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Synthetic Biology as an Engineering Science? Analogical Reasoning, Synthetic Modeling, and Integration

Abstract

Synthetic biology has typically been understood as a kind of engineering science in which engineering principles are applied to biology. The engineering orientation of synthetic biology has also received a fair deal of criticism. This paper presents an alternative reading of synthetic biology focusing on the basic science oriented branch of synthetic biology. We discuss the practice of synthetic modeling and how it has made synthetic biologists more aware of some fundamental differences between the functioning of engineered artifacts and biological organisms. As the recent work on the concepts of noise and modularity shows, synthetic biology is in the process of becoming more "biology inspired".

1. Introduction

Systems biology and synthetic biology form related, highly interdisciplinary fields sharing largely the same analytic tools. What sets them apart is the focus of synthetic biology on the design and construction of novel biological functions and systems. Synthetic biology is often understood in terms of the pursuit for well–characterized biological parts to create synthetic wholes,[1] and as such has typically been understood as a kind of engineering science in which engineering principles are applied to biology. This view is shared by the public understanding of synthetic biology as well as the practitioners themselves. According to Jim Collins[2], who introduced one of the first synthetic networks, a toggle-switch, in 2000: "[…] synthetic biology was born with the broad goal of engineering or 'wiring' biological circuitry – be it genetic, protein, viral, pathway or genomic – for manifesting logical forms of cellular control."

The engineering orientation of synthetic biology has received a fair deal of criticism. In a recently published article on systems and synthetic biology Calvert

1 Church, G. M., "From Systems Biology to Synthetic Biology", in: *Molecular Systems Biology* 1, 2005.0032, doi:10.1038/msb4100007, Published online: 29 March 2005.

2 Khalil, S. A. and Collins, J. J., "Synthetic Biology: Applications Come to Age", in: *Nature Reviews Genetics* 11, 2010, pp. 367–379.

H. Andersen et al. (eds.), *New Challenges to Philosophy of Science*,
The Philosophy of Science in a European Perspective 4,
DOI 10.1007/978-94-007-5845-2_14,

and Fujimura[3] claim that "[t]he research programme that expresses this objective [of rendering life calculable] in perhaps its most extreme form is *synthetic biology*". Furthermore, they posit that "synthetic biology aims at construction, whereas the objective of systems biology is to understand existing biological systems" (*ibid*.). We wish to present an alternative reading of synthetic biology that pays attention to the epistemic dimension of the material practice of the discipline. Taking into account the impressive array of interview and other data on which Calvert and Fujimura's study was based, we find it astonishing that they neither recognize the basic science oriented approach of synthetic biology nor distinguish between the influences of engineering vis-à-vis physics on synthetic biology. Namely, a more basic science oriented branch of synthetic biology has developed alongside the more engineering and application oriented approaches. This basic science oriented branch of synthetic biology targets our understanding of biological organization by probing the basic "design principles" of life. The design and exploration of gene regulatory networks constructed from biological material and implemented in natural cell environment is exemplary of this kind of approach. Interestingly, this kind of study has directly affected synthetic biology: biology in all its complexity has begun to occupy the centre stage. Important engineering notions on which synthetic biology has been grounded, such as noise and modularity, have been reinterpreted and some analogies drawn to engineering have been questioned. In the following we will study some aspects of this development through consideration of work at the Elowitz lab, which is one of the leading synthetic biology laboratories.[4]

2. Analogical reasoning and combinatorial modeling

2.1 Physicists advertising the use of engineering concepts in biology

In synthetic biology one can distinguish two main approaches: an engineering approach and a basic science approach. The engineering approach, which aims to design novel biological parts or organisms for the production of, for instance,

3 Calvert, J. and Fujimura, J., "Calculating Life? Duelling Discourses in Interdisciplinary Systems Biology", in: *Studies in History and Philosophy of Biological and Biomedical Sciences,* 42, 2011, p. 160.

4 One of the authors spent four years in the Elowitz lab at the California Institute of Technology observing the daily research practice in this lab.

vaccines,[5] biofuels,[6] and cancer-killing bacteria,[7] is often construed as comprising the whole field of synthetic biology. Less visible than the engineering approach is the basic science approach, which uses synthetic biology, especially synthetically designed biological parts, as a tool for investigating the basic design principles of gene-regulatory networks.[8] When this line of research took its first steps, one of the main desiderata was to reduce the complexity of biological systems. The reason for this strategy was not necessarily due to the reductive vision of the scientists in question but rather their aim of studying some aspects of biological organization *in isolation*. This was deemed indispensable for the purposes of testing various possible design principles, as well as exploring the concepts, methods and techniques imported to systems and synthetic biology from other disciplines, notably from engineering and physics.

