



Contents lists available at ScienceDirect

# Studies in History and Philosophy of Biological and Biomedical Sciences

journal homepage: [www.elsevier.com/locate/shpsc](http://www.elsevier.com/locate/shpsc)

## Modeling systems-level dynamics: Understanding without mechanistic explanation in integrative systems biology

Miles MacLeod<sup>a,\*</sup>, Nancy J. Nersessian<sup>b</sup><sup>a</sup> Centre of Excellence in the Philosophy of Social Sciences, Department of Political and Economic Studies, University of Helsinki, P.O. Box 24, 00014, Finland<sup>b</sup> Department of Psychology, Harvard University, 1160 William James Hall, 33 Kirkland St., Cambridge, MA 02138, USA

### ARTICLE INFO

#### Article history:

Received 19 May 2014

Received in revised form

22 October 2014

Available online 25 November 2014

#### Keywords:

Systems biology

Mechanistic explanation

Understanding

Systems-level understanding

Abstraction

Complexity

### ABSTRACT

In this paper we draw upon rich ethnographic data of two systems biology labs to explore the roles of explanation and understanding in large-scale systems modeling. We illustrate practices that depart from the goal of dynamic mechanistic explanation for the sake of more limited modeling goals. These processes use abstract mathematical formulations of bio-molecular interactions and data fitting techniques which we call top-down abstraction to trade away accurate mechanistic accounts of large-scale systems for specific information about aspects of those systems. We characterize these practices as pragmatic responses to the constraints many modelers of large-scale systems face, which in turn generate more limited pragmatic non-mechanistic forms of understanding of systems. These forms aim at knowledge of how to predict system responses in order to manipulate and control some aspects of them. We propose that this analysis of understanding provides a way to interpret what many systems biologists are aiming for in practice when they talk about the objective of a “systems-level understanding.”

© 2014 Elsevier Ltd. All rights reserved.

When citing this paper, please use the full journal title *Studies in History and Philosophy of Biological and Biomedical Sciences*.

Systems biology has provided an important motivation and material for extending philosophical conceptions of mechanistic explanation to dynamic systems (see Bechtel, 2011; Bechtel & Abrahamsen, 2005, 2010; Brigandt, 2013; Fagan, 2012; Levy & Bechtel, 2013). Our aim in this paper is to explore typical cases of model-building in systems biology research that depart from standards of dynamic mechanistic explanation. These departures are practically and pragmatically motivated by the many constraints systems biologists face. Studying these departures opens up a window on a very rich largely unexplored set of practices afforded by the power of modern computational and mathematical techniques of approximation and abstraction, particularly in connection with parameter-fixing. These practices allow modelers to extract reliable information and achieve some form of understanding of systems despite errors and inaccuracies in their

representations. In this paper we investigate how these practices operate, how to situate them with respect to mechanistic explanation, and what kind of understanding they produce.

Our analysis will draw upon cases from a 4-year ethnographic investigation of labs working in the bottom-up stream which self-identify as doing “integrative systems biology,” a form of systems biology that aims to integrate computational and mathematical methods with experimental biology. These labs focus both primarily on modeling metabolic networks and to a lesser extent on gene regulatory networks and inter-cellular interaction. We conducted unstructured interviews and field observations, followed by semi-structured interviews to focus on specific issues, and attended lab meetings, which varied in frequency depending on the lab. Researchers in these labs are mostly graduate students and mostly come from engineering backgrounds. These labs are nonetheless diverse in other ways. The first, Lab G, is composed only of modelers (engineers of various kinds and applied mathematicians), some of whom model biological pathways for various purposes, while others work on generating mathematical methods for parameter-fixing or structure identification. These modelers work in

\* Corresponding author.

E-mail addresses: [miles.macleod@helsinki.fi](mailto:miles.macleod@helsinki.fi) (M. MacLeod), [nancynersessian@fas.harvard.edu](mailto:nancynersessian@fas.harvard.edu) (N.J. Nersessian).

collaboration with molecular biologists from outside the lab. The second, Lab C, comprises mostly researchers who do both modeling and experimentation in the service of building their models, although usually with some collaborative support from molecular biologists outside the lab for theoretical guidance. Our claims about modeling in this paper derive from our analysis of ethnographic interviews around the model-building processes and practices of the modelers in both these labs, as well as the literature in this stream of systems biology.<sup>1</sup>

We find that in practice 1) systems biologists often frame limited predictive and explanatory goals with respect to complex target systems, which can be met without dynamic mechanistic explanations of how these systems function; and 2) these goals prescribe problems that are tractable using mathematical and computational techniques of parameter-fitting. These techniques rely upon layers of top-down abstraction and approximation that draw out desired relationships from a mechanism but compromise the accuracy of the resulting simulation model with respect to other aspects of the mechanism. These processes thus tend to render opaque the role that the underlying mechanism of parts and interactions plays in producing the phenomena of interest.

