Varieties of Noise:

Analogical Reasoning in Synthetic Biology

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Abstract:

The picture of synthetic biology as a kind of engineering science has largely created the public understanding of this novel field, covering both its promises and risks. In this paper, we will argue that the actual situation is more nuanced and complex. Synthetic biology is a highly interdisciplinary field of research located at the interface of physics, chemistry, biology, and computational science. All of these fields provide concepts, metaphors, mathematical tools, and models, which are typically utilized by synthetic biologists by drawing analogies between the different fields of inquiry. We will study analogical reasoning in synthetic biology through the emergence of the functional meaning of noise, which marks an important shift in how engineering concepts are employed in this field. The notion of noise serves also to highlight the differences between the two branches of synthetic biology: the basic science-oriented branch and the engineering-oriented branch, which differ from each other in the way they draw analogies to various other fields of study. Moreover, we show that fixing the mapping between a source domain and the target domain seems not to be the goal of analogical reasoning in actual scientific practice.

Keywords:

Synthetic biology, interdisciplinarity, analogical reasoning, engineering sciences, complex systems, noise

1. Introduction

One of the most visible and active protagonists of synthetic biology, Drew Endy, opened his Testimony to the Committee on Energy and Commerce with the following description of the research undertaken in his lab: "One current 'holy grail' is to implement a genetically encoded 8-bit information storage system. Our deliverable is similar to a computer's memory chip or a USB flash drive that you might use with a digital camera, […].[1] Another prominent synthetic biologist Jim Collins, who introduced in 2000 one of the first synthetic networks, a toggle-switch, argues along the same lines writing that "[…] 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." (Khalil & Collins, 2010).

A recurrent theme in Endy's, Collins', and many other synthetic biologists' reflections and statements on synthetic biology consists of making biology an engineering science. For them engineering sciences, such as mechanical or electrical engineering, function as model sciences for synthetic biology. This picture of synthetic biology has also created a public understanding of this novel field, covering both its promises and risks—such as the development of bacteria to produce biofuels or to kill cancer cells—or the recreation of dangerous viruses by terrorists.

In this paper, we argue that the actual situation is more nuanced and complex. Many of the analogies drawn to engineering by synthetic biologists are merely hypothetical and under debate and investigation. A prominent example of this is provided by the assumption of the modular organization of biological systems, which is one of the cornerstones of synthetic biology. It seems to be needed for engineering purposes, as it allows the integration of functional biological units into organisms such as bacteria. Another critical point regarding the engineering aims of synthetic biology is related to the goal of designing controllable systems. In the light of recent research, non-genetic variability in the form of stochastic fluctuations, which are summarized under the term of

[1] http://med.stanford.edu/scopeblog/Endy.Testimony.05.27.2010.pdf (Accessed 22 January 2013).

noise in synthetic biology, appears to be essential for biological systems. Yet at the same time it limits how well the engineered synthetic systems can be controlled. Stochastic fluctuations that can be caused for example by the small number of molecules in the cell, are an inherent property of biological as well as synthetic systems. This highlights, as we will show, a major tension between the engineering of biological systems and the functioning of naturally evolved biological systems.

Moreover, even though engineering concepts, such as robustness, standardization, redundancy, and noise, form the key concepts of synthetic biology, it is often forgotten that in synthetic biology analogies are not only drawn to engineering. In fact, synthetic biology is a highly interdisciplinary field of research located at the interface of such fields as physics, chemistry, biology, and computational science. All of these fields provide concepts, metaphors, mathematical tools, and models that are utilized by the scientists by drawing analogies between these different fields of inquiry. The analogies drawn are not only positive; negative analogies are also made.

In the following, we will highlight some aspects of the heterogeneous interdisciplinary research practice of synthetic biologists by considering the analogies they make to other disciplines. We will pay particular attention to the emergence of the functional meaning of noise, which marks an important shift in how engineering concepts are employed in this field. The notion of noise serves to highlight the differences between the two branches of synthetic biology: the basic science-oriented branch and the application/engineering-oriented branch. These branches differ from each other in the way they draw analogies to various other fields of study and the extent to which they rely on positive analogies to engineered systems.

As regards the discussion on analogical reasoning in the philosophy of science and cognitive science, our study shows that negative analogies play a much more important epistemic role than these discussions would lead us to expect. Moreover, fixing the mapping between a source domain and the target domain seems not to be the goal of analogical reasoning in actual scientific practice. What is striking is the transient, broad, and tentative nature of analogical reasoning; one can discern a continuous dialectic between often very general positive and negative analogies, prompting scientists to retrieve resources from different fields and disciplines in an effort to better understand the problems they face and the objects under investigation.

2. Analogical reasoning and interdisciplinary exchange

In the philosophy of science, analogical reasoning has often been discussed in the context of knowledge generation: in scientific discovery and theory development and hypothesis formulation. The important role of analogies in the aforementioned activities has generally been recognized, but the epistemic status of analogies has been a matter of disagreement. Whereas some philosophers have considered analogies as only heuristic tools, others have proposed that scientific theories and models could be approached through the idea of analogy (e.g. Harre, 1970; Hesse, 2001; Nersessian, 2002a; Bailer-Jones, 2009). According to this view, which Hesse (2001) has dubbed the analogical conception of theories, scientific models (or theories) are considered as analogs to their real-world targets. Nancy Nersessian describes the analogical modeling process as the evaluation of how well the "constraints of a model fit the salient constraints of a target problem" (Nersessian 2002a, p. 138).[2] As our interest is in understanding interdisciplinary exchange, we focus on analogical comparisons between different fields of inquiry. From this perspective, analogical reasoning provides modelers with a powerful cognitive strategy to transfer concepts, formal structures, and methods from one discipline to another. Mary Hesse's work, especially Hesse (1966), provides a locus classicus for this debate.[3] Her distinction between positive, neutral, and negative analogies offers a handy tool for studying the analogical process. For Hesse, positive analogies refer to those properties that the two analogs have in common, whereas negative analogies refer to known differences between them. Neutral analogies, in turn, refer to the properties whose commonality or difference has yet to be established; they

[2] Nersessian's account of analogical reasoning is closely linked to the cognitive science discussions on mental modeling and (mental) model-based reasoning (see Nersessian, 2002b).

[3] In the writings of Hesse and Nersessian, the ideas of models as analogs of real-world targets and analogies between two domains of inquiry often coalesce. This is justified by the idea that an analog from one field can serve as a model of another field, as Hesse's well-known example of the billiard ball model of the "dynamic" theory of gases shows.

thus provide epistemic potential for further inferences and theoretical development. They suggest specific questions to study and possibilities to extend the theory.

Hesse also puts forth two other classifications. She distinguishes between *material* and *formal* analogies, and *horizontal* and *vertical* relations. A *formal* analogy exists between two domains if the relations between certain elements within one domain are identical or at least comparable to the relations of the corresponding elements in another domain. This would mean, for example, that the relations could be described by the same equations. *Material* analogies, in turn, require the two domains or analogs to have at least certain properties in common. For Hesse, they are pre-theoretic analogies between observables. As regard properties, there can be *horizontal* and *vertical* relations between them. Horizontal relations refer to corresponding (similar) properties of the two domains, whereas vertical relations are relations between the properties *within* a domain. The two domains are formally analogous if they are similar with respect to their vertical relations.

Hesse's aforementioned distinctions come close to cognitive scientist Derdre Gentner's influential theory of analogy (1983).[4] She distinguishes between attributes and relations and claims that an analogy does not necessarily become stronger only if the two analogs share more attributes. Instead, she thinks that in analogy the key similarities are those that lie in the relations that hold within the domains, thus viewing analogy as structure mapping between the source and target domains (see also Gentner & Markman, 1997). In targeting the connectedness of knowledge, she focuses on what Hesse calls vertical relations. Both Gentner and Hesse emphasize the importance of the analogical transfer of the *relations* within the domain, which is what Gentner calls *systematicity*. Such systematicity shows "an implicit preference for systems governed by "higher order relations" such as causal, mathematical, or functional relationships (Gentner & Holyoak, 1997). From the perspective of modeling, it is important to note that systematicity is a central feature of mathematical and computational models, which typically study the dynamic behavior of a system of interconnected variables (Knuuttila, 2011).

[4] Apart from philosophy of science and cognitive science, there is an important body of research on analogical reasoning in artificial intelligence entitled "case-based reasoning" (see Schank, 1982; Aamodt & Plaza, 1994).

