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Bernadette Bensaude-Vincent

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Bernadette Bensaude Vincent  
Université Paris 1/IUF  
17 rue de la Sorbonne  
75005 Paris France  
Bernadette.Bensaude-Vincent@univ-paris1.fr

### **Discipline-Building in Synthetic Biology**

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#### Abstract

Despite the multidisciplinary dimension of the researches conducted under the umbrella synthetic biology, the founders of this new research area in the United States adopted a disciplinary profile to shape its institutional identity. In so doing they took inspiration from two already established fields with very different disciplinary patterns. The analogy with synthetic chemistry suggested by the term ‘synthetic biology’ is not the unique model. Information technology is clearly another source of inspiration. The purpose of the paper focused on the US context is to emphasize the diversity of views and agendas coexisting under the disciplinary label synthetic biology, as the two models analysed are only presented as two extreme postures in the community. The paper discusses the question: in which directions the two models shape this emerging field? Do they chart two divergent futures for synthetic biology?

Keywords: engineering, synthetic chemistry, synthetic strategies, open source, biobricks, epistemic pluralism.

## **Introduction**

All practitioners of synthetic biology agree that this emerging field combines knowledge from a large number of disciplines, including molecular biology, engineering, mathematics, chemistry, and physics. Synthetic DNA, xeno-DNA, minimal genomes, and protocells could arguably be presented as exemplars of the current movement of Converging Technologies prompted by the nanotechnology wave. Yet they belong to a special branch of biology often coupled with systems biology.<sup>1</sup> Despite its multidisciplinary dimension, synthetic biology follows the traditional model of academic disciplines.

In their effort to build a community of practitioners and stabilize the emerging field, the pioneers of synthetic biology have looked for analogies with well-recognized fields, in order to establish synthetic biology as a legitimate discipline. They shape a disciplinary identity of their research field by using quite different models such as chemistry and information technology.

The name itself ‘Synthetic Biology’ became an official label on the occasion of the Synthetic Biology 1.0 Conference organized in June 2004, at MIT by Drew Endy and Tom Knight, both members of the department of Biology and Biological Engineering of this Institute. The phrase “synthetic biology” (*biologie synthétique*) had been introduced a long time ago, in 1912, by a French physico-chemist Stéphane Leduc. (Leduc 1910 and 1912) However it seems that this antecedent did not play any role in the choice made in 2004. There is no historical link between the early 20<sup>th</sup>-century attempts at engineering life-like systems and the new branch of biology emerging in the early 21<sup>st</sup> century. Leduc and other engineers of living systems such as Jacques Loeb are rediscovered but it would be counterfactual to

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<sup>1</sup> See the journal *Systems and Synthetic Biology* created in 2007. <http://www.springer.com/biomed/journal/11693>

present them as the ancestors of today's synthetic biology. (Fox Keller, 2002, Bensaude-Vincent, 2009).

So where does this word come from? The analogy with the field of synthetic chemistry, which emerged in the mid-nineteenth century is quite obvious. To what extent synthetic chemistry can be seen as a disciplinary model for synthetic biology? If this model turns out to be in competition with rival models does it preclude the unity of the emerging discipline of synthetic biology?

Beginning with a brief report on how the term "synthetic biology" came into use, this paper will survey the discourses of emergence and point to a competition between two models. Finally it will discuss the significance of these rival models for the further developments of synthetic biology.

Before trying to describe the on-going process of discipline building in the synthetic biology community a few words about why this identity work matters may clarify the aims and perspective of this paper. From the large literature about discipline building (Gingras, 1991; Nye, 2002; Molyneux-Hodgson and Meyer, 2009), one can retain that it is a three-fold process: A research field first nucleates around individual trajectories; then it is stabilized through a number of "community making devices" such as annual conferences, journals, learned societies, chairs and academic curricula, textbooks; along the process of institutional establishment the emerging community shapes its social identity through the views developed by practitioners in their public presentations about novelty, references to the past and visions of the future.

This paper will focus on the views developed by synthetic biologists about novelty, their visions of the past and of the future rather than on their actual practices or institutional strategies, which are more relevant for a sociological analysis of discipline building. This paper rather seeks to characterize the epistemic choices of discipline builders, and to

emphasize the role of their discourses about the past and the future. Such discourses are not just a sort of ideological wrapping or external façade isolated from epistemic choices. They are integral parts of the process of discipline building, which is heavily loaded with values and visions. Such discourses are crucial for stabilizing the social and cultural identity of a discipline, and they are shaped by the local contexts as much as by the objects and instruments of investigation. This is one reason why this case study is limited to the US context.<sup>2</sup>

The social discourses of identity have two major functions. First they serve a purpose of legitimation. There is no historical necessity for the emergence of a discipline. In particular, synthetic biology is not the “natural outcome” of molecular biology and a range of alternative pathways could have been chosen for the establishment of the various research programs gathered under the umbrella ‘synthetic biology’. Many candidate disciplines or sub-disciplines vanish or merge in already established communities in the course of the discipline-building process. One major function of the social identity discourses is precisely to avoid such failures by forging a kind of historical necessity in order to establish and legitimize the field.