It is remarkable, in the first place, that engineers and physicists did start to experiment, explore, and tinker with biological systems. To be sure, there are plenty of examples throughout history, of physics and physicists having an important impact on theoretical work in biology. Yet, during the emergence of synthetic biology something rather new happened: physicists entered biology labs or even opened their own labs and started working at the bench. This movement of physicists into molecular biology labs was largely enabled by the standardized molecular biology kits, which became available by that time. With these kits, no longer was it essential to know all the details and steps of polymerase chain reactions (PCR) – a method to amplify a small number of copies of DNA – one could simply follow the instructions that came with the kit. Performing experiments in molecular biology was suddenly much easier. Another peculiar feature of synthetic biology is that even though the basic science approach has been heavily physics-influenced, many of the central concepts come from engineering. This raises the question of what triggered this use of engineering concepts by physicists. Why does one not immediately recognize "the physicist" behind this line of research?

Interestingly, physicists themselves have argued against the use of concepts taken from physics in describing and analyzing biological systems. Physicists

5 Ro, D. K., Paradise, E., Quellet, M., Fisher, K., Newman. K., Ndgundu, J., Ho, K., Eachus, R., Ham, T., Kirby, J., Chang M. C. Y., Withers, S., Shiba, Y., Sarpong, R. and Keasling, J., "Production of the Antimalarial Drug Precursor Artemisinic Acid in Engineered Yeast", in: *Nature* 440, 2006, pp. 940–943.

6 Bond-Watts, B. B., Bellerose, R. J. and Chang, M. C., "Enzyme Mechanism as a Kinetic Control Element for Designing Synthetic Biofuel Pathways", in: *Nature Chemical Biology* 7, 2011, pp. 222–227.

7 Anderson, J. C., Clarke, E. J., Arkin, P. A. and Voigt, C. A., "Environmentally Controlled Invasion of Cancer Cells by Engineered Bacteria", in: *Journal of Molecular Biology*, 355, 2006, pp. 619–627.

8 E.g. Elowitz M. B. and Leibler, S., "A Synthetic Oscillatory Network of Transcriptional Regulators", in: *Nature* 403, 6767, 2000, pp. 335–358; Gardner, T. S., Cantor, C. R. and Collins, J. J., "Construction of a Toggle Switch in Escherichia coli", in: *Nature* 403, 6767, 2000, pp. 339–342.

began discussions about the appropriateness of transferring concepts from physics to biology already in the mid-1990s. These discussions lead to programmatic articles such as "From molecular to modular cell biology" published in 1999 by Leland Hartwell, John Hopfield, Stanislas Leibler and Andrew Murray.[9] All four authors, two of whom are physicists (John Hopfield and Stanislas Leibler) and the other two biologists (Leland Hartwell and Andrew Murray), have made important contributions in their respective fields of research. In this article, the four authors argue for turning away from the prevailing reductionist approaches in molecular biology that "reduce biological phenomena to the behavior of molecules".[10] According to the authors, these approaches fail to take into consideration that biology-specific functions cannot be attributed to one molecule, but that "[…] most biological functions arise from the interaction among many components".[11] To describe biological functions, they go on to claim, "we need a vocabulary that contains concepts such as amplification, adaptation, robustness, insulation, error correction, and coincidence detection".[12]

To be sure, Hartwell et al.[13] paint a too reductionist picture of molecular biology and they seem to ignore early attempts to apply engineering concepts to biology – often side-by-side with concepts adapted from physics.[14] But the key point is that Hartwell et al. argue against the use of concepts taken from physics when considering biology, and instead suggest plundering the engineering lexicon. Analogies to engineered artifacts were considered appropriate as such items are typically constructed to fulfill a certain *function* – like the parts of biological organisms. This stance helped to create a collective identity for physicists entering into synthetic biology and shape the research practice of this emerging research field – a field that was attributed with a, somewhat misleading, radical novelty. However, a closer look at the development of synthetic biology reveals that it was not long before researchers began to question the validity of these engineering concepts, and subtly the meanings of the concepts began to change when applied to the design, manipulation, and exploration of synthetic biological systems.

