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RESEARCH ARTICLE

Designing de novo: interdisciplinary debates in synthetic biology

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Abstract Synthetic biology is often presented as a promissory field that ambitions to produce novelty by design. The ultimate promise is the production of living systems that will perform new and desired functions in predictable ways. Nevertheless, realizing promises of novelty has not proven to be a straightforward endeavour. This paper provides an overview of, and explores the existing debates on, the possibility of designing living systems de novo as they appear in interdisciplinary talks between engineering and biological views within the field of synthetic biology. To broaden such interdisciplinary debates, we include the views from the social sciences and the humanities and we point to some fundamental sources of disagreement within the field. Different views co-exist, sometimes as controversial tensions, but sometimes also pointing to integration in the form of intermediate positions. As the field is emerging, multiple choices are possible. They will inform alternative trajectories in synthetic biology and will certainly shape its future. What direction is best is to be decided in reflexive and socially robust ways.

Keywords Synthetic biology · Design · Innovation

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Introduction

Synthetic biology is often presented as a promising knowledge field. A crucial novelty that it brings, differing from previous genetic engineering, is that it aims at producing novelty by design. The ultimate promise of synthetic biology is the production of living systems that perform new and desired functions in predictable ways (Silver 2009). The success of such an endeavour relies on the possibility of turning biology into an engineering discipline, and engineers and biologists are collaborating in such a program. However, how to realize the promise of turning biology into engineering and how to perform design de novo are not unproblematic endeavours. This paper provides an overview of, and explores the existing debates on, the possibility of designing living systems de novo as they appear in interdisciplinary talks in the field of synthetic biology. Multiple and sometimes competing views make up this young knowledge field. As the field is emerging, multiple choices are possible. They will inform alternative trajectories in synthetic biology and will certainly shape its future. That being a central argument of this paper, it is organized into four sections. The first section of the article introduces the issue of designing de novo as central to the emergence of synthetic biology as a new knowledge field. The second section provides an overview of interdisciplinary debates between engineering and biological views within the field. A third section revisits and broadens such interdisciplinary debates. Referring to some of the literature on synthetic biology in the social sciences and the humanities, the arguments presented in this section aim at broadening the debate and pointing to some ultimate sources of disagreement. Differing views on what life is and how it works lay at the basis of controversies on the possibility of designing living systems de novo as they appear in interdisciplinary talks between engineers and biologists. The last section presents some possible ways in which differing views may lead to differing lines of action and trajectories in the field.

In the field of synthetic biology, the scope of interdisciplinarity is opening up as a number of projects in Europe and the US are required to integrate views from the social sciences and humanities in different ways .[1] Coming from two different fields (i.e. social sciences and biology), the authors' approaches and experiences of the field of synthetic biology are of a very different kind. However, in the course of our talks we found that similar concerns emerged in different ways within the different disciplines that study and make up synthetic biology, including our own. The arguments below build on the literature on synthetic biology and on our experiences working in the field.[2] We present a spectrum of views and arguments, identifying a range of controversial opinions that are at the origins of synthetic biology and that we repeatedly came across within the literature and in our discussions with researchers in the field. Concerns with the possibility of designing systems and functions de novo appear mainly in the 'bio-engineering' approach to synthetic biology, and may also concern 'minimal genome' strategies (Deplazes 2009). That being the scope of the paper, we do not intend to be exhaustive, yet we do intend to show the heterogeneity that makes up this emerging field, provide an overview of the points in debate, and relate them to possible lines of action.

Designing de novo in synthetic biology

The term synthetic biology refers to a wide range of endeavours "embodying an equally wide range of aims, and having correspondingly various relations to the activities generally included in the discipline of biology" (Fox Keller 2009). In spite of such heterogeneity (Anonymous 2009; Anderson et al. 2012; O'Malley et al. 2008; Mukherji and Oudenaarden 2009), a widely accepted definition of synthetic biology presents it as the design and construction of novel biological entities, "and the re-design of already existing ones" (Calvert 2010; see also Mukherji and Oudenaarden 2009). In an attempt at including the diversity of approaches, aims, and practices of synthetic biology, such a definition points to fundamental ambiguities at the very basis of this emerging field. To be sure, it is clear that the ambition of designing functions that cannot be found in nature is quite different from modifying already existing natural systems. Nature-mimicking construction and novel design are quite different endeavors. Indeed, a range of biological systems, from relatively simple ones such as a virus to entire bacterial genomes, has been constructed by chemical synthesis. Yet, designing de novo entails a far more radical action from an epistemological and moral point of view for it involves the creation of a new kind.

