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Generative models: Human embryonic stem cells and multiple modeling relations

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ABSTRACT

Model organisms are at once scientific models and concrete living things. It is widely assumed by philosophers of science that (1) model organisms function much like other kinds of models, and (2) that insofar as their scientific role is distinctive, it is in virtue of representing a wide range of biological species and providing a basis for generalizations about those targets. This paper uses the case of human embryonic stem cells (hESC) to challenge both assumptions. I first argue that hESC can be considered model organisms, analogous to classic examples such as *Escherichia coli* and *Drosophila melanogaster*. I then discuss four contrasts between the epistemic role of hESC in practice, and the assumptions about model organisms noted above. These contrasts motivate an alternative view of model organisms as a network of systems related constructively and developmentally to one another. I conclude by relating this result to other accounts of model organisms in recent philosophy of science.

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1. Introduction

This paper deals with model organisms, an important variety of concrete model. Since the early 20th century, biologists have concentrated experimental research efforts on a few select organisms: the fruit fly *Drosophila melanogaster*, the nematode worm *Caenorhabditis elegans*, the laboratory mouse *Mus musculus*, *Escherichia coli* bacteria, and a small number of others. These 'classic model organisms' are indisputably central to biological and biomedical practice. Research on them provides the experimental basis for much of 20th and 21st century biology, contributing to the field's enormous advances in genetics, molecular biology, and medical research. However, philosophical study of model organisms does not play a correspondingly central role in philosophy of science, although models and modeling are increasingly prominent topics. The philosophical literature on models and modeling is overwhelmingly focused on abstract or theoretical models (e.g., Giere, 1988; Godfrey-Smith, 2006; Parker, 2009). In many important treatments, model organisms are an afterthought at best.[1]

The literature on model organisms is, conversely, not centered within philosophy. It is instead profoundly interdisciplinary, involving history, anthropology, social and cultural studies of science, and biology as well as philosophy.[2] This literature is mainly in

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[1] For example, Godfrey-Smith (2006) discusses two ways of conceptualizing model systems: as "abstract mathematical objects," and "as "imagined concrete things"—things that are imaginary or hypothetical, but which would be concrete if they were real" (734–735). Model organisms, evidently, fall into neither category. At the Models and Simulations 6 conference (Notre Dame, May 9–11, 2014), the present paper was, to my knowledge, the only paper dealing with model organisms on the program.

[2] Influential case studies of model organisms include: Kimmelman (1993) on maize, Mitman and Fausto-Sterling (1993) on the flatworm *Planaria*, Kohler (1994) on *Drosophila melanogaster*, Ankeny (1997) on *C. elegans*, Creager (2002) on tobacco mosaic virus, Löwy and Gaudillére (1998), Rader (2004) on *Mus musculis*, and Leonelli (2008) on *Arabidopsis thaliana*. Important collections of model organism cases include Clarke and Fujimura (1993) and Creager et al. (2007). More general treatments are provided by Ankeny and Leonelli (2011), Bolker (1995, 2009), LaFollette and Shanks (1995), Levy and Currie (2014), Steel (2008); the last three are discussed further below. This brief list is of course only a small selection of the large interdisciplinary literature on model organisms, a thorough survey of which is beyond the scope of this paper.

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the form of case studies, often historically rich and detailed with respect to scientific practices and their social context. Many such studies exemplify integrated history and philosophy of science, and defy classification along traditional disciplinary lines. Although philosophers of biology have made important contributions to this literature, discussions of models and modeling in general philosophy of science remain largely insulated from it.[3]

The broad aim of this paper is to challenge this dialectical division. I do so by criticizing two ideas about model organisms that are commonly met with in discussions of models and modeling in general philosophy of science, using the case study approach that is common in the model organism literature.

The first idea is that model organisms, as such, do not play a distinctive epistemic role in science. This notion, though rarely made explicit, is crucial in justifying the neglect of model organisms in general philosophy of science. If model organisms function as other models do, then they require no special philosophical examination; more general treatments of abstract or concrete models are all that is needed. Weisberg (2013) offers a very clear statement of this idea:

> Model organisms are obviously an important class of models, but I think that they can be accommodated in the framework I have presented thus far [a tripartite typology of concrete, mathematical, and computational models] because model organisms are concrete models. Although they are not constructed [built],… they are concrete systems that resemble concrete targets. The special properties of model organisms discussed above [i.e., having generalized target systems, being studied by means of empirical experiments rather than mathematical analysis] are not unique to model organisms, but are ubiquitous features of modeling practice. For example,… many models have generalized target systems… In addition, other kinds of concrete models besides model organisms are studied by doing experiments (16–17).