Second, the identity work is useful to attract funds and enrol scientists because they shape a vision of the future, an ideal type? This is why the models chosen for building a new discipline matter. They provide a sort of “paradigm”. But what happens when the practitioners of an emerging discipline promote various disciplinary models? Can a discipline be built on the basis of epistemic pluralism? (Chang, 2011)

### **1. 2000- A puzzling coinage**

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<sup>2</sup> International comparisons could help refining our understanding of the role of such discourses in discipline building. According to Molyneux-Hodgson and Meyer, 2009, the process of community building in the United Kingdom does not mobilize such disciplinary models. Rather it seems to be based on a science policy effort to i) catch up with the United States (with the not-lagging-behind argument); ii) building a network of existing communities and; iii) creating a sense of global collective.

Naming is a crucial step in discipline building, for demarcation purpose and for achieving visibility. (Powell, O'Malley, Müller-Wille, Calvert and Dupré, 2007) According to Luis Campos's inquiry on the coinage of synthetic biology', this phrase won over two rival candidate labels: 'constructive biology' and 'intentional biology'. (Campos, 2009) All three words emphasize the introduction of design in biology, albeit with quite different connotations.

'Constructive biology' was meant to emphasize the contrast with traditional biology, viewed as essentially observational and descriptive. The phrase came out as early as 1999 to refer to bio-inspired robotics and it seems to be mainly used by biologists working close to the Artificial Intelligence (AI) community: "Constructive biology (as opposed to descriptive biology) means understanding biological mechanisms through building systems that exhibit life-like properties. Applications include learning engineering tricks from biological systems, as well as the validation in biological modelling". (Nahaniv et al. , 1999) AI biologists share a number of concerns and practices with synthetic biologists. Yet the robotics community is quite distinct from the circle of researchers who promoted synthetic biology as a discipline. Only those synthetic biologists who are engineering minimal cells, with the expectation to explore the origins of life or the source of individuality do occasionally use the phrase 'constructive biology'.<sup>3</sup>

The alternative 'intentional biology' was a more serious candidate, since it had been the founders of the discipline - Robert Carlson, Roger Brent and Drew Endy – had used this phrase as early as 2000. The adjective 'intentional' was meant to emphasize the predictive

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<sup>3</sup> For instance George Church a professor at Harvard Medical School who is involved in a number of synthetic biology projects, used the term "constructive biology" to state his personal commitment: "The biggest questions I'm asking myself, at least in the laboratory, are: "What is it that makes us individuals?" That's what we call the personal genome project. Its aim is holistic, in contrast to the usual single disease or tissue. The second is: how do we engineer biology? which can be called our "constructive biology" or "biological design" efforts. The two might intersect quite nicely in the form of personalized medicine".

[http://blogs.nature.com/ng/freeassociation/2006/07/george\\_church\\_on\\_constructive.html](http://blogs.nature.com/ng/freeassociation/2006/07/george_church_on_constructive.html)

power acquired by biology thanks to the introduction of methods borrowed from engineering, as Carlson clearly stated:

“When we can successfully predict the behavior of designed biological systems, then an intentional biology will exist. With an explicit engineering component intentional biology is the opposite of the current, very nearly random applications of biology as technology”. (Carlson, 2001, 1)

However, when the phrase ‘intentional biology’ was publicised in the meeting “After Genome 6. Achieving an Intentional Biology” organized by Carlson in Tucson, Dec 2000, it raised intense criticisms from the biologists attending the meeting. It was perceived as a tacit criticism of current biotechnology as it had developed rather randomly since the 1970s.. (Campos, 2009, p. 18). Thus “the word ‘intentional biology’ went over like a lead balloon” reported Endy, who never fully endorsed the phrase ‘synthetic biology’. Even after its general acceptance in 2004 at the SB 1.0 Conference, he preferred to use “engineering biology” in his foundational paper. (Endy, 2005)

According to Campos, the alternative label ‘synthetic biology’ was suggested in 2001, by Carlos Bustamante, a biologist at Berkeley, where Carlson was a research fellow in the Molecular Sciences Institute until 2002.<sup>4</sup> Strikingly Bustamante has developed a distinct approach, typical of bionanotechnology rather than of mainstream synthetic biology. His group is involved in single-molecule manipulation and detection with optical tweezers and single-molecule fluorescence microscopy. They investigate the behaviour of biomolecular motors, molecular mechanisms of control of transcription in prokaryotes. For this purpose they make extensive use of Scanning Force Microscopy (SFM), a technique emblematic of

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<sup>4</sup> The mission of this Institute retains the predictive turn of Carlson’s Intentional Biology: “to predict the behavior of cells and organisms in response to defined genetic and environmental changes. For instance, its Alpha project (2001-2009) aims at “predicting the quantitative behavior of a eukaryotic regulatory network in individual cells in response to perturbations”.

nanotechnology. Bustamante's laboratory is not even mentioned among the Synthetic biology labs listed at the conference SB 2.0, in 2006.

If the proponent of the label synthetic biology did not belong to the core group of American scientists who promoted this discipline along the Synthetic Biology X.0 conferences (2004, 2006, 2007, 2008, 2011), how are we to understand that this phrase eventually came to prevail and acted as a signpost for bringing together research groups into a community?

