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Prospects and problems for standardizing model validation in systems biology

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A B S T R A C T

There are currently no widely shared criteria by which to assess the validity of computational models in systems biology. Here we discuss the feasibility and desirability of implementing validation standards for modeling. Having such a standard would facilitate journal review, interdisciplinary collaboration, model exchange, and be especially relevant for applications close to medical practice. However, even though the production of predictively valid models is considered a central goal, in practice modeling in systems biology employs a variety of model structures and model-building practices. These serve a variety of purposes, many of which are heuristic and do not seem to require strict validation criteria and may even be restricted by them. Moreover, given the current situation in systems biology, implementing a validation standard would face serious technical obstacles mostly due to the quality of available empirical data. We advocate a cautious approach to standardization. However even though rigorous standardization seems premature at this point, raising the issue helps us develop better insights into the practices of systems biology and the technical problems modelers face validating models. Further it allows us to identify certain technical validation issues which hold regardless of modeling context and purpose. Informal guidelines could in fact play a role in the field by helping modelers handle these.

Contents

1. Introduction

The number and diversity of computational models which are used to study biological processes at molecular, intercellular and physiological levels is steadily growing. The field of systems biology unites scholars from very different backgrounds, and consequently styles of building models vary greatly. As Jeremy Gunawardena has highlighted, systems biology will need to start “harmonizing [the] cacophony” of “concepts and techniques that are coming into the subject from the physical sciences and computer science” (Gunawardena, 2010; 42). And indeed, there have been many efforts over the past years to implement certain standards in systems biology, in the form of modeling languages, such as the systems

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biology markup language (SBML), and the collection of models in standardized formats in publicly available databases (e.g. the biomodels database). Most of these efforts, however, concern purely syntactical aspects of modeling and are not concerned with model validation. The need for standards for validation has been explicitly expressed by the systems biology community as well (Klipp et al., 2007).

Model validation refers to the process of establishing whether a “model reliably reproduces the crucial behavior and quantities of interest within the intended context of use.” (Rykiel, 1996; 226) Standardization of any model-building and assessment process has much to recommend it, since it could improve clarity and communication within a field, thus promoting both productivity and efficiency. Standardized testing schemes for systems biology models could greatly facilitate the accumulation of knowledge in the field through the development of model databases which inform their users in common transparent terms on the extent of the reliability of a model without having to take this reliability on trust or investigate it themselves. Agreed upon standards could further help establishing a basis for safe reliable use of models given their increasing role in the design and testing of medical technologies and treatments, and at least in some such contexts systems biologists see a patent need for standardization (see Viceconti et al., 2016).

However, it is possible that setting standards for model validation is neither an achievable nor helpful goal for systems biology to aspire to generally, at least at this point in its development. The nature and complexity of living systems might make it intrinsically difficult to achieve the same kind of standardization achieved for instance in engineering disciplines. In this contribution we would like to discuss the prospects and problems for standardizing model validation in systems biology. By listing various challenges our goal is not to dismiss standardization out of hand but merely to point to various obstacles that any drive to standardize validation might have to contend with. We begin by exploring what is meant by validation and what previous discussions on the concept of validation contribute to discussions over standardization (Section 2). We then motivate the desirability for validation standards in systems biology (Section 3). In the fourth section of this paper we discuss both the practical and technical problems that standardization faces, given the current situation in systems biology. We close with some cautious recommendations regarding the prospects of standardization. Our reasoning for the most part is philosophical in nature, that is, we are mainly concerned with the current methodological practices in the field and the rational concepts underpinning validation. We develop the technical details only when necessary. A further part of our analysis is based on the results of an ethnographic study led by Nancy Nersessian of model-building practices in two systems biology labs.

2. Validation of models in science and engineering

Philosophy of science has investigated various aspects of scientific modeling. For example, a major discussion in philosophy of science concerns the kind of structures models are and the degree to which the primary purpose of scientific models is representational or inferential (see Suárez, 2004). Philosophy has also addressed extensively the relations between model and theories, and the role models in play in scientific discovery processes (see Frigg and Hartmann, 2012). Much less has been written about the proper or effective bases or procedures by which models can be justified or verified for their given purposes. The most important exception to this are philosophical debates about the validity of robustness analysis as a source of empirical evidence on the accuracy or reliability of a model's results (Weisberg, 2006). Otherwise, however, the literature on model validation has often focused on more abstract or fundamental questions. For example, validation has been discussed as a special case of fundamental philosophical problems such as induction or theory confirmation (for an overview see Kleindorfer et al., 1998). In a particularly influential article in this spirit Oreskes et al. (1994) argue that validation is a fundamentally misleading concept because it is impossible to establish the truth of a model. Calling a model “validated” is risky and falsely misrepresents models as “true” or “false” to policy-makers. According to this stance, models can only be falsified, and their primary role in science is heuristic, i.e., for the purpose of developing hypotheses. Of course there is a legitimate worry here. Models can be given too much credibility and authority through uncritical labeling of models as “valid”. However, this analysis of validation has been criticized as of little use for practical decision making based on computational models in engineering and technology, in which engineers seek a principled epistemic basis upon which to make decisions about how to use and rely on the models they build (e.g. Oberkampf and Roy, 2010). In scientific contexts it seems unproductive to narrowly frame the issue of validation in terms of truth or falsity alone, and philosophers of science might benefit from more pragmatic approaches. On the issue of how models should be represented in the environmental sciences Peterson (2006) for instance constructs a practical system by which modelers can represent uncertainty and the sources of it to policy-makers. Küppers and Lenhard (2005) demonstrate the importance of constructing independent standards for validating social science models as opposed to natural science models, given the nature of the phenomena and practices social science deals with.

Our principal interest, like that of Küppers and Lenhard above, is not in higher level philosophical debates over the status of models but in the practical conditions by which models can be justified for a particular set of goals and how well practices in systems biology and the nature of biological systems afford the possibility of standardized validation procedures. We follow Carusi (2014) and Carusi et al. (2012) by treating it as important to understand the constraints on practices in order to comprehend how well these might align with robust and recognized validation procedures. Before going further then, it is wise to develop some broad understanding of the meaning of validation, and what is commonly thought relevant to it in scientific circles.

Rykiel (1996) discusses validation of simulation models with an eye to the requirements of scientific practice. A validation judgment, according to him, is an assessment of the accuracy of a model and of whether that accuracy justifies reliance on the model for at least certain goals or ends. Rykiel writes with ecology in mind but many of his findings apply generally. For instance validation assessments or procedures may take many forms in practice. Models of a system may be validated operationally, according to how well models fit the available data on that system's behavior. Such validations can be complex, involving procedures like sensitivity analysis or other form of statistical analysis, which try to discover how robustly and precisely a model mimics a system. As Rykiel puts it, these kinds of validation focus on performance (rather than representational accuracy directly) as their principal goal, and models can be tweaked or engineered to produce better performance without necessarily improving the degree to which a model soundly captures reality.

Secondly, a model can be validated to the degree to which it does capture the known properties and structure of the phenomena it models. Rykiel calls this conceptual validity. Validation in this sense uses available theories and knowledge of phenomena to assess whether a model captures accurately what is known of the phenomena and to assess how well the abstractions and idealizations the model relies on might assist or compromise its ability to