Philosophy of Science (2022), **89**, 908–917
doi:10.1017/psa.2022.60

PSA PHILOSOPHY OF SCIENCE ASSOCIATION

PHILOSOPHY OF SCIENCE

SYMPOSIA PAPER

(Un)Easily Possible Synthetic Biology

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(Received 15 October 2021; revised 05 March 2022; accepted 02 May 2022; first published online 25 May 2022)

Abstract

Synthetic biology has a strong modal dimension that is part and parcel of its engineering agenda. In turning hypothetical biological designs into actual synthetic constructs, synthetic biologists reach toward potential biology instead of concentrating on naturally evolved organisms. We analyze synthetic biology's goal of making biology easier to engineer through the combinatorial theory of possibility, which reduces possibility to (re)combinations of individuals and their attributes in the actual world. While the last decades of synthetic biology explorations have shown biology to be much more difficult to engineer than originally conceived, synthetic biology has not given up its combinatorial approach.

1. Introduction

At face value, synthetic biology appears to offer straightforward purchase into biological possibility. In turning hypothetical biological designs into actual synthetic constructs, synthetic biologists may have, in so doing, realized some previously unactualized biological possibilities. Yet, the task of engineering biology is challenging at the outset. Biological systems are results of evolution: idiosyncratic, context-dependent, and tangled with piecewise adaptations. What kind of modal ontology, then, underlies the synthetic strategy of biology made, if not easy, at least *easier*?

We use the combinatorial theory of modality (Armstrong 1986, 1989) to analyze the notion of possibility native to synthetic biology. We argue that it can better accommodate the agenda of synthetic biology than the notion of biological possibility based on abstract combinatorial spaces (e.g., Dennett 1995; Huber 2015). The latter tends to put too much emphasis on the elements and their combinability, formally conceived, while Armstrong's theory also emphasizes the importance of structural universals. We treat the design principles of synthetic circuits as structural universals, arguing that they are central for the rational engineering approach in synthetic biology. This approach seeks to standardize biological parts, assembling them into circuits according to first-principle designs that are often transferred to biology from physics and engineering.

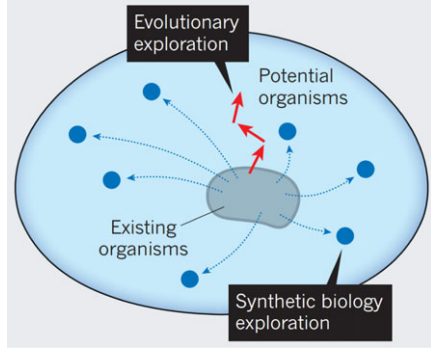

Figure 1. The expansion of biology from natural organisms to potential organisms (Elowitz and Lim 2010, 890).

The last two decades of synthetic biology experimentation have shown, however, that rational engineering of biology is far less easy than originally conceived. First, the biochemical peculiarities of biological parts and simple synthetic constructs, and their interactions with the rest of the cell, make their recombination challenging. Second, the analogies to electronic circuits that have already proven limiting when it comes to bacteria have largely been left behind in the recent research on the organization of multicellular organisms. Yet, although synthetic biology research has questioned many of its earlier assumptions, its commitment to a combinatorial approach appears to remain unwavering.

2. Spaces of the (biologically) possible

In a programmatic article published in *Nature*, two leading synthetic biologists, Michael Elowitz and Wendell Lim, argue for an "*expansion of biology* from a discipline that focuses on natural organisms to one that includes potential organisms" (Elowitz and Lim 2010, 899). Biology should follow the example of physics and chemistry that study "the physical and chemical principles that govern what can or cannot be, in natural and artificial systems" (ibid). While many areas of biology, like evolutionary biology, do also engage in modal reasoning, Elowitz's and Lim's goal is more ambitious. They highlight how forward engineering of new behaviors using well-understood genetic components and simple design principles can help extend biological research beyond naturally evolved organisms and their evolutionary paths. Figure 1, taken from their article, encapsulates the main goal of the expansion of biology through synthetic biology: taking biology to some other directions than evolution. This goal has often been combined with that of improving biology. While the results of natural evolution are unduly complicated due to the process of random mutations of already existing designs, rational engineering promises simpler and more optimal designs. In Figure 1, evolutionary explorations follow a steady, stepwise path, while synthetic biology explorations offer *potential* (marked by *dashed* lines) short cuts to other areas of the space of possibilities, not reachable by evolution.