From a philosophical perspective, it can be argued that the synthetic biologists who undertook a basic science approach did not adopt the engineering concepts and vocabulary uncritically: they actually used the genetic circuits they engineered to study, apart from the fundamental organization of biological systems, also the engineering concepts used in this endeavor. Thus there is an interesting *reflexive*

9 Hartwell, H. L., Hopfield, J. J., Leibler, S. and Murray, W. A., "From Molecular to Modular Cell Biology", in: *Nature* 402, 1999, C47–C52.

10 Hartwell, H. L., Hopfield, J. J., Leibler, S. and Murray, W. A., "From Molecular to Modular Cell Biology", in: *Nature* 402, 1999, C47.

11 *Ibid*.

12 *Ibid.*

13 *Ibid.*

14 Jacob, F., and Monod, J., "Genetic Regulatory Mechanisms in the Synthesis of Proteins", in: *Journal of Molecular Biology* 3, 1961, pp. 318–356.

twist to this endeavor, which is enabled by a new type of model – the synthetic model – developed in this field, *and* the characteristic way in which it is used. Synthetic models are typically triangulated in a combinatorial fashion with mathematical models and experiments on model organisms. In the following we discuss how the practice of combinatorial modeling has lead scientists to discover important differences between the control mechanisms of biological and engineered things.

2.2 Providing control in engineered and biological systems

Control is of central importance in engineered as well as in biological systems. However, already early on it was discovered that there are fundamental differences between controlling the behavior of biological systems and that of engineered artificial systems. Engineered systems typically rely on autonomous control mechanisms. A thermostat is a good example. In this case the room temperature (input) is measured, compared to a reference temperature (output), and in the next step the heater is changed in such a way that the room temperature is adjusted to the reference temperature. The biological solution is more elegant and makes use of internal oscillating cycles that interact and harmonize the behavior of the parts of biological organisms by coupled oscillations. Biological systems need cyclic organization, since they use the matter and energy of their environments to reconstruct and organize themselves.[15] In this biological systems differ crucially from artificial engineered systems – a point addressed by Brian Goodwin in 1960s. Goodwin was an early mathematical modeler of oscillatory feedback mechanisms and he proposed the first model of a genetic oscillator, showing that regulatory interactions among genes allowed periodic fluctuations to occur. Goodwin contrasted the behavior of genetic oscillators with engineered control systems writing: "The appearance of such oscillations is very common in feedback control systems. Engineers call them parasitic oscillations because they use up a lot of energy. They are usually regarded as undesirable and the control system is nearly always designed, if possible, to eliminate them".[16] Thus decades before the emergence of synthetic biology, it was already clear that biological organisms organize their behavior differently than the engineered artefacts.

Goodwin's model and its extensions have been used as basic templates for other models of oscillatory behavior, including the circadian clock (see Bechtel this volume). Instead of one clock it actually consists of a large orchestra of "clocks"

15 To which extent biological organisms gain control over their functioning by self-organization arising from interacting oscillations is an open question. Living systems do also rely on such decoupled controllers as genes (see Bechtel, W. and Abrahamsen, A., "Complex Biological Mechanisms: Cyclic, Oscillatory, and Autonomous", in: C. A. Hooker (Ed.), *Philosophy of Complex Systems. Handbook of the Philosophy of Science*, vol. 10. Oxford: Elsevier 2011, pp. 257–285, for an excellent discussion on the role of different oscillations in biological systems).

16 Goodwin, B., *Temporal Organization in Cells.* London: Academic Press 1963, p. 5.

that on the basis of oscillations on a molecular level synchronize the functions of the organs in a biological organism.[17] Although in comparison to circadian clocks the humanly engineered control systems, such as thermostats, appear rather simple, they are still thought to have something important in common: both make use of feedback mechanisms. One of the most basic assumptions in the modeling of control in biological systems is that they make use of feedback mechanisms. Such feedback mechanisms are typically modeled using non-linear equations, which give rise to oscillations. Yet up until recently, researchers have been uncertain whether the kinds of feedback systems depicted by the various mathematical models proposed are really realizable in biological systems. Namely, that the well-established ways of mathematically creating feedback systems used by physicists[18] may not represent the way naturally evolved organisms organize themselves. But with the advent of synthetic biology, synthetic models could be created and then it was possible to demonstrate that feedback mechanisms in biological systems can indeed lead to the kind of oscillatory behavior exhibited by circadian clocks.

