(Re)Engineering Biology Abstracts
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Non-traditional Engineering of Desired Weak Emergent Properties of Synthetic Cells
Mark A. Bedau

Various kinds of synthetic cells are produced in synthetic biology. Top-down synthetic biology genetically modifies simple natural cellular life forms to make (partly) synthetic cells. Bottom-up synthetic biology uses nonliving materials to make synthetic protocells. Both forms of synthetic biology engineer synthetic cells so that they have certain desired global properties. Those properties are typically produced by very complex causal webs, and some call them "weak" emergent properties (Bedau 1997). Synthetic biology uses many methods adapted from traditional engineering to create desired emergent properties, including Edisonian trial and error (Martin et al. 2003), standardized genetic components (Mutalik et al. 2013a,b), genome refactoring (Temme et al. 2012), and synthetic genomes (Gibson et al. 2010). But it uses engineering methods that are non-traditional. One non-traditional method is in vitro (directed) evolution, which produces desired genetic material through an artificial evolutionary process (e.g., Yokobayashi et al. 2002). Other methods apply tools from contemporary machine learning (Caschera et al. 2011), and similar non-traditional methods could be adapted to systems biology and bio-medical engineering. Both methods are especially useful for engineering desired weak emergent properties, because of the complex causal webs underlying these properties. The non-traditional methods explain the central role of synthesis in synthetic biology.

Why Phytobricks?: How synthetic biologists are engineering plants
Dominic Berry

The majority of laboratory work within synthetic biology has been directed towards single-celled organisms, but from the outset synbio has promised to revolutionise the manipulation and design of more complex organisms. In recent years efforts have been made to integrate a cadre of plant scientists, and the most conspicuous aspect of this work is the introduction of a new iGEM track dedicated entirely to plant synthetic biology, which will be launched in time for the 2016 jamboree. The iGEM (International Genetically Engineered Machine) competition is an international student competition that has run annually since 2003. The growth of the latter, which today involves thousands of students and hundreds of institutions, and the integration of more complex organisms, are taken to demonstrate synbio's flourishing.

However, at the same time as plant science is being integrated into synbio, there is also evidence that plant scientists are maintaining a distinct identity for themselves within synthetic biology. Based on interviews with those scientists responsible for creating the plant iGEM track, and laboratory observations of plant synbio in practice, this paper is dedicated to answering the question: in a field inspired by engineering ideals such as modularity and orthogonality, why Phytobricks?

The Synthetic Method between Engineering and Science: A new paradigm for the scientific exploration of the frontiers of life?
Leonardo Bich and Luisa Damiano

This talk will focus on the synthetic method, an emerging approach at the crossroads between engineering and science that develops pioneering insights from organizational biology, cybernetics and systems theory. The specificity of this method, based on the idea of 'understanding by building', is that it directly involves engineering into the scientific comprehension of biological processes through the construction of 'synthetic models': 'functioning artefacts' that incorporate scientific hypotheses to produce the phenomena under inquiry, and can be used as means to test the underlying theories.

In this presentation we will mark out the theoretical, epistemological and methodological features of this approach, illustrating how it can be considered capable to generate a new research paradigm for biology: new methodological procedures associated to new theoretical and epistemological frameworks. We will support our analysis by focusing on case studies from research on minimal life, i.e., current studies on compartments involving different forms of synthetic modelling. The main goals are two:
-To identify limits and possibilities of these applications of the synthetic method through comparisons with other methodological approaches integrating engineering into biology;
-To establish whether in this context we can talk of a new and pluralist research paradigm, or a transition towards it.

An Engineering Paradigm: Whose paradigm?
Mieke Boon

As the organizers of this conference suggests, there are good reasons to talk about an engineering paradigm, rather than considering the life-sciences as fundamentally different to other experimental sciences as they bring engineering approaches to biology. In this paper, I will focus on the paradigm of science maintained by philosophers. This paradigm determines which problems, ideas, approaches and answers are considered relevant and adequate in the philosophy of science. Indeed, the shift towards an engineering paradigm is obvious from changes of concepts employed by philosophers when they talk about the life sciences. The recognition by philosophers that scientific practices such as the life sciences incorporate engineering approaches, has several of the typical characteristics of a changing paradigm. This paper aims to analyze the content and appropriateness of the emerging engineering paradigm, focusing on typical Kuhnian aspects such as: ontological presuppositions on the general subject-matter studied in experimental sciences; fundamental epistemological values; normative ideas on the aims of science; assumptions on the character of scientific knowledge; and paradigm examples of science. It will be defended that, in many cases, the engineering paradigm is more appropriate for understanding both contemporary and historical scientific practices.