However, in light of Hesse's examples it seems that material analogy provides a *basis* for constructing formal analogies (cf. Bailer-Jones, 2009, p. 58). Nersessian (e.g. 2002a) argues on the basis of her detailed historical reconstruction of Maxwell's work that he formulated the mathematical representation of the electromagnetic field concept by making use of imaginary models of fluid medium, drawing inspiration from continuum mechanics and machine mechanics. As he progressed in this theorizing, his conception of the aetherial medium became more abstract, yet traces of his earlier analogical reasoning remained in his thinking, creating a formal inconsistency in his equations that was only later eliminated.

With respect to our case on genetic regulatory networks, this is an important point; they are conceptualized in terms of electric circuits—and often referred to as "genetic circuits"—which has made genetic regulatory networks amenable to further conceptualization and formalization. Thus it seems that drawing material analogies to other kinds of systems, or employing theoretical concepts, such as noise, depicting certain *other* kinds of systems or behaviors, is needed to mobilize and animate formal analogies and give them theoretical content. There is also interesting empirical evidence from cognitive science that supports the importance of material analogies, although, as we have already seen, cognitive scientists prefer relational analogies. To give an example, the more complex the task of establishing an analogical relationship between two domains becomes, the more people rely on similarity-based comparisons on the level of manifest features (see Holyoak, 2005). Jee et al. (2010) note that in teaching students a highly unfamiliar topic, analogies made with *both* structural and concrete similarity are more likely to be most instructive (p. 5–6).

To summarize, in the discussion on analogies one can discern the following common features[5]:

[5] Cognitive scientists' approach on modeling can be summed up as a process of four stages: *retrieval* of one or more analogs (from memory), structural alignment or *mapping*, analogical *inference*, and (possibly) generalization, resulting in new relational categories or schemas (see e.g. Gentner & Holyoak, 1997; Holyoak, 2005).

- Analogy is approached in terms of similarity and familiarity: one makes sense of a domain in terms of a better known, more familiar domain that is thought to be similar to the domain in question
- Analogical relationship is conceptualized as a mapping between target and source domains; the focus is on the shared structure (and, possibly, dynamics) of the two domains
- An important goal of analogical reasoning is to provide plausible, although fallible inferences about the target. Neutral analogies provide resources for further theoretical development.
- Analogy enables the mathematization of the target domain in terms of relational generalizations that may yield abstract schemas common to both source and target.

We find all of these points important and relevant to scientific practice; however, on the basis of our case study on synthetic biology we would like to extend this conception of analogical reasoning in the following ways: Firstly, it seems to us that negative analogies carry more epistemic weight than earlier discussion on analogies leads us to expect (see, however, Morgan, 1997; Shelley, 2002a & 2002b). As we will show, in modeling gene regulatory networks both positive and negative analogies, especially to engineering, were drawn often in parallel, showing that analogical reasoning does not primarily trade with possible similarities, but instead juxtaposes similarities with differences in subtle ways. Secondly, this dialectical process of drawing both positive and negative analogies implies that more often than not the goal of analogical reasoning is not to fix a mapping between source and target domains. Rather, analogical reasoning is more transient and preparatory in nature, a tool used by scientists to conceptualize and grasp novel and less known phenomena. Both of these features of analogical reasoning, the importance of negative analogies and the transient nature of analogical reasoning point towards the inadequacy of the source-target pair as the basic unit of analysis of analogical reasoning. In light of our case, analogical reasoning taking place in science weaves together a heterogeneous fabric of knowledge, tools, methods, and concepts from different disciplines. This is attested to also by the way synthetic biologists mathematize their objects of investigation.

Rather than abstracting a common structure shared by the source and the target, synthetic biologists, like researchers in many other fields of computational science, draw their theoretical templates from the repository of formal systems studied in the context of complex systems theory and applied in a variety of disciplines to a wide range of entirely different phenomena.[6]

Let us also note, in anticipation of our case, that this heterogeneous process can be strongly driven by specific goals, as corroborated by the engineering-oriented branch of synthetic biology. The multi-constraint approach to analogical reasoning (Holyoak & Thagard, 1989) takes this goal-drivenness of analogical reasoning into account. However, according to their account, the pragmatic considerations function as an additional constraint to be satisfied simultaneously with constraints arising from similarity of corresponding elements and structural parallelism. In contrast, in the engineering-oriented branch of synthetic biology the molding of the target according to an analogy to engineered systems has become a goal in itself, although scientists agree that biological and engineering systems function in fundamentally different ways. Here, as we will see, it is perhaps most appropriate to talk about *forcing an analogy*.

3. Two different approaches to noise: the basic science-oriented approach and the engineering/application-oriented approach

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, vaccines (Ro et al., 2006), biofuels (Bond-Watts, 2011), and cancer-killing bacteria (Anderson et al., 2005), is often construed as comprising the whole field of synthetic biology. Less visible than this engineering approach is the basic science approach, which uses synthetic biology,

[6] This implies an interesting link between analogical reasoning and the widespread use of cross-disciplinary formal templates in science. Examples of such formal and computational templates that can be applied to different problems in various domains are, for instance, the Poisson distribution, the Lotka-Volterra equations and different agent-based models (see Humphreys, 2004; Knuuttila & Loettgers, 2012).

especially synthetically designed biological parts, as a tool for the investigation of gene-regulatory networks (e.g. Elowitz & Leibler, 2000; Gardner et al., 2000).

Scientists following the engineering approach often have a background in engineering and/or computational science, whereas scientists following the basic science approach usually come from physics. In the following, we will show how the different scientific backgrounds give rise to specific commitments regarding, for example, the goals of the research, the way analogies are drawn, the types of concepts introduced from other fields, the interpretation of results, and the assumptions made about, for example, organizational structures of biological systems.

These different commitments of the engineering and basic science-oriented branches of synthetic biology do not necessarily lead these two branches to proceed independently from each other. Instead, the two research areas overlap in various ways. For example, both branches make use of engineering concepts and aspire to understanding the organizational structures of biological systems in order to develop novel biological parts and systems. But, as we are going to show, the motivation for why and how the engineering concepts are introduced is different, and moreover, analogies to them are often drawn in different ways. The aims of gaining insights into the basic structural organization of biological systems and the development of novel biological systems are weighted differently in the two branches. In the basic science approach, the exploration of the *design principles* of biological organisms[7] precedes the exploration of the possible applications of this knowledge. To be sure, the scientists in this branch of synthetic biology engineer synthetic biological systems, but they have characterised their approach as "basic science through engineering" (Cookson et al., 2009). The engineering branch proceeds the other way around: by first engineering novel biological systems and parts, and in a process of doing so, or at a later phase, exploring the structural organization of biological systems.

The recent research on the notion of noise provides an illustrative and from a scientific viewpoint a highly important example of the similarities and differences

[7] The term "design principle" itself is a term adapted from engineering. In synthetic biology the search for design principles has largely occupied the place of theory. See especially the discussion in sections 3.2 and 3.3.

between the two approaches. Synthetic biologists in the engineering-oriented branch usually proceed as engineers do and treat noise as a nuisance that one should get rid of. By contrast, since the 2000's, there has been an ongoing lively discussion in the basic science-oriented branch of synthetic biology concerning the functional aspects of noise. In the work of these researchers, noise has retained the older meaning as a nuisance, but they also address its functional role, believing it to be a crucial and distinctive characteristic of biological processes.

In what follows we will elaborate the various interdisciplinary influences and instances of analogical reasoning that have shaped synthetic biology by first portraying the motivations of the scientists in the basic science-oriented branch for introducing engineering concepts into biology. This original program, as we will see, led also to the questioning of its suitability for modeling biological systems. In Section 4, we will focus on the engineering and application-oriented branch and investigate the reasoning of its scientists regarding biological systems and how they try to come to terms with the problem of noise.

