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Can biological complexity be reverse engineered?

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ABSTRACT

Concerns with the use of engineering approaches in biology have recently been raised. I examine two related challenges to biological research that I call the synchronic and diachronic underdetermination problem. The former refers to challenges associated with the inference of design principles underlying system capacities when the synchronic relations between lower-level processes and higher-level systems capacities are degenerate (many-to-many). The diachronic underdetermination problem regards the problem of reverse engineering a system where the non-linear relations between system capacities and lower-level mechanisms are changing over time. Braun and Marom argue that recent insights to biological complexity leave the aim of reverse engineering hopeless - in principle as well as in practice. While I support their call for systemic approaches to capture the dynamic nature of living systems, I take issue with the conflation of reverse engineering with naïve reductionism. I clarify how the notion of design principles can be more broadly conceived and argue that reverse engineering is compatible with a dynamic view of organisms. It may even help to facilitate an integrated account that bridges the gap between mechanistic and systems approaches.

1. The virtues and pitfalls of reverse engineering

Reverse engineering methodologies are currently gaining terrain in biological fields such as systems biology and neuroscience. In response to these developments, experimental biologists have raised concerns regarding the associated quest for design principles that they take to imply an assumption of a rather static and modular design of organisms. A workshop in Konstanz brought together philosophers and biologists to discuss the implications of research methodologies in the life sciences.[1] This paper focuses in particular on concerns raised regarding reverse engineering of biological networks.

The experimental biologists Erez Braun and Shimon Marom (2015) provide fascinating insights to biological complexity by stressing how living systems are characterized by a (deep) two-way degeneracy and lack of separation of time-scales. Against this complexity, they criticize so-called reverse engineering approaches for investigating biological systems as if these were programmed and fully decomposable engineered systems, designed to conduct pre-designed functions. This paper clarifies and supports their criticism of naïve reductionism, but questions the argued discrepancy between reverse engineering and systemic approaches.

The notion of reverse engineering has its origin in the attempt to copy or further develop the design underlying a functional system in hardware and software engineering without access to the design protocol (Chikofsky & Cross, 1990). Although the aim to design functional systems is primarily seen in synthetic biology and bioengineering, reverse engineering has currency in many other biological fields where it commonly refers to the process of '(detailed) examination of a functional system, in the face of limited *a-priori* knowledge of its design principles' (Braun and Marom, 2015).[2] In the abovementioned definition I have bracketed the requirement of a *detailed* examination. This requirement marks an

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[1] "Philosophers meet Biologists: Experimental Studies of Population Phenomena", organized by the Zukunftskolleg, University of Konstanz, May 2013.

[2] This definition differs from how reverse engineering is understood in the literature on adaptationism. For clarification see (Green, Levy, & Bechtel, 2015).

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important difference between Braun and Marom's view on reverse engineering as a reductionist strategy and the account I develop in this paper. For Braun and Marom, 'design principles' seem to refer to the results of fine tuning (and selection of) specific control parameters engineered to lock the system in a given dynamic state.[3] In contrast, the view I develop is inspired by reverse engineering in systems biology where abstraction is central. In this context, design principles typically refer to general features of functional organization that are independent of system-specific contexts or particular molecular parameters. My aim in this paper is to take seriously the challenge posed for (reductionist) reverse engineering, while nuancing the description of reverse engineering approaches through examples from systems biology.

It is worth noting that the call for engineering approaches often reflects a wish for an alternative to the reductionist study of isolated molecules and pathways. The goal is to identify organizational patterns that may otherwise be lost in the preoccupation with molecular details. If the same principles can be applied in the design of different types of engineered systems from cars to computers or airplanes, it seems likely that some principles are shared among different biological systems or even among engineered and biological systems (Braillard, 2010). This objective to identify shared formal criteria for functional design is not new. It dates back at least to the early days of control system theory and modern cybernetics, where feedback control was formalized as a basic principle for maintaining stable states and oscillations (Wiener, 1948). But reverse engineering methods have recently become increasingly widespread in data-intensive biological fields concerned with the identification of non-random connectivity patterns in biological networks. When un-aided pattern detection is not analytically feasible, mathematical models can guide the search for relevant structure-function relations (Levy & Bechtel, 2013).