Nature as a Toolbox: A New Look at the Concept of Levels of Organization
Daniel Brooks

Despite its pervasiveness, the concept of 'levels of organization' has received little attention in its own right. In this presentation I will argue that, contrary to recent claims of its uselessness, the 'levels' concept can easily be revealed as a uniquely effective and flexible conceptual tool tailored to perform a wide host of scientific tasks. Indeed, far from any reified "layer-cake" image, 'levels' as depicted in actual scientific usage arguably represents nature itself as a toolbox, from which scientists are free to select the parts with which to construct their solutions to the problems they engage in their investigations.

The key to this approach will be a usage-based reconstruction of 'levels' that reveals a fragmentary concept that balances a striking variation in conceptual content between instances of use with a remarkably conserved and unifying significance attributed to it across these instances. This significance, captured by the "epistemic goal" motivating its usage, is its ability to structure explanatory problems. This heuristic, usage-based treatment of levels does not diminish the concept's general importance to science, but rather allows for its use in, and usefulness for, scientific practice to be better contextualized to particular tasks encompassing varying breadths of activity.

Crash Testing an Engineering Framework in Neuroscience: When Does the Idea of Robustness Break Down?

Mazviita Chirimuuta

In this paper I discuss the concept of robustness in neuroscience. Systems biologist Kitano (2004) defines robustness as, "a property that allows a system to maintain its functions against internal and external perturbations." Thus, in order to determine whether or not a system is robust, one must specify its function, and also specify the kinds of perturbation it faces. Various means for making systems robust have been discussed across biology and neuroscience (e.g. copy redundancy and fail-safes). It is obvious, but still worth emphasising, that many of these notions originate from engineering.

I will argue that the framework borrowed from engineering aids neuroscientists in (1) operationalizing robustness; (2) formulating hypotheses about how the system achieves robustness; and (3) showing how robustness may be precisely quantified. Furthermore, I will argue that the use of the engineering framework in neuroscience gets stretched, perhaps to breaking point, when applied to systems where (1) there is no principled distinction between processes for robustness and processes which continually maintain the life of the cell; (2) where perturbations are a regular occurrence rather than anomalous events; and (3) where one should not conceive of the system as seeking to maintain a steady state (O'Leary et al).

Reprogramming and the Repressilator

Melinda Fagan

Synthetic biology is touted by proponents as a novel approach to studying life. However, some philosophers have noted significant continuities with experimental biology (O'Malley 2009, Bechtel 2011, Knuutila and Loettgers 2013). This paper builds on their arguments by comparing an exemplar of synthetic biology, the Repressilator, to induced pluripotent stem cell lines (iPSC) produced by "direct reprogramming" – a traditional experimental method. This focused comparison exhibits significant continuities between synthetic and experimental biology. The two cases involve very similar aims, biological materials, 'wet' experimental methods, and results. Both the Repressilator and reprogrammed iPSC are

engineered systems consisting of genetic regulatory networks constructed and inserted into cultured cells, which induce changes in cell phenotype.
These methodological parallels undercut the distinction between synthetic and traditional biology in terms of "forward- and reverse-engineering." However, there are some important differences between the two cases. The Repressilator and cell reprogramming, I argue, differ with respect to (i) the source of transcription network organization, and (ii) the roles of pre-defined 'programs' in constructing the system and generating results. I discuss some broader implications of these results, with emphasis on the social organization of 'engineering biosciences.'

<u>Crosscutting Biology and Engineering via Fractals</u>
Luis Favela

Fractals are a potentially rich source of theories and methods that can facilitate interdisciplinary work among biologists and engineers. Fractals are scale-free, self-similar structures, whereby the global structure is maintained at various scales of spatial and temporal observation. Fractal methods can mathematically reveal structure in variability that is often disregarded as noise or "averaged away" by traditional linear and additive statistical analyses. As such, phenomena can be misrepresented if outliers are trimmed or are understood solely in terms of the average of its features. Fractal analyses are, at least in some cases, better suited to capture phenomena that do not conform to Gaussian distributions. Engineers have applied fractal analyses to work on antenna signals, force on chains and their effect on materials, Internet traffic, and urban structure planning. Biologists have applied fractal analyses to research on tree and bronchial tube branching, neuron dendrites, breathing, and heartbeats. As is evident by this brief list of examples, fractal concepts and methods are substrate neutral and can facilitate understanding regardless of the material composition or causal mechanisms related to a phenomenon. These benefits make fractals a good contender for facilitating interdisciplinary work among biologists and engineers.