How should this space be understood? Elowitz and Lim do not explicate how they conceive of the space of biological possibilities while other philosophers and scientists have taken up the charge. Dennett (1995) lays out a huge space for all possible DNA

https://doi.org/10.1017/psa.2022.60 Published online by Cambridge University Press

sequences in his "Library of Mendel," by defining biological possibilities as follows: "x is biologically possible if and only if x is an instantiation of an accessible genome or a feature of its phenotypic products" (Dennett 1995, 118). The Library of Mendel is basically a *logical* space consisting of *descriptions* of genomes, whose standard codes in known living systems consist of only four characters (A, C, G, and T). It is noteworthy that Dennett allows for alternative genetic systems as well, which would lead to other spaces of possibilities (Koskinen 2019). Evolutionary biologist Andreas Wagner has similarly invoked the metaphor of the library in depicting the spaces of evolutionary explorations (e.g., Wagner 2014). His libraries include the library of protein genotypes, the library of regulatory genotypes, and the library of metabolic genotypes. Evolution explores these libraries through evolving populations.

Both Dennett and Wagner note that these kinds of libraries are hyperastronomical in size. The possible states in such spaces exceed by far the number of atoms in our universe, and the time the evolutionary process would need to visit all possible states would take longer than the existence of our universe. This poses the serious question of how life could have evolved and enabled such a diversity of life forms on earth. Clearly, libraries of these kind do not yet capture biological possibility, though they do address an important aspect of synthetic biologists' understanding of it. What is important is the combinatorial nature of these libraries, and how such a combinatorial approach relates to the idea of biology made easier: Engineering new biological functions could be achieved by assembling standardized biological modules. How these modules are supposed to be assembled, is a problem that is heightened by the vastness of libraries and the problem of dynamics. We suggest that Armstrong's combinatorial theory of possibility better captures the notion of biological possibility inherent in the combinatorial synthetic biology agenda. What is more, the constraints of Armstrong's theory of possibility also illuminate the challenges of the idea of biology made easier.

3. The combinatorial world of Armstrong

Like Dennett's and Wagner's notions of biological possibility, Armstrong's combinatorial theory of possibility (Armstrong 1986, 1989), is based on combinations of basic components. Yet it also goes beyond library metaphors in addressing the questions of assembly and dynamics, although the latter only to a limited extent. The combinatorial theory of possibility aims to reduce the possible to the actual. A combinatorialist is both a naturalist and an "actual-world chauvinist" (Armstrong 1989, 56) tracing "the very idea of possibility to the idea of combinations—*all* the combinations which respect a simple form—of given, actual elements" (Armstrong 1986, 575). Such combination also covers the notions of contraction and expansion, which are important notions when it comes to evolutionary processes and synthetic biology (see the following text for more on expansion).

The actual world of a combinatorialist consists of (1) a set of things, or individuals, that can be characterized by (2) a set of properties and relations, and (3) the distribution of these properties and relations, which exhaustively specifies which individuals have which properties and in which relations they exist with one another (see Kim 1986). Once the individuals and their attributes (properties and relations) are fixed, all other worlds can be generated from them by combination and recombination.