3.1 Replacing physics concepts with engineering concepts

A remarkable feature of synthetic biology is the high number of engineers working in the field, especially in the engineering and application-oriented segment. One could even get the impression that engineers have replaced physicists in this field, emulating the earlier influence that physicists like Max Delbrück and Erwin Schrödinger had on molecular biology (e.g. Luria & Delbrück, 1943; Schroedinger, 1944). Furthermore, superficially at least, it seems that as part of this development the concepts and methods of physics were replaced by those of engineering. Engineering concepts such as circuits, robustness, redundancy, and noise are crucial markers in the emerging field of synthetic biology. Yet, the situation is not straightforward and may be better captured in terms of a multilevel reconfiguration of the various disciplines (molecular biology, physics, engineering, and computational science) that have contributed to synthethic biology specific concepts, methods, and techniques. From this perspective much of the interdisciplinary exchange is inconspicuous and opportunistic, proceeding on the level of scientists adapting whatever concepts and tools from other disciplines that help them to better understand their objects of investigation.

One important observation in this context is that physicists, like Alexander van Oudenaarden and Michael Elowitz, still make up an important and influential group in synthetic biology. A look at the research agendas of their groups shows that for them synthetic systems mostly serve as a tool for analyzing structural-functional relationships in gene regulatory systems. But why does one not immediately recognize "the physicist" behind this line of research. The reason, we suggest, is the seemingly engineering orientation of their research. The question then becomes, why is there such a strong engineering *flavor* to their research?

It may come as a surprise that physicists themselves have been arguing against the use of concepts taken from physics, often finding them inappropriate for describing and analyzing biological systems.[8] An example of this is provided in a paper published in 1999 by Leland Hartwell, John Hopfield, Stanislas Leibler, and Andrew Murray entitled *From molecular to modular cell biology*. All four authors, two of whom are physicists (John Hopfield and Stanislas Leibler) and the other two biologists (Leland Hartwell and Andrew Murray), are well-known scientists who 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, which "reduce biological phenomena to the behavior of molecules" (Hartwell et al., 1999, C47). According to the authors, this reductionist approach fails 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" (Hartwell et al., 1999, C47). 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." (Hartwell et al., 1999, C47). The key point here is to note that this argument seeks to spell out why a *functional* understanding of biological systems

[8] There is a long debate among physicists concerning the question on the appropriateness of concepts from physics in the context of biology. See for example Alfred Lotka (1925) and Brian Goodwin (1963; see also below).

should induce us to suplement the concepts taken from physics with concepts that are more attuned towards the functioning of biological systems. Engineered artefacts are thought to fit the bill because they are also designed to fulfill specific functions.

It is also noteworthy that the authors' depiction of molecular biology does not take into consideration the earlier contributions that applied engineering concepts to biology, which were often applied side by side with concepts from physics. For instance, the famous Operon model (Jacob & Monod, 1961) shows that approaching biological functions in terms of networks had already been done decades earlier in biology. Thus, the authors sacrificed historical accuracy in favor of formulating a stringent research program. Indeed, statements and articles like theirs helped to create a collective identity for physicists entering synthetic biology and to shape the research practice of this new research field, emphasizing also, somewhat misleadingly, the novelty of the field.[9]

Taking a look at the analogies drawn in the article, the authors' stress on negative analogies (on a very general level, though) is striking. By making the argument that concepts from physics fail to describe the functional aspects of biology, the authors draw a negative analogy to physics. A further negative analogy is drawn to molecular biology by disapproving the reductionist approach of molecular biology. On the other hand, these negative analogies entail a positive analogy to engineering, enabling the introduction of engineering concepts and metaphors into synthetic biology. Moreover, it implies another positive analogy, that is, one to the mechanistic tradition in biology through the authors' focus on mechanisms based on *interacting* genes and proteins.[10] This latter positive analogy was not made explicit in the article, but the earlier work on the circadian clock[11] rhythms had already modeled gene regulatory systems on the basis of feedback loops (Goodwin, 1963), which are familiar from mechanical and electrical engineering, where feedback mechanisms play an important role in the design of control mechanisms. In the following paragraph, we study Goodwin's model, which brings engineering concepts and

[9] It has become a part of the rhetorical repertoire of synthetic and systems biologists to portray molecular biology as a reductionist science and systems biology as a way of overcoming this "old-fashioned tradition" (see Calvert & Fujimura, 2011).

[10] For the mechanistic discussion on gene regulatory networks, see Bechtel (2011) and Knuuttila & Loettgers (in press).

[11] The circadian clock refers to the day and night rhythms of organisms.

a non-reductionist mechanistic approach together—serving as an example of the motivations underlying the introduction of engineering concepts into biology.

3.2 The Goodwin model as an example of a gene regulatory network

Researchers in the basic science-oriented branch of synthetic biology focus on how genetic networks regulate themselves. Control is essential to all biological processes. One of the most common ways of providing control is by a feedback mechanism. Mahlon Hoagland and Bert Dodson describe its importance as follows: “Feedback is a central feature of life. The process of feedback governs how we grow, respond to stress and challenge, and regulate factors such as body temperature, blood pressure and cholesterol level. The mechanisms operate at every level, from the interaction of proteins in cells to the interaction of organisms in complex ecologies.” (Dodson & Hoagland, 1995).

The already-mentioned Jacob’s and Monod’s Operon model (1961) of prokaryotic gene regulation gave impetus to other scientists like Brian Goodwin, who studied gene regulatory networks such as the network in Figure 1, where a gene suppresses itself.

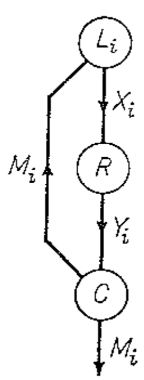

FIGURE 1.

Figure 1. Illustration of a negative auto-regulation feedback loop (Goodwin, 1963, p. 23).

The main structure of the model forms a negative feedback loop, consisting of a genetic locus L_i, synthesizing messanger RNA (*mRNA*) in quantities represented by the variable X_i. The *mRNA* leaves the nucleus and enters the ribosome, which reads the information from the *mRNA* and synthesizes proteins in quantities denoted by Y_i. The proteins are connected to metabolic processes. At the cellular locus C, the proteins influence a metabolic state by, for example, enzyme action, which results in the production of metabolic species in quantity M_i. A fraction of the metabolic species travels back to the genetic locus L_i where it functions as a repressor.

This mechanism leads to oscillations in the protein level Y_i regulating biological processes such as the circadian rhythm. Goodwin described the mechanism by a set of differential equations, which were due to the feedback mechanism of non-linear character. Such systems display complicated behavior, and no analytical solutions exist for them. Goodwin was, however, able to show by performing very basic computer simulations that the change in the concentrations of protein Y_i and *mRNA* forms a closed trajectory. This means that the model system is able to perform regular oscillations. These kinds of oscillations produced by the negative feedback loop are essential for modeling periodic processes, such as the circadian rhythm, but, as Goodwin explained, were unwanted from the perspective of an engineer. "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." (Goodwin, 1963, p. 5).

Consequently, starting from an engineering paradigm and drawing a positive analogy to engineered systems, Goodwin ended up drawing also a negative analogy to engineering and to how, for example, negative feedback works in thermostats. They measure the room temperature (input), compare it with a reference temperature (output), and then change the heater so that the room temperature is adjusted to the reference temperature. By contrast, control in biological systems is established in a different way, by oscillating feedback mechanisms.

Even though the network structures and elements—positive and negative feedback loops—had been introduced and used already early on in the study of biological organization, of which the pioneering work of Goodwin gives an illustrative example, the truly distinctive feature of synthetic biology lies in the materiality of the synthetic models and the engineered biological systems. Manipulating and working with biological components have forced researchers to question the analogies drawn to engineered systems. In the following section, we will consider the effects of being able to engineer a synthetic model out of biological components. We will introduce one of the first and most famous of the synthetic models, the *Repressilator*. Using this example, we will discuss how deviations in the dynamics of the synthetic model from those predicted by the mathematical model led to the emergence of a functional meaning of noise.

3.3. The Repressilator as an example of synthetic model

The *Repressilator* was introduced in 2000 by two physicists, Stanislas Leibler and Michael Elowitz. The *Repressilator* is an engineered oscillatory genetic network, which consists of three repressor genes, where each repressor inhibits the expression of the following gene, leading to oscillations in the protein levels. Figure 2 presents a sketch of the *Repressilator,* depicting the basic structure of the synthetic system.

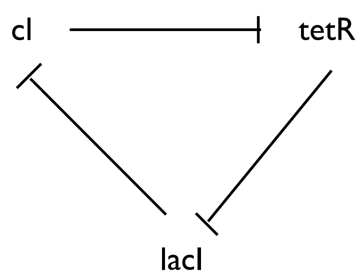

Figure 2. Diagrammatic depiction of the *Repressilator*. In this system, the three repressor genes cl, tetR, and lacI repress each others' expression.