<u>Reconciling Specialties of Engineering and Biology</u>
Elihu Gerson and Alok Srivastava

Participation of multiple specialties in a single project raises potential problems of cooperation that must be reconciled if the project is to continue. Participating specialties face trade-offs posed by the need to accommodate others. Understanding the reconciliation process in a general way requires developing means for analyzing these trade-offs that are not limited to particular contexts. We suggest two dimensions of such contexts. The explication spectrum lists the phases a research project might enter over the course of its life. The translation spectrum marks the distinctions separating basic research results from products or services in general use.

Understanding the ways in which different specialties influence one another depends on the ways that researchers negotiate and revise their own approaches as they learn the limits, requirements, and potential of complementary approaches. Researchers employ many tactics to align their positions on the explication and translation dimensions. Two kinds of reconciliation tactic seem to be especially common: developing appropriate standards and creating coordination mechanisms. The reconciliation tactics used are improved over time, so that joint research becomes better integrated and more reliable. We illustrate our approach with examples of standardization processes and coordination mechanisms drawn from various intersections of biology and engineering.

The Multifaceted Potential of Affordance-based Reverse Engineering in Biology

Dominic Halsmer

The concepts of reverse engineering and affordances have been combined to produce a fruitful synergy with the potential for advancing systems biology. The idea of affordances has found utility, not only in design engineering, but also in affordance-based reverse engineering (ARE). In this context, an affordance is something that is provided to the end user of an engineered device, by virtue of some relationship between the user and the device. In more complex systems, this is extended to include a relationship between parts of a system that play a role in ultimately providing a capability to the end user. These part-to-part affordances are critical in analyzing the depth of functionality that characterizes biological systems, especially at the microscopic level. Researchers in evolutionary biology have also found the concept of affordance to be helpful in understanding the evolutionary process. Affordances can assist in clarifying the process of niche construction. Hence, it seems clear that ARE has the potential to contribute at both the microscopic and macroscopic levels. Furthermore, affordances merely provide a statement of capability that persists because of key biological relationships. Thus, it is metaphysically neutral, and as such, more in keeping with the concerns and limits of science.

The Machine Analogy in Synthetic Biology

Sune Holm

A widespread and influential characterization of synthetic biology emphasizes that synthetic biology is the application of engineering principles to living systems. Furthermore, there is a strong tendency to express the engineering approach to organisms in terms of what seems to be an ontological claim: organisms are machines. In the paper I investigate the ontological and heuristic significance of the machine analogy in synthetic biology. I argue that the use of the machine analogy and the aim of producing rationally designed organisms do not necessarily imply a commitment to the identity of organisms and machines. The ideal of applying engineering principles to biology is best understood as expressing recognition of the machine-unlikeness of natural organisms and the limits of human cognition. The paper suggests an interpretation of the identification of organisms with machines in synthetic biology according to which it expresses a strategy for representing, understanding, and constructing living systems that are more machine-like than natural organisms.

Abstraction and Model Construction in Systems and Synthetic Biology

Tarja Knuuttila and Andrea Loettgers

The prevalent view on abstraction among philosophers of science is that of omission. Whereas idealizations are thought to introduce distortions to a scientific representation, abstraction is understood in terms of abstracting away from the details of a system. According to this tradition a model is a highly selective depiction of the underlying mechanism of a phenomenon, or some basic causal factors, taking into account only those features that make a difference.

We argue that the idea of abstraction as omission does not often capture what goes on in actual *model construction*. From the perspective of modeling heuristic one should make a distinction between cases in which one abstracts away from most of the details of a phenomenon of interest from those that start from an abstract mathematical mechanism describing a general pattern of interaction often adapted from other scientific disciplines—such as physics and engineering in the case of biology. We will illustrate this point by examining how systems biologist Uri Alon has made use of optimality principles in modeling gene regulatory networks.

