Studies in History and Philosophy of Science 56 (2016) 113–121

Contents lists available at ScienceDirect

Studies in History and Philosophy of Science

journal homepage: www.elsevier.com/locate/shpsa

Using computational models to discover and understand mechanisms

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ARTICLE INFO

Article history:
Available online 19 November 2015

Keywords:
Computational modeling;
Mechanistic explanation;
Circadian rhythms;
Discovery;
Understanding;
Design principles

ABSTRACT

Areas of biology such as cell and molecular biology have been dominated by research directed at constructing mechanistic explanations that identify parts and operations that when organized appropriately are responsible for the various phenomena they investigate. Increasingly the mechanisms hypothesized involve non-sequential organization of non-linear operations and so exceed the ability of researchers to mentally rehearse their behavior. Accordingly, scientists rely on tools of computational modeling and dynamical systems theory in advancing dynamic mechanistic explanations. Using circadian rhythm research as an exemplar, this paper explores the variety of roles computational modeling is playing. They serve not just to determine whether the mechanism will produce the desired behavior, but in the discovery process of hypothesizing mechanisms and in understanding why proposed mechanisms behave as they do.

1. Introduction

Many areas of biology (physiology, cell and molecular biology, etc.) have been slow to embrace computational modeling (fields such as population genetics and neuroscience being exceptions). The focus of research has been on developing and applying experimental techniques to develop accounts of mechanisms thought to be responsible for phenomena such as gene expression, metabolism, and cell division. Accounts of mechanistic explanation advanced by philosophers (Bechtel & Abrahamsen, 2005; Bechtel & Richardson, 1993/2010; Machamer, Darden, & Craver, 2000) have emphasized the importance of characterizing parts and operations that, when organized appropriately, are able to generate the phenomena of interest. Little, though, has been said about how researchers connect their understanding of parts and operations with the phenomenon to be explained. When they hypothesize mechanisms with parts organized in relatively simple ways, researchers are able to rely on mentally rehearsing the operations proposed to evaluate whether they could generate the phenomenon. For example, by imagining the execution of each successive step in the textbook description of protein synthesis one can imagine how a polypeptide chain is generated that matches the sequence of codons on the DNA. Mental operations mirror the causal operations proposed to operate in nature. Computational modeling was not needed to understand how these mechanisms (which are the focus of what I refer to as *basic mechanistic explanations*), could account for the phenomenon.

In the late 20th century the mechanisms proposed in fields such as cell and molecular biology became more complicated as more parts and operations were identified. This alone, however, was not sufficient to lead biologists to turn to computational modeling, as even with lots of parts, they could still rehearse the succession of operations mentally to determine whether the proposed mechanisms sufficed to generate the phenomenon. Rather, the need for computational models became more serious with the development of accounts of mechanisms in which the operations were no longer organized sequentially but featured multiple feedback loops. The need became even greater when the operations appealed to could only be described by non-linear mathematical equations. Humans, including scientists, perform poorly in predicting the behavior of non-linear processes and keeping track of multiple interactions due to feedback loops, especially if they operate on multiple timescales. To overcome these limits, scientists often develop

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http://dx.doi.org/10.1016/j.shpsa.2015.10.004
0039-3681/

mathematical characterizations of the different operations and employ these in computational models that simulate how hypothesized mechanisms will behave. Mechanisms whose behavior can only be accounted for with computational modeling and analytic tools such as those offered in dynamical systems theory no longer count as basic mechanistic explanations but fall in the hybrid category of dynamic mechanistic explanations (Bechtel & Abrahamsen, 2010, 2012). The goal of this paper is to elaborate on the roles computational models play in dynamic mechanistic accounts.

In this paper my main focus is on mechanistic explanations (explanations in which proposed mechanisms play a central role).[1] Evaluating explanations often involves predicting (or retrodicting) what would happen if the explanation were correct. The most basic use of computational modeling in biology involves prediction—predicting whether a proposed complex mechanism would produce the phenomena for which it is posited as an explanation. I will introduce this role for computational modeling in Section 2. Much of scientific research, however, is involved not in evaluating, but in discovering explanations (proposing possible mechanisms). The very factors that made it important to employ computational models to determine how a proposed mechanism would behave have also led researchers to employ them in the discovery process. In this paper I will illustrate such use of computational modeling in proposing a mechanism (Section 3) and in proposing how a given mechanism might be embedded in another (Section 4). A common, although not a necessary, goal of explanation is to provide understanding—making it intelligible to us why the proposed mechanism would account for the phenomenon. As proposed mechanisms become complicated and complex, one can predict how a mechanism will behave through computational modeling without understanding why it will behave that way. Acquiring understanding often requires abstracting from the details of a mechanism to uncover basic design principles it employs (Green, Levy, & Bechtel, 2014; Levy & Bechtel, 2013). In Section 5, I discuss the use of computational modeling in identifying the basic design principles that enable a mechanism to generate a phenomenon.