The vision of *radical novelty* is often mobilized in the media, and it generates not only hype, but also public reactions (Rinaldi 2012). In the literature, it is not always clear what novelty may refer to, whether it is the production of new functional behavior or new systems. Furthermore, de novo is sometimes used as synonymous with being made *from scratch*, and it is sometimes assumed that when systems are made from scratch, functional novelty will arise. Since its origination, a recurrent point in discussion within the field has been whether synthetic biology actually uses novel assembling techniques that substantially differ from those deployed in molecular biology and biotechnology, or whether it rather introduces a new approach, although doing so by using already existing techniques (De Lorenzo 2010a; Morange 2009). Emphasizing design, some have even pointed to a paradigm shift, while others have argued that synthetic biology is merely a buzzword used to produce a hype effect (Potthast 2009). To illustrate this controversy on the novelty of the field: BioBricks are iconic constructions in synthetic biology. The term BioBrick refers to DNA sequences with well-defined functions. They are projected to be standard interchangeable parts that can be used in a range of biological systems and will work in a predictable fashion. Yet, it is not unproblematic to establish how BioBricks perform novelty by design. On the one hand, BioBricks are technically and physically classical constructs, such as the ones that have been used in molecular cloning for decades; on the other hand, their expected standard behavior makes the difference with the *ad hoc* design of genetic constructs in biotechnology. Another much discussed example was the first "synthetic cell", as it was named (Bedau et al. 2010). The novelty here was that, for the first time, a chemically synthesized bacterial genome, based on a known native genomic sequence, was synthesized to be functional (Gibson et al. 2010). This outstanding result can be considered the first step towards the construction of further rationally designed synthetic cells. Nevertheless, it was questionable as to whether the construct was genuinely new, not only because the synthesized genome was functioning in a naturally existing cell, but also because the sequence of the

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[1] For instance, the last European funding scheme: FP7 KBB. 2013.3.6-02 Synthetic Biology Towards Applications (http://www.2020-horizon.com/Synthetic-Biology-towards-applications-i1060.html) research on the ethical, legal, and social implication was requested as a component of proposed research projects.

[2] The second author of the paper is a biologist by training, working in the field of synthetic biology, and has been an advisor of iGEM teams since 2008. The first author of the paper does social studies of science. Although this is not an ethnographic paper, the paper benefits from the ethnographic experiences of the author, including talks and interviews with engineers and biologists in the field. She was also an advisor of the Valencia-Biocampus iGEM team in 2012.

synthetic genome was for the most part a copy of an existing one (Giuliani et al. 2011). To mention just one more remarkable achievement of synthetic biology: metabolic pathways have been re-wired in astounding ways, to the extent that the *artemisinin project* (Dietrich et al. 2009) achieved the synthesis of a precursor of the antimalaria drug artemisinin in yeast and *Escherichia coli*. Acknowledged as a milestone within the field of synthetic biology, this successful project relied to a large extent on tinkering and trial and error rather than rational "design". It could be argued that the project introduces a novel approach with a focus on "circuitry" (characterizing metabolic pathways as circuits). Perhaps the most remarkable novelty of the artemisinin, and other similar projects for the production of drugs and biofuels in microorganisms, is the aim of turning biology into a substrate of industrial engineering (Keasling 2009), particularly "to formalize the process of designing cellular systems in the way that traditional engineering disciplines have formalized design and manufacture, so that complex behaviours can be achieved for practical ends" (Arkin and Fletcher 2006). For biology to truly become an engineering discipline, first projecting desired functions and then realizing them, it would have to follow principles of rational design such as standardization, decoupling, and abstraction (Endy 2005). Yet, the task to turn biology into a matter of industrial design is far from being an easy one. While materials such as iron have quite predictable behaviours, living systems are known to be quite variable in their functioning. In some views, this versatility makes life appear as an exciting and promising material (Isaac et al. 2006; Endy 2005). But such variability can also make biology difficult to engineer (Anderson et al. 2012; Serrano 2007). To what extent such versatility of life can be engineered is a crucial point of debate within the field of synthetic biology.