2.3 Synthetic models and the combinatorial strategy

One of the defining strategies of the basic science oriented approach is the combinatorial use of mathematical models, experiments on model organisms – and synthetic models. The basic idea of this combinatorial modeling strategy is shown in Figure 1, which is taken from a review article on synthetic biology by Sprinzak and Elowitz.[19] As the upper part (a) of the diagram suggests, in combinatorial modeling the results gained from the three different epistemic activities inform each other.

17 See e.g. Bechtel, W. and Abrahamsen, A., "Dynamic Mechanistic Explanation: Computational Modeling of Circadian Rhythms as an Exemplar for Cognitive Science", in: *Studies in History and Philosophy of Science* 41, 2010, pp. 321–333; Bechtel, W. and Abrahamsen, A., "Complex Biological Mechanisms: Cyclic, Oscillatory, and Autonomous", in: C. A. Hooker (Ed.), *Philosophy of Complex Systems. Handbook of the Philosophy of Science*, vol. 10. Oxford: Elsevier 2011, pp. 257–285.

18 See e.g. Strogatz, S., *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*. Cambridge (Mass.): Perseus Books, 1994.

19 Sprinzak, D. and Elowitz, M. B., "Reconstruction of Genetic Circuits", in: *Nature* 438, 7067, 2005, pp. 443–438.

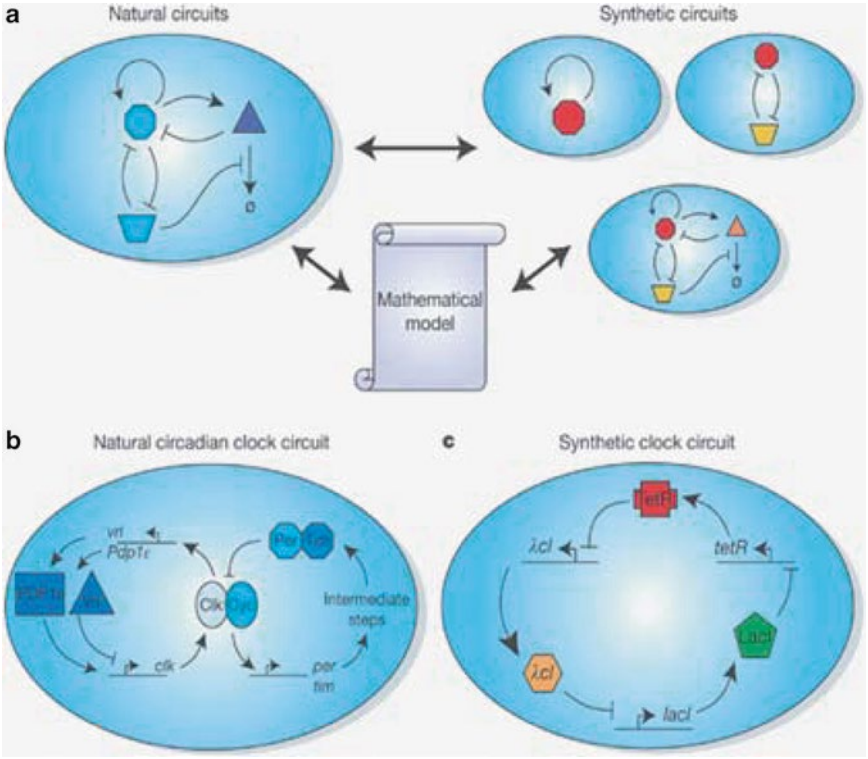

Figure 1. Combinatorial modeling according to Sprinzak and Elowitz (2005).

Why do researches make use of such a combinatorial modeling strategy in studying the organizational principles in biology? A clue can be found from the lower part (b) of the diagram. The left hand side of the diagram depicts our present understanding of the "natural gene regulatory circuit" of the circadian clock of *Drosophila* (fruit fly) consisting of interacting genes and proteins and the right hand side a synthetic model of the circadian clock, the *Repressilator*, to be introduced in the next section. The diagram indicates the two main differences between the natural and the synthetic system:

1. The natural system exhibits a much higher degree of complexity than the synthetic system.
2. The synthetic circuit has been designed by using different genes and proteins.

Consequently, synthetic models have the advantage of being less complex than model organisms. On the other hand, in comparison with mathematical models they are of the same materiality as biological systems (although the *Repressilator* was constructed from different genetic material than the naturally occurring circadian clocks, a point to which we will return below). This fact of being of the

same materiality as natural systems is crucial for the epistemic value of synthetic modeling. Roughly, it means that synthetic models are expected to work in the same way as biological systems. This very materiality of synthetic models has led researchers to discover new features of the functioning of biological systems, features that were not anticipated by mathematical modeling, or experimentation with model organisms.