To illustrate these different roles of computational modeling, I will focus on modeling in chronobiology, the field of biology devoted to understanding circadian and other biological rhythms. Circadian rhythms are endogenously generated oscillations that are entrainable to the light/dark cycle of the local environment and regulate a wide range of physiological and behavioral activities by restricting expression of specific genes to particular times of day. Research in the early 20th century demonstrated that these rhythms were endogenous by showing that in the absence of cues from the environment, organisms would exhibit rhythms slightly different than 24 h (hence, the rhythms were named *circadian* from *circa*, about, and *dies*, day). Much of the pioneering research in the later decades of the 20th century on the mechanism responsible for circadian rhythms was conducted on animals (especially fruit flies and mice), but circadian rhythms have also been demonstrated and studied in plants, fungi, and cyanobacteria. I begin with research on animal circadian rhythms as that makes apparent the conditions under which computational modeling first became important but also how it followed on the articulation of proposed mechanisms. In subsequent sections I turn to research on circadian rhythms in cyanobacteria where modeling has played a central role in the discovery of the responsible mechanism and in understanding how it produces the phenomenon.

2. Modeling to establish a proposed mechanism's sufficiency

The proposal of a mechanism for circadian rhythms in animals built on experimental findings that suggested the nature of the mechanism. Through a screen of mutant fruit flies for disrupted or altered circadian rhythms, Konopka and Benzer (1971), discovered strains of flies that exhibited shortened or lengthened rhythms or were arrhythmic. They traced the mutation in all strains to a single gene they named *period* (*per*). Discovering how the gene figured in generating circadian rhythms had to await the development of cloning techniques. In pioneering research applying these techniques to circadian rhythms, Hardin, Hall, and Rosbash (1990) determined that concentrations of both *per* mRNA and the protein PER oscillated with a period of about 24 h, and that the phase of peak PER concentration lagged about four hours behind that of *per* mRNA. This led them to propose a mechanism involving a negative feedback loop (known as a transcription–translation feedback loop or TTFL) in which, after it is synthesized, PER is transported back into the nucleus where it inhibits (by a then unknown process) the transcription of *per* (see Fig. 1).

The idea of oscillations resulting from negative feedback was familiar in engineering and it is relatively easy to rehearse mentally the operations of the mechanism to understand how it could give rise to the oscillations in the concentrations of *per* mRNA and PER: When concentrations of PER are low, the gene *per* is not inhibited and it is transcribed into *per* mRNA, which is then translated into PER. This causes concentrations of PER to increase, but as they do so, more is transported back into the nucleus where it inhibits the process of transcription. As less PER is synthesized and what there has been synthesized is broken down, concentrations of PER drop again. But as they do so, the inhibition on *per* transcription is reduced and more PER is once again synthesized. Although such an account reveals how this mechanism could generate oscillations, it is compatible both with the oscillations gradually dampening and the mechanism settling into a steady state where the transcription and translation of PER is just sufficient to match its degradation and with the oscillations being sustained indefinitely, which is required if the oscillation in PER concentration is to explain circadian rhythms. Determining which happens requires tracking quantitatively the concentrations of PER. This is made even more difficult because sustained oscillations require one or more non-linear operations, which are very challenging to keep track of in mental rehearsal.

Five years after the TTFL explanation was first proposed, Goldbeter (1995) produced a computational model to show that the proposed feedback mechanism would not dampen but would exhibit sustained oscillations. The basic structure of his model had in fact been introduced several decades earlier by Goodwin (1963),

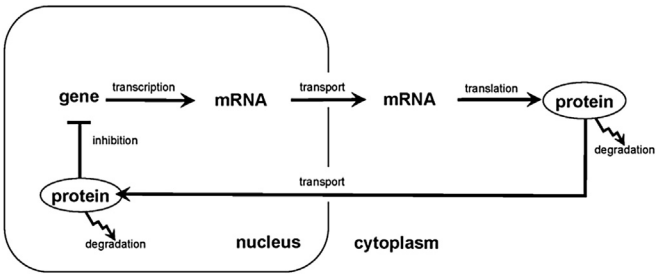

Fig. 1. The transcription–translation feedback loop (TTFL) proposed to explain circadian rhythms in fruit flies. See text for details.

[1] Mechanistic explanations are a species of explanation and there are other types of explanation scientists employ. Even in the fields of biology I discuss, explanations sometimes take the form of historical analyses or network analyses (which situate the responsible mechanism in a larger context).