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While Armstrong views the world in terms of individuals, properties, and relations forming a single spatio-temporal system, he is wary of thinking of it as "a tinker-toy construction from three different parts" (Armstrong 1989, 577). Instead, these "elements" should be understood as abstractions from what he calls "states of affairs," and only by "selective attention may [they] be *considered* apart from the states of affairs in which they figure" (ibid., 57). For reasons of space, we will consider neither this complication of Armstrong's theory any further nor the question of whether there could be a fixed base ontology of simple individuals, which do not have any proper parts. For instance, Kim (1986) thinks that Armstrong would need to posit such a base. Armstrong allows, however, that it is contingent matter whether it is "structures all the way down," and whether any individuals, properties, and relations might be "indefinitely complex" (ibid. 586). What is important for our purposes is to note that the combinatorial Armstrongian world is structured, likely in very complex ways. It does not boil down to the virtually uncountable arrays of simple elements in the Mendelian library.

Indeed, Armstrong distinguishes between conjunctive and structural properties. For instance, F & G would be a *conjunctive property*, where F and G are properties. The Mendelian library in its concentration in all possible genomes (and their phenotypic products) seems to be an example of a space made up of such conjunctive properties. *Structural properties* are more complex, involving relations, where any number of parts could presumably stand in various kinds of relations to each other. In addressing structural properties, Armstrong talks about structural universals that do not have a mereological composition. While Armstrong allows for *expanding* the world by more individuals, the same does not apply to universals. There are no "alien" universals. Such requirement follows directly from Armstrong's actualism: The building blocks of worlds need to be instantiated by actual individuals.

The molecule methane provides a stock example of a structural universal. Methane is composed of four hydrogen and one carbon atoms, which form covalent bonds in-between them. Fisher explains methane's status as a structural universal as follows: "If methane is instantiated, the molecule that instantiates it has five spatiotemporal parts. These parts must instantiate certain universals: four of the five parts instantiate hydrogen, and the remaining part instantiates carbon" (2018, 2). Lewis (1986) has argued against structural universals, among other things, on the basis that methane has only one universal called "hydrogen" and not four. In response, Armstrong has revised his earlier account according to which complex universals are mereological wholes, analyzing them rather as states of affair, and claiming that such states are subject to nonmereological composition. The consequent philosophical discussion has engaged in offering various theories that attempt to explain the compositional nature of structural universals (see Fisher 2018). Regardless of how this problem may be solved, the notion of structural universals is crucial for understanding the synthetic biology agenda of designing novel biological functions, parts, and organisms.

4. Structural universals and the synthetic biology program

In their construction of synthetic systems, synthetic and systems biologists make heavy use of the idea of general principles governing biological control and

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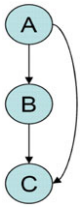

Figure 2. Example of a network motif in form of a feed-forward network. *Note*: See http://www.clipartbest.com/clipart-RTG6Geeyc.

development. The original program of synthetic biology was premised on the idea that biological circuits would follow some general design principles in an analogy to electrical circuits—a hypothesis that is only partially supported by the progressing synthetic biology research, as we will discuss in the following text. In the notion of a design principle, the structure and dynamics come together, as Alon has put it: "The structure of biological circuits—the precise way that their components are wired together—provides them with special dynamical features" (Alon 2006, 2). Alon has further assumed that complex circuits are assembled from recurrent patterns of so-called network motifs. They are basic connectivity structures that occur much more often than would be the case if they occurred by chance (Milo et al. 2002). Figure 2 shows an example of such a network motif, a feed-forward loop. It can be defined as "pairs of source and target nodes that have two or more internally disjoint connecting paths" (Berka 2012, 75). In a biological context, such loops can, for example, speed up the manufacture of proteins that are not transcription factors. In the network depicted by Figure 2 there are three spatiotemporal parts, of which, for example, A and B can represent transcription factors that bind to the receptor C. A feed-forward network is a small structure in which A directly regulates C or using an intermediate transcription factor B.