2.4 The Repressilator *and the emergence of the functional meaning of noise*

The *Repressilator* is one of the first and most famous synthetic models. It is an oscillatory genetic network, which was introduced in 2000 by Michael Elowitz and Stanislas Leibler.[20] The first step in constructing the *Repressilator* consisted in designing a mathematical model, which was used to explore the known basic biochemical parameters and their interactions. Next, having constructed a mathematical model of a gene regulatory network Elowitz and Leibler performed computer simulations on the basis of it. They showed that there were two possible types of solutions: "The system may converge toward a stable steady state, or the steady state may become unstable, leading to sustained limit-cycle oscillations".[21] Furthermore, the numerical analysis of the model gave insights into the experimental parameters relevant for constructing the synthetic model and helped in choosing the three genes used in the design of the network.

The structure of the *Repressilator* is depicted in the following diagram:

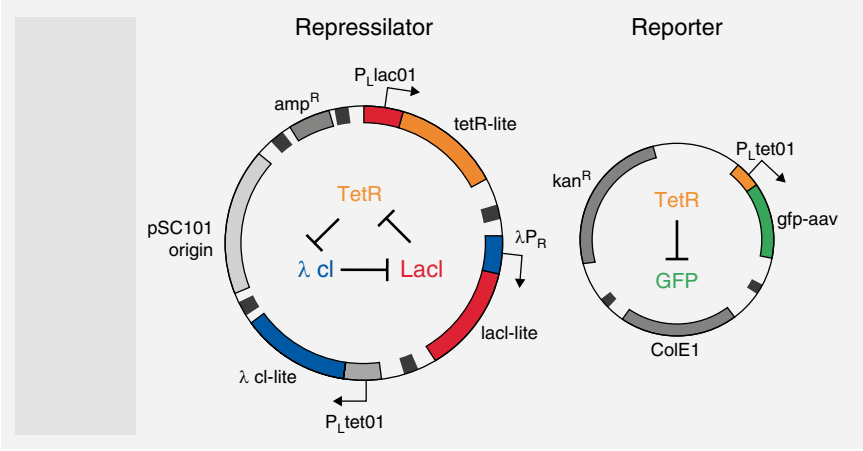

Figure 2. The main components of the *Repressilator* (left hand side) and the *Reporter* (right hand side) (Elowitz and Leibler 2000, p. 336).

20 Elowitz M. B. and Leibler, S., "A Synthetic Oscillatory Network of Transcriptional Regulators", in: *Nature* 403, 6767, 2000, pp. 335–358.

21 *Ibid.,* p. 336.

In the diagram the synthetic genetic regulatory network, the *Repressilator,* is shown on the left hand side and it consists of two parts. The outer part is an illustration of the plasmid constructed by Elowitz and Leibler. The plasmid is an extra-chromosomal DNA molecule integrating the three genes of the *Repressilator*. Plasmids occur naturally in bacteria. In the state of competence, bacteria are able to take up extra chromosomal DNA from the environment. In the case of the *Repressilator,* this property allowed the integration of the specific designed plasmid into *E. coli* bacteria. The inner part of the illustration represents the dynamics between the three genes, *TetR*, *LacI* and *λcI*. The three genes are connected by a negative feedback loop. The right hand side of the diagram shows the *Reporter* consisting of a gene expressing a green fluorescent protein (GFP), which is fused to one of the three genes of the *Repressilator*. The GFP oscillations in the protein level made visible the behavior of transformed cells allowing researchers to study them over time by using fluorescence microscopy.

The construction of the *Repressilator* was enabled by the development of new methods and technologies, such as the construction of plasmids and Polymerase Chain Reactions (PCR). On the other hand, the construction of synthetic models has so far been limited to simple networks such as the *Repressilator* whose construction components (and their number) had to be chosen in view of what would be optimal for the behavior under study.[22] This means that such networks need not be part of any naturally occurring system. For example the genes used in the *Repressilator* do not occur in such a combination in any biological system but were chosen and tuned on the basis of the simulations of the underlying mathematical model and other background knowledge in such a way that the resulting mechanism would allow for (stable) oscillations.

