Axiomathes (2019) 29:363–382
https://doi.org/10.1007/s10516-019-09415-4

ORIGINAL PAPER

Model Organisms as Simulators: The Context of Cross-Species Research and Emergence

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Received: 6 October 2018 / Accepted: 14 January 2019 / Published online: 24 January 2019

Abstract
Model organisms are a living form of scientific models. Despite the widespread use of model organisms in scientific research, the actual representational relationship between model organisms and their target species is often poorly characterized in the context of cross-species research. Many model organisms do not represent the target species adequately, let alone accurately. This is partly due to the complex and emergent life phenomena in the organism, and partly due to the fact that a model organism is always taken to represent a broad range of diverse organisms. More often than not, model organisms are taken as a reference point for an extrapolation to be made to the unknown characteristics of other species. I propose to view model organisms as analogue simulators which represent the emergent phenomenon in the context of cross-species research. A model organism represents a wide range of species by simulating their molecular microstates which underlie various emergent phenomena. I show that although model organisms represent the target species inadequately at many levels of complexity, they have epistemic values as a simulator in virtue of which the emergent phenomenon can be modeled dynamically, a virtue that is hardly attainable by non-dynamic models.

Keywords Model organisms · Simulation · Simulators · Emergence · Cross-species · Scientific representation · Models · Modeling

1 Introduction

Model organisms as a specific type of scientific models are living material models which are far more complex than other standard scientific models. Although model organisms are relatively simple and genetically easy to be manipulated as compared to experimental organisms, its representation of a wide range of diverse species is never straightforward. Unlike other types of non-living models which comprise

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more or less fixed model assumptions and entities, a model organism is a complex living model which consists of a wide range of distinct dynamic variables—ionic concentration, transcriptional and translational profiles, cellular activities, and so forth—that constantly change their values during the process of modeling, and vary from one individual organism to another. Although some of these variables are controllable to a certain extent in the laboratory, many of them are not subject to synergistic control, let alone to manipulate them precisely for laboratory purposes. These constantly changing dynamic variables render model organisms a dynamic model, which can be used to study the dynamic features of the target species. This characterization of a dynamic model is in agreement with William Bechtel's notion of a dynamic model which provides an avenue for the "exploration of the mechanism's dynamics" (2010, p. 321). Model organisms as dynamic models are used to study cellular and molecular processes in the target species. What is important in biological research is to learn about *the process which is leading to an outcome* (i.e., the temporal dimension of modeling which treats model organisms as a dynamic model), instead of focusing on the final outcome of a biological mechanism (i.e., the atemporal dimension of a model organism, which I shall call the non-dynamic aspect of a model organism).

The fact that many intricate networks of cellular and molecular processes occur as an emergent phenomenon, such as vesicle formation and neuronal spikes, has rendered the model organism an incredibly complex scientific model. Although the standardization of model organisms and the advancement in genetic engineering have warranted the production of laboratory strains of model organisms with desired characteristics (Ankeny and Leonelli 2011; Leonelli and Ankeny 2012), the micro-dynamic aspect of a model organism such as the proteomic profile varies across individual model organisms. Besides, a model organism is taken to represent a broad range of diverse species, which are very different in terms of morphology, genetic constitutions, and habitats. Although many species share a common ancestry and their genomes are highly similar, inference from the genetic and proteomic profile of one organism to another is not straightforward because the molecular and cellular disparities exist beyond the gene sequence.[1] Despite genetic mechanisms that are shared among various species do provide universality to a certain extent at the fundamental level, model organisms are a less reliable basis for extrapolation at the epigenetic level (Bolker 1995). The disparity in molecular, cellular, biochemical and morphological aspects of organisms has rendered inferences from model organisms to other species problematic.

Despite the widespread use of model organisms in scientific research, the representational relationship between model organisms and their target species is often poorly characterized in the context of cross-species research. Given the disparity between species, many model organisms do not represent the target species adequately, let alone accurately. This is partly due to the complex and emergent life

[1] Organisms with highly similar genes might differ in various cellular and molecular characteristics, such as mutation rate, synonymous codon usage, protein expression profiles, RNA regulations, and epigenetics.

phenomena in the organism; and partly due to the fact that a model organism is always taken to represent a broad range of diverse organisms. In view of the fact that many cellular and molecular processes and phenomena are emergent, it is particularly challenging to use a single model organism to represent a hodge-podge of species. Although scientists sometimes use more than one model organism in cross-species research to offset the limitation of one-to-many representation, epigenetic factors and emergent cellular factors still present a hurdle for an adequate model representation. The inadequacy of representing the emergent phenomenon in cross-species research has well been recognized by scientists:

> However, the average rate of successful translation from animal models to clinical cancer trials is less than 8%. Animal models are limited in their ability to mimic the extremely complex process of human carcinogenesis. (Mak et al. 2014, p. 114)