There is a variety of research programs gathered under the umbrella synthetic biology. In her attempt at "piecing together a puzzle", Ana Deplazes distinguishes five different approaches: Bioengineering, aiming at making biological parts, devices, and systems, synthetic genomics, aiming at making chassis through DNA synthesis, protocell synthesis, unnatural biology, aiming at synthesizing exotic DNA, and in *silico* biology, aiming at designing organisms. (Deplazes, 2009) Bioengineering is only one approach among four others, though they receive most attention in the press and in the media. There is a striking imbalance between the small emerging community of bioengineers gathered around Drew Endy, Jay Keasling, Rob Carlson who took the initiative of the conferences Synthetic Biology X.0 and the huge number of research groups of chemists, biochemists, biophysicists, who bring their own practices and cultures in the field.<sup>5</sup>

For the small group of bioengineers who worked hard to promote synthetic biology as a discipline, synthetic biology proceeds from the fusion of two worlds: molecular biology which provided access to the building blocks of life and computational technologies pioneered by cybernetics. (Carlson, 2010, p. 6) Whilst it is clear that they do not take inspiration from chemistry, the parallel with synthetic chemistry is nevertheless acceptable for them in so far as it usually comes with two revolutionary claims: synthetic biology will

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<sup>5</sup> Among the groups who publish in the five fields mentioned by Desplazes are: Eric Kool's group at Stanford, Carlos Bustamante's group at Berkeley, Jack Szostak's group working on protcells at Harvard, David McMillen's group at University of Toronto, and Steve Benner's group or the famous Craig Venter's group.



deeply affect our lives and the world as synthetic chemistry did in the past; and synthetic biology will provide safer and cleaner substitutes for chemicals. (Keasling, 2008) In other words, the message conveyed by this label could be: Synthetic biology is bound to overtake synthetic chemistry.

If a consensus could be reached around ‘synthetic biology’ because this phrase served the ambitions of all research groups working in the field, does it mean that they have similar research agendas, visions and models? As it is nearly impossible to survey the research agendas of all groups, the paper will now focus on two extremely contrasted visions of the field developed by two specific groups.

## **2. 2005- Two visions of synthetic biology**

Among the most cited papers, two articles published in 2005 promote diverging views of synthetic biology inspired by two different models. Drew Endy’s famous paper “Foundations for Engineering Biology” seeks to promote foundational technologies inspired by computer engineering. (Endy, 2005) By contrast Steve Benner’s and A. Michael Sismour’s article “Synthetic Biology” provides a review of the field modelled on chemistry. (Benner, Sismour, 2005) Interestingly both Benner and Endy are concerned with disciplining synthetic biologists: Benner considers that discipline prevents them from always reaching the conclusion that they want to reach? (Benner, 2010) Endy considers that the engineers have to follow basic rules.

Endy’s paper introduces engineering methods into biology. Trained as an engineer in Civil and Environmental Engineering, Endy did a PhD in Biochemical Engineering at Dartmouth devoted to modelling the behaviour of a virus, bacteriophage T7, attacking E-Coli bacterium. (Jha, 2005) As too many parameters were out of control to predict the actual

behaviour of the virus, he figured out that an artificial virus with a simplified synthetic genome containing only functional genes would lead to a more predictable model. He then moved to the Biological Engineering Department at MIT where he worked to make biology easier to engineer. Endy seeks to import in biology the methods of engineering. He shares this objective with the group of scientists who promoted synthetic biology as a new discipline.

Endy derives three methodological rules from engineering: standardization, decoupling and abstraction. (Endy, 2005) Standardization presupposes the full description and characterization of biological parts. Decoupling is a strategy for simplifying a task by dividing it into manageable independent operations. Abstraction consists in dealing with each level of complexity separately, regardless of their interactions. Although the last two rules could have been taken from Descartes *Regulae ad directionem ingenii*, they were derived from electronic circuits engineering. Drew Endy, as well as Rob Carlson, and Roger Brent, the trio who supported the label 'intentional biology', took inspiration from both electronic circuits and software engineering. Their program rests on the creation of a data base, a collection of well-characterized biological parts that can be assembled in devices and systems. For Endy, decoupling and abstraction are not just rules for the direction of the mind since he recommends a strict division of labour between the various tasks. This engineering approach, emphasizing standardization, modularization, interoperability, transparency and reliability can be viewed as a continuation of "engineering ideal in American culture". (Rabinow, Bennett, 2007)

When Endy moved from MIT to Stanford in 2008 his research program reinforced the close connection between biological engineering and computer engineering. Among other projects his lab is working on a project of engineering genetically encoded memory systems with the view to store information within living cells. Thus engineering is the top priority. As Evelyn Fox Keller argues, for Endy "synthetic biology's role is not in understanding

organisms as they have evolved, but possibly (...) in understanding how to remake these organisms to better and more efficiently serve our ends as human users". (Fox Keller, 2009, 296)

Whereas Endy's paper was presented as the dawn of a new era, Benner and Sismour reviewed an already existing area of research. For them synthetic biology has been around for about 20 years. Benner who has been trained as a chemist performed the first synthesis of a gene in 1984 and later used organic synthesis to prepare a chemical system capable of Darwinian evolution. Accordingly, he is legitimate in claiming that he initiated synthetic biology as a field. For him, synthetic biology is basically an extension of bio-inspired chemistry. Based on his experience as a chemist, his group has used organic synthesis methods to create artificial molecules capable of behaving like biological entities, typically enzymes. Benner's main argument is that synthesis complements analysis. While analytical results will never suffice to overthrow a theory, synthesis alone is powerful enough to bring about paradigmatic changes. In his view, synthesis is first and foremost a tool for making discoveries. His model is Robert Woodward's synthesis of Vitamin B12 in the 1950s, which was like "sending a man on the moon". The synthetic route was a long multi-step process, which provided not only a useful molecule but above all a "better understanding of chemical bonding". Similarly in synthetic biology the failed efforts to synthesize non-ionic DNA backbones provided a better understanding of the significant role of repeating charges in the functions of DNA. The emphasis on the cognitive role of synthesis does not hamper its practical utility. The paper proudly mentions that the synthesis of artificial DNA led to branched DNA diagnostic assays developed by the industrial chemical manufacturer Chiron and Bayer diagnostics.