Summing up: above we have described how with the formation of synthetic biology a new tool was introduced into the research on biological organization: the construction of novel engineered genetic networks specially designed for answering certain kinds of theoretical questions. Mathematical models were unable to settle the question of whether the various network designs proposed, e.g. in the context of circadian clock research, could actually work in biological organisms. This problem was aggravated by the fact that the model templates, methods and concepts used were not originally devised with biological organisms in mind. Neither could this problem of the generality and foreignness of the theoretical tools used be conclusively settled by experimentation since the work with model organisms had to deal with the immense complexity of even such simple model organisms as *E. coli.* Moreover, experimentation relies on mathematical modeling in the interpretation of experimental results. Thus even though empirical research has progressed considerably over recent decades with respect to studying the genes and proteins involved in the circadian clock phenomena, for example, the

22 In the case of the *Repressilator* the order in which the genes are connected to each other, turned out to be crucial, too.

results are often inconclusive. Synthetic models, like the *Repressilator* are partly able to fill the gap between mathematical modeling and experimentation on model organisms by offering a tool for identifying possible network design principles, and showing whether they might be realizable in biological organisms. Moreover, by implementing the synthetic genetic network into a cell it is exposed to some further constraints of natural biological systems, thus providing insight into the modularity of the circadian mechanism. Interestingly, the *Repressilator* sparked a new line of research as a direct result of its limited success. In contrast to the mathematical model underlying it, the *Repressilator* did not show the expected behavior: regular oscillations. Instead, the oscillations turned out to be noisy. Computer simulations suggested that stochastic fluctuations could be the cause of this noisy behavior. This led researchers to explore the meaning of noise in the context of biology. An exploration that in itself highlighted further differences between engineered artefacts and biological systems. Whereas in engineering noise is usually regarded as a disturbance, the recent research in synthetic biology indicates that in biological organisms noise also plays a functional role. Biological systems appear to make good use of noise in diverse processes, including development,[23] differentiation (e.g. genetic competence[24]), and evolution.[25] Apart from internal noise, there remained the possibility that the noisy behavior could also have been caused by external noise coming from the cell environment. This in turn means that the *Repressilator* was probably not so modular as it was supposed to be, that is, it did not form as isolated a module in its host system as was expected. Indeed, apart from noise, modularity is another engineering concept whose limits have been questioned by recent research in synthetic biology.

3. The second wave of synthetic biology: Aiming for integration

3.1 Investigating the modularity assumption

Modular organization is among the most basic and important assumptions of synthetic biology, but also one of the most contested ones. Since its beginning synthetic biology has faced the following dilemma regarding the assumption of modular organization: on the one hand, synthetic biology relies on the assumption of modular organization in view of its aim to design autonomous modules of

23 Neildez-Nguyen, T. M. A., Parisot, A., Vignal, C., Rameau, P., Stockholm, D., Picot, J., Allo, V., Le Bec, C., Laplace, C. and Paldi, A., "Epigenetic Gene Expression Noise and Phenotypic Diversification of Clonal Cell Populations", in: *Differentiation* 76, 1, 2008, pp. 33–40.

24 Çagatay, T., Turcotte. M., Elowitz M. B., Garcia-Ojalvo. J. and Süel, G. M., "Architecture-Dependent Noise Discriminates Functionally Analogous Differentiation Circuits", in**:** *Cell* 139, 3, 2009, pp. 512–522.

25 Eldar, A. and Elowitz, M. B., "Functional Roles for Noise in Genetic Circuits", in: *Nature* 467, 2010, pp. 167–173.

interacting components that would give rise to a specific function/behavior. On the other hand, each synthetic biological system also functions as a test to which extent the assumption of the modular organization is justified.

Looking at more recent developments in synthetic biology it seems that synthetic biologists, forced by the insights they have gained from designing and constructing synthetic systems, have begun to reconsider the assumption of modularity. They have left behind the *strictly* modular organization and allowed for some interaction between the components of a module and the other constituent parts of the cell in which it is embedded. This more close integration of synthetic systems with the host cell means a loss of control over the performance of the synthetic system but it also opens up new possibilities for the design of synthetic systems. This situation is very similar to the case of noise. Noise in biological systems also has two sides: from the engineering perspective it means losing partial control over the performance of a synthetic system, but, on the other hand, noise also has a functional component that improves the performances of an organism. Thus for synthetic biology the critical point is how to make use of noise in the design and engineering of synthetic systems, or in the case of modular organization, how to integrate the components of synthetic systems with those of the host cell to support the performance of the synthetic system. Nagarajan Nandagopal and Michael Elowitz[26] put forward one possible strategy. The two authors explicate what they mean by integration on the systems level by referring to a work by Stricker et al.[27] on a transcriptional oscillator. The design of this oscillator is even simpler than that of the *Repressilator* – it just consists of two genes: an activator and a repressor. The expression of either gene can be enhanced by the activator protein and blocked by the repressor protein. Both proteins function as transcription factors for both genes. Concerning the dynamic of their model system, Stricker et al. made the interesting observation that unintended interactions of the synthetic system with the host cell actually improved the oscillatory behavior of the system by making the oscillations more precise.

