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Introduction

Introduction: Philosophers meet biologists

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> Constructing a machine that works (such as a highly parallel computer) is an engineering problem. Engineering is often based on science but its aim is different. A successful piece of engineering is a machine which does something useful. Understanding the brain, on the other hand, is a scientific problem. The brain is given to us, the product of a long evolution. We do not want to know how it might work but how it actually does work. This has been called "reverse engineering"—trying to unscramble what someone else has made—but … it is reverse engineering on the products of an alien technology. And what a technology!
>
> Francis Crick
> "The recent excitement about neural networks"
> *Nature* 337 (12 January 1989), 129–132 (132).

1. The biological challenge

This special section involves an intense interaction between philosophy of science and current experimental biology. Our original goal as philosophers was to contribute to understanding experimental methodology and explanatory approaches to processes of self-organization and evolutionary adaptation in which functions play an essential role. The occasion for this encounter is provided by two sets of experiments performed by **Erez Braun** and **Shimon Marom** during the past 15 years. These experiments focus on the exploratory behaviour of biological systems as they seek to cope with severe *novel* challenges. Importantly, the systems are not "pre-wired" or "pre-designed" to accommodate such challenges that force them into an exploratory dynamics. The principal experimental idea is then to track the dynamics of a system under such conditions during adaptation. What makes the experimental work under review critical to philosophical discussion is the generalization at which the experimenters have arrived with two different realizations of biological systems, namely, yeast cells and neural networks.

The search for uncovering universal aspects, rather than system-specific features, is the motivation for conducting these experiments in two different biological realizations. Clearly, a system of microorganisms operates on a completely different level from that of a system of neurons linked in a network and, yet, preliminary results from the two systems suggest, so the experimenters argue, that universal biological features may be revealed at these two enormously different scales.

A system of microorganisms. Erez Braun worked with genetically modified yeast cells that were changed such that the synthesis of the essential amino acid histidine was placed under the control of a gene responsible for the utilization of galactose. Without technical intervention the production of histidine is completely unrelated to the galactose mechanism. This latter mechanism is inactivated in a medium rich in glucose. As a result, in an environment lacking histidine and containing glucose, histidine is in high demand but cannot be produced. Under such conditions, the manipulated yeast cells were forced to find a solution to the problem and develop a novel regulatory mode. They could only survive if they managed to relaunch the blocked synthesis of histidine. The observation was that a considerable fraction of the yeast cells adapted quickly to the new constraints. Braun argues that this set of experiments shows that inherited adaptation can result from physiological responses which reflect cellular plasticity. In light of this result, so the argument goes, the view that regards the genome as a "programme", the environment as an "input signal", and the phenotype as a "logical output" of the cellular "computing device" should be revisited.

A system of neurons. The second set of experiments concerns a population of neurons. When many neurons are extracted from the brain, placed together *in vitro* and given appropriate nutrients, they extend axons and dendrites, forming numerous synaptic connections, and develop complex patterns of activity. A large-scale randomly connected network of cortical neurons is found to exhibit preferred modes of response to a given input. Shimon Marom imposed a challenge on such a neural network that demands a specific but arbitrarily defined target response which has a low default probability. The observation was that these neural networks meet this challenge within a surprisingly short period of time and converge quickly toward the required target response. Marom places emphasis on his observation that there seems to be no preferred time scale for describing the processes representing this activity of self-organization. Consequently, as he argues, temporal response patterns cannot be used for distinguishing between different levels of organization, such as microscopic and macroscopic configurations.

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The two sets of experiments deal with different biological systems, but both exhibit, so the claim goes, the same pattern of adaptation by self-organization. What makes biological populations special and distinct from inanimate objects is the fact that in the former class self-organization can be interpreted in terms of functions. A mechanism that fulfils a certain function can be viewed as the endpoint of a process that realizes an objective, which is determined by environmental constraints. This functional adjustment is produced by some sort of higher-level coordination which, in itself, is not pre-designed.

Braun and Marom inferred two universal features from these two sets of experiments, namely, (1) two-way degeneracy, or "deep degeneracy," as they call it, and (2) a lack of time scale separation or the property of being scale free. The first feature has to do with the causal microscopic–macroscopic relation, or rather the absence of such a relation. Many-to-one degeneracy is supposed to say that the same function can be performed by different physiological mechanisms, while one-to-many degeneracy means, conversely, that the same physiological component can play a multiplicity of functional roles. As Braun and Marom argue, many-to-one degeneracy is typical of physical systems, while the hallmark of biological systems is the converse degeneracy from one (microscopic) to many (macroscopic) features. Deep degeneracy, or two-way degeneracy, brings the two relations together and is supposed to express a many–many relationship between functions and their realizations. This complex relationship thwarts, in the view of Braun and Marom, any attempt to reduce higher-level biological properties, or systems properties, to the nature and interaction of their component parts.