I do not deny that model organisms do represent their target species adequately in certain domains, such as providing genuine insights into the questions of genetic modifiers and of the mechanisms of tumor growth (Cheon and Orsulic 2011). The problem that I shall consider in this paper is that model organism representation is not straightforward in the context of cross-species research, given the prevalence of emergence in life phenomena. Although in certain domains a model organism could be an adequate representation of its target species in virtue of gene sequence similarity, the very same representational relationship may not hold in some other domains. This is the case in cancer biology where a mouse model is successful in basic immunology—a domain in which the mouse genes and human genes are relatively similar, but fails frequently in clinical contexts where gene similarity does not warrant an adequate representation of the complex pathological state of human patients by drawing the relevant inferences from a mouse model. In many instances, the gene profile of a model organism that is designed to be similar to its target species does not warrant an adequate representation, as evidenced in the case of humanized mouse models which fail to represent human diseases adequately.[2] Although a gene profile that is similar to that of the target species renders a model organism a promising tool in certain domains of investigation, it may be an inadequate model in others. I shall call this the dilemma of model organism representation—the success of which is domain-relative.[3]

The dilemma of model organism representation is mainly due to species-specific differences between the model organism and the target species in the representation

[2] Mark Davis warns that although humanized mouse modeling is promising, 'it should not be assumed that such mice are equivalent to a human immune system in any respect unless it is demonstrated to be so by a variety of objective measures.' (2008, p. 836).

[3] Biologists are aware of this dilemma of representation. They recognize that the success of a model organism (and an animal model) representation is domain-relative. Lampson (2013) suggests to use an animal model to answer specific questions rather than broad questions in order to make the model more successful. Cheon and Orsulic (2011) claim that an ideal mouse model of human cancer needs to fulfill a list of stringent criteria in various domains, some of which are drug response, chemoresistance, and histopathology.

of the emergent phenomenon. It is implausible to draw a reliable and an accurate inference based on the genetic and molecular data of a model organism to a broad range of target species in the face of emergent phenomena. These data, when interpreted and deployed in the context of a non-dynamic modeling approach, do not explain or predict the emergent phenomena in the target species adequately. In a mouse model of cancer (which is a typical non-dynamic modeling approach as conceived by philosophers), a reliable representation is hard to attain given various differences between mice and humans. The emergent phenotype of cancer in mice is often found to be different from that of human patients. For example, humans have a tendency to be more susceptible to developing cancer than mice due to longer life span and having larger number and size of cells (Heljasvaara and Pihlajaniemi 2011). Besides, the fact that the tumor spectrum and karyotypes are distinct between the two species renders the laboratory mice more prone to developing mesenchymal tumors, while humans to be more susceptible to epithelial carcinomas (Heljasvaara and Pihlajaniemi 2011). In addition, numerous distinct homeostatic and histological factors in the two species present an obstacle for direct inference from the clinical outcome of a mouse model to human patients. Given the fact that disparities exist between mouse models and humans though they do share a great number of homologous genes, and that an inference from a mouse model to humans is never straightforward in the non-dynamic modeling activity, it is dubious that a mouse model (and any model organism) can be used as a reliable model for human cancers.

To account for the dilemma of model organism representation in relation to the pervasive emergent phenomenon and a wide range of diverse target species, I propose to view model organisms as analogue simulators. A simulation is the process of using a model to study the behavior of a system over time, which is a dynamic modeling approach in contrast to the non-dynamic modeling approach. In principle, I agree with Robert Rosen that "[i]n the context of natural science, we can characterize a class of material systems by requiring that all of their models be simulable." (Rosen 2000, p. 268; see also Rosen 1991).[4] Current philosophical understanding of the modeling activities involving model organisms is to take model organisms as a non-dynamic model—viz., to represent the emergent states of a target species without temporal dimension (e.g., see Meunier 2012; Ankeny 2000). This view fails to capture the microscopic changes at the molecular levels along the temporal dimension of an emergent phenomenon. Microscopic changes in the model organism over time may account for the emergent processes and macro-level phenomena in the target species. Therefore, a dynamic representational approach (i.e., simulation) is critical to capture the emergent phenomenon which is prevalent in the target species. I do not contend that a dynamic representational approach to organism modeling may decisively solve the problems of representation mentioned above; what I am arguing for is that this approach is more apt in representing the emergent biological processes in the cross-species context.

[4] I thank an anonymous reviewer for pointing me to Rosen's works. Rosen's mathematical works in theoretical biology have been embraced and clarified by his student Louie (2014).

Apart from what has been mentioned above, one may reasonably ask what are the further justifications of the proposal to view model organisms as simulators rather than as a type of conventional non-dynamic model.[5] There are at least four reasons.[6] First, although model organisms possess many characteristics of a typical non-dynamic model, viewing model organisms as a simulator "extends modeling practices in a variety of ways"[7] (Morrison 2009, p. 40) that is useful as an exploratory strategy to gain novel insights about a phenomenon (Burian 2007; Steinle 1997). Second, a model organism is always manipulated by biologists in a dynamic way in which its molecular and cellular variables are fluctuated, over time, in representing a phenomenon across a wide range of target species (for example, see Wightman et al. 1993).[8] It is time for the philosophy of model organism to reflect this dynamic practice of biologists. Many of these dynamic variables give rise to various emergent phenomena that can only be interpreted along the temporal dimension. For example, the expression of the *per* gene (which is responsible for circadian rhythms) is fluctuated throughout a day, which results in the circadian oscillations (which is an emergent phenomenon) in an organism.[9] In view of the fact that a model organism consists of a large quantity of dynamic molecular and cellular variables that gives rise to a complex network of emergent phenomena, it would be more appropriate to treat a model organism as a dynamic model—viz., as an analogue simulator. Third, simulating a system that exhibits the phenomenon of emergence, as argued by Bedau (2012), provides a novel type of understanding than the experiments and conventional scientific modeling. By taking model organisms to be a simulation of the target species, the complexity of the target phenomenon can be simulated as patterns of emergence, which is the phenotype displayed in the laboratory. Fourth, the model-target relationship as characterized by the traditional view of non-dynamic model organism modeling is an inadequate account in the face of the dilemma of model organism representation. As discussed above, the success of representing the target species by a model organism is domain-relative. It is now apt to change the perspective from viewing the model organism modeling as a non-dynamic representation of the emergent phenomenon in the target species to viewing such a modeling activity as a dynamic representation.