In reality, this system is far more complex. Genes are complex entities. The biochemical parameters and processes are usually not fully known and are estimated on the basis of empirical results and/or mathematical models. Furthermore, the synthetic model is not an isolated object, but is imbedded in a larger biological system. In the case of the

Repressilator, *Escherichia coli* bacteria functioned as the host system. Consequently, one had to assume that the dynamic of the *Repressilator* was undisturbed from the rest of the processes taking place in *E. coli*. Whether this is really the case or not is difficult to prove, but synthetic biologists in general operate on the assumption of the modular organization of a biological system. In the case of the *Repressilator,* this particular synthetic system is assumed to make up a module in the bacteria that can be studied in isolation from the rest of the cell. This means that construction and implementation of synthetic systems, such as the *Repressilator,* not only allow researchers to study structural-functional relationships in biological systems, but also to explore the appropriateness of engineering concepts, such as modularity, in modeling the design principles of biological systems.[12] This proved to be important in the case of the *Repressilator*, as we will describe below.

In constructing the *Repressilator,* Elowitz and Leibler attempted to find a design principle in biological systems that would lead to stable oscillations, like those observed in circadian clocks. The mathematical model, which functioned as a blueprint for the design of the synthetic model, predicted stable oscillations: "the system may converge toward a stable steady state, or the steady state may become unstable, leading to sustained limit-cycle oscillations" (Elowitz & Leibler, 2000, p. 335). However, the synthetic model did not exhibit the behavior predicted by the mathematic model. The oscillations in the protein level, which were made visible by connecting one of the three repressor genes of the network to a green fluorescent protein (GFP), leading to oscillations in the intensity of the light emitted by the GFP, showed irregularities. Figure 3 provides an example of such single-cell observations. The arrow in (a) and (b) indicates a single *E. coli* bacterium over a period of time within a growing population of bacteria. The analysis of the intensity of light emitted from the single bacterium via the GFP led to the oscillations depicted in Figure 4. Temporal oscillations occurred within a period of about 150 min, which is three times longer than typical cell division time. This means that the state of the network is transmitted to the progeny cells. The irregularities in the oscillatory behavior occur in the output "both from cell to cell, and over time in a single cell and its

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[12] On the centrality of modularity for the "first wave" of synthetic biology, see Purnick & Weiss (2009). Khalil & Collins (2010) add "modularity" to their glossary of the basic concepts of synthetic biology.

descendants" (Elowitz & Leibler, 2000, p. 336). Figure 5 shows a comparison of the time courses in the fluorescence of three sibling cells. One observes a shift in the phase of the oscillations and a difference in the period of the oscillations.

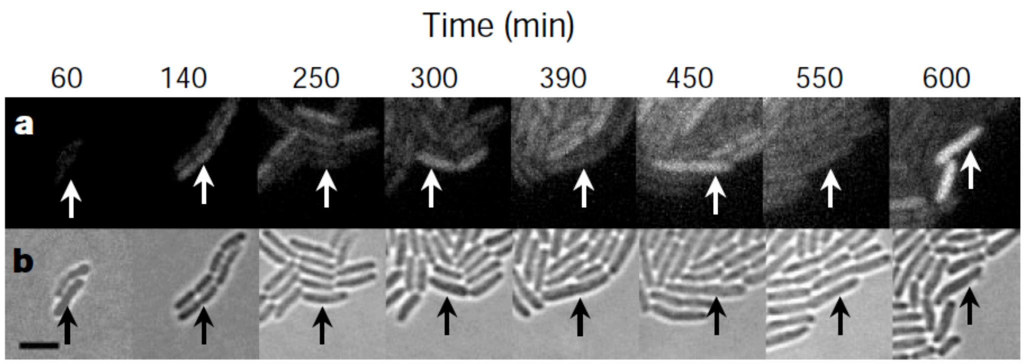

Figure 3. The row of pictures in a) and b) shows a growing population of *Escherichia coli* bacteria over a time period of 600 min. In a) and b), different microscopy techniques have been used, but the populations are the same. The arrow points to a single cell followed over the time period (Elowitz & Leibler, 2000).

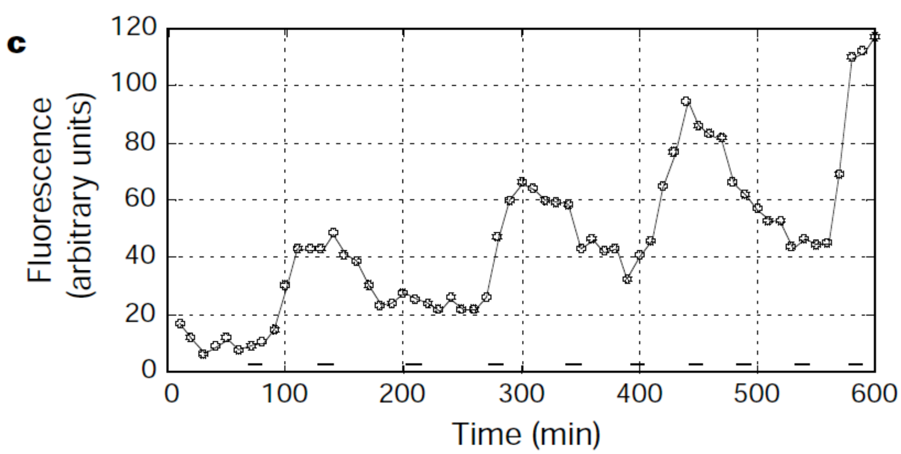

Figure 4. Oscillations of the single cell indicated in Figure 3.

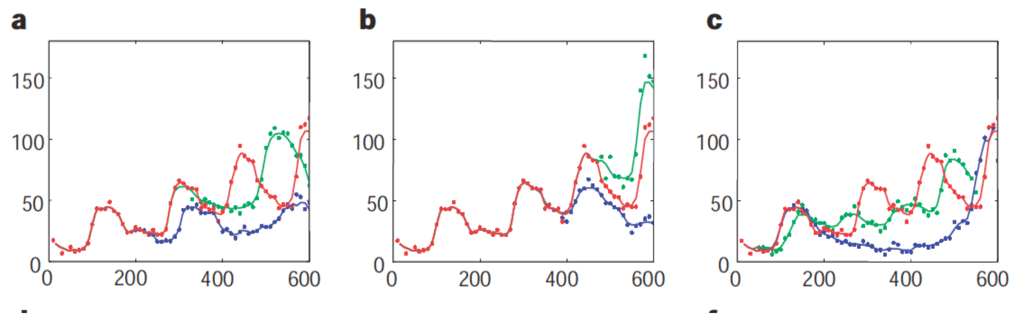

Figure 5. Comparison of the oscillations observed in sibling cells. The red graph shows the fluorescence of the cell from the figure 3. The blue and green graphs illustrate the fluorescence of two sibling cells. The comparison of the three graphs shows a clear shift in the period and phase of the oscillations (Elowitz & Leibler, 2000).

What could be an explanation for these variations in the oscillations among the cells of the population of *E. coli* bacteria? In designing the *Repressilator*, Elowitz and Leibler used a deterministic model. A deterministic model does not take into account stochastic effects such as stochastic fluctuations in gene expressions. As already argued by, for example, Spudich and Koshland (1976), stochastic fluctuation could be due to the low number of molecules in cells.[13] However, at that time no means existed for the direct observation of such fluctuations on a molecular level. This only became possible when GFP was introduced in the 1990's. Performing computer simulations on a stochastic version of the original mathematical model, Elowitz and Leibler were able to reproduce similar variations in the oscillations as observed in the synthetic model. This led researchers to the conclusion that stochastic effects may play a role in gene regulation—which gave a rise to a new research program attempting to identify sources of noise in biological systems and the effect of noise on the dynamics of the system.