The second issue concerns the time scale among processes occurring at different levels of organization. Braun and Marom observe that there is *no* such scale separation: microscopic structures operate over time scales that are traditionally attributed to macroscopic structure and *vice versa*. The lack of time scale separation is characteristic of complex systems. Scale-free processes are affected by events from the distant past and may continue into the future with no terminus. As a result, scale-free processes extend across different levels of organization and defy, for this reason, attempts to explain macro-processes through underlying micro-processes. The mechanisms underlying scale-free processes are therefore dispersed across a variety of entities, interconnections, and levels of organizations and do not exhibit clear boundaries. As a result, such macro-phenomena do not admit of a micro-explanation. Put differently, no relevant level of organization can be identified at which the mechanism supposed to produce a given phenomenon operates. Two-way degeneracy and the lack of timescale separation militate against both reductionism and reverse engineering.

While generalization and the comprehension of universal features is a chief goal of science, Braun and Marom observe that "much of biology is about specificity, telling the origins of *differences* between species, phenomena, capacities." From this perspective, the two universal claims, namely, two-way degeneracy and the lack of timescale separation, raise the suspicion that something is amiss: these generalizations could be artefacts of the particular approaches to biological systems. In other words, the chosen relevant system variables are not the correct ones; the choice could be the result of misleading methodologies. Braun and Marom question the possibility of uncovering the design principles underlying a mechanism on the basis of its overt effects. Their argument relies on underdetermination and multiple realizations. Biology, they claim, is not technology. "The business of biology *as a basic science* is not to uncover a plausible mechanism but rather to discover the actual design principles underlying the natural phenomenon; this is where the naïve version of reverse engineering in particular, and naïve reductionism in general, epistemically fails" (see the above motto). Their concerns cluster around three themes: reverse engineering, mechanism and function.

2. The responses of the philosophers

Three philosophers, **Sara Green**, **William Bechtel** and **Ulrich Krohs** have taken up the challenge and grappled with these difficulties. They subject the claims to philosophical scrutiny under the question headings, respectively, Can biological complexity be reverse engineered? Can mechanistic explanation be reconciled with scale-free constitution and dynamics? And, finally, Can functionality in evolving networks be explained reductively? The overall result of this exchange is relevant, in our view, to the understanding of the science of biology and its practice as well as to the role of philosophy in this scientific quest. In anticipation of our conclusion, we may note that—in this meeting of philosophers and biologists—the coordination of the two different disciplinary approaches has been frustrated and rendered ineffectual. No interdisciplinary endeavour emerged, and the protagonists were arguing at cross-purposes.

Sara Green takes up the challenges which Braun and Marom raise regarding the possibility of reverse engineering and the anti-reductionist sentiments they associate with their objections. These objections indicate that the pattern of behaviour which a system exhibits leaves room for a variety of principles or mechanisms that might produce this behaviour. Green refers to a similar debate in systems biology where the prospects and limitations of engineering approaches have also centred on methodological pitfalls associated with the search for so-called design principles. This comparison shows that insights can be transferred across these domains.

Green stresses the need to distinguish between the *soundness* of engineering approaches and the *productivity* of their associated heuristic. For instance, false models often lead to productive insights, and negative analogies can result in valuable knowledge on how organisms and artefacts differ. Searching for design principles may be a fruitful heuristic even if no simple general principles can be found. We must therefore not only base the evaluation of this strategy on the correctness of its underlying assumptions but also on the relation between the research aim and its heuristic value. Whereas Braun and Marom's criticism aims at engineering approaches in general, Green restricts the criticism to the unreflected use of engineering metaphors and design analogies. In her view, the choice we have is not a choice between biased and neutral methodologies but between being aware of biases and ignoring them.

Further, as Green points out, subjecting the system at hand to a more detailed or fine-grained analysis may well produce data that are able to distinguish between alternative hypotheses about the underlying mechanisms. The concerns which Braun and Marom raise regarding the underdetermination of the true mechanism by the pertinent observations, may be due to the schematic character of their example. They deal with a toy model, while real-world biological systems can be put to more extensive scrutiny. The latter may well succeed in distinguishing the true mechanism from its merely possible alternatives. Consequently, the failure which Braun and Marom bring to the fore may have more to do with the particulars of their case than with the features of reverse engineering in general.

In addition, associating reverse engineering with "naïve reductionism" is misguided. Rather, studying engineering-inspired approaches in systems biology reveals that important characteristics of organisms, such as the robustness of functions against distortions, is mostly due to organizational features at various systems levels. That is, understanding patterns of behaviour and regularities of systems change does not so much require the detailed