated by the lack of definition of risk and of operational approaches to assess them. There was also a too large focus on synbio objects apprehended independantly of their ecosystem. We should take more in account the interaction of the objects with the environment.

Social scientist: it was really mutual learning!

The workshop featured a student event where they have presented or played games and fictions, available at this page.

All comments are welcome at this page (or to sacha.loeve@univ-paris1.fr).

The second Paris-Freiburg workshop on Worldviews and Values in Synthetic Biology will be held in Freiburg in July 2-3, 2015, immediately before a theatre performance weekend, thus enabling participants of the workshop to visit the theatre performances and conversely enabling students involved in the theatre project to become part of the workshop discussions.