If mechanistic explanations are not the target, then there is important question to be asked about what it is this kind of systems biologists is aiming for. We will suggest that such modelers aim for understanding in terms of how to intervene on certain network elements in order to influence network dynamics. They aim for predictively accurate or robust mathematical representations of the dynamic relationships between a limited selection of variables from a system. This form of understanding is pragmatic in the sense that it aims for control (Lenhard, 2006), but is also pragmatic in the sense that it is a response to the significant constraints modelers face. It trades away the accuracy and detail of a mechanistic account, which would demonstrate the links between parts, organization, and system-level properties or phenomena, for limited but achievable information on the relations between specific key parts and the over-all dynamics of the system. This information serves the expressed goal of systems biology to achieve mathematical accounts of system-level dynamics, and indeed can be used to interpret what systems biologists mean in practice when they say they aim—in contrast to molecular biologists—at a “systems-level understanding.”

This paper proceeds as follows. First, we outline the goals and practices of systems biology in general to provide some insight into the problem-solving context. Second, we briefly detail recent developments in the philosophical discussion of dynamic mechanistic explanation in relation to systems biology. Third, we examine with the aid of our own case studies how the attitudes of modelers and model-building practices in systems biology diverge from the objective of mechanistic explanation. Finally, we argue that nonetheless, these systems biologists often claim their mathematical models provide a form of non-explanatory understanding of dynamic relationships amongst variables, which is essential to their ability to construct models and handle complex systems.

## 1. Systems biology

As many commentators have pointed out systems biology is a diverse field characterized by different methods and practices (Calvert & Fujimura, 2011; O'Malley & Dupré, 2005). One can best

understand what unifies these practices as a shared commitment to model complex biological systems using computational and mathematical resources and to an often loosely specified idea of a “systems approach.” Although dynamical systems theory and even the notion of “systems biology” have longer historical roots, the modern incarnation is about 20 years old, born of the widespread availability of adequate computational power, developments in mathematical and algorithmic techniques, and the development of mass data production technologies (Kitano, 2002; Krohs & Callebaut, 2007; O'Malley & Dupré, 2005). Such technologies include in particular high-throughput data technologies which collect dense dynamic information from a system. One of the prime methodological innovations of modern systems biology has been to integrate engineering with biology by integration engineering concepts of “system,” and its mathematical methods for analyzing large-scale systems, with modern-day computational processing and high-throughput technologies for data collection.

Systems biology positions itself against traditional biological fields like molecular biology. The latter apply experimental techniques to measure molecular properties, often *in vitro*, discover interactions, and build pathways. Rather than studying molecules and their interactions systems biology studies the dynamic behavior and properties of the systems they form. The need for a “systems approach” is supported with several philosophical claims in this regard. Firstly one of the central claims of systems biology is that properties and biological functions of components are dependent on their participation within systems (Kitano, 2002; Westerhoff & Kell, 2007). Secondly since parts and operations are typically determined and modified within the bounds of large-scale systems, only at this scale can predictively accurate models be constructed to guide control and intervention on systems (e.g., for medical purposes). Operating with small-scale representations and smaller pathways risks neglecting many important interactions these pathways have with external elements and networks that control and ultimately determine their dynamics. Because of the complexity and sensitivity of large-scale networks (arising from the many interacting components and nonlinearities in the form of feedback relations), they need to be represented mathematically. Only mathematical analysis can draw out the dynamic features and the control relationships of such networks. The qualitative approaches of molecular biology simply cannot be effective in obtaining this information. All systems biologists more or less, thus, share a commitment to modeling system dynamics mathematically (see also O'Malley and Dupré, 2005; 1273).

That said, many quite distinct pursuits take the name “systems biology,” ranging over different biological subject matter from genes up to ecological systems and over different methodological approaches, such as “top-down” and “bottom-up streams” approaches (Krohs & Callebaut, 2007; Westerhoff & Kell, 2007). The former aim to reverse-engineer system structure from dense data sets and the latter, to build models from lower-level data on pathway structure and component interactions. Thus, these streams represent quite distinct methodological approaches. For modelers in both streams, the predominant standard for a good model is often first and foremost predictive accuracy. Data are often left out of the model-building process to then test (“validate”) the model and build faith in its robustness, although other arguments are often used to establish robustness as we will see. If a model can be validated this way, then inferences can be put forward regarding intervention and control based on analysis of the model.

A significant component of systems biology, however, is concerned not with large-scale modeling, but discovering design motifs or small sub-networks that exhibit a particular function that is reproduced and reused across different biological systems and different species. (Alon, 2007; Green & Wolkenhauer, 2013; Levy &

<sup>1</sup> This research is funded by the US National Science Foundation which requires following human subjects' regulations, so we use numbers to name the researchers of each lab. Also, many of the researchers are non-native English speakers, which accounts for the grammatical errors in the quotes.

Download English Version:

<https://daneshyari.com/en/article/1162192>

Download Persian Version:

<https://daneshyari.com/article/1162192>

[Daneshyari.com](https://daneshyari.com)