In their review of synthetic biology, Benner and Sismour distinguished two trends: in addition to the use of chemical synthesis to reproduce emergent behaviours, they point to

another research program seeking to assemble interchangeable biological parts into systems. This could be a recognition of Endy's modular approach to synthetic biology. In fact this trend is illustrated by biomimetic chemistry in protein engineering, aimed at reproducing isolated behaviours of natural bio-systems. Its main result according to Benner is a knowledge gain, which allowed Benner to go beyond Watson and Crick model of nucleic acids structure. The new model emphasizing the role of sugar and phosphate backbone in molecular recognition opened up new theoretical perspectives as well as new opportunities for personalized medicine.

### **3. Lessons from history**

Disciplinary histories have often been used by scientists as a tool for shaping emerging fields. The memory of heroic figures, founding events, and clichés helps building a community of practitioners and implicitly conveys goals and values. (Graham, Lepenies, Weingart, 1983; Abir-Am, Elliott, 1999) Synthetic biology is no exception. Both disciplinary models make extensive use of historical vignettes.

It seems that the advocates of the computer engineering model found few resources in the short history of this discipline as they preferably turn to other engineering disciplines. For instance, in his attempt to shape the future of biology as a technology Carlson finds inspiration in the history of aeronautics. (Carlson, 2010) He draws at least three methodological lessons from it. First, reducing complexity is a necessary condition for success. In his view the pioneers of aviation succeeded when they eliminated the mechanisms they were unable to understand and reproduce. "No biological engineer will success in building a system de novo until most of that complexity is stripped away, leaving only the barest essentials". (Ibid. p. 6) A second key for success was the quantitative approach, with

models to be tested. Aviation with aircrafts heavier than air proceeded from knowledge of the physics of flight and practical experience with flight was a kind of test of theoretical models. (Ibid. p. 7, 21, 40-41) And the third lesson is jointly taught by the history of aviation and computers: Innovation comes from outside academic circles and big industrial labs, so garage biology should be encouraged. (Ibid. , p. 176)

The chemical model benefits from more direct parallels with the history of nineteenth century synthetic chemistry. For instance, Yeh, and Lim (2007) compared the recent shift from molecular biology to synthetic biology to the transition that chemistry underwent in the mid-nineteenth century from a science focused on the determination of nature and proportions of compounds (through analysis) to a science aimed at synthesising new compounds. The latter generated the flourishing industry of fine chemicals that synthetic biology is said to overthrow in the near future. Twentieth-century biology is thus reconfigured as an analytic (rather than descriptive) science for the purpose of presenting the development of synthetic biology as the ineluctable consequence of the analytical phase.<sup>6</sup>

Without entering into any detailed historical survey, the paper gives a superficial glimpse of the history of nineteenth-century chemistry, relying on a selection of almost legendary figures of past chemistry. (Bensaude-Vincent, 2009) In the usual ‘whig’ manner, the authors select the episodes that can serve the point they want to make. In this case they argue that synthesis is a necessary complement of analysis for the advancement of knowledge. “Before the time of Wöhler and Berthelot the understanding of even simple molecules was as naïve as our current understanding of complex biosystems” (Yeh and Lim, 2007: 522). The paper minimizes the amount of knowledge acquired by twentieth-century biologists in order to stress the historical necessity of synthetic biology. “The history of organic chemistry suggests that synthesis will be a necessary complement to analysis in order for biologists to

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<sup>6</sup> To systems biology also, chemistry may provide a model as suggested by Pawan K Dhar’s paper (2007) who argued that a bio-periodic table using protein fold as the fundamental unit in biology would allow to compute higher-level interactions from component properties.

truly understand the mechanisms of complex living systems". (Ibid. : 523) Thus a first benefit of the chemical analogy is that it can be used for legitimating projects and investments in synthetic biology.

More lessons could have been inferred from this historical parallel for the benefit of the synthetic biology community. In particular, since chemical synthesis has been promoted in the nineteenth-century both as a cognitive method and as a source of material goods, since heavy investments from industrial companies were coupled with intensive academic research, the parallel could be used for legitimating the dual nature of synthetic biology: as a promising technology attracting venture capitals or industrial investments and as a cognitive enterprise aimed at improving our understanding of life. The parallel could also serve to dismiss the potential concerns raised by the entanglement of cognitive and commercial purposes since a number of nineteenth-century synthetic chemists coupled an academic career with positions in industrial companies.<sup>7</sup>

However the dual cognitive-commercial profile of synthetic biology is not a priority for the authors, who do not bother about potential conflicts of interest arising between the ethos of academic research and industrial interests. They accordingly develop a particular view of nineteenth-century chemistry exclusively focussed on the cognitive dimension of synthesis. As it emphasizes the limitations of analytical knowledge, the paper claims that nineteenth-century synthetic chemists did not know the composition and the structure of the substances that they synthesized. However disputable this claim might be<sup>8</sup>, it matters because it conveys the view that it is perfectly legitimate to make things without fully understanding what you

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<sup>7</sup> The life of Adolph von Baeyer could serve as an exemplar of the benefits that can be expected from intertwining academic and industrial careers. This organic chemist, former student of Kekulé, played a key role in industrial chemistry take-off, while conducting a prestigious academic career. A Professor at the University of Munich and later at the University of Strasburg, he was awarded the Nobel Prize for Chemistry in 1905. At the same time he was working at the corporate laboratory of BASF, where he and his pupils managed to achieve the industrial synthesis of indigo after years of research and many patents (see Haber, 1958, Reinhardt, 1996).