[5] It is a common understanding among philosophers of biology to take model organisms as a type of living model rather than a type of simulator. I surmise that one of the main reasons is that model organisms share many characteristics of the models. Another reason could be that the term 'simulator' has always been associated with 'computer simulation', despite the fact that it can be used to refer to analogue simulators such as a wind tunnel. In the literature, model organisms are always regarded as a material model (see Meunier 2012; Huber and Keuck 2013).

[6] In this paper, I can only provide a cursory explanation of these four reasons. A detailed defense of them requires a separate paper. My aim in this paper is to focus on the representation of the emergent phenomenon in the context of cross-species research.

[7] Though Morrison is speaking in the context of computer simulations, it is applicable in the context of analogue simulations.

[8] There is no reason to claim that only a computer simulation is dynamic but an analogue simulation is not. Engineers and scientists do recognize the dynamic nature of analogue simulations, such as a physical wind tunnel simulation. See Ahmad et al. (2005).

[9] See Bechtel and Abrahamsen (2010) for a philosophical analysis.

In this paper I shall focus on the molecular and cellular aspects of the use of model organisms in cross-species research, without investigating the macro-aspects of the deployment of model organisms such as its use in the clinical procedural simulation.[10] I focus on the issue of how an analogue simulation of the target species can exhibit the patterns of emergence in various life phenomena that cannot be easily achieved if we were to take model organisms as a non-dynamic model as traditionally conceived. In Sect. 2, I shall make clear in what sense a model organism is a simulator. In Sect. 3, I discuss the phenomenon of emergence in the context of cross-species research that involves model organisms. In Sect. 4, I argue, with a case study, that the view of model organisms as simulators can accommodate the representation of an emergent phenomenon in the target species. I conclude in Sect. 5.

2 What Kind of Simulator Model Organisms are?

To articulate that model organisms are simulators is by no means to uphold the view that model organisms should be viewed as a computer simulator, or functioning like a computer simulator. In view of the fact that model organisms are living beings, I adopt a general meaning of simulation which is defined by Winsberg (2009), according to which digital computation is excluded from the definition. According to Winsberg, a simulation is "*any system* that is *believed or hoped* to have dynamical behavior that is similar enough to some other system such that the former can be studied to learn about the latter." (Winsberg 2009, p. 836. My emphasis). On this interpretation, model organisms function as a simulator because they are dynamically similar to the target species in terms of genetic profiles and cellular functions in many respects. It seems no reason that the critic would demand a further justification for viewing model organisms as a simulation of the target species, because in accordance with Winsberg's definition, the molecular profiles of a model organism are dynamically similar to that of the target species, and various cellular activities (which accounts for the emergent phenomenon) are believed or hoped, on scientific ground, to be dynamically similar to that of the target species.[11] The relevant aspects of the target species could be learned by investigating a model organism.

A simulation, according to Winsberg's definition, can be *any* system that is *believed or hoped* to fulfill the requirements of dynamicity and similarity. I contend that a simulation, in order to be credible, is to be based on a scientific ground if a

[10] In an animal model of clinical research, specific diseases and pathological conditions can be simulated via adroitly implemented procedures. For example, aortic stenosis in many species could be simulated using supracoronary banding of the aorta of an animal model (Gross 2009, p. 207; Yarbrough et al. 2012). This type of procedural simulation involves relatively large equipments as compared to the molecular and cellular approach.

[11] According to Winsberg's definition of a simulation, what qualifies something as a simulation can be the fact that the object in question is actually functioning as a simulator (e.g., a computer simulation of the big bang), or that the object in question is *hoped* or *believed* to function as a simulator. He writes, "Any object that we study because we *think or hope* it is dynamically similar enough for us to learn about basins of fluid by studying it is a simulation of a basin of fluid." (2009, p. 836; my emphasis).

simulator is believed or hoped to have the dynamical behavior that is similar to its target system. A simulation is a credible simulation of a specific target system only if it is following a scientific protocol, or with a belief or hope that it is a credible simulation that is scientifically justifiable. With this qualification, a revised version of Winsberg's definition of a simulation is given below:

> **SIMU**: a simulation is *any system* that is *believed or hoped*, on scientific ground, to have the dynamical behavior that is similar enough to some other system such that the former can be studied to learn about the latter. Such similarity is underpinned by the common function possessed by the simulator and the simulated.[12]