Insofar as it brings the promise of novelty by design, synthetic biology is often presented as a promising emerging field, yet most of its promises are still to be realised (Porcar et al. 2011; Knight 2005; Kwok 2010; Potthast 2009). As often presented, the potential of synthetic biology relies to a large extent on realising the possibility of turning biology into an engineering discipline (Endy 2005). Still, there is no agreement on how biology should be turned into engineering. In discussions between engineering and biological views, a crucial point in debate is on the possibility of designing living systems de novo. The next section provides an overview of such a debate.

Controversies: engineering and biological views

To realize the promise of designing new systems with novel functions, and to design those systems from scratch, both biologists and engineers in the field would agree that at least two conditions are necessary: the parts of the system have to be well characterized and there has to be a sufficiently well defined set of rules for assembling the parts (i.e. BioBricks or other forms of DNA standards). Such agreement opens two kinds of debates: on the nature of the parts and on assembling strategies.

Discussions on the "parts" have largely focused around the issues of standardization and modularity. A crucial question is whether those parts are, or can be made into, interchangeable, reusable, and connectable modules (Shetty et al. 2008). To work as real modular parts with defined functions, the parts should be orthogonal, that is, context independent (De Lorenzo 2010b). In a broad sense, the debate revolves around the issue of whether modularity is a natural property, or whether it is an abstraction imposed by engineers to simplify the design of complex systems. The spectrum of views in relation to this point may go from those who see modularity as a property of living systems (Anderson et al. 2012; Silver 2009), to more skeptical views. A common intermediate argument is that biology presents relative modularity (Arkin and Fletcher 2006; De Lorenzo 2010a, b). However, this, one could say, is a "biology type of argument" since in engineering modularity is not a relative property. Rather it introduces a fundamental premise on how the modules that make up a machine interact. Another possible argument here, a kind of an "engineering argument" this time, is that even when biological systems do not display natural orthogonality, and even if modular and standard parts cannot be found as such in nature, by manipulating biology *as if* it was modular, it will eventually become so. The vision here is orthogonal living systems co-existing with non-orthogonal systems (and perhaps mixing?).

In the discussions on modularity, a central question is that of context independency. A variable range of views and understandings can be found in relation to this point. Here the spectrum of opinions goes from engineering views that would tend to characterize contextual relations as non-desired noise, to others that would tend to see cellular contexts as a site where relevant, if not crucial, phenomena occur. A conciliatory midway view is that, to some degree, the context should be included in synthetic biology designs and constructs (Carrera et al. 2012; Cardinale and Arkin 2012). Although this is an accepted position, disagreements may arise when proposing concrete ways of doing this in practice. One proposal is to standardize the context itself (i.e. minimal cellular chassis), reducing the number and complexity of contextual relations. Insofar as the aim here is to produce controlled and predictable contexts, this can be seen as an engineering kind of solution to the problem of contextuality. If the context is to be engineered, an unavoidable problem will arise: where do the limits of the context lie? This is a problem of scaling. A possible view here is that in living systems different scales exist, one including the other in an increasing complexity structure not unlike a living Matryoska. In biological systems a key source of complexity is the interconnections across scales (Noble 2008). In this view, one can possibly conclude that, "engineering any part of an organism must at some level take the entire organism into account" (Adrianantoandro et al. 2006). Yet, attempts at including the complexity of the "entire organism" in design practices will be difficult to conciliate with engineering ideals, where a "good design is a simple one". A wide range of opinions may also appear in relation to the issue of complexity, from those who understand living systems as inherently interconnected and complex (Schille 2011), to those who believe that complexity can be avoided by starting the construction of living systems from scratch (Purnick and Weiss 2009), and that "an alternative to understanding complexity is to get rid of it" (Tom Knight, quoted in Ball 2004). As differing views express, an unresolved tension between simplicity and complexity articulates foundational debates in synthetic biology.