In allowing noise a functional meaning, this new research program actually drew a *further negative analogy* to engineered control systems (the first is attributable to the idea that oscillations produce control in biological systems, as Goodwin suggested). Yet

[13] More generally, the step from a deterministic model to a model that includes stochastic elements has been quite a common move in computer modeling in the 1980s and 1990s. For instance, algorithms like simulated annealing have been very successful—despite their initial counterintuitiveness—as stochastic elements seem to deviate from optimality. We are grateful for the anonymous reviewer for pointing this out to us.

at the same time, researchers at the Elowitz lab found other kinds of systems, also engineered ones, to which positive analogies could be drawn: they turned their attention to concrete excitable systems such as neural networks and lasers, where noise had already been found to play a functional role. In regards to this line of research the collaboration of a postdoc at the Elowitz lab, Gürol Süel, together with a physicist Jordi Garcia-Ojalvo from the Universitat Politècnica de Catalunya turned out to be of great importance. In their work on the response to stress of the bacteria *Bacillus subtilis* they drew an analogy between the excitable dynamics of lasers and neurons and the behavior of gene regulatory networks. Süel and Garcia-Ojalvo interpreted the competence state of bacteria as an excitable state, which could be entered by means of noise in the form of stochastic fluctuation in gene expression (Süel et al., 2006).

4. Analogical reasoning and noise in the engineering approach

Also in the application-oriented branch of synthetic biology, the functional role of noise is presently recognized as an important part of the functioning of biological systems. However, instead of providing an interesting new research object in its own right, it usually poses a serious challenge for the attempt to design novel biological systems that can function in a reliable and predictable fashion. This branch of synthetic biology does not aim to mimic biological systems but to engineer novel systems with specific functions, which need not be brought about in the same ways as in naturally evolved systems. Because of this goal, and also due to the close ties with engineering, noise is predominantly regarded as a disturbance within this branch, to the extent that it reduces control over the designed biological systems. Much effort has therefore been invested in strategies to avoid or reduce noise.

Consequently, it may not come as a surprise that analogies are drawn in a different way and to different kinds of systems than in the basic science-oriented component of synthetic biology. In the engineering and application-oriented branch of synthetic biology, engineered systems as well as the practice of engineering serve as models for how to engineer reliable biological systems. This practice can be justified by the idea that actual biological systems are flexible enough to allow for the realization of different engineering paradigms. But it is also possible that the variability we observe in biological systems is of such a basic importance that it cannot be avoided and the task of engineers is to find such ways of dealing with it that take into account this specificity of biological systems. In the next sections, we will lay out this dialectic and the related tension in the engineering-oriented branch of synthetic biology.

4.1 Role of noise in purposeful engineered biological systems

In the context of engineering, one recognizes many different forms of noise, like the unwanted signals in information theory that interfere with the signal containing the information to be transmitted, or acoustic noise in the form of meaningless and very loud sounds, or electric noise such as random fluctuations in electric currents. An entire field in engineering—*reliability engineering*—is devoted to the study of the reliability of engineered systems as well as to the development of strategies and architectures to make an engineered system function in a reliable fashion (Elsayed, 1996). How can reliability, then, be achieved in the case of engineered biological systems?

Drew Endy (2005) discusses at length how the field of synthetic biology should be organized, or, as he puts it, how synthetic biology could become a truly engineering science. In his proposal, Endy draws a positive analogy to the construction of buildings. He argues that the success of the construction process depends on: "(1) the existence of a limited set of predefined, refined materials that can be delivered on demand and that behave as expected, (2) generally useful rules (that is, simple models), and (3) skilled individuals with a working knowledge and means to apply these rules" (ibid., p. 450). But, as we have already seen, biology-specific difficulties hinder the application of these three rules to biology. These difficulties are according to Endy: "(1) an inability to avoid or manage biological complexity, (2) the tedious and unreliable construction and characterization of synthetic biological systems, (3) the apparent spontaneous physical variation of biological system behavior, and (4) evolution" (ibid., p. 450).

In this scheme, noise would fall under the "spontaneous physical variation of biological system behavior". Variations and fluctuations, like the genetic fluctuations discussed above, are intrinsic to biological systems. These fluctuations, or, as they are generally called, noise, make it difficult to engineer reliable systems. Endy, drawing yet another analogy to engineering, suggests that the problem could be handled by introducing the following practices: standardization, decoupling, and abstraction. Standards, he writes, "underlie most aspects of the modern world. Railroad gauges, screw threads, internet addresses, 'rebar' for reinforcing concrete, gasoline formulations, units of measure, and so on" (ibid., p. 450). In the same fashion as we make use of standards in these different parts of our daily life, Endy wants to introduce standards for biological components. [14] By "decoupling" he refers to how complicated/complex problems are separated into simpler parts. "Abstraction," in turn, reduces complexity by organizing biological functions hierarchically. The basic idea of how to reduce biological complexity is depicted in Figure 6.

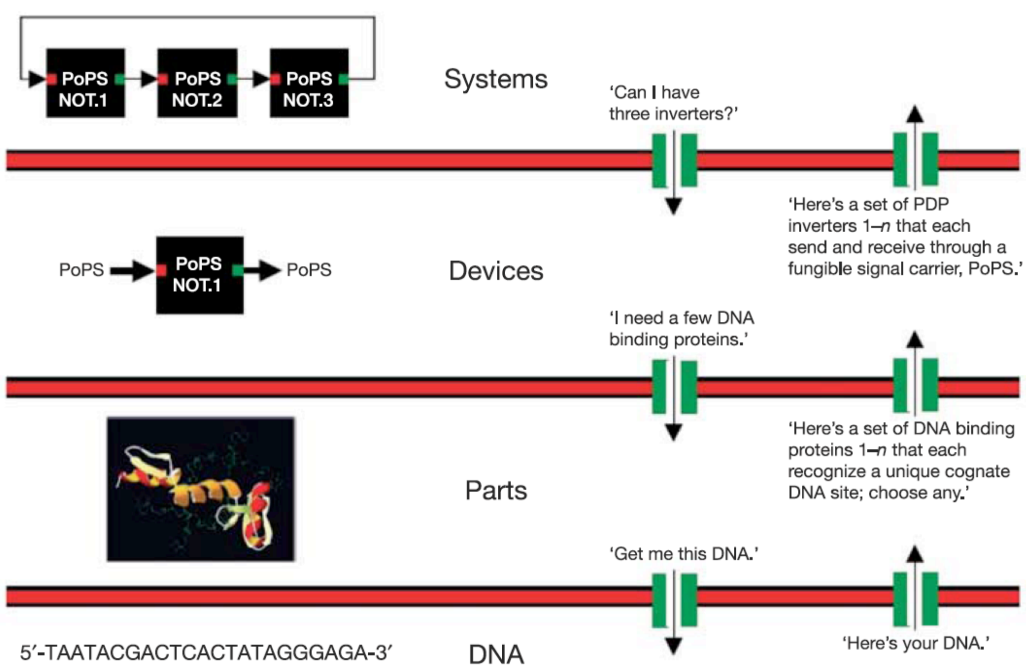

Figure 6. The diagram shows Endy's idea of an abstraction hierarchy that would support the

[14] An example of this agenda is given by BioBriks, which catalogs standardized biological parts/components. See: http://partsregistry.org/Catalog (Accessed November 1 2011).

engineering of integrated genetic systems (Endy, 2005, p. 451).

According to Endy, the "information describing biological functions might be organized across levels of complexity using abstraction hierarchies […]." (ibid., p. 451). This form of hierarchical organization would be based on exchanges of information across levels, allowing individual scientists to work on any of those levels simultaneously without needing to take into account the details of the other levels. It is quite obvious, however, that this kind of scheme to transform biology into an engineering science does not really make any room for noise introducing uncertainty into the biological systems, and it is difficult to see how noise could be handled by this framework.

4.2 The cell as a computer

Instead of the construction metaphor, one can approach biological systems through an analogy to computing. As in other areas of molecular biology, it has become very common in synthetic biology to describe biological systems as information processors, inviting the drawing of analogies between biological systems and computers. However, the analogical reasoning has also been bidirectional; computer systems have functioned as a source of inspiration for modeling biological systems, and vice versa, biological systems can provide clues for developing computational systems. For instance, biological systems can "process" a great amount of information in parallel. Take, for example, pattern recognition. Inspired by how the brain processes information, scientists such as John Hopfield have investigated alternative ways of processing information than the traditional symbolic one (Hopfield, 1982; Loettgers, 2007).