Notably, **SIMU** is not specific about what constitutes a simulator. The advantage of endorsing **SIMU** is that it can accommodate for a simulator which is not actually simulating but believed or hoped (based on valid scientific reasons) to simulate a target system. By taking model organisms as simulators they are not required to be known to be actually similar to their target in order to play the role as a model organism; rather, they are model organisms in virtue of the fact that they are hoped or believed, on scientific ground, to be similar to their target species.[13] The notion of model organisms as simulators is built upon the prevalent notion that model organisms are a specific scientific model.[14] In addition, this loose definition of simulation is favorable especially when a model organism taken as a simulator is used in an exploration-driven experiment which is not driven by hypotheses. An exploration-driven experiment is common in molecular and cell biology (Burian 1997, 2007; Elliott 2007; Franklin 2005; Ratti 2015), where the outcome of an experiment cannot be anticipated due to the uncertainty of the domain of study in virtue of the complexity of life phenomena—the prevalence of emergent phenomena. The exploration-driven experiment, such as model organism research in the cross-species context, may not always establish an actual similarity representational relationship with the target species, as I have argued in Sect. 1 that some model organisms are not similar to their target species in many respects. However, scientists always *believe*, *or hope*, that their model organism is dynamically similar to the target species so that the representational relationship can be firmly established. **SIMU** which does not require a model organism to have actual, but believed or hoped, similarity relationship with the target species is a favorable definition for model organism studies which are an exploration-driven research brimming with uncertainty in the research outcome.

[12] My view is similar to Rosen's idea that the basis for system analogy which underlies modeling is the common function of two systems under comparison (Rosen 2000, p. 280).

[13] Not to discount the fact that model organisms are similar to some target species, despite they are not (but hoped to) similar to a wide gamut of others.

[14] I thank an anonymous reviewer for pointing out that a simulator needs to be a model of the target system to warrant the structural congruence between both systems.

As articulated recently by Dardashti, Thébault and Winsberg, an analogue simulation (model organisms belong to this category)[15] "allows certain inaccessible phenomenology in the target system to be probed by *experimentation* on the analogue." (2017, p. 56. My emphasis). As an analogue simulator, model organisms are handled in the ways of *experimentation* rather than of computer algorithmic processes. Experimenting on a model organism is always a convenient way to learn about the inaccessible phenomenology in the target species. One such example is the use of squid giant axon, in the early days of neuroscience, in modeling the neuronal activity of human brains. Squid axons which are relatively much larger than human axons provide an accessible research platform for the study of the relatively inaccessible neuronal activities in human brains. Squid axons were probed experimentally and acted as an analogue simulation for human axons. By investigating squid axons experimentally along the temporal dimension, the findings of the neuronal properties of squid axons are extrapolated to the neuronal properties of human axons by taking the squid axons as a simulator. It is natural to view squid axons as a simulator because scientists believe that the biochemical properties of a squid neuron are similar to that of human neurons. As dictated by **SIMU**, given that the same biochemical principle is underlying the mechanism of neurotransmitters and neural circuits in both squid and human neurons, the squid neuron is believed to have the dynamical behavior that is similar enough to human neurons such that the former can be studied to learn about the latter.

A simulator does not need to faithfully emulate every single detail of the dynamical behavior of the target system. Following Humphreys (1991), I contend that simulators provide approximate solutions rather than exact solutions to the problem at hand.[16] On this interpretation, simulations aim at providing an *insight* rather than an exact result—an insight which is relevant and desirably profound but need not be an accurate representation of the target phenomenon.[17] In view of the fact that simulations always provide an approximate solution in the form of an insight about the target system, it is also sometimes deemed as a complementary approach to the experimentation that is aimed at producing accurate solution. Computational biologists and experimental biologists always take simulations to complement experiments in ways of providing important predictive insights (Ulmschneider and Ulmschneider 2010; Pradel and Ewbank 2004), a salient characteristic which is shared by model organism studies in the sense that the research performed on a model organism cannot completely replace the experimental work performed on the target species.

[15] Dardashti et al. (2017) enumerate a list of prospective cases of analogue simulations in physics. I do not embrace their conditions for an analogue simulation because their account requires mathematical accuracy and syntactic isomorphism between the simulator and the target system, which is inappropriate for the case of model organisms as a simulation of target species.

[16] Although Paul Humphreys's paper argues for computer simulations, it is applicable to analogue simulations as well.

[17] I contend that the scientific insight provided by model organisms is more important than the exact result that can be extrapolated to the target species. Like a climate simulation model, the significance of model organisms as a simulator lies in the insights learned from the experimentation rather than in the practical solution provided.

In other words, one cannot understand every detail of a target species by merely depending on the result from the investigation of a model organism. More often than not, what is revealed in a model organism about a target species is very limited in terms of the specific details, and may not be generalizable to a wide array of other species. The experimental work on the target species is indispensable if one wishes to fully understand them.[18] In short, the insight about the target species provided by a model organism can be used to guide, rather than replace, the experimental work on the target species.