A recurrent argument in favor of engineering living systems de novo is that since there is so much functional complexity in living systems, it will be easier and more effective to design living systems from scratch and in a simpler way than trying to substantially modify naturally existing systems (Adrianantoandro et al. 2006). This is an argument in favor of simple and rational design. A key issue here is how *emergence* is differently understood from engineering and biological approaches. Ever since Darwin's theory of evolution was broadly accepted as paradigmatic in biology, most biologists accept the role of natural selection as the main mechanism for the *emergence* of new biological forms and functions. Systems biology inherits this paradigmatic idea and gives it a more complex turn, emergence appearing as a systemic property that ultimately allows for new functions to originate (Bok von Wûlfingen 2009). At the basis is the same idea: that non-predictable behavior, as emergence and mutations, is not the exception but the normal way of evolving for living systems (Moya et al. 2009). Conceptualized in this way, evolutionary mechanisms may be difficult to conciliate with principles of rational design; as in engineering, the incidence of an emerging behavior is to be controlled and reduced for the well-functioning of the system. Nevertheless, some envision developments in the field, particularly through the use of digital methods, that will enable to turn evolutionary mechanisms such as adaptation and selection into the object of design, eventually enabling the engineering of whole ecosystems and a programmed type of evolution (Smolke and Silver 2011). On the extreme end of the spectrum, some may argue that life resists rational design, emphasizing the unpredictability and variability of living systems by mechanisms such as mutation, natural selection, and emergence. This might be deduced from the detailed and holistic studies on *Mycoplasma pneumoniae* (one of the bacteria with the smallest genome), which reveal an unexpected transcriptomic and proteomic complexity (Kühner et al. 2009; Yus et al. 2009; Güell et al. 2009) In this view, when released in natural environments synthetic systems will either be prone to die or evolve in unexpected ways. An in-between position promotes the combination of rational design and directed evolution strategies, including directed evolution (Porcar 2009). These strategies combine the potency of rational design (i.e. the insertion of a desired gene coding for an heterologous protein) with the "creativity" of evolution by subjecting engineered strains to repeated rounds of mutation or DNA recombination and Darwinian-like (survival of the fittest) selection (Romanini et al. 2012; Schaerli and Isalan 2013).

Further debate on complexity focuses on the rules and grammars for the assembling of the parts into more complex devices and systems (Cai et al. 2009; Heinemann and Panke 2006) How does one assemble the simple parts so as to perform novel and desired functions? An important question here is to what extent the notion of "hierarchies" can be applied to the organization of living systems just as it is applied in engineering, or if living systems follow different organizational patterns. As with modularity, again, a key question is whether some sort of hierarchical organization exists in nature or whether it could be artificially produced. Differing views can be found as to the question of how systems are organized, and consequently, how new functional behaviors may emerge. The problem of assembling, thus, is not of an easy nature and manifests in multiple sets of challenges. Some leading figures in the field have diagnosed the problem in terms of "design gap" (Smolke and Silver 2011), arguing that even when synthetic biologists have become quite good at constructing simple devices, they still need to develop ways to assemble systems to behave in predictable and desired ways over time (i.e. to follow a design). To fulfill such a promise, considerable effort is being put into the development of programming languages and software for assembling the parts (MacDonald et al. 2011; Blakes et al. 2011; Kaznessis 2009). Such a digital toolkit is expected to allow the design of systems that will ultimately work in a programmed manner (Smolke and Silver 2011). The successful realization of such a toolkit would entail a "second wave" in synthetic biology (Purnick and Weiss 2009), where tinkering and trial and error would finally be replaced by planned rational design.

To sum up: the vision of a Lego biology in which standard biological parts are assembled into devices and systems has generated a lot of controversy, particularly around the question of to what extent engineering principles such as standardization, abstraction, and decoupling can be applied to the making of biological systems (de Lorenzo and Danchin 2008). While from a biological view the endeavor of imposing principles of rational design on the making of living systems may appear to entail fundamental difficulties, from an engineering approach these difficulties can be considered a mere technical problem. In the latter case, the realization of the promises of synthetic biology will depend on the development of a technological toolkit (software, more efficient automated technologies for DNA synthesis, etc.). In practice one can find a wide range of positions regarding the possibility of engineering biology by applying principles of rational design, and therefore the possibility of *designing* de novo. Discussions of to what extent general principles of rational design can be transferred to the domain of biology present further implications and problems: how to translate those general principles of design into more concrete rules and procedures for the design of specific living systems? This question does not appear explicitly in debates between engineering and biological views, yet it has been pointed out by philosophers and sociologists of science (See Mackenzie 2010). To illustrate this point: The repressilator is a specific design that has been widely discussed as becoming an iconic design of synthetic biology. The repressilator is a synthetic genetic regulatory network implemented in *E. coli* and is constructed with three genes, with gene expression connected in a feedback loop, in such a way that each gene represses the next gene and is itself repressed by the previous gene of the loop (Elowitz and Leibler 2000). The outcome of the circuit is the oscillatory expression of a green fluorescent protein which mimics, to a certain extent, natural circadian clocks. An argument here is that the concrete design principles of a pendulum are well known (Gramelsberger 2012), and furthermore there are natural dynamics in living systems that resemble the oscillatory movements of a pendulum, such as the circadian clocks mentioned above; so if design implies novelty by definition: what is designed in the repressilator? Other iconic examples in synthetic biology are switches and simple sensing mechanisms, for which the same argument can be applied: although they are certainly useful for enlarging the inventory of the functional elements that can be combined into more complex systems, it can be argued, that they lack novelty per se.