<sup>8</sup> For historians of chemistry this claim is highly controvertible. Marcellin Berthelot for instance emphasized that through synthesis chemistry had become a predictive science and illustrated its predictive power with Adolphe Wurtz's work on glycols. (Berthelot, 1897, p. 190-192).

are doing. “A critical lesson here is that a complete understanding of chemical principles was not a prerequisite for the emergence of synthetic chemistry. Rather, synthetic and analytical approaches developed in parallel and synergized to shape our modern understanding of chemistry.” (Ibid.,523) The analogy allows synthetic biologists to explore all kinds of combinations without being able to control and predict the outcome, for lack of understanding of the principles. In a way, the chemical model gives a moral license to play the sorcerer’s apprentice. As explorers of uncontrollable powers, synthetic biologists cannot always be held accountable for what they do.

Although they are obviously more concerned with academic research, the authors cannot completely overlook that part of current research efforts in synthetic biology are application-driven. “In today’s world, many tend to link synthetic chemistry with the production of drugs. Indeed, it was abundantly clear to early chemists that synthetic products could improve human health, but their initial efforts actually led to an industrial explosion in an unexpected direction.” (Ibid. :523) They nevertheless find in this other face of nineteenth-century chemistry a new example to claim as much academic freedom as possible. They use the episode of William H. Perkin who discovered a synthetic dye (mauve), while he was conducting research on quinine, an antimalaria drug, to emphasize the role of unexpected results. They also claim that this classical case of serendipity was the starting point of the booming synthetic dyestuff industry in the late nineteenth century. Thanks to this simplistic *raccourci* (which overlooks the complexity of the process leading from aniline to alizarin dyes and from laboratory discovery to industrial process) Yeh and Lim suggest that unexpected results are the rule rather than the exception. Hence a third lesson drawn from the history of synthetic chemistry:

“Synthetic biologists (and their funding agencies) must move forward with an open mind. The progress of synthetic biology cannot be myopically linked to only a few

obvious targets; instead, we must be prepared for a variety of potential industrial and therapeutic applications, including unexpected ones that we have not yet foreseen.” (Ibid.: 524)

Thus the parallel with synthetic chemistry is meant to secure a large autonomy for synthetic biologists.<sup>9</sup> Unlike the champions of an engineering view of synthetic biology, the chemistry model seeks a better understanding biology through synthesis. Looking back at the two simultaneous papers published in 2005 and at the lessons drawn from a historical parallel one gets the impression that two independent communities with their own goals, visions and ideals are using the same label ‘synthetic biology’ without interfering. Significantly Benner has never been invited as a keynote speaker in the annual conferences (most of them organized by the biobricks community) until SB 5.0 in June 2011. Are there two different synthetic biologies running parallel or do they really share common projects? Should we acknowledge the possibility of constructing a discipline on the basis of epistemic pluralism?

#### **4. Alternative models?**

Although Endy’s conviction that synthesis can be made easier through a modular approach is clearly inspired by electronic circuit engineering, it meets the view of synthesis as reverse analysis which comes from chemistry. In this respect it is noticeable that Endy does not take literally the computer metaphor for living systems. Unlike cybernetics-inspired biologists who claim that any aspect of biology can be examined computationally”, he does not advocate a computational program. Whereas many systems biologists could pronounce a cybernetic credo “if you can’t compute it, you don’t understand it”, Endy and his disciples

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<sup>9</sup> Yet as Andrew Maynard, a scientific advisor for Synthetic Biology Project at the Woodrow Wilson International Center for Scholars pointed out in his comment of Yeh and Lim’s paper, the historical precedent of synthetic chemistry could teach synthetic biologists quite different lessons. (Maynard, 2008) The damages and hazards due to a number of synthetic chemicals could be used for raising concerns and invite synthetic biologists to a more precautionary attitude in order to secure a sustainable development of synthetic biology.



rather believe in Feynman's credo "what I cannot create, I do not understand".<sup>10</sup> Ironically Endy's strategy from the simple-to-the-complex as exemplified in the sequence from biological parts, to devices, and systems could have been inspired by a famous nineteenth century synthetic chemist, Marcellin Berthelot. There is a striking analogy between Berthelot's program of gradual synthesis and Endy's biobricks approach. For Berthelot the development of synthetic chemistry would not depend on inspiration or intuition, but requires a gradual step by step procedure. (Berthelot, 1897) Starting with the elements carbon and hydrogen to synthesize binary compounds – the hydrocarbons - that constitute the backbone of all organic assemblies; then synthesizing ternary compounds (alcohols); follow up with the synthesis of quaternary compounds through combinations of lower compounds, and so on. Similarly Endy advocates a step-by-step approach moving from independent parts, to devices and then to systems. The champion of synthetic chemistry and the champion of synthetic biology share the conviction that the rational simple-to-complex method of design is the key to success.