The choice of the graph theoretical framework as a key representational strategy reflects how reverse engineering is often conducted at a high level of abstraction. Displaying regulatory connections as nodes and edges affords a topological analysis that abstracts from the details of what these units represent to identify functional capacities that relate to the architecture of the network. For instance, many real-world networks seem to share general characteristics such as the small-world effect and scale-free connectivity distribution (Barabási & Oltvai, 2004; Bechtel, 2015). It is highly contested how much biological information one can derive from topological analysis and whether the scale-free distribution exemplifies a biological design principle (Arita, 2004; Keller, 2005). But many biologists agree that there is a connection between the robustness of biological networks and their non-random connectivity distribution and hierarchical structure (Steinacher & Soyer, 2012). Other examples of design principles are bi-stable switches (Tyson, Chen, & Novák, 2003) and overabundant sub-circuits in gene regulatory networks, called *network motifs* (Alon, 2007a, see below). To some researchers, such findings provide optimism that there is simplicity in the apparent complexity of biological systems (Alon, 2007c; Csete & Doyle, 2002).

The quest for design principles reflects a hope that key properties of biological systems can be understood without knowing all the lower-level causal details. This is not only a point about practical convenience but also about the relevant level of analysis. The cancer biologist Lazebnik (2002) provocatively compared biomedical research strategies to the attempt to fix a radio by atomizing the system into component parts and studying these in isolation. If the malfunction of the system is connected to the orchestrated organization of parts and processes, searching for broken molecular components is bound to fail. Lazebnik therefore proposes an engineering approach to investigate how the components are wired together as a functional whole. Lazebnik's original choice of example however also clarifies why reverse engineering is often considered a reductionist strategy. Biological systems do not function like a pre-designed radio; there is no simple and static "wiring" of a living cell. Critics are concerned that engineering approaches underestimate biological complexity when assuming that living systems are similar.

To exemplify, topological network analysis is sometimes advertised as a bias-free decomposition strategy, in contrast to hypothesis-driven functional analysis. But choices of structural criteria — often inspired by design principles in electronic networks — also imply a bias. It is typically possible to fit several structural modules to a given data-set, and researchers cannot assume any tight overlap between structural and functional modules (Krohs, 2010). While the problem of underdetermination is a general problem in science, the challenge is particularly apparent in fields where data-intensive modeling is only loosely integrated with experimental analysis (Krohs, 2012). These methodological concerns are complemented by a more fundamental worry that biological design principles may not exist at all (Marom et al., 2009). The inherent plasticity, degeneracy and evolvability of the functional organization of living systems indicate that methodologies and conceptual frameworks from engineering should not be uncritically applied in biology.[4] An important question is therefore whether there are better strategies for facing not only the challenge of 'synchronic degeneracy' (the many to many mappings between lower-level functional organization and system behavior) but also of what I shall call 'diachronic degeneracy' (the change of these relations over time).[5]

To discuss the prospects of reverse engineering methodologies, I compare the concerns raised by Marom and Braun to a similar debate in systems biology. I first draw on two examples to illustrate the problem of 'synchronic underdetermination' for reverse engineering of biological networks (Section 2.1). I then discuss whether the biases can be accounted for via evidence calibration and by increasing the resolution of the analysis (Section 2.2). While this seems to be a feasible solution if the system is relatively stable over time, Section 3 highlights the challenges associated with what I call the 'diachronic underdetermination problem'. This problem relates to the prospects of identifying design principles at the background of changes to cross-level relations over developmental and evolutionary time-scales. Section 4.1 and 4.2 reexamines the merits of engineering approaches against this challenge. Section 5 demonstrates how reverse engineering can be productively combined with a systemic approach. Section 6 concludes with some general remarks on the prospects of reverse engineering methods in biology.

2. Engineering approaches and synchronic underdetermination

2.1. Reverse engineering biological networks

To illustrate the problem with synchronic underdetermination, this section examines two attempts to reverse engineer biological

[3] For a discussion of the use of the notion of design principles and other functional terms in Braun and Marom's papers, see Krohs (2015).

[4] In the context of evolution biology, design thinking has been criticized for having adaptationist implications. I have discussed the relation between design approaches and adaptationism elsewhere (Green, 2014; Green, Levy, et al., 2015), and this paper instead concerns the challenges for reverse engineering associated with synchronic and diachronic degeneracy. I shall, however, discuss the role of reverse engineering in evolutionary studies in Section 5.

[5] I thank Ben Sheredos for suggesting these terms to cover the challenges addressed.