In the work of the synthetic biologist Ron Weiss, we find both of these approaches. Starting with mathematical modeling and computer simulation, Weiss tried to implement digital logic circuits into biological systems, and by doing so, drew an analogy from information processing by digital computers to biological systems. In 1999, Weiss, who has a strong background in computational science, published together with

George E. Homsy and Tom Knight an article entitled “Toward *in vivo* Digital Circuits” (Weiss et al., 1999). The three authors propose in this article: “[…] a mapping from digital logic circuits into genetic regulatory networks with the following property: the chemical activity of such a genetic network *in vivo* implements the computation specified by the corresponding digital circuit.” (ibid., p. 2). These specially designed genetic networks were supposed to be programmed in such a way that they would allow specific functions to be performed. Or as the authors describe it: “This would allow us to fit biological cells with digital ‘prostheses’ that enable the cell to perform user-specified computational processes. Programmable computation in living cells would be an enabling technology for a host of applications such as drug and biomaterial manufacturing, nanomachine assembly, sensor/effector arrays, programmed therapeutics, and as a tool for studying genetic regulatory networks.” (ibid., p. 1).

What Weiss et al. are envisioning is perhaps more appropriately described as *forcing an analogy* than as drawing an analogy. This is also expressed by their goal of “implementing meaning” to introduce something from outside into the system and to make the system controllable in a known way. This element of control is central for the engineer. The idea of implementing logical digital circuits into biological systems was not, however, realized (from mathematical models/computer simulations into actual biological systems). The authors simulated biochemical networks in terms of digital networks in which signals represented the synthesis rate of DNA binding proteins. A repressor fused to a structural gene was modeled on logic gates such as an inverter. The protein binding to the repressor functions as an input, repressing the production of the protein linked to the structural gene representing the output. Thus the behavior of biological processes was translated into a digital logic. But, interestingly, as we shall see below, with the advent of actually designing biological genetic networks the perspective of the researchers started to change and biological systems increasingly became a source of inspiration.

4.3 Biological entities replace mathematical entities

With the possibility of engineering simple gene regulatory networks the idea of implementing logical digital circuits into genetic circuits was replaced by the idea of basic functional modules, which could be used in designing complex biochemical networks. The assumption of the modular organization of biological systems became central for the research practice of synthetic biology. It enabled synthetic biologists to focus on the design of simple networks of genes and proteins that are linked to a specific function and could be arranged into more complex networks of interconnected modules. Being able to manipulate and work with biological components encouraged scientists like Weiss to attempt designs inspired more by biology than by digital computers. This does not mean that the goal was to mimic biological systems but rather to come up with more biologically inspired designs, which would function in a specific and robust way. In an article "Synthetic biology: new engineering rules for an emerging discipline" (Andrianantoandro et al., 2006), Ron Weiss and his co-workers contrasted the approach taken by biologists with that by synthetic biologists in the following way: "Biologists are familiar with manipulation of genes and proteins to probe their properties and understand biological processes. Synthetic biologists must also manipulate the material elements of the cell, but they do so for the purpose of design, to build synthetic biological systems. Synthetic biologists design complex systems by combining basic design units that represent biological functions." (ibid., E2).

An example of such a basic design principle that could form a module in a larger more complex network is shown in Figure 7, taken from Purnick and Weiss's article "Second wave of systems biology: from modules to systems" published in 2009 (see also Andrianantoandro et al., 2006). The gene regulatory network depicted is a dual-feedback oscillatory circuit. It consists of a transcriptional repressor (*lacI)* (blue box), a transcriptional activator (*araC*), and a reporter in the form of a green fluorescent protein (*yemgfp*). Each of the three components of the oscillator is located downstream of a promoter region $(P_{lac-aral})$. The positive feedback is mediated by the protein AraC binding to the promoter region of the activator *araC.* The negative feedback is mediated by LacI and IPTG, a protein that is induced and can be controlled from outside. The reporter allows[15] the researchers to observe the oscillations in protein production. The idea of coupled positive and negative feedback loops is more akin to the functioning of biological systems than, for example, the engineering-inspired negative feedback design of the *Repressilator*. Indeed, Andrianantoandro et al. (2006) describe the oscillatory design of their synthetic system as follows: "[it] can produce oscillations in a manner *similar to transcriptional regulatory control mechanisms in certain circadian rhythms*" (ibid., p. 413, emphasis added). This comment is revealing in that the authors, instead of treating engineered systems as model systems, refer to biological systems. It shows, we suggest, that the experience of working with actual biological components and systems has changed the way the originally engineering-motivated synthetic biologists draw their analogies. They are increasingly looking for designs that are "biology-inspired."[16]

James Collins described this shift in how noise is recognized and treated in synthetic biology in an interview we made in the following way: "In molecular biology in particular, the systems that we're dealing with are intrinsically very noisy. And many of us have explored and characterised the noise […] thinking about ways how you could filter it, but I think what we've seen is now a shift—towards recognising that it's a feature and not a bug of the system. And that it may be best to accommodate it by acknowledging it's there, and/or to harness [that is] could you harness the noise for example, using it as a feature or property of the system. That could produce additional functionalities such as the ease of switching and exploring different stable states."[17] But as Collins also pointed out, such attemps to make use of noise in engineering biological systems are still in their infancy.

In sum, we have showed above how, by drawing analogies to engineering, synthetic biologists import such engineering concepts as feedback mechanisms, modularity, and robustness; but when it comes to the question of how the processes are controlled, negative analogies to engineered systems become more prominent. Positive analogies to the behavior of naturally evolved biological model systems are drawn

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[15] See Loettgers (2009) for a concise depiction of the sophisticated experimental process through which Glossop et al. (1999) established the second (positive) interlocked feedback loop in the circadian clock of *Drosophila*.

[16] This is even reflected by the names of the research institutes such as the *Wyss Institute of Biologically Inspired Engineering* at Harvard.

[17] Interview on 1 February 2012.

instead—although as the example of lasers shows, new engineering analogs are utilized as well.

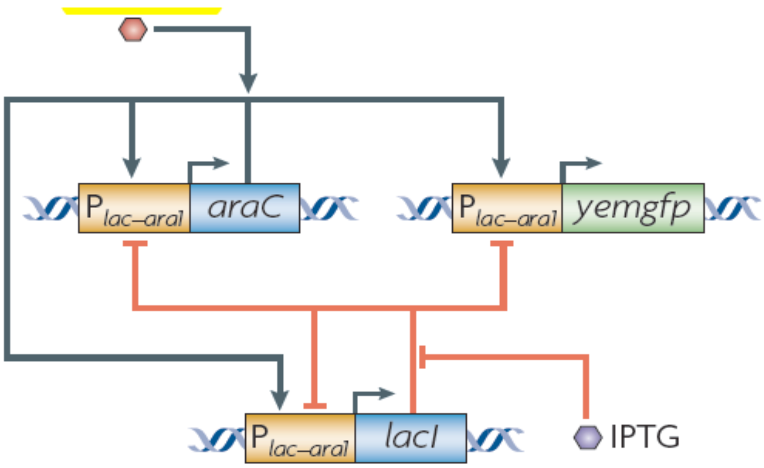

Figure 7. A dual-feedback oscillatory circuit by Ron Weiss and his colleagues (Purnick and Weiss, 2009, p. 413).[18]

Dealing with material objects has a further effect. Synthetic biologists have realized the challenges introduced by such details as the structure of proteins, their binding sites and strength, and the cellular environment in which the module is designed and supposed to function. As a result, in the context of designing actual biochemical networks/modules instead of surrogates in the form of mathematical models or computer simulations, the analogy to computer systems enters in a different way. Synthetic biologists such as Weiss still approach biological systems in terms of information processing, but draw instead a negative analogy between the ways in which digital computers and biological systems perform computation.

Adam Arkin and Daniel Fletcher have elaborated this point in their review article "Fast, cheap, and somewhat controllable" (Arkin & Fletcher, 2006). The two synthetic biologists identified as a major challenge of synthetic biology "the difficulty of predicting what biological components will do, even when the parts are readily obtainable and much is known about them individually. On this issue, lessons learned from engineering bridges, boats and planes are of little help, because the operating

[18] Note how much this diagram still resembles those depicting electrical circuits.

conditions under which biological systems function are significantly different from those of familiar macroscopic systems." (ibid., p. 114.3). A useful engineered biological system is one that could be totally controlled and that functions in a predictable way. According to Arkin and Fletcher, this is where the gap between engineered systems and biological systems becomes most obvious. "Thermal fluctuations that drive stochastic behavior can typically be ignored or managed in traditional engineering, but often not in cells. And *in situ* evolutionary changes in parts and control systems are simply not problems for inanimate objects—not so for biology. In fact, biology's success—its ability to grow and evolve new solutions and test fitness through competition—has depended on just those behaviors that frustrate predictability. Any engineering of biology to serve our needs must recognize, understand and manage this drive towards variation and the evolutionary competition with other organisms." (ibid., p. 114.3).