Indeed Berthelot never achieved his grandiose programme to synthesize the complex compounds found in living organisms from the four elements, carbon, oxygen, hydrogen, and nitrogen. Similarly, up to now, Endy and his group have not achieved the synthesis of any biological system. The gulf between actual practices and the ideal of rational design creates another rapprochement between the chemical model and the computer model. Just as synthetic chemists working at the bench make molecules partly by chance, in a manner combining logic, tricks, and serendipity, (Hoffmann, 1995) so do synthetic biologists. Although synthetic biologists want biology to be rational and elegant, the few devices and organisms that have been successfully synthesized were made from pre-existing systems, through a lot of tinkering, trials and errors, and iterations. As Maureen O'Malley convincingly

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<sup>10</sup> O'Malley (2009) revisits the meaning of Feynman's too famous quotation and discusses its relevance for synthetic biology.

argues on the basis of a few examples lots of tinkering and kludging are involved in assembling the pieces to make a device (O'Malley, 2009). In this respect like in many others, synthetic biology is close to computer engineering where the term 'kludge' (combination of klumsy, ugly and dumb) originated.<sup>11</sup>

If the chemical model and the computer engineering model inspire similar strategies of synthesis, is it because they rely on the same metaphysical assumptions? Indeed the advocates of the chemical model consider DNA molecules as a code programming a number of operations. Nature is viewed as a source of code rather than as a source of raw materials. In other terms for all synthetic biologists, life is information. They also give prominence to functions over structure, they all look at the building blocks as functional units performing specific operations.<sup>12</sup>

From an epistemological perspective they equally share Feynman's credo that knowledge is acquired through creation or synthesis. (Schmidt, 2009) However the computer engineering model rests on the ideal: knowing before assembling. For Endy and his colleagues synthetic biology should follow engineering methods beginning with specification. The design process starts with a detailed description of the explicit requirements of a product. In the following stage, engineers attempt to combine existing parts, devices or systems in a way that will yield a product meeting those specifications. The parts should be plain clear and the assembly process is entirely predictable. It is intentional biology because the object of design results from a combination of intention and prediction. While knowing is a precondition for making in the engineering view of synthetic biology, it is not necessarily

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<sup>11</sup> Computer engineers use pieces of software ('patches',) to fix problems or clear up programs from all sort of bugs that hamper or diminish their performances. Bugs are often generated by various layers of language in a programme. Just as the genetic programme keeps vestiges of its evolution, computer programmes are full of traces of earlier stages without a source code or which no longer fit in the most recent language.

<sup>12</sup> Their shared concern with functionalities relies on the many different meanings of the term 'function'. Functionalizing most often means implementing useful tasks, sometimes creating chemical bonds and more rarely integrating an entity in a larger system to contribute to the emergence of new properties in the system.

understanding. As the purpose is not representing life as it is, or how it evolved, knowing rather means coming out with a framework of life for our intervention into it.

By contrast the chemical model being more about gaining a better understanding of life through synthesis requires making without fully knowing. If synthesis allows making discoveries and paradigm shifts, as Benner argued in his 2005 paper, it is because synthesis is much more than a process of reverse analysis confirming analytical results. If the authors emphasized that they needed a moral license to combine things without being able to predict the result, it is because synthetic chemists know how many detours, skills, tacit knowledge and tours de force are involved in the art of synthesis. (Hoffmann, 1995) As chemical syntheses rely on inner dynamics of molecules and interactions between them and with their environment, they are rather opaque processes. To chemists, Endy's ideal of interchangeable biological parts looks naïve as it makes no allowance for intrinsic interactions between dissolved molecules. With the experience of more than a century of molecular design chemists know that interoperability is a major challenge.

## **5. Divergent social practices**

Because of their unequal ratios between knowing and making, the two models of synthesis do not engage the designer's responsibility in the same manner. Whereas the algorithmic approach to synthesis inspired by engineering requires a blueprint of the process to make it predictable, the chemical approach always allows surprise, hazards and opportunities to occur. The engineers-designers of biological devices can be held fully responsible for their predictable results while the chemists-designers have to go through trials and errors and pilot plants before a synthetic process can be safely handled. Material

ingredients – whatever they be - have a spontaneous behaviour and need to be tamed through a long process of acclimatization and domestication.

In addition, the two trends have divergent views on ownership and sharing. The tradition inherited from chemical and pharmaceutical industries encourages biosynthetic chemists to patent their products at each stage of the process and they are in favour of proprietary databases. As soon as industrial or medical applications are in view they are made for profit. For instance Benner's career illustrates a clear-cut distinction between profitable tools or platforms for pharmaceutical industries and cognitive enterprises. On the profit side, he founded biotech start-ups such as EraGen Biosciences and the MasterCatalog of protein modules used as a proteomics platform by the Genome Therapeutic Corporation. The non-profit side is Benner's research at the Foundation for Applied Molecular Evolution (FAME), a centre for innovative research at the crossroad between molecular and planetary sciences in search for extraterrestrial life.

By contrast, synthetic biologists inspired by engineering work seek to secure simultaneously the academic and industrial futures of synthetic biology through open source. It is not just a variation about precisely where to draw the line on public versus private ownership. (Oye, Wellhausen, 2009) There is a disagreement within the US community of synthetic biologists about whether or not private property is necessary to spur innovation. Rob Carlson challenges the established demarcation line between upstream open academic research and downstream private applications. He advocated the combination of academia and industry from the beginning:

“The course of labor in biological technology can be charted by looking at the experience of the computer and internet industries. Many start-up companies in Silicon Valley have become contract engineering efforts, funded by venture capital, where workers sign on with the expectation that the company will be sold within a few years,

whereupon they will find a new assignment. The leading edge of the biological technology revolution could soon look the same”. (Carlson, 2001)

Endy, Tom Knight and Randy Rettberg created a data base of biological parts – the Registry of Standardized Biological Parts - at MIT and at the same time encouraged young people to practice synthetic biology. The collection increases thanks to the students teams involved in the annual International Genetically Engineered Machine Competition (iGEM). The participants are given biological parts stored in the registry at the beginning of summer and they have to combine them for designing a device or a system to be presented at the big Jamboree in Cambridge in autumn. They subsequently return the products of their designs to the registry.