Opening up the scope of the debate: views from "abroad"

In the previous section we have provided an overview of some of the controversies regarding the possibility of d*esigning living systems* de novo as they appear in debates between engineering and biological views in synthetic biology. The cross talks between engineering and biological views focus on parts and systems and on how they relate, and thus, how they can be assembled. Issues of concern are modularity, context-independency, and emergence. Although opinions on such issues are quite divergent, we have also identified a number of middle positions that point to a will for consensus and to find working solutions. The idea that a "relative modularity" can be found in nature is but one example, however not exempt of problems. How to develop strategies to specify such *in between* (engineering and biology) positions remains unclear. In spite of fundamental controversies, the community of synthetic biologists appears as a "community of promise" (Brown 2003): joined by the shared expectation that, in one way or another, living systems will be designed to perform novel and desired functions.

Sometimes questioning synthetic biology's innovative ambitions, but also imbuing them with reality, scholars from the social sciences and the humanities have been included in a number of synthetic biology projects in Europe and the US, broadening the interdisciplinary scope of the field. What the specific contributions of such disciplines may be has been usefully discussed (See Calvert and Martin 2009; Rabinow and Bennett 2012). Our paper supports the idea that those disciplines can contribute by "opening up" current debates to broader questions, disclosing what is many times only assumed in such debates (Stirling 2008; Calvert and Martin 2009; Delgado et al. 2012). By pointing to the sources of disagreement, these disciplines can also contribute to conceptual developments in synthetic biology, particularly in relation to the issue of *designing* de novo. The following lines suggest some places where such contributions could start.

Looking at the scholarly traditions of engineering and biology seems to be a good place to start searching for clues on differing understandings of notions of systems as they inform debates in synthetic biology. Not the least, engineering has been concerned with producing performance and functions by producing things. Producing explanations about how the system works is an effect, rather than the main goal, of design activities in engineering disciplines (Schyfter 2013). On the other hand, even for the most applied branches of biology, producing knowledge about how life works has been the main goal of research activities (Knorr-Cetina 1999; Rheinberger 1997). Perhaps for that difference in purpose, when looking at systems, engineering strategies have placed the focus on sorting out ways to assemble a set of parts (Vincenti 1990; Law 2002) that have been previously characterized with set if stable properties. When transferred to biological domains, and particularly as it is used nowadays in some strands of systems biology, the notion of system emphasizes interactions, rather than placing the emphasis on the functioning of isolable parts (Boogerd et al. 2007). Especially in some approaches to systems biology, a recurrent argument is that the function of the system is more than the sum of functions of the parts integrating the system (Bok von Wûlfingen 2009). How to conciliate the emphasis on isolable parts with the emphasis on complex interactions remains a challenge for synthetic biology. This tension appears implicit in debates on how to address and tackle contextuality, as presented in the previous section. At the basis of cross talks on contextuality lies a divergence of views on how living systems function. Again, a historical approach to the notion of systems and how they have been articulated and used in the fields of biology and engineering can help to bring to light such divergences. After *the rise* of artificial intelligence research, both biological and cybernetic systems started to be described as being organized on the basis of complex non-linear and auto-regulated dynamics. Although cybernetic ideas about the complexity of the system were transferred to the understanding of how biological entities are organized, the most central question remained unsettled: how does complexity arise in the first place? (Fox Keller 2007). While in cybernetic systems complex organizational rules (including self-organization rules) are given by an external agent (engineer), living systems generate complexity in a spontaneous, mainly evolution-driven fashion. This is, by combining a sort of "informal" organization (Moreno 2007) in which mutations and the blind mechanism of natural selection are at the origins of biological diversity. This means that while living systems can generate new functions, cybernetic systems cannot generate new functions by themselves, unless they are programmed to do so (Trogemann 2010). A promising vision mobilized in the field of synthetic biology is that of programmable living systems, but to what extent can living systems be programmable and self-organizing? And what kind of self-organization would that be? These fundamental questions about the nature of systems remain open. Disagreements on how living systems are organized, and consequently, on how novel functions may arise, relate to two further questions that are central for conceptual development in synthetic biology but that have not been openly addressed in debates between engineers and biologists in the field yet: (1) If emergence is at the origin of new functional behavior, can emergence itself be engineered? And, (2) In designing de novo, who is the designer? The following lines present some clues to open up those questions.

