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When one model is not enough: Combining epistemic tools in systems biology

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ABSTRACT

In recent years, the philosophical focus of the modeling literature has shifted from descriptions of general properties of models to an interest in different model functions. It has been argued that the diversity of models and their correspondingly different epistemic goals are important for developing intelligible scientific theories (Leonelli, 2007; Levins, 2006). However, more knowledge is needed on how a combination of different epistemic means can generate and stabilize new entities in science. This paper will draw on Rheinberger's practice-oriented account of knowledge production. The conceptual repertoire of Rheinberger's historical epistemology offers important insights for an analysis of the modelling practice. I illustrate this with a case study on network modeling in systems biology where engineering approaches are applied to the study of biological systems. I shall argue that the use of multiple representational means is an essential part of the dynamic of knowledge generation. It is because of—rather than in spite of—the diversity of constraints of different models that the interlocking use of different epistemic means creates a potential for knowledge production.

1. The role of models in knowledge generation

This paper focuses on the use of models in scientific practice and reflects on knowledge generation through the integrative use of multiple models and epistemic frameworks. Despite the diversity of models—from mathematical representations to living model organisms—the categorization under the same name has relatively recently been justified by their common function as investigative instruments that mediate between theory and the world (Morgan & Morrison, 1999). The broad definition implies that anything that can be used as a facilitator of scientific reasoning through representation of target objects or of hypothetical systems may be called a model. However, models are involved in several complex relations, and there is no simple linear relation between target and representation. Of importance is not only the connection between models and their targets, but also the dynamic relations between different models. Rather than analyzing how models represent targets, I shall argue for the importance of understanding how and why models are combined in iterative processes. A characterization of the virtues of models that only takes into account how single models represent target objects has the limitation that it cannot account for how scientists learn about the world with the use of highly idealised and unrealistic models.[1] Instead, models may be more adequately described as epistemic tools; as artefacts constructed for the purpose of manipulation and specifically constrained by their representational means and use in a concrete scientific context (Knuuttila, 2011). I exemplify this with a case study on network modelling in systems biology where models are used in a spiral-like fashion to develop insights about organizing principles for biological networks.

I focus on how models work at the intersection of the known and the unknown. Models are needed when research is in a state of dealing with unknown phenomena, and where unmediated evidence for the features of target phenomena is not a possibility (Rheinberger, 1997). Since models serve a variety of different epistemic goals in research and signify different representational

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[1] The traditional representationalist account has mistakenly seen structural similarity as a privileged type of representation in modeling. But representation, in the sense of "standing for", can cover a range of very different and context-specific relations. I therefore prefer to understand representation in a very broad sense in order to embrace *different* representational strategies used in the modeling practice.

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means, a pragmatic account of models must take the variety of model functions into account (Leonelli, 2007). I propose that models are primarily informative from a relational perspective where they are connected to other models. The activity of modeling thus has an inherent systemic nature in being coupled to other models and entities, and the modeling activity should be seen in the context of how different models are brought together (see also Knuuttila & Loettgers, 2011; Weisberg, 2006; Wimsatt, 1981; Winther, 2006). The consequence of this view is that relations between different models are just as important as relations between targets and models.

In exploring the use of multiple models in systems biology I shall draw on the conceptual repertoire of Rheinberger's historical epistemology where modeling is understood as the activity of 'shuttling back and forth between different spaces of representation' (Rheinberger, 1997, p. 108). I provide an integrated account where modeling is understood as a matter of constructing, manipulating and comparing representations in a spiral-like fashion where a whole body of models interact. I first underline the aspects of Rheinberger's conceptual framework that I find particularly useful for understanding modelling and its relationship to experimental practices. Section 2 addresses this issue with a case study from systems biology where a variety of models are used to reverse engineer a biological network in search for design principles. Section 3 examines how methods and models from engineering and biology are integrated and combined in a search for design principles. Finally, I relate the account of this paper to recent philosophical accounts and discuss what is gained by employing this framework for discussing the role of models.