Using Evolution to Engineer Microbiomes
Nicolae Morar & Brendan Bohannan

The concept of 'engineering', which implies the application of science to solving certain problems involved in the design of structures and systems that respond to human needs, has been recently attached to biology, genetics, and ecology. Two specific ways of engineering biological networks have emerged. Genetic engineering consists of creating and programing cells to perform particular functions, e.g. release quantities of insulin when a body needs it. In contrast, evolutionary engineering selects for a particular state of a property (e.g. a particular function), where changes in the 'parts' and their interactions are occurring as a by-product of this selection. These two forms of biological engineering are underlined by two different logics. While the former focuses on selecting units of life, the latter highlights the importance of evolutionary constraints. However, both forms of engineering have underplayed two important facts about animals and plants: 1) organisms include a diverse community of microbes that colonize them & 2) microbiomes are not passive players but contribute to host function and fitness. The engineering of biological systems can no longer afford to overlook the importance of microbial processes. Hence, our question: could the manipulation of the microbiome of an organism have an effect on host function, and thus, impact host fitness?

The Epistemology of 'Good Enough': Pragmatism and Engineering Knowledge in Synthetic Biology
Pablo Schyfter

Synthetic biology is a field in-the-making, without any consensus identity, ambitions, practices, or principles. However, one contingent advocate a field of 'authentic' engineering with a biological substrate. For these practitioners, settling the field hinges on delivering a new engineering modelled on and congruous with the old.

As the sociology of knowledge and science studies have demonstrated, epistemic systems, practices and products result from collective practice, and contribute to the formation of scientific and technological groups. As such, the pursuit of engineering standing is in part a pursuit of engineering knowledge.

Sociological and philosophical studies of synthetic biology demand an epistemology of engineering knowledge. I posit that pragmatist epistemology from the works of John Dewey and William James can serve in concert with the sociology of knowledge to develop and deliver an epistemology of knowledge-making and knowledge-use in engineering.

Engineering knowledge is something employed, rather than an end in itself. Pragmatism argues that truthfulness is usefulness, and the sociology of knowledge enables empirical study of how utility is defined, pursued, and evaluated collectively. Using synthetic biology as a case study, I demonstrate the value in this epistemological partnership, and the character of engineering knowledge as knowledge 'good enough' to use.

Understanding Biological Systems through Mathematical Modeling

Eberhard O. Voit

The hallmark of biological systems is complexity, which is the consequence of enormous numbers of molecular components and nonlinear processes, non-intuitive system responses, threshold effects, and emerging properties that often cannot fully be explained. A true comprehension of this complexity would require cohesive theories, which however do not exist at present. A first step toward such theories is the exploration of complex systems with computational models, which can aid our understanding of at least certain features of such systems. I will discuss the following aspects of biological systems modeling:

1. Models are non-unique; some are more useful than others, if they answer pertinent questions.
2. Models should be interlocking within biological levels, but differ in granularity between them.
3. Each level may require unique modeling frameworks; other model types may connect levels.
4. Models of biological systems cannot be formulated in terms of first principles from physics, because their governing processes are too convoluted.
5. All biological models are mesoscopic; there is no feasible bottom or top.
6. Engineering approaches may be useful, but require caution, because the superposition principle seldom holds in biology.

I will analyze these aspects and demonstrate them with models in the context of schizophrenia.

Fundamental Engineering Principles of Natural and Artifactual Design

William Wimsatt

Several features are deeply anchored characteristics of both natural evolved and artifactual systems. *Scaffolding* occurs when a structure or behavior is utilized to make possible, easier, or faster the attainment of a goal. Generative *entrenchment* is the building of dependent structures, processes or behaviors (SPB's) on earlier SPB's in a way that facilitates their addition to (and scaffolding) an adaptive structure. This thereby makes the primary SPB's more essential, their loss more severe in its effects, making entrenched elements more conservative in evolutionary processes, and affecting more and less likely directions of evolutionary change. Scaffolding and entrenchment are endemic to the evolution of complex systems, in biology, in technology, in cognition, and in culture. *Robustness* is the relative insensitivity of system performance to different arrangements or specifications or modifications of its parts. *Modularity* is a last design principle of biological and technological systems and facilitates independent modification and recombination to create new kinds of systems. These last two properties, however, are realized in different ways in evolved and artifactual systems. I consider the implications of these characteristics for architectural similarities and differences between newly designed engineering artifacts and those natural or artifactual systems that have undergone an evolutionary processes, and how these fundamental architectural properties themselves evolve.