I do not deny that model organisms are a type of scientific model when I propose to view model organisms as an analogue simulator in the context of cross-species research. Being a model and being an analogue simulator are not mutually exclusive, as the Phillips machine and wind tunnels are two prominent examples of analogue simulators-cum-models. What I wish to argue in this paper is that it is more appropriate to view model organisms as simulators in the face of the emergent properties of life phenomena in the target species. Although I accept the view that model organisms are a type of model, it is not of the same kind as other standard scientific models. As Ankeny and Leonelli (2011) have pointed out, model organisms are neither true models that faithfully mirror their target, nor simplifying models that represent only certain aspects of their target. Ankeny and Leonelli also stress that the findings of non-analogous features in the cross-species research are more fundamentally problematic than other types of scientific models in virtue of the fact that model organisms are assumed to be comparable with other organisms at the most basic level. Model organisms differ from other experimental systems in that they are deployed as an intact unit (i.e., the whole organism) in the investigation of a particular biological process. Although they are made up of living materials, model organisms are not natural given the extensive amount of standardization and genetic customization to which they are imposed. Given these unique characteristics of model organisms, Ankeny and Leonelli claim that model organisms are *a unique way of doing science* that is distinct from a typical scientific model and a typical experimental system. This unique way of doing science, I propose, can be best captured by taking model organisms as an analogue simulator.

It is not uncommon that philosophers and biologists speak, in a vague way, of model organisms as analogue simulations of biological processes without paying enough attention to: (1) the emergent phenomenon that is prevalent in these biological processes; and (2) the temporal dimension of these simulable biological processes. Rachel Ankeny views model organisms as "actual simulations of biological processes shared by other organisms" (2001, p. S255) without further elaborating on how the simulation of the target phenomenon can be achieved. It seems that Ankeny implies the similarity relationship to be held across species (in terms of biological processes) when she takes model organisms as simulators. According to Ankeny, the

[18] Though the finding garnered from model organism studies may not be generalizable to all respects of life phenomena and to all species, it is still critical in providing useful insights into many domains. Besides, it is not always necessary to specifically experiment on a particular organism to learn about it when such insight can be obtained reliably from model organism studies.

epistemic basis of reasoning from a model organism to the target species is not proceeding along the line of causal reasoning. Instead, Ankeny suggests that the reasoning structure in model organisms assumes a form of case-based reasoning which is more generalizable, according to which "from base cases through to the target cases of interest using constant, multidirectional feedback loops" (p. S259). Huber and Keuck (2013) admit, in a footnote, that animal models could be described as analogue simulations in view of the fact that the temporal dimension comes into play in animal models. However, Huber and Keuck's paper is not aimed to develop in that direction. In the clinical context, biomedical practitioners often speak of animal models as a simulation of the clinical conditions and stages in the target species (see Cobrinik 2013; Sivakumar and Couldwell 2013). In the basic biological research, biologists often take model organisms as an analogue simulation of the conserved molecular and cellular mechanism that may be applied across species (see Evans et al. 2003; White 2015; Ikami et al. 2017). Model organisms are taken as a simulator in the sense that they are the exemplary animal that possesses more or less similar fundamental features with the represented species.[19]

Before I conclude this section, I would like to address a common worry about taking model organisms as a simulator. The critic may point out that if model organisms are taken as simulators rather than experimentations as traditionally conceived, there would be a risk of vitiating the inference power from model organisms to the target species, for only experiments "have greater potential to make strong inferences back to the world." (Morgan 2005, p. 317). This view, however, is grounded in the idea that experiments are more similar to the target systems because they are versions of the real world, or that the experiment consists of the same material as that of the target system; whereas simulation models are artificial constructs that are dissimilar to the target system in the real world (Morgan 2005). I believe that such view has confounded ontology with epistemology. Bueno (2014) argues that simulations can be as good an inferential apparatus as the experiment. He contends that simulations play an important role as an inferential device to represent the target phenomenon in the absence of the causal interaction with the target system. In principle, there is nothing that can stop the inference from the result of a simulation to the cause in the reality (Bueno 2014), a feature that is characteristic of an experimentation that traces the output of an instrument to the cause in the target phenomenon. In view of the fact that simulations can be as successful as experiments in virtue of the reliability of the simulation techniques (Winsberg 2010), taking model organisms as simulations would not vitiate its inferential capacities in representing the target species. As argued by Winsberg (2010), the trustworthiness or reliability

[19] This is evidenced in an investigation of the regulation of DNA replication timing during mammalian development. The researchers used a mouse model to simulate the replication mechanism in mammals. The similarity between the mouse model and other species, which is a characteristic feature of simulation, is revealed in the following paragraphs: "Furthermore, changes in replication time are linked to changes in sub-nuclear organization and domain-wide transcriptional potential, and tissue-specific replication timing profiles are *conserved* from mouse to human, suggesting that the program has developmental significance. Hence, these studies have provided a solid foundation for linking megabase level chromosome structure to function […]" (Pope et al. 2010, p. 127; my emphasis).

of an experiment or simulation "is depend[ing] on the *quality* of the background knowledge and the skill with which it is put to use, not on which *kind* [simulation or experiment] it belongs to." (p. 70; Original emphasis).