In sum, we have described how in the process of drawing positive and negative analogies the functional meaning of noise emerged, simultaneously revealing the characteristic tension in synthetic biology between engineering and biology. As we have shown, this tension is attributable to the question of how far one can carry analogies drawn between electrical and mechanical engineered systems and biological systems. The neat analogy between the levels of organization of computing systems and biological systems displayed, for example, by Andrianantoandro et al. (2006) in Figure 8 breaks down since it does not take into account the variation and evolutionary aspects crucial for understanding life.

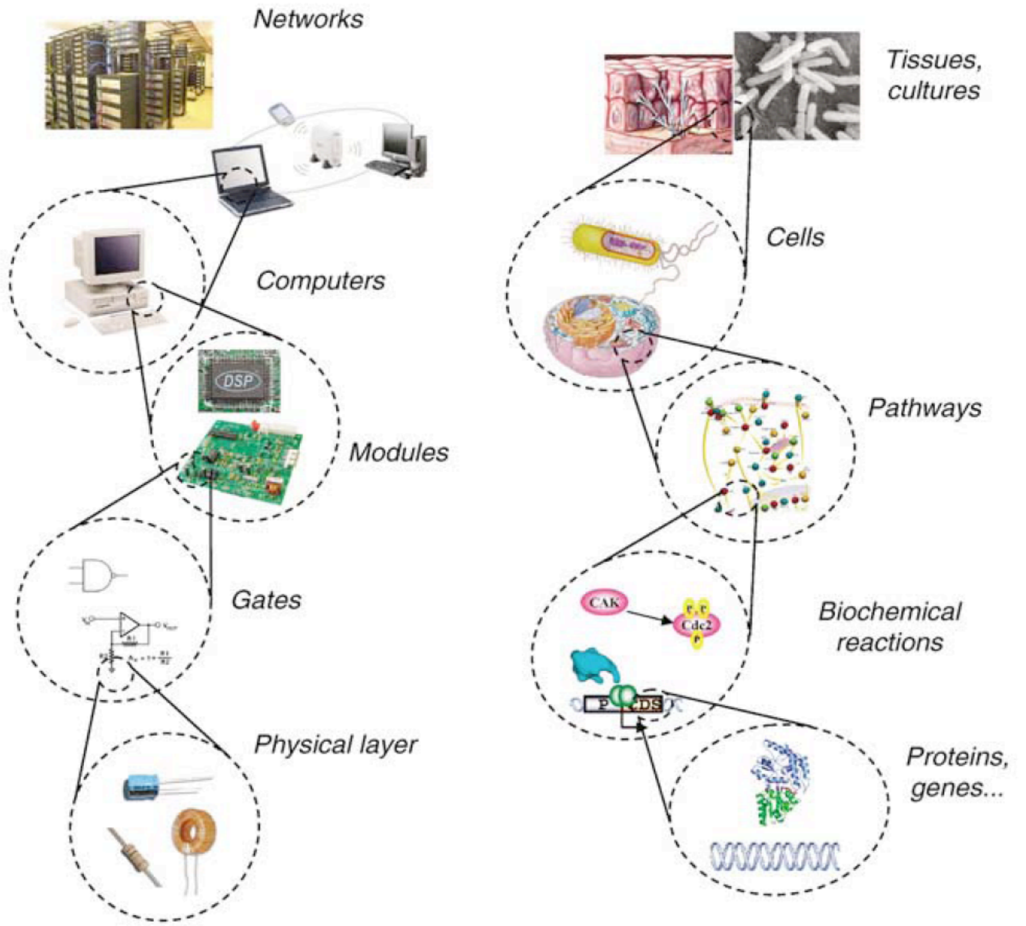

Figure 8. A depiction of an analogy between the levels of organization of computing systems and biological systems (Andrianantoandro et al., 2006, p. 2).

5. Discussion

Above, we have discussed the various ways in which researchers in the area of synthetic biology make use of analogical reasoning. The basic science-oriented and engineering-oriented branches of synthetic biology differ from each other in this respect, which is reflected by the place and role of the notion of noise in their theoretical research practice. Although the scientists in both branches employ heavily engineering concepts—which are imported by drawing analogies between biological, and electrical and mechanical engineered systems—the arguments they present are different, as are the types of concrete systems on which the biological systems are modeled. That is, although the researchers in both branches of synthetic biology use the same kinds of methods and formal tools for modeling the phenomena, the material analogies they draw to various kinds of concrete systems are partly different.

The basic science-oriented branch of synthetic biology builds its modeling endeavor on the engineering notion of a feedback control mechanism. Indeed, synthetic biologists frequently use the term "genetic circuits" for genetic regulatory networks, thus invoking the notion of an electric circuit. However, the mathematical templates used to model the dynamics of gene regulatory networks are taken from the study of complex systems, which is a formal field of study with applications in various disciplines. Despite the reliance of the basic science approach on the notion of a feedback loop, the further progress and the direction that the present research has taken are largely due to the negative analogies drawn between artificial and biological control systems. Firstly, already Goodwin (1963) suggested that oscillations (conceptualized as noise in artificial systems) in fact provide the means by which biological systems regulate themselves. A further negative analogy as regards the role of noise in artificial vis-á-vis biological systems was drawn as a result of synthetic modeling. Although the mathematical model that was used as the basis of the construction of the *Repressilator* exhibited regular oscillations, the *Repressilator* did not.

In principle, there are two ways of dealing with the observed noise, indicative of the differences between the engineering-oriented and the basic science-oriented branches of synthetic biology: On the one hand, one can pursue the positive analogy between artificial and biological systems by treating the fluctuations as a disturbance and trying to find ways of making the system more robust by changing its architecture. This approach is chosen by the engineering-oriented branch of synthetic biology, which uses different strategies to isolate and eliminate the various sources of noise. The basic science approach, by contrast, has chosen the opposite direction, drawing a further negative analogy to artificial control systems. Recognizing noise as an intrinsic part of biological systems, the researchers in this field have started to study the sources and impact of noise on biological systems. As a result of these studies, noise has also been assigned a functional role; it supports the various functions of biological systems.

That the engineering approach sees noise as something that should be eliminated does not mean that in principle researchers in this branch would deny that noise could have a functional meaning—this view is merely discordant with their engineering aims. Scientists working in the engineering-oriented branch of synthetic biology are constrained by their aim to come up with engineered biological objects, such as bacteria, that could be used for specific purposes, e.g. the production of vaccines and biofuels. From this perspective, noise contradicts the goal of designing reliable and predictable systems. These engineering-specific constraints become even more critical when it comes to engineering such biological objects as cancer cell-killing bacteria, which are brought into the human body and interact directly with parts of it. In this context, any kind of behavior deviating from the one for which the bacteria was designed, i.e. destroying a specific kind of cell, could lead to serious damage. The scientists in the basic science branch of synthetic biology are not "limited" by these engineering constraints. Their focus is, as we have seen, on gaining more insight into the basic design principles underlying specific functions such as the circadian rhythm. The big open question is whether the presently intensively studied topic by the basic science approach, the functional meaning of noise, and the non-genetic variations producing it, pose a serious obstacle for applying the engineering approach to biology. [19]

Regarding the philosophical and cognitive science discussion on analogies, we believe that the research practice of synthetic biology discussed above shows the fruitfulness of adopting this perspective to scientific reasoning. However, our discussion also reveals two related features of analogical reasoning that have received insufficient attention to date in the discussion on analogical reasoning. Firstly, neither the cognitive science discussion nor the philosophical discussion has adequately targeted the importance of negative analogies for scientific reasoning. Secondly, it appears to us that the goal of analogical reasoning *is not* the fixing of a mapping between the target and the source systems. Instead, analogical reasoning displays a subtle juxtaposition of positive

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[19] One way to justify the attempt to eliminate noise is to invoke the fact that on the population level the effect of stochastic fluctuations usually averages out.

and negative analogies, where the analogies drawn are often rather tentative and also general in nature. Moreover, the way that the material and formal analogies—often adapted from different areas of study—are used side-by-side highlights the heterogeneity of analogical reasoning.