Consequently, and in contrast with the traditional aim of designing isolated modules, the interactions between synthetic systems and the host cell need not always be a bad thing, but could be advantageous as well. Having pointed this out, Nandagopal and Elowitz proceed to call for synthetic systems "that integrate more closely with endogenous cellular processes".[28] With this step, they suggest, the field would move away from its original aim of designing "autonomous genetic circuits that could function as independently as possible from endogenous

26 Nandagopal, N. and Elowitz, M. B., "Synthetic Biology: Integrated Gene Circuits", in: *Science* 333, 2011, pp. 1244–1248.

27 Stricker, J., Cookson, S., Bennet, M. R., Mather, W. H., Tsimring, L. S. and Hasty, J., "A Fast, Robust and Tunable Synthetic Gene Oscillator", in: *Nature* 456, 2008, pp. 516-519.

28 Nandagopal, N. and Elowitz, M. B., "Synthetic Biology: Integrated Gene Circuits", in: *Science* 333, 2011, pp. 1244–1248.

cellular circuits or even functionally replace endogenous circuits".[29] Nandagopal and Elowitz use a three-partite picture (Figure 3) to depict what they think will be one of the big changes in the practice of synthetic biology: "Future progress will require work across a range of synthetic levels, from rewiring to building autonomous and integrated circuits de novo".[30]

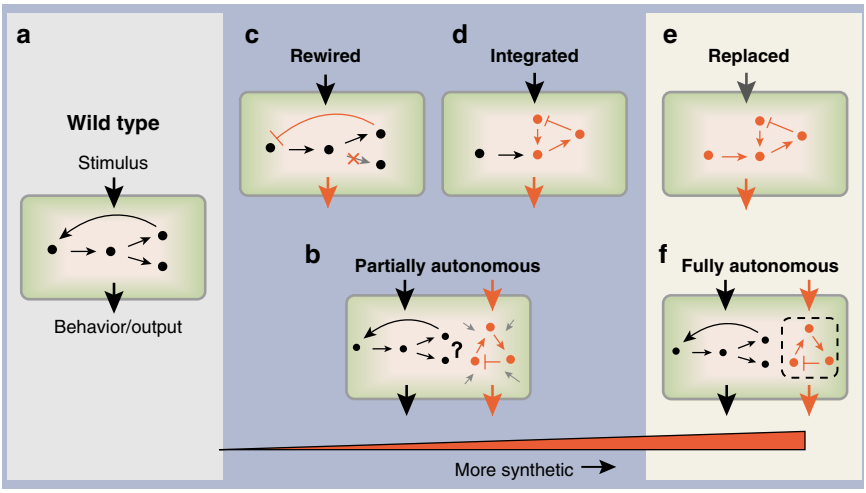

Figure 3. The continuum of synthetic biology (Nandagopal and Elowitz 2011, p. 1244).

In the diagram depicted in Figure 3 Elowitz and Nandagopal introduce what they call the "continuum of synthetic biology". In this continuum one moves from the wild type towards fully autonomous synthetic systems increasing the degree of the synthetic part of the system. How is this increase in the synthetic part achieved? There are several options. One can follow the "traditional" approach of designing an assumedly modular genetic circuit and introducing it into the wild type. As the example of Stricker et al. nevertheless showed, unintended interactions can occur (gray arrows) that could be difficult to control. An alternative approach, propagated by Nandagopal and Elowitz, consists in first rewiring the genetic circuit in the wild type and then in a second step implementing a synthetic circuit into the rewired circuit. This rewiring of the existing genetic circuits offers, firstly, a way to explore the design principles on which the genetic circuit is based and, secondly, a possibility of using these insights to avoid unintended interactions with the host cell. As has been shown in a number of studies in which the strategy of rewiring

29 *Ibid.* p. 1244.
30 *Ibid*. p. 1244.

has been used, the actual biological design principles often are counter-intuitive.[31] Nature appears to have used solutions which differ from those of engineers.