“The Registry is based on the principle of "get some, give some". Registry users benefit from using the parts and information available from the Registry in designing their engineered biological systems. In exchange, the expectation is that Registry users will, in turn, contribute back information and data on existing parts and new parts that they make to grow and improve this community resource”. (<http://partsregistry.org/MainPage>)

The “get some, give some” principle, taken from the open source movement in software engineering is the basis of the creation of the Biobricks Foundation, a not-for-profit organization aimed at promoting data sharing, open technical standards, and the free availability of the biological parts. Thus as Stephen Hilgartner emphasizes, the Biobricks Group tries to promote a new regime of sociability through biology. The regime of openness subverts the current practice of patenting every step, it also challenges the divide between amateurs and experts, its ambition is to generate a new social order (Hilgartner, 2010, 3) The coupling of data production and social reorganization is a major component of Carlson’s programme of intentional biology. As early as 2001 in a paper entitled “Open source and its

impact on industry” he claimed that bio-engineering would become so cheap and easy that it would be accessible to amateurs, and since 2001 he has actively encouraged garage biology. The promotion of amateur science is even encouraged by some universities: Johns Hopkins University shares the conviction that synthetic biology is so easy that it is accessible to beginners with no prerequisite, and no disciplinary background. It offers an interdisciplinary Build-a-genome Course in the undergraduate curriculum, which suggests that medical students could get rid of the biological heritage. (Cooper EM, et al., 2012)

The project of subverting the hierarchy between experts and laypersons is not necessarily inspired by democratic ideal. As Hilgartner argues, the discourse of openness in synthetic biology has no clear political agenda:

“BioBrick regime, while potentially well-suited to create a significant community resource of available parts, looks like a relatively conventional IP-minimalist regime. As such, it does little to address increasingly pressing questions about how property rights in emerging technology impinge on democratic decision making. » (Hilgartner, 2010, p. 19).

In contrast to European synthetic biologists who are aware of the public resistance to GMO crops, Endy and Carlson are not open to public debates or stakeholders meetings. They are not concerned with all the discussions and experiments going for promoting democracy in technology. (Callon et al. 2001, Feenberg, 2010). They are more in favour of a self-regulation of the scientific community about issues of safety and security. The series of Syn. Bio conferences and the Synthetic Biology Research Center are working in this direction. While participatory democracy is not even envisaged, government regulations are strongly criticized. In discussing issues of security and safety, Carlson develops the example of illegal drugs to argue that all regulations are leaky, not only inefficient but even counterproductive:

“Regulation is therefore causing a shift from distributed, domestic production to foreign centralized, criminal organizations”. (Carlson, 2010, p. 125)

Moreover, despite the subversion of academic hierarchies, the regime of openness is not really engaged in a social revolution. The main objective is cost reduction for the industrial take off of synthetic organisms. The history of work organisation in capitalism has taught us that cost reduction goes hand in hand with the simplification of operations, and a subsequent deskilling of workers which allows their replacement by machines and a cost reduction for maximum profit. Although the discourses about the iGEM competition are all about creativity, fun and excitement, the students provide a cheap way to fill the library of biobricks and to foster the process of cost reduction. Indeed students are not robots, but the replacement of technicians by automata has been very quick in DNA sequencing and the subsequent cost reduction over the past decade has been spectacular: from \$5000 for one million of bases in 2001 to \$0.08 in 2011.

Carlson’s future prospect of open source bioengineering is inspired by a rejection of the current patents held by big pharmaceutical companies, which slow down innovation. However Carlson’s criticism of biocapitalism does not mean that he wants to promote an alternative to capitalism. (Rajan, 2006) Far from trying to step away from market economy Carlson advocates an open, free, deregulated market. He is convinced that the market push will drive the future of synthetic biology: “Where there is a market there will always be attempts to supply it, even when the product is both legally and culturally frowned upon”. (Carlson, 2010, p. 126) Carlson consequently advocates a deregulated and open innovation based of creative entrepreneurs and small firms rather than big pharmaceutical companies: “The development of fundamentally new technology in a market economy requires and explicitly depends upon the participation of small firms and entrepreneurs.” (Ibid. p. 134)

The assumption underlying Carlson's vision and the Biobricks project is that easiness and openness will enlarge the number of users and consequently bring added value to synthetic biology. This *credo* drove the spectacular diffusion of computer technologies under the auspices of the so-called Moore's law predicting the rate of increase of computing power and of costs decline. Carlson formulated a similar projection for synthetic biology (known as Carlson's curve) predicting that the sequencing of a human genome for \$1000 in 2020. Computer industry provides the roadmap for synthetic biology with an exponential rate of development and a flourishing industrial future in a deregulated market economy. Similarly the source of value in open biology will be the electronic information that specifies the biological function. "When it eventually becomes possible to synthesize DNA at will for minimal cost and to run the 'program' in an organism at one's choice, there may well be no market for the object defined by the program. In that world the value of DNA truly becomes its informational content. The only money that would exchange hands in transaction would be to pay for the DNA synthesizer and for reagents and raw materials to run the synthesizer" (Carlson, 2010, p. 217)