Network motifs, as well as more complex network structures, can be considered structural universals in Armstrong's terms.[1] They are abstract structures that can be instantiated by different kinds of entities. Such entities can be considered universals as well, being, for example, transcription factors in this case. Differing from the structure of the methane molecule, the feedforward loop depicts a network that is of a dynamic character. Its dynamic is not visible in the visual depiction of a feed-forward loop, but can be described, for example, by differential equations.

The idea of combining standardized genetic parts according to such general design principles has been formative for synthetic biology. The beginning of synthetic biology has often been dated back to the publication of the first two synthetic circuits in *Nature* in 2000 (Cameron, Bashor, and Collins 2014). One of these circuits was a synthetic toggle switch (Gardner, Cantor, and Collins 2000) and the other one was the repressilator, a ring oscillator implementing a negative feedback loop between transcriptional repressors (Elowitz and Leibler 2000). Later on, it was shown that the addition of a positive feedback loop to the negative feedback loop would increase the robustness and tunability of oscillations (Stricker et al. 2008). Results such as these led to the expectation that synthetic biologists could rewire and reprogram

[1] Wagner (2014) also appears to ascribe to structural universals in praising the tightness of the "nexus between math and reality" (220).

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organisms for useful ends. The other part of the rational engineering agenda of synthetic biology has been provided by the goal of accumulating standardized genetic parts, from which engineered circuits could be assembled. A notable step in this direction was the *Registry of Standard Biological Parts* founded in 2003 at the Massachusetts Institute of Technology. The registry records many types of biological parts, such as DNA, plasmids, primers, promoters, and ribosomal binding sites, as well as devices such as reporters and inverters.[2]

Although network motifs are dynamic in character, their treatment as structural universals tends to sidestep many important features of biological circuits. The entanglement of topology and dynamic in the network structure provides for additional possible behaviors targeted in the more recent research in synthetic biology. Stochastic fluctuations, that is noise, in gene expression serve as an example. Enzymes and proteins, which activate and inactivate genes are only present in low numbers in cells, which leads to fluctuations in gene expression. The question is whether such noise plays a different role in biology than in engineered systems, where it is largely considered as a nuisance to be eliminated (Knuuttila and Loettgers 2014). The research on noise, as well as many other developments within synthetic biology show that biology may not be as easily engineered as originally conceived.

5. (Un)easy possibilities, variously constrained

With "easy possibility," modal epistemologists refer to particular kinds of objective possibilities. Some x is easily possible if it is objectively possible that x obtains or exists, assuming that things are roughly similar to how they are. Easy possibilities have local restriction conditions; in scientific contexts, they can include relevant entities and causal dependencies, as well as technological availabilities. As most restriction conditions are unknown and may remain so, one way around this problem is to invoke "accessibility relations" instead of restriction conditions (Strohminger and Yli-Vakkuri 2019, 1160).

Synthetic biology makes heavy use of accessibility and similarity relations. Apart from utilizing novel molecular biology technologies and the wealth of accumulating biological data, synthetic biology has been premised on the assumption that the functioning of biological organisms is similar to that of engineered artifacts, relying on modularity and some basic and generalizable principles that it shares with physics and engineering. This combinatorial approach has unquestionably contributed to the perception of easily possible synthetic biology. The (rational) recombination of actual, well-characterized biochemical parts according to some universal connectivity structures has been expected to make accessible such regions in the overall space of biological possibilities that could not be attained by evolutionary explorations (given their historical and entrenched nature).

The more than two decades of synthetic biology has established, among other things, that it is possible to construct genetic circuits from biological parts, endowing them with novel functions. These successes of synthetic biology have provided evidence for the design principles used, thus adding to our knowledge on what is

[2] http://parts.igem.org/Main_Page.

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biologically possible. Yet, the successes of the combinatorial program of synthetic biology have only been partial: Synthetic systems have turned out to be only somewhat functional, and experimentally opaque. It is often difficult to find out why synthetic constructs perform differently than expected. Consequently, it remains unclear whether the design principles applied really amount to any structural universals governing actual and possible life.