1.1. A conceptual framework for understanding modeling

Scientific reasoning is never as clear as it appears in published papers. During the process of knowledge generation the relevant representations are neither known nor readymade for comparison. When modelling is used for gaining knowledge about a (partly) unknown object the process is not an approximation to something already stable. New research objects are unstable in the sense that their properties and boundaries only indirectly accessible for observation. Accordingly, the process of stabilizing a new entity happens indirectly through relations to different bodies of already certified knowledge and by production of new representations for comparison and integration. This process is often an iterative cycle of modelling and experimentation, where a series of representations with different constraints are combined. The constraining relations of epistemic tools are historically situated in what Rheinberger calls an experimental system (Rheinberger, 1997, 2007, 2009). With this notion Rheinberger captures Bachelard's description of the instruments of modern science as 'theories materialized'. The idea is that the technicalities of an experimental system productively constrain scientific reasoning by determining the realm of possible representations (Rheinberger, 1997, p. 20). His notion of experimental system is broad and includes instruments, models, and material and theoretical entities with varying degrees of scientific stability. *Stability* is here an indicator of how well the scientific objects, instruments or concepts are accepted by the scientific community and is thus an epistemic, rather than an ontological, category.

The focus on stability is important for understanding the role of models in research since models occupy a middle position in the continuum between two types of objects that experimental systems consist of. These are differentiated by their different degrees of (epistemic) stability:

1. *Technical objects* provide the stable context for experimentation. They can be material objects, concepts, systems of accepted knowledge, or instruments. Rheinberger defines technical objects as 'answering machines', since they work as unquestioned tools to produce answers about epistemic objects.
2. *Epistemic objects* are unstable entities existing at the boundary between the known and the unknown. These represent the conception of physical structures or processes that are objects of investigation in a specific context at a particular time. Through the embodiment of what one 'does not yet know', epistemic objects thus work as 'question generating machines' that drive science forward.

Whereas technical objects set the boundary conditions for the possible representations within the experimental system, epistemic objects are only vaguely present in the context of a research project. They do not (yet) appear as stable scientific facts, methods or entities but are brought into existence within the context of an experimental system that embeds and constrains them. Knowledge production is spiral-like and takes the form of a continuous transformation of epistemic entities to technical entities, if they can become sufficiently stabilized through a process Rheinberger calls *resonance* (Fig. 1, resonance will be clarified below). In this process models play a key role because they are situated at the interface of technical and epistemic objects, or between the known and the unknown. On one hand, models must include sufficiently

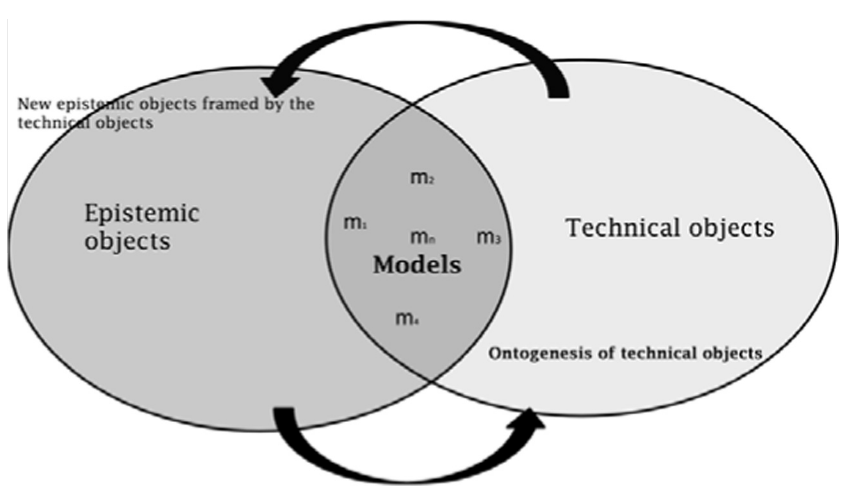

Fig. 1. Knowledge generation: a self-correcting spiral of oscillations between representations.