The question about emergence ultimately refers to the issue of what the nature of life may be and the possibility of turning biological matter into an engineering material. To be sure, synthetic biology's promise of turning biology into engineering relies on the premise that living systems are *engineerable matter*: "biology is to serve as a substrate for engineering as much as inanimate materials provide the basic stuff for civil, mechanical and electrical engineering" (Schyfter 2012). In turning the versatile and dynamic character of life into the object of design (Bensaude-Vincent 2007), synthetic biology introduces unprecedented challenges for engineering: what appeared before as intangible and limiting, is now promising and exciting. Yet, to what extent living matter can be conceptualized and performed as a mere material for engineering, just as iron and silicon, is a matter of discussion. In this regard it has been argued that design in synthetic biology entails, not only a number of practices and approaches, but also principles of design that have often been invoked as "a way of abstracting away the uncertainties and intricacies of biology" (Mackenzie 2010, p 183). Design in synthetic biology, thus, is often used as a black box that impedes discussions about the different ontologies of living and non-living matters. Such lack of distinction may be the source of practical problems when synthetic biologists try to design living things with novel functional behavior. For engineers to be able to design novel functions they need some knowledge of basic and stable properties of the materials they are working with so that they are able to specify the problem in engineering terms (Vincenti 1990). Yet, a main difference between engineering materials such as iron or silicon and engineering living systems is that, while the first have properties that are then used to produce functions, the second already have functions. In non-living systems the distinction between property and function is often obvious. For instance, in the case of computers it is easy to distinguish hardware and its properties from the software that enables the functioning of the system. For the case of biological systems, there has been a lot of debate about to what extent it makes sense to distinguish between structure and function, if at all. The idea that the function of the gene is encoded in the gene sequence, and later on, that it is embedded within gene-regulatory networks, has been central to developments in molecular biology (Fox Keller 2009). The distinctions and relations between structure, property, and function are more straightforward in engineering. This has a direct effect on organization of design practices. In industrial engineering, a common way of proceeding is by first identifying a desired function and then the best material to perform such a function. Next, in a quantitative fashion, the properties of the materials are modeled to perform the function before the design is actually realized. However, in biological approaches the distinction between properties and functions of living systems is often unclear. Are "self-reproducing", "self-repairing" and "self-organizing" properties/functions of living systems? One could bring this question even further and ask: is "living" a state, a property, or a way of functioning of biological systems? (See DeLanda 2011; Deplazes and Huppenbauer 2009). Conceptual distinctions on this point are often absent in debates between engineering and biological views in the field. Yet, in designing de novo, such distinctions are important as it should be clear what is to be engineered and what is to be the novel product of engineering.