Weisberg here argues that model organisms are like other (inanimate) concrete models in their representational role, relation to targets, and mode of usage by scientists. Having subsumed them to a more general class of models, Weisberg does not mention model organisms again in the book. The idea that model organisms function as other models do, that their epistemically significant properties are "ubiquitous features of modeling practice," underwrites their marginalization in his otherwise inclusive account. Weisberg's approach is representative of many prominent treatments of models and modeling by philosophers of science (e.g., Giere, 2004; Godfrey-Smith, 2006).

The second idea to be criticized in this paper is that model organisms' main epistemic role is to represent, and thus support generalizations about, a wide range of biological targets. The exact range of targets is thought (reasonably) to vary across cases, but to be typically large: all mammals, say, or all vertebrates, all sexually-reproducing species, all eukaryotes, or even all living things. Some broad range of targets is required, if model organisms are to function as sources of evidence for significant biological generalizations. Weisberg, again, states this view of model organisms' role very plainly:

> If we consider the kudzu plant as a model organism, then its target is a very wide range of actual and possible invasive plant species. We are supposed to be able to generalize about what we learn from kudzu in order to understand and prevent future invasions (2013, 16).

On this view, model organisms provide evidence for general claims about some broad class of organisms, actual and possible, such that those models' targets correspond to the scope of the generalization so supported. Although few would argue that this is model organisms' *only* scientific role, it is the one most often noted by philosophers of science. Weisberg (2013) identifies the issue of generalized targets as "[o]ne of the foci of the literature about model organisms" (16). Ankeny and Leonelli (2011) preface their study of model organisms (discussed further below) by referencing this role: "In the most general terms, model organisms are non-human species that are extensively studied in order to understand a range of biological phenomena" (313). Huber and Keuck (2013) also characterize model organisms' role in biology (but not biomedicine) in these terms ("Biology makes use of model organisms in order to draw general conclusions for general biology;" 386). Levy and Currie (2014) base their account of model organisms (also discussed below) on the premise that model organisms support inferences about some broad class of targets ("empirical extrapolations") in virtue of being representative of that class.[4]

These two ideas are independent, but they go together well. It does seem there is a basic role all models play, whether concrete or theoretical, living or virtual: to be used as tractable surrogates for some target system scientists wish to understand. If model organisms are distinguished from other models only in virtue of their generalized biological targets, then their epistemic role is much like that of other models (idea #1). This is, roughly, the line taken by Weisberg. Levy and Currie (2014), in contrast, endorse the second idea but not the first. They defend this position by arguing that generalizations based on model organisms involve different inferences than generalizations based on theoretical models—clearly an epistemologically significant difference. A shared premise in this debate is that model organisms' primary function is to represent a wide range of biological targets so as to support generalizations about them (idea #2). Many contributors to the interdisciplinary literature on model organisms, in contrast, reject both ideas as simplistic or inadequate. Discrepancies between the two discussions arise in part from a methodological split between the general abstract approach favored by many philosophers of science and that of richly detailed, specific case studies of model organisms. Although the argument of this paper is critical, its overall aim is conciliatory: to bring these two literatures bearing on model organisms into closer alignment.

To do so, I engage the above two ideas about model organisms, which are prevalent in general philosophy of science, in terms of a particular case, which adds to the existing interdisciplinary literature on model organisms. This case concerns human embryonic stem cells (hESC). hESC are one kind of stem cell, distinguished from others by their organismal source (an early human embryo) and developmental properties (pluripotency, or the ability to give rise to any kind of cell found within a mature human organism). They are artificial biological entities, constructed and maintained in laboratory culture. Nonetheless, I argue, they exhibit many features of model organisms. Section 2 summarizes the characteristic features of classic model organisms, based on the case study literature

[3] Exceptions (e.g. Ankeny & Leonelli, 2011) are discussed below.

[4] More precisely, Levy and Currie (2014) argue that generalizations from a model organism to a target class are justified by circumstantial or phylogenetic evidence that the model is in fact representative of the target class with respect to the traits of interest, rather than by "explicit and known analogies between model and target" (1). The latter justification they take to be characteristic of theoretical models. I return to Levy and Currie's account in Section 5.