Problems are often easier to tackle in the abstract. Synthetic biology, if anything, shows this to be the case—things tend to get messy at the lab bench. Synthetic biologists have to juggle multiple constraints at the same time. Some of the constraints relate directly to the techniques and methods of the construction process and, therefore, may be considered independent from objective biological possibilities. Such constraints are expected to change over time with technological and methodological progress. Others are due to the biochemical properties of the parts: their standardizability, actual combinability, and resultant dynamic, as well as the dependence of synthetic systems on the cellular environment and its metabolic system. Then there are the difficulties of relating the properties and interactions of the molecular components to mathematical models that often provide blueprints for synthetic systems, and also the primary means for studying their behaviors (e.g., Knuuttila and Loettgers 2013). Moreover, through the triangulation of mathematical and synthetic modeling, the biological features become entangled with concepts and analogies embodied by mathematical models, often transferred from other domains, especially from physics.

Most of the challenges synthetic biologists have been tackling in recent research relate to the increasing complexity of the synthetic systems, as the research has moved from bacteria to different cell types and multicellular organisms and addressed the stochastic nature of cellular processes. When it comes to making use of synthetic biology in multicellular organisms, one of the challenges results from transporting synthetic circuits into cells (Gao et al. 2020). Here, special attention needs to be paid to preventing the circuits from becoming integrated into the host genome.

Perhaps paradoxically, the program of synthetic biology, based on the notion of modularity of biological entities and design principles adapted from electrical engineering and physics, has been accumulating evidence against these very assumptions, becoming more biology inspired in the process. Apart from addressing more complex designs and noise, the modular architecture has also been questioned. Whereas earlier research in synthetic biology sought to construct as many well isolated modules as possible, it has become clearer that the interactions of the synthetic modules with the rest of the cell environment may make their functioning more robust (Cookson, Tsimring, and Hasty 2009). However, in complex synthetic systems consisting of several circuits, components of the different circuits may interfere with each other, disrupting the function assigned to them.

6. Future "unintuitive" designs

Especially the turn from bacteria to multicellular organisms has prompted synthetic biologists to explore more complicated novel designs. An illustrative example is provided by the recent research of the Elowitz lab at California Institute of

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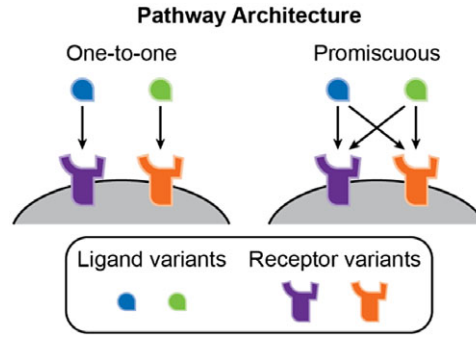

Figure 3. Comparison of the key–lock interaction with the promiscuous signaling pathway (Su et al. 2020).

Technology on signaling pathways in the development of multicellular organisms. They develop differently than do bacteria: embryonic development crucially depends on accurate, timely, and specific communication between cells. Research in developmental biology has discovered several highly preserved developmental pathways such as Notch, WNT, BMP, and Hedgehog. These pathways raise the question of how such a limited number of pathways can provide high precision cell-cell communication in diverse life forms.

The Elowitz lab, among some other labs, has approached this question as an information processing problem, focusing on the coding and deciphering of information through making use of experiments in addition to mathematical and synthetic modeling. Li and Elowitz focus on "'communication codes' through which information is represented in the identities, concentrations, combinations and dynamics of extracellular ligands" (Li and Elowitz 2021, 1). Specifically, they aim to shed light on "how signaling pathways decipher these features and control the spatial distribution of signaling in multicellular contexts" (ibid.). What is intriguing about their approach is that ligands, which are proteins binding to receptors, are not approached as "messages," but rather as "messengers." In the beginning, Elowitz and team found it confusing and difficult to make sense of the signaling pathways in development. In contrast to the common understanding according to which ligands bind to receptor sites in a key-lock like fashion, they found "promiscuous" binding of ligands and receptors.