The question of whether it is possible to turn the emergent properties of life itself into the object of design is a crucial one. As it appeared in the debates above, engineering views diverge when it comes to conceptualizing and valuing emergence. Since the rise and general acceptance of Darwinian evolution, there is a shared understanding within the different biological fields that life entails a certain degree of systemic unruliness as lack of clear functional direction is at the basis of Darwinian evolution (Dupre 2003). In the form of mutation and unexpected changes, such unruliness is at the basis of the emergence of new functions. This has an effect both at the level of the parts, and also in the overall functioning of the system. For instance, it is difficult to establish one part-one function relations in biological systems since one part of the system may have more than one function (even if not performed at a particular point in time), some parts may have no function, and new functions may emerge (Fox Keller 2003). Furthermore, in biological systems, what appears as dysfunctional in the first place may become functional if the context changes, and what appears as having no function may become functional under different conditions. And yet, in the tradition of engineering, emergent behaviors are usually unwanted ones. How to conciliate such differing views on the origins of functional behaviors in living systems is a central challenge for synthetic biology: is the "messiness" of life in the form of variable forms of emergence, mutations, and other forms of systemic noise a condition or an impediment for the appearance of new functions? The answer to this question of course depends on who is assigned the role of the designer of the system. As debates in the section above point to, by emphasizing rational design, design in synthetic biology may question natural selection as the mechanism at the origin of functions. Whether synthetic biology points to a paradigm shift, by moving away from a Darwinian view on evolution to just produce *some other* kind of living systems (some other non-natural nature), is a broad and central question suggested by some authors in the philosophy and sociology of science (Deplazes and Huppenbauer 2009; Calvert 2010), yet it remains to be openly discussed in debates within the field. However, if the purpose of synthetic biology is not to just produce a new kind of life (i.e. orthogonal), but to engineer natural life to perform new functions, issues such an emergence and context will have to be taken seriously. To this end, the challenge of synthetic biology will not only be to turn biology into engineering, but also to develop more biological forms of engineering (Rabinow and Bennett 2012).

The debate on emergence and on how new functions may arise in living systems ultimately refers to the question of who is the designer, as pointed out above. The intentional, purpose-driven, and even dream-driven, character of synthetic biology is often emphasized in engineering views in the field. Non the less, work on the history of synthetic biology reports how the term "intentional biology" was considered to give name to the field in its origins. The term would be used to refer to the potential of the field to produce living systems that 'would behave as intended, rather than displaying random and mystifying behaviors often encountered when genetically modified organisms are introduced into new environments or set loose in the wild' (Robert Carlson quoted in Campos 2010, p 17). In engineering, design *pursues* a purpose; engineered systems always function to fulfill someone's expectation. In rational design a function is always with-purpose and an external agent produces the functionality of the system. Building on a Darwinian paradigm, however, biologists would tend to agree that, "in the wild", life is made by no one and for no one. Biological systems have functions, but no obvious purpose a priori. An obvious and much discussed epistemological and ethical question for debate is to what extent life can be produced for utilitarian *purposes* (Boldt and Muller 2008). Beyond that discussion, differences in conceptualizing functionality in relation to purpose will inform discussions on whether functions are new or old. In this regard, a lack of neat distinctions on what is *new* and what is *old* is quite apparent when looking at the functional behaviors of the living things produced in synthetic biology. To illustrate this point, in 2010, one of the authors of this paper (MP) supervised an iGEM team in Valencia, Spain. The team produced a BioBrick consisting of a yeast "prionic switch". In talks with the students, we realized that while biotech students tended to understand this BioBrick as a 'modified prionic protein that works *as if* it was a switch'; engineering students understood it as a switch made on the basis of organic stuff. This is an important difference in understanding: prioritizing function and utility; engineering students characterized the BioBrick as a switch. From an engineering view, switches are designs that are made to accomplish certain purposes and expectations. In contrast, from a biological view, prionic proteins do not correspond to any pre-given purpose, but in a sense carry in themselves the reason of their own functioning (quite dysfunctional by the way), a result of Darwinian evolution. While focusing on purpose and utility, one could have concluded that the BioBrick presented functional novelty, yet focusing on the prionic protein and its functioning from a biological view, novelty is not so obvious. This example is mentioned to illustrate that the question of whether biology produces functional novelty is not straightforward, but ultimately depends on the background and expectations of those involved in the specific design activities. As we argue in the next section, differing views on the possibility of designing living systems de novo lead to differing expectations and paths of action for synthetic biology.

Concluding: paths of action for synthetic biology

Synthetic biology is emerging as a fundamentally diverse field, where differing views on what life is and how it functions co-exist. Along with such diversity, there are a range of different opinions on how the promises of synthetic biology are to be realized and different explanations of why the great expectations have not been met yet. Such explanations suggest differing lines of action and imply a certain positioning in relation to the future (Table 1). For instance, if from an extreme engineering view, life can be thought of as a material that primarily functions as any other material and to which modular functionality can be applied, one could thus construe that synthetic biology has not accomplished its promises yet, mostly because of a lack of technical means. In this line of thought, it has been argued that developments of synthetic biology depend on making more efficient, faster, and cheaper DNA synthesis technologies (Carlson 2010). If one believes so, the obvious recommendation for policy makers would be more investment in technological development. This kind of thinking often entails a vision of breakthroughs in synthetic biology as being just around the corner, or at least relatively close. For those who emphasize that living systems are fundamentally complex and interconnected, the breakthroughs in synthetic biology may not only depend on technological development. Rather, a possible diagnosis of the problem here would be that of incomplete biological knowledge. A logical line of action to take here would be more investment in systemic approaches to life, with expectations of mid- to long-term developments.