It is reasonable to anticipate that the critic might argue that the fundamental difference between experiments and simulations is ontological. Guala (2002) holds that the fundamental difference between simulations and experiments is ontological rather than epistemological. The relation between the simulating and the simulated system is formal; whereas the experimental systems and the target systems are grounded in the same material. In a simulation, the simulating and the simulated system consist of different materials. What characterizes a simulation is the abstract and formal similarity relation that holds between a simulator and its target. The critic may point to the fact that model organisms indeed share the same type of material (e.g., cells) with the represented target species. Therefore, argues the critic, it is more reasonable to categorize model organism studies as experimentations instead of simulations. To reply to this line of argument, it is noteworthy to point out that no two species are sharing the same type of emergent properties and processes despite the fact that they are made up of the same material. The different configuration of genetic regulatory mechanisms and the emergent characteristics of many cellular and molecular processes render any two species distinct ontologically at the emergent level.[20] In view of the fact that model organisms are ontologically distinct from the target species at the emergent level, and that model organisms and their target species bear a formal similarity in the genetic and other fundamental biological aspects in the context of cross-species research, we may view model organisms as simulators rather than the traditionally conceived non-dynamic experimental systems. Further, viewing model organisms as simulators, as argued above, is not mutually exclusive with the view that model organisms are experimental systems. Even we grant that model organisms and their target species are ontologically grounded in the same material, it is still plausible to view model organisms as a simulation-cum-experimentation.

3 Emergence and Model Organisms

Emergence is a phenomenon commonly found in complex systems. In biology, the notion of emergence was coined to designate the unpredictable or novel properties of a system that cannot be reduced, ontologically or explanatorily, to the individual properties of the constituents (Mayr 1982; Humphreys 1997; Wimsatt 2000; Reid 2007; Johnson 2010). The higher-level biological process is always emerged from

[20] It is analogous to the view that although two physical objects (say, water and ice) consist of the same material (i.e., atoms), they may possess different chemical properties due to the different configuration of the atoms, therefore renders them ontologically distinct at the chemical level. This is similar to my claim that a model organism and its target species are distinct ontologically at the emergent level, for the same molecular and cellular components in both organisms have different configurations when giving rise to phenotypes. After all, all objects are made up of the same material—atoms. It is the configuration of the material that matters.

the interaction of the constituent parts "in the absence of a pre-programmed blueprint." (Mitchell 2003, p. 6). One distinctive feature of emergence is that a sequence of emergent states of a phenomenon can be characterized dynamically (i.e., temporally), therefore making the formation of emergent properties temporally tractable. Simulation, which characterizes the target system in a dynamic way, is the best option to probe into an emergent phenomenon when there are no theoretical shortcuts to predict the development of a higher-level function from lower-level properties (Bedau and Humphreys 2008).[21] In view of the fact that model organisms are used to investigate the emergent properties and phenomena of the target species, it is appropriate to view the experimental work involving model organisms as a simulation of the emergent properties of the target species.

To understand a phenomenon at the functional level, it is important to characterize the differentiation between local properties and global properties along the temporal dimension. For instance, in protein folding various conformational states (i.e., the global properties) that are observed at different transient temporal points emerge from the interaction of the constituent atoms (i.e., the local properties). This dynamic nature of emergence is best studied via simulations rather than the traditional non-dynamic experimentations[22] (See Abundo et al. 2002; Fersht 2008; Enciso and Rey 2011). The non-dynamic experimentation is always constrained by the experimental data which are "limited in scope and generally correspond to *averages over both time and space*." (van Gunsteren et al. 2008, p. 149; my emphasis). What is important in characterizing an emergent phenomenon is not the availability of the averaging data, but the availability of each transitional data of an emergent phenomenon. Investigating into the transitional data at each critical temporal point of an emergent phenomenon allows one to simulate the emergent state of a target species based on the finding obtained in model organisms. By tracing the transitional data at a much narrowed timescale, one is able to understand better the process of an emergent phenomenon. As argued by Nersessian and MacLeod (2017), simulation is a linchpin of the investigation into a complex system, without which the understanding of the target system is only superficial at best. In certain field such as systems biology, simulation plays an essential exploratory role in guiding the experimentation and model building process, and "makes possible the exploration of quite complex systems for generalities that can form the basis of a theory […]" (Nersessian and MacLeod 2017, p. 124).[23]

[21] For example, Weber (1999) holds that simulations can be employed to explore the putative routes of *emergence* of the immune system.

[22] Simulation studies in protein folding are indispensable because experimental studies are unpromising in virtue of the low-resolution structural data yielded with sufficient temporal resolution (Freddolino et al. 2010). In addition, it was reported that physical models of protein folding are lagging behind simulations and bioinformatics approaches (Dill et al. 2007). In characterizing the emergent nature of protein folding, Thirumalai et al. (2010) conclude that both theoretical framework and simulations (which employ a variety of coarse-grained models) are significant in making testable predictions for protein folding.

[23] Johannes Lenhard (2007) argues that simulation takes a form of exploratory cooperation between experimentation and theoretical modeling, in the sense that simulation models are determined by the data and dependent on the right fundamental equations of theoretical models. Simulation is set to run through a process of iterative reciprocal comparison between experiment and model.