As a consequence of the rewiring strategy the resulting engineered circuit is only partially independent. However, for the engineering purposes as high modularity as possible is usually sought because of its controllability. In order, then, to get an independent circuit that would be based on the insights gained from the exploration of the rewired circuit one would integrate the function of the rewired circuit design into an autonomous genetic circuit. This strategy allows for suppressing unwanted interactions with the host cell but also implementing interactions which support the function in question. In more general terms, the proposed strategy tries to balance the need for control and the possibility of taking advantage of the interactions with the host cell. In such a way the engineering of synthetic systems becomes increasingly inspired by biological systems – a point that has recently been stressed by several synthetic biology research programs.[32]

3.2 The call for disciplinary integration

According to the latest developments in synthetic biology, the field seems to be ready for new challenges. From a stage in which the main goal consisted in exploring the applicability of engineering principles in the context of biology, the synthetic biologists working in the basic science branch are moving forward towards more concrete applications. Or as the Ruder, Lu and Collins put it:

> The field initially arose from the combined efforts and insights of a small band of engineers, physicists, and computer scientists whose backgrounds dictated the early directions of synthetic biology. For the field to reach its full clinical potential, it must become better integrated with clinicians.[33]

Thus the above-mentioned integrational approach in the exploration of the basic design principles of biological organization is accompanied with the call for integration also on the disciplinary level.[34] In order to find novel ways and strategies for instance in medicine, synthetic biologists feel that they need the support and know-how of clinical researchers. Combining the integration efforts on these two

31 See e.g. Çagatay, T., Turcotte. M., Elowitz M. B., Garcia-Ojalvo. J. and Süel, G. M., "Architecture-Dependent Noise Discriminates Functionally Analogous Differentiation Circuits", in**:** *Cell* 139, 3, 2009, pp. 512–522.

32 See e.g. http://wyss.harvard edu/viewpage/264/a-new-model. Accessed at 5 January 2012.

33 Ruder, W. C., Lu, T. and Collins, J. J., "Synthetic Biology Moving into the Clinic", in: *Science* 333, 2011, p. 1251.

34 O'Malley and Soyer argue that systems and synthetic biology provide good examples of the various kinds of integrative pursuits taking place in contemporary science, see O'Malley, M. A. and Soyer, O. S., "The Roles of Integration in Molecular Systems Biology", in: *Studies in History and Philosophy of Biological and Biomedical Sciences*, 2011, pp. 58-68.

fronts is an ambitious aim, but synthetic biologists find in such fields as clinical research, a lot of potential for the application of their specific engineering approach. The long list of possible clinical applications includes the treatment of infectious diseases and cancer, as well as vaccine development, microbiome engineering, cell therapy, and regenerative medicine.[35]

For instance, in cancer research synthetic biology could design and produce special bacteria, which would be able to identify and kill cancer cells. The possibility of targeting only cancer cells would have the advantage of avoiding the side effects of traditional cancer therapies, such as the damage of healthy tissue. Ruder, Lu and Collins[36] argue that for these developments to take off, synthetic biologists have to integrate their research and engineering efforts into the research done in clinical labs. Synthetic biologists believe that the experiences they have accumulated in the manipulation of synthetic biological systems empower them to offer clinical practice biologically inspired and hopefully also practically implementable solutions.

4. Conclusion

Above we have argued that in contrast to the popular image of synthetic biology as a discipline attempting to force biological systems into an engineering mold, the exploration of the differences between engineering and biology has been one of the central foci of the basic science approach to synthetic biology. The materiality of synthetic biological systems and the possibility of directly manipulating biological components has provided many valuable insights into biological organization as well as pointed towards the limitations of any single-minded engineering approach. What seems in our opinion to be too easily glossed over by the critics of synthetic biology is the fact that in engineering synthetic biological things synthetic biologists are at the same time also exploring the assumptions on which this endeavor is built. This reflexive element in their endeavor has, in a relatively short time, made synthetic biologists aware of some fundamental differences between the functioning of engineered artifacts and biological organisms. As the recent work on the concepts of noise and modularity show, synthetic biology is in the process of becoming more "biology inspired". These new insights do not make the engineering of synthetic biological systems an easier task – rather, they increase our awareness of the difficulties and challenges to be encountered.

35 Ruder et al., *ibid.* p. 1249.
36 *Ibid.*

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