For example, in the case of the BMP (bone morphogenetic protein) pathway, 11 different ligands exist that form pairs or dimers of the same or different proteins, which again can bind to even more complex structures of proteins. These ensembles of proteins bind to receptors, which themselves have substructures and, by doing so, turn genes on or off in the process of development. Promiscuous binding shows that the ligands are not very choosy when it comes to receptors. The same ligand can bind to different receptor subunits, as shown in Figure 3, which compares a one-to-one pathway to a promiscuous one.

Synthetic biologists have dubbed such designs as these "unintuitive" (Eldar and Elowitz 2010) when compared to the familiar engineering designs. However, conceived as messengers, BMPs are able to mediate messages between different kinds of cells. In fulfilling their task, the BMPs follow some combinatorial rules, which imply some kind of design principles. Understanding them might allow researchers to probe

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and design different developmental pathways leading to novel biological organisms and functions.

Promiscuous binding prompts the question of how such a complicated signaling process could encode information and regulate the development in multicellular organisms. And what is the role of combinatorialism in this complex dynamic? It seems clear that one virtue of combinatorialism is precisely that it allows for the complexity of multiple layers that make the BMP system more precise and robust. Moreover, promiscuous ligand-receptor bindings can yield more complex patterning and versatility in cell types with fewer signals. Consequently, despite the complexity and unintuitiveness of the organization of systems like the BMP pathway, the combinatorialist program used to study them has remained intact. In fact, the BMP system, as examined by the Elowitz lab, is more radically combinatorial than what would have been expected: Instead of any inherent bindings, the components of the system can be assembled in manifold ways. But this does not mean that anything goes. The scientists identified several combinations of ligands and receptors functioning as messengers.

There is one thing, however, that may need to go: the fixed repertoire of universal design principles. As the case of promiscuous binding shows, the simple and intuitive design principles transferred from physics and engineering likely do not apply to biology as such. In the case of network motifs, some specific function is assigned to each structure (even though its realization depends on biochemical parameters and the environment). In contrast, in the case of BMPs serving as messengers, different combinations of ligands and receptors form multiple relationships to each other that nevertheless are able to transport the same message between two cells. As a result, biological possibilities appear less easy to be engineered. The design principles may be highly unintuitive, as well as change and get extended over time, and the advancing research in synthetic biology has shown that their applicability strongly depends on the system and environment in which they are applied.

7. Conclusion

We have argued that the idea of rationally engineering novel biological functions, parts and organisms is based on a combinatorialist metaphysics. In this regard, the combinatorial theory of possibility of Armstrong fares better than the notion of biological possibility presented by Dennett. Armstrong's theory also addresses, apart from the idea of combining modular biological parts, the design principles governing their connectivity. Some central limitations of Armstrong's theory also prove revealing with respect to the idea of biology made easy. Especially the assumption of a fixed set of structural universals—or a fixed set of simple design principles in terms of systems and synthetic biology—appears difficult to maintain. Biology seems to trade with complexity, for good reason. Could this complexity be reduced to combinations of more basic modular circuits, like network motifs? The recent work on promiscuous binding points to the contrary, although it is still firmly grounded on a combinatorialist approach. Nevertheless, it is also combinatorialism with a difference: a multitude of different structures and functions emerging from the different combinations of biological entities.

Acknowledgments. This project received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 818772). Tarja Knuuttila also acknowledges funding from the Swedish Research Council, grant no. 2018-01353.

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Cite this article: Knuuttila, Tarja and Andrea Loettgers. 2022. "(Un)Easily Possible Synthetic Biology." *Philosophy of Science* 89 (5):908–917. https://doi.org/10.1017/psa.2022.60