According to the genetic principle, individual organisms within a species vary in their genetic properties. This genetic variation leads to the functional differences across genetic backgrounds that make the accurate prediction of phenotypic profiles a major challenge in experimental biology (Gasch et al. 2016). The phenotype is emerged from, yet cannot be purely reduced to, the genetic properties. The inference from model organisms to target species becomes unreliable given the large gap of the genetic variation between two different species. The studied phenomenon that emerged in the model organism may not be the similar one in the target species. However, by tracing the temporal profile of the emergent phenomenon via a simulation, it is plausible to identify and compare the states of the model organism and the target species, a strategy that may reduce the inferential gap between the model organism and the target species.

To trace the temporal profile of an emergent phenomenon, it is required to change the perspective of experimentation by incorporating the notion of natural variation into the molecular and cellular studies of model organisms. Natural variations as a critical parameter in model organisms include, but not limited to, the "variation in gene expression, protein function, molecular interactions, and network organization." (Gasch et al. 2016, p. 148). These natural variations constitute an emergent phenomenon and affect the variation of the phenotypes of interest. In the process of manipulating a model organism by tracing the natural variations across the temporal dimension (which is an activity of an analogue simulation), the emergent characteristics of the phenotype of interest can be captured in detail for a reliable inference to be made from the model organism to the target species.

Now the question is how to simulate the natural variations of model organisms in an analogue way—viz., to trace the natural variations across temporal dimension. As I have made clear in the previous section, to view model organisms as simulators is not to contending that model organism studies should be carried out in the form of computer simulation. Rather, I articulate that model organisms can be manipulated as an analogue simulator to simulate the natural variations. There are many domains in model organism research to which the analogue simulation can be applied. I shall focus on a case study in gene regulation in Sect. 4. Before doing so, it will be a boon to make a more explicit connection between emergence and simulation by discussing Mark Bedau's notion of weak emergence.

Bedau (1997) articulates a notion of weak emergence which is applicable to life phenomena.[24] He has formulated weak emergence in terms of an emergent state which is only derivable by simulation. He defines weak emergence as: "Macrostate P of [a system] S with microdynamic D is *weakly emergent* iff P can be derived from D and S's external conditions but only by simulation." (1997, p. 378; original emphasis). I shall quote at length his elaboration of this definition:

[24] Bedau argues against the traditionally stronger notion of emergence according to which a strong form of downward causation is involved. He maintains that this type of emergence is irrelevant in science (Bedau 1997).

> Weak emergence applies in contexts in which there is a system, call it *S*, composed out of "micro-level" parts; the number and identity of these parts might change over time. *S* has various "macro-level" states (macrostates) and various "micro-level" states (microstates). *S*'s microstates are the intrinsic states of its parts, and its macrostates are structural properties constituted wholly out of its microstates. Interesting macrostates typically average over microstates and so compresses microstate information. Further, there is a microdynamic, call it *D*, which governs the time evolution of *S*'s microstates. Usually the microstate of a given part of the system at a given time is a result of the microstates of "nearby" parts of the system at preceding times; in this sense, *D* is "local". (1997, p. 377)

What is characteristic of the weak emergence of a phenomenon is that a *simulation* is required to derive the macrostate's behaviors from the microstates. Simulations are performed by iterating a system's microstates given the initial conditions and the external conditions. Simulation provides an avenue for scientists to grasp the macrostate of a complex system that is beyond the reach of traditional experimentations and modeling (Bedau 1997, 2012). For Bedau, it is implausible to study a complex system in nature without the aid of simulations. The roles of simulations in manifesting a weak emergent phenomenon are twofold: first, simulations "produce artificial examples of weak emergence." (Bedau 2012, p. 91); second, they "play a crucial role in helping us understand natural examples of weak emergence." (Bedau 2012, p. 91). These two roles are interconnected in such a way that an artificial example of weak emergence generated by simulations can facilitate our understanding of the naturally occurring weak emergence.

In view of the fact that Bedau's view of simulation is compatible with **SIMU**, which is a general definition of simulation applicable to model organisms, Bedau's view of the role of simulation in explaining the emergent phenomenon can be extended to the view of model organisms as simulators. Model organisms, which are subjected to standardization and genetic manipulations,[25] are used as a simulator in helping us to understand the naturally occurring emergent phenomena in the target species. I revise Bedau's definition of weak emergence to accommodate emergent phenomena in the cross-species model organism research:

EM Macrostate *P* of a model organism *M* with microdynamic *D* is *emergent* iff *P* can be derived from *D* and *M*'s external conditions but only by **SIMU**

In view of the fact that model organisms are artificially constructed to a certain extent through genetic and molecular manipulations, **EM** is compatible with Bedau's claim that biological phenomena and properties "can be captured as emergent phenomena in *artificial life models*." (Bedau 1997, p. 393; my emphasis). In

[25] Model organisms are artificially constructed in the laboratory through various genetic and molecular manipulations. In terms of the artificiality of model organisms, emergent phenomena observed in model organisms are comparable to Bedau's view that simulations "produce artificial examples of weak emergence" (Bedau 2012, p. 91).