Carlson's strong advocacy of open-source and deregulated bioeconomy has a paradoxical and certainly unintentional consequence. In his effort to secure the most promising future for synthetic biology, he provides weapons to its critics and opponents. In his book *Biology is Technology*, one can find the most severe critical analysis of the state of the art in synthetic biology. From an economic perspective synthetic biology as it is now is not sustainable. In particular, Carlson undermines the commercial future of the most celebrated prowess. Keasling's work on malaria through ad hoc engineering and tinkering is too expensive to be realistic from a commercial production. (Ibid. p. 100-101) Just for Venter's experimental assembly published in 2008, \$ 2 million have been spent and much more is needed for a second step and hundred times more for scaling up (Ibid. p. 104-105).



Carlson also unwillingly casts doubts on the economic potentials of the Registry of Standard Biobricks when he confesses that most biological parts designed by students in iGEM competitions do not work, that only a few standard parts are well characterized. (Ibid. p. 96) He emphasizes such defects as proofs that synthetic biology is still in its infancy and that it needs to mature in a near future.

## **Conclusion**

Synthetic biology provides an interesting case study for understanding the complex process of discipline-building, because of the paradoxes in its early development, which may impact on its future. Choice of a disciplinary profile despite the multidisciplinary practices, choice of a label ‘synthetic biology’ which does not mirror the programme of those who work hard at the promotion of the new discipline. It is important to stress that synthetic biology in the USA is not a monolithic block.

The contrast between the two disciplinary models presented in this paper is just an example of the epistemic pluralism, which dominates the field. Different research groups have different agendas, different relations to the past, and different visions of the future. Along the lines of synthetic chemistry, the new discipline looks like the continuation and completion of twentieth-century biology. It opens an era of plenty both for the advancement of knowledge and for practical applications. It is not disruptive as it legitimates the pursuit of academic research together with industrial enterprises, and commercial profits. By contrast the engineering model supports claims of a radical break in the biological research tradition. In encouraging amateur practice and openness it seems to disrupt the academic regime of knowledge production as well as the regime of intellectual property that covers biotechnological products. It develops a new mode of knowledge sociability and economy.

If epistemic pluralism is a major feature of emerging fields like synthetic biology, how are we to interpret it? Is it a temporary state of a discipline in its infancy prior to the implementation of a dominant paradigm? In this case the two disciplinary models of synthetic biology would be competing for primacy in a kind of Darwinian selection. Or should we consider the coexistence of various epistemic cultures a typical feature of “normal science” in a time when research is driven by instruments, by economic interests and science policy? In this case epistemic pluralism would be the hallmark of a post-academic regime of knowledge production.

Although Carlson insists that synthetic biology is still in its infancy there is no hint of any rivalry that would suggest a Darwinian competition. There are certainly tensions between the groups of practitioners and maybe some scepticism about the research agendas of rival groups, but to my knowledge there are no attempts at disqualifying them. The choice of a disciplinary profile did not raise any concern for constructing a coherent framework out of the diversity of epistemic cultures. Pluralism is not perceived as threatening the future of the discipline. On the one hand, the discrepancy between the two models here described is qualified because they are just two extremes in a wide spectrum of research agendas, as mentioned in the introduction. On the other hand, the potential conflicts between the proponents of the two models have been neutralized for at least two reasons.

First, they converge in the belief that despite the current obstacles and bottlenecks, in the future synthetic biology will bring about solutions to all current issues, from the origin of life, extra-terrestrial life, to the production of renewable energy and cheap medicine. This technological optimism reminiscent of the scientific credo of nineteenth-century chemists, contrasts with moderate expectations in public opinion, who seem to favour a moratorium on synthetic biology products. (<http://www.genengnews.com/gen-news-highlights/gen-poll-majority-favors-moratorium-on-synthetic-bio-products/81246614/>)

Second, applying open source ideals to biology and encouraging amateur practices has not so far disrupted the course of professional research and the fierce competition between industrial countries. As long as sophisticated and expensive technical platforms equipped with up-to-date instruments are needed for achieving reliable syntheses, garage biology will remain a hobby for young creative people (or for eccentric millionaires). Noble discourses about freedom, creativity and the annual festive jamborees in Cambridge are far from sufficient to initiate a democratization process. Despite the discourses and the promises, the discipline grows in the USA with no democratic basis and no concern for democratization.

Whether the regime of openness initiated by the Biobricks Foundation can prevent the kind of monopolies that prevailed in former biotechnology, such as GMO crops, remains an open question. Will the champions of openness stop the race for patents? Will they secure the free availability of all products, and not-for-profit initiatives? Or alternatively will all synthetic biologists follow on the path of Craig Venter's mad pursuit of spectacular synthetic *tours de force*, and patent applications covering general aspects in order to conquer a position of monopoly? Or will the community split up with a fraction continuing the patent regime that presided over the development of industrial chemistry since the nineteenth-century and another fraction taking advantage of the emergence of this new technology to create a new social order? The future of synthetic biology is still open, and may not be entirely in the hands of synthetic biologists. It depends partly on industrial investments, on science policy, not only in the United States but in Asia and Europe as well. However is likely that epistemic pluralism will continue to rule this discipline for a while and that synthetic biology will never be a replica of synthetic chemistry, never become a "discipline as we know it".

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