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Introduction

Introduction: Philosophers meet biologists

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Giora Hon (University of Haifa)
Martin Carrier (Bielefeld University)

> 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 reconstruction of the underlying mechanisms, but rather the grasp of their large-scale architecture. In this way, reverse engineering may not fall prey to misleading local subtleties. This systems-oriented approach suggests that reverse engineering should not be confounded with naïve reductionism.

Green acknowledges Braun and Marom's objections but warns against throwing out the baby with the bath water. She reflects on the difficulty in distinguishing between the productive and limiting aspects of research strategies, and emphasizes the increased awareness that can be obtained from the analyses of such strategies. Overcoming the biases harboured by these approaches requires calibration with other sources of independent evidence. This task is philosophical as well as scientific, and collaboration between the two domains can therefore be fruitful.

William Bechtel notes that Marom raises doubts regarding the viability of mechanistic explanations of biological (and psychological) phenomena by arguing that many such phenomena are scale-free in the sense that there is no distinct duration in which the assumed mechanism produces the effect in question. Being scale-free means that the mechanism does not have a clear onset and an unambiguous termination. Rather, a certain pattern of activity may depend on events in the distant past and affect events in the remote future. This stands in contrast to the period of activity of some phenomenon as it is traditionally assumed. Bechtel observes that Marom uses this consideration as an argument against the possibility of invoking mechanisms for explanatory purposes since mechanisms are typically regarded as sequences with a clearly defined start and finish.

Indeed, fundamental to the mechanistic approach is the decomposition of a system responsible for a phenomenon into parts and operations that are organized so as to generate that phenomenon. As indicated, one principal difficulty is the lack of well-delineated temporal boundaries differentiating a mechanism from its environment. Bechtel draws a parallel between Marom's temporal sense of being scale-free and the more established spatial sense. In a scale-free system, a given phenomenon may influence seemingly distant entities and may be affected, conversely, by these entities. Such mechanisms are not delineated by well-defined boundaries and may therefore dissolve into a diffuse network of causal influences with no distinct borders.

The antidote, as suggested by Bechtel, is an instrumentalist rather than a realist understanding of mechanisms. What counts as a mechanism and how it is individuated depends on the explanatory purposes which these mechanisms are intended to serve. Mechanisms are idealizations, that is, they deliberately involve simplifying falsehoods. Delineating mechanisms does not mean cutting nature at its joints, but rather carving foci of interest from this seamless whole. This process is tantamount to featuring certain influences and neglecting others, thereby creating boundaries in an interconnected world. The mechanistic approach should not be abandoned; rather, the imposition of temporal and spatial boundaries often generates accounts of mechanisms that are accurate to a first approximation. This first approximation includes the most salient features and is subsequently modified and refined by integrating components and influences that seemed too far-off initially in temporal or spatial respect. It is true, delineating a time window in which one characterizes the functioning of a mechanism is an imposition made by scientists, and one must be prepared to recognize that the effects one is trying to explain may be due to processes outside that time window. But iterative strategies of this sort work with scale-free mechanisms in spatial respect; they should also be helpful for dealing with temporally scale-free processes. To be sure, if mechanistic explanations are supposed to capture real mechanisms as they operate in nature, then Marom's objection that scale-free processes and interactions are difficult to explain mechanistically holds. If, however, mechanisms are considered idealizations that impose temporal and spatial boundaries on the processes studied, then these mechanisms can be extended according to the explanatory purposes at hand. This is how mechanisms can account after all for scale-free relations. In sum, notwithstanding Marom's objections, Bechtel argues for the viability of mechanistic explanations of scale-free phenomena.

The main thrust of Krohs's paper concerns the analysis of Braun and Marom's ascriptions of biological functions. Krohs develops a concept of functions that is suitable for unifying seemingly diverse features that Braun and Marom appeal to in characterizing functions. Krohs argues that passages suggesting a causal role account of functions in the sense of Cummins and passages specifying a more demanding normative concept of functions can be brought into harmony and integrated with each other if a design-based concept of functions is attributed to Braun and Marom. This concept is understood as a reconstruction of Braun and Marom's actual talk about functions, but Krohs also claims that his design-based account is superior as a philosophical theory of functions. Krohs presents the design of a system as the ensemble of types of component activities, and the function of a component is given, then, by its role in the system according to the system's design. This design concept of functions, as Krohs claims, can capture Braun and Marom's use of functions better than the standard etiological concept does, since one of their crucial points is that the adaptive response of yeast does not proceed via selection processes.

Krohs is highly critical of many biological claims entertained by Braun and Marom. In particular, it has not been convincingly demonstrated, in his view, that an alternative mechanism of processing yeast was created by the rewired cells; nor was it established how frequent the claimed switch to the new physiological regime emerged. In addition, labelling the relevant effects as "population phenomena" is misleading, in Krohs's opinion, since some effects are attributed to changes in individual cells, while others are said to go back to interactions among cells. Populations in the biological sense of organisms distinguished by common ancestry are not part of either picture. Moreover, Krohs casts doubt on the originality of various interpretations which Braun and Marom offer. In particular, the claimed two-way degeneracy between structure and function is the same thing as the by now familiar claim of a many—many relationship between the two. Specifically and in contrast to what Braun and Marom suggest, mere multiple realizability of biological functions is in accordance with standard reductionist accounts in the philosophy of biology.

3. The significance of this interdisciplinary encounter

In our original plan we had expected that the meeting at the Zukunftskolleg in Konstanz, and the subsequent publication of this special section would demonstrate how a combination of experimental expertise with the rigor of philosophical critique would sharpen conceptual analyses that are vital to the understanding of natural phenomena and to the design of productive experimental schemes. We prepared the ground for a collaboration in an interdisciplinary spirit, but our expectations remained unfulfilled. In the ensuing exchange of arguments the scientists and the philosophers both kept to their positions without finding a common ground.

Braun and Marom expected the philosophers to respond constructively to what they considered fundamentally novel issues in the study of biological systems. The biologists hoped that the philosophers would join forces and grapple together with the very problems they had identified as part of a long-term intellectual history regarding reduction and levels of organization. They wanted to enlist the philosophers in their attempt to find novel methodologies which might help circumvent the problems they had encountered. However, all Braun and Marom got are objections they consider to be of a biological rather than a philosophical nature. By contrast, the philosophers complain that the biologists overstrain their case because they are not sufficiently familiar with the state of philosophical discussions. This applies to reverse engineering in Green's case, to the property of being scale free in Bechtel's account, and to reductionism in Krohs's analysis. The biologists claim they have discovered unsurmountable barriers to traditional practices, while the philosophers respond that these difficulties have all been well thought through and indeed resolved.

Braun and Marom sought philosophical support for what they consider problematic methodologies which in their view are essentially misleading. What they learnt from the philosophers is that these difficulties are well known and could be overcome by applying due care and increased awareness of the relevant constraints. The biologists wanted to rethink their practices, but they were told by the philosophers that there is no need to do so—one should simply press on with the traditional practices. This was not the moral the biologists expected to hear from philosophers. Have the philosophers missed something? We leave it to the reader, indeed, to the philosophy community, to decide.