A different vision can be that living systems and non-living systems work in radically different or even incommensurable ways. A logical conclusion would be that the concepts used in engineering disciplines are not sufficient or not appropriate to describe and design living systems. One possible proposal would thus be re-conceptualizing engineering to suit biology, or a sort of biologization of engineering. In this line of thought, the discussion would not be focused on determining whether living systems are more or less modular, orthogonal, and so forth, but rather new conceptual tools should be generated. For instance, a renewed notion of "system" that joins together engineering and biological views could be negotiated. In order to promote such conceptual work, engineers and biologists would have to collaborate in a truly interdisciplinary fashion and on a long-term schedule. In this interdisciplinary conceptual work, philosophers and sociologists of science would also contribute valuable knowledge. Another possible vision is one in which one thinks of living systems as being radically variable, open, and uncertain. This easily connects with the idea that the promises of synthetic biology have not been accomplished yet due to an intrinsic limitation of human knowledge. We would have to accept, if we follow this point of view, that it is not possible to have a complete knowledge of life. When the inherent incompleteness of scientific knowledge is emphasized, a coherent way of acting would be on the basis of precaution and humility (Jasanoff 2007). Relatedly, one would have to accept that the future is uncertain and that it is difficult to foresee when/if the promises of synthetic biology will be met. In our discussions with biologists and engineers in the field of synthetic biology, we have not found much emphasis on these kinds of arguments, but rather they are

Table 1 Synthetic biology, multiple views and paths for action

View	Why not yet?	Possible policy recommendation	How far is the future?
Living systems are fundamentally complex and interconnected	Incomplete biological knowledge	More funding for systems biology, systems ecology…	Long term/mid-term future
Life as a material. It can be used as a substrate for engineering	Technology is not yet there	More funding for developing a technological toolkit for synthetic biology	Mid-term/short term future
Living systems and non-living systems function in differing/incommensurable ways	Engineering needs to be reconceptualized/biologization of engineering?	Promoting conceptual work through interdisciplinary collaborations	Mid-term/long-term future
Living systems function in radically variable, open and uncertain ways	Intrinsic limitation of human knowledge	Precaution and humility	Don't know. The Future is uncertain
The intrinsic value of life	It is inappropriate to think of life as a substrate for engineering	Open debates on values and worldviews	Emphasis on the present

more commonly found among philosophers and sociologists of science and complexity theorists. To different degrees one can also recognize this view among policy makers supporting precautionary approaches. Public views also have a role within current synthetic biology policies and they will possibly influence the future(s) of this emerging field. For instance, the ETC group and over a hundred civil society organizations have called for a moratorium on synthetic biology (Pennisi 2012). In this view, synthetic biology is alleged to be "extreme engineering" (ETC 2007), entailing a non-proper way of "playing" with life. It is easy to envision environmentalist, indigenous, and religious groups emphasizing the intrinsic value of life and opposing the idea that life can be used as a mere substrate for utilitarian purposes as engineers use other materials. Here, the focus of the debate is not only on future risks and uncertainties, but also on present inappropriateness. A proper policy recommendation in this regard could be promoting ethical debates and transparent science communication exercises where scientists have the chance to make explicit the values and worldviews involved in their research (Boldt and Müller 2008). Up to this point, we have intended to provide a catalogue of different positions and views in relation to synthetic biology, its promises, and future prospects (Table 1). In practice, the different views and opinions in the controversies of synthetic biology may not appear separated.

This article has provided an overview of debates on the possibility of designing de novo as they emerge in the field of synthetic biology. Different views co-exist within the field, sometimes as controversial tensions, but sometimes also pointing to integration in the form of intermediate positions. Such diversity does not need to be reduced for the field to develop, but rather diversity can be seen as enriching this field. Nevertheless, depending on how such tensions are negotiated, the field may take different directions. What direction is best is to be decided in reflexive and socially robust ways.

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