1) Epistemic importance of negative analogies

As our case shows, apart from the positive analogies, one should pay attention to the negative analogies. The focus on negative analogies, we suggest, reveals the heterogeneous nature of analogical reasoning, which is largely neglected by the traditional approach. The reason why so little attention has been given to negative analogies in the literature on analogical reasoning might be because a negative analogy, by itself, does not seem to add to our knowledge apart from being used as some kind contrast case (see, however, Shelley, 2002a & 2002b; and Morgan, 1997).[20] Nevertheless, the situation changes if one enlarges the unit of analysis from the source-target pair to cover other domains and bodies of work that could give negative analogies a tentative interpretation and point towards further study.

In the case of the notion of noise, the irregular oscillations of the *Repressilator* prompted researchers to search for theoretical tools and methods as well as exemplary systems from other fields and disciplines in order to interpret the negative analogy. The functional understanding of noise had already emerged in physics, from which synthetic biologists adopted the majority of their modeling methods. Especially the work in statistical physics provided a well-understood concept of stochastic fluctuations and associated formal templates, such as Poisson variations, for the study of the non-deterministic fluctuations observed in biological systems (cf. Ozbudak et al., 2002). In

[20] To be sure, there is some existing literature on negative analogies. Shelley 2002a and b discusses the use of various kinds of negative analogies in science and philosophy. His focus is somewhat different from ours, however: he aims to show that analogical reasoning furnishes a type of inferential reasoning of its own and its value is not just heuristic. Cognitive scientists, in turn, mention negative analogies when discussing comparisons between *two similar examples from the same or related domains* that are alike in most respects. The purpose of a negative analogy is then to contrast or distinguish (e.g. Jee et al., 2010; Holyoak, 2005). See also the discussion of Gentner and Markman (1994) on *alignable differences*: the idea is that attributing similarities also requires differences. We do not regard this work as being easily applicable to scientific research, which is usually far from being able to align similarities and differences in the way described by cognitive scientists. In the light of our cases, this seems not to be the goal of scientific reasoning either.

the case of the Elowitz lab, the emerging research program focusing on noise led to new collaborations of which the most important was the cooperation with physicist Jordi Garcia-Ojalvo, who had studied excitable systems in the context of complex systems (Lindner et al., 2004). By perceiving biological systems as complex systems, scientists in the basic science-oriented branch of synthetic biology draw analogies to such systems as neurons, lasers, and coupled oscillatory systems. The complex behavior of these systems has been intensively studied by scientists coming from physics, mathematics, and computer science. On the other hand, as discussed above, the engineering-oriented approach relies more on analogies to engineered artefacts and their construction processes. Yet, even in this case, working with actual biological materials has made researchers more wary of hasty analogies to engineering.

2) Transient and heterogeneous nature of analogical reasoning

The research practice of synthetic biology points towards the transient, heterogeneous, and programmatic nature of analogical reasoning in science. In contrast to the prevailing literature on analogy, more often than not, establishing a mapping between a source and a target system seems not to be the goal of analogical reasoning. Rather, the analogies drawn are usually tentative and even very general—to the extent of being programmatic—and one can discern a continuous and subtle dialectic between the negative and positive analogies drawn. Why has this characteristic of analogical reasoning escaped cognitive scientists—and even philosophers of science? One plausible answer is suggested by Nersessian and Chandrasekharan (2009). In their account of hybrid analogies in neuroscience, they stress the importance of the construction processes for the epistemic value of analogical reasoning. They place analogy at that “end of a creative continuum” that deals with “extremely complex instances spread over time“ (ibid., p. 187). Cognitive science, according to them, has thus far studied “ready-to-hand problems”, but such an approach is obviously too simplified with respect to actual scientific problems.[21]

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[21] When cognitive scientists have considered science, they have typically been interested in science education, dealing with teaching students already established scientific knowledge (e.g. Jee et al., 2010).

We suspect, however, that there is also a more philosophically inclined reason for the neglect of the transient and dialectical nature of analogical reasoning—a reason that also underlies the inattention to negative analogies. Namely, both the neglect of negative analogies as well as the stress on establishing a fixed mapping between the source and the target systems seem to be vestiges of representational ideals still present in the thinking about analogies. In mapping, a similarity relationship is established that is akin to a representational relationship, which has conventionally been taken as the hallmark of knowledge. Furthermore, the stress of Gentner and other cognitive scientists on the *mapping of structure* comes close to the structural conception of scientific representantion in that for both it is ultimately the underlying structures that matter (e.g. French & Ladyman, 1999)—that is precisely what the recent practice-oriented approaches to modeling and representation have sought to avoid (e.g. Giere, 2010; Knuuttila, 2005; Mäki, 2009; Suárez, 2010). It seems to us that the goal of highlighting the role of analogies in science is to make room for the constructive and imaginative moment of scientific reasoning; the different semantic-cum-structuralist accounts fixated on the structural relationships between the source and target systems fail to pay attention to this. Furthermore, as such accounts attempt to ground representation in an isomorphic or partially isomorphic relationship between the source and target systems, they have no need to consider the background information. Analogical reasoning, on the other hand, is highly dependent on various sources of experimental evidence and theoretical foreknowledge (see, e.g., Shelley, 2002a & 2002b; Nersessian, 2002a).

As regards the heterogeneity of analogical reasoning, it is interesting to note how the material (or concrete)[22] and formal analogies alternate in it, as pointed out by Hesse (1966) and Nersessian (e.g. 2002a). To be sure, the analogies drawn to engineering sciences or engineered systems in synthetic biology do not focus on shared individual properties, rather concentrating on the "organizational level"—(e.g., the analogy to how computing is organized in different levels or the analogy to the organizational structure of traditional engineering science). Yet, it is interesting to note how analogies are still drawn to material systems, especially in the explorative phase of analogical reasoning

[22] We have been using "material" and "concrete" as synonyms, as is the case with the discussion on analogical reasoning.

(see also Nersessian, 2002a). As the research program stabilizes, it tends to trade in its theorizing more directly with formal structures without the recourse to concrete systems that could function as analogs.

6. Concluding remarks

Above, we have studied how via analogical reasoning synthetic biologists utilize the theoretical results, tools, methods, templates, and concepts of other fields and disciplines. The relatively recent practice of synthetic modeling, the engineering of genetic regulatory networks from biological substrata, has been of crucial importance in this respect; it has significantly changed the attitude of the researchers in the field of systems and synthetic biology towards the analogies drawn to engineering. The materiality and the specific properties of biological systems exploited by synthetic modeling have caused scientists to question the earlier analogies and replace them with new analogies believed to be closer to the functioning of biological systems. We have also discussed how analogical reasoning typically makes use of concrete and formal analogies simultaneously. In synthetic modeling, the analogical reasoning goes one step further, becoming truly material. Yet, it is not a question of mere instrumental "thing" knowledge (Baird, 2004), as opposed to theoretical knowledge, since here the engineered things are constructed to investigate the theoretical assumptions underlying synthetic biology. And even the practice of the engineering-oriented branch of synthetic biology of forcing an analogy (to engineered systems) has epistemic implications in probing how far the analogy between engineered and biological systems can be extended.

Lastly, let us note yet another role engineering plays in synthetic biology. Namely, with the introduction of synthetic modeling and novel imaging methods researchers began to realize the complexity of the question of noise. The new methods revealed non-genetic fluctuations at the single-cell level (Elowitz et al., 2002). Such fluctuations had remained "invisible" at the previously studied population level, where they typically average out, whereas the new methods disclosed a large number of hitherto unrecognized non-deterministic fluctuations. This raises the question of why the notion of noise was extended in such a way. Why should researchers continue talking about noise when referring to these non-deterministic fluctuations and their possible functional roles? This certainly reflects the influence of engineering sciences on biology and the background of many synthetic biologists in the research of complex systems. However, there seems to be another more profound reason, related to the interdisciplinary transfer of concepts and tools typical of modeling. As discussed above, the application of engineering notions and modeling methods of physics to biology by way of analogical reasoning is not unproblematic. The sources of the fluctuations in biological organisms are largely unknown in all but a few cases, as is also their exact impact on the dynamics of biological systems. One reason for the use of the notion of noise is precisely this uncertainty; noise functions both as an umbrella term and as a place holder for the emerging research on different forms of fluctuations, their sources, and their consequences for the dynamics of biological systems.

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