EM, macrostate *P* of a model organism can be a phenotypic trait or a process, and microdynamic *D* can be the underlying molecular or genetic players. An emergent phenomenon in the target species can only be learned by simulating the similar biological processes in model organisms. Simulating the model organism's microdynamic is indispensable because "[i]n practice, we have no alternative but to simulate the system's micro-level behavior, if we want to observe what macro-behavior will emerge." (Bedau 2012, p. 97). In next section, I shall argue, with a case study, that the view of model organisms as simulators can accommodate the representation of an emergent phenomenon in the target species.

4 Simulating Alzheimer's Disease: Using *Drosophila* as an Analogue Simulator

In Sect. 3, I have argued that model organisms can be manipulated as an analogue simulator to simulate the natural variations of model organisms across the temporal dimension, such as variations in gene expressions and molecular interactions. I shall focus on a case study in gene regulation in this section. I aim to show that emergent phenomena in the target species can be learned by taking model organisms as a simulator in simulating the similar biological processes. Taking model organisms as a simulator involves only the perspective change in the epistemic function of model organisms, switching from viewing model organisms as a non-dynamic scientific model to viewing them as an analogue simulator, rather than the change in scientific methodology.

Drosophila is a paradigmatic model organism in the cross-species studies of many neurodegenerative disorders. Regardless of the differences between brains in *Drosophila* and humans, the existence of many common signaling pathways in the pathogenesis of neurodegenerative disorders makes *Drosophila* an ideal analogue simulator for scientists to learn about the disease development in human patients. The pathogenesis of neurodegenerative disorders in organisms is a complex emergent process (i.e., macrostate) derived from the synergistic interaction of many genetic players and signaling pathways (i.e., microdynamics of microstates). In the following case study, I shall take *Drosophila* to act like a material hardware,[26] and the transgenes (which are genes transferred via genetic techniques from human genes to the *Drosophila* genome) to act like a simulation software that aims to simulate the gene-associated behaviors in the target species (i.e., human patients). I shall assume that the term 'simulation software' is an appropriate analogy, for the transgene in the *Drosophila* is an exact copy of the gene found in the human. The transgene is simply a copy of the same gene transferred from the human to the *Drosophila*, a scenario analogous to the act of copying a file from one computer to another. Besides, my interpretation of the function of a transgenic *Drosophila* is consistent with my definition of a simulation, viz., **SIMU**. Transgenes that are transferred into a *Drosophila*

[26] It is not uncommon that philosophers treat organisms as machines. See Nicholson (2014) and Holm & Powell (2013).

are identical with that of the target species in terms of the genetic constitution. However, the chromosomal and molecular milieu in which the transgenes are embedded is homologous, rather than identical, with that of humans. The temporal dimension of the expression of the relevant genes and the signaling pathways in *Drosophila* is similar to that of human patients. This similarity relationship between the transgenic *Drosophila* and human patients allows scientists to use the former to learn about the latter through analogue simulation.

Drosophila is a widely used model organism in the study of Alzheimer's disease, which is a neurodegenerative disorder associated with progressive memory loss. Modeling Alzheimer's disease in *Drosophila* is challenging because many of the critical genes and factors implicated in the disease are not conserved in *Drosophila* (Bilen and Bonini 2005). Among many molecular events that are implicated in the pathogenesis of Alzheimer's disease, accumulation of amyloid-β (Aβ) peptides in the brain is a telltale sign of the progression of the disease. Because Aβ cannot be expressed in *Drosophila*, the transgenic *Drosophila* strain carrying human Aβ is used to study the pathology involved. Iijima et al. (2004) constructed a transgenic *Drosophila* model to study the pathological effects of human Aβ40 and Aβ42 peptides in Alzheimer's disease. Iijima and colleagues found that both Aβ40 and Aβ42 cause progressive loss of learning ability in the *Drosophila*. The scientists used Pavlovian olfactory associative learning as an experimental setup to simulate the human patients' learning ability in the *Drosophila*. The *Drosophila* were trained by being exposed to electroshock paired with one of the two odors for 60 s following a second odor without electroshock for another 60 s. The learning ability of the transgenic *Drosophila* was observed by the percentage of the *Drosophila* making the correct choice of odor (Iijima et al. 2004, p. 6623).

The progressive loss of learning ability in the *Drosophila* is an emergent phenomenon that can be investigated by simulating, in an analogue way, the underlying mechanism, which is found to involve the accumulation of Aβ40 and Aβ42. According to **EM**, the progressive loss of learning ability is a macrostate of the *Drosophila* that can be derived from the mechanism of the accumulation of Aβ40 and Aβ42, which is a microdynamic that governs the time evolution of the interaction between the microstates Aβ40–Aβ42 and other enzymes, and from the relevant physiological conditions (e.g., specific hormone regulation) that serve as the external conditions. Such derivation of the macrostate as an emergent phenomenon, according to **EM**, can only be attained by **SIMU**. According to the definition of **SIMU**, the emergent phenomenon in *Drosophila* (i.e., the progressive loss of learning ability) can be extrapolated to human patients because the dynamic behavior of the former is similar to that of the latter—the former can be studied to learn about the latter. The dynamic behavior of the Aβ40- and Aβ42-expressed *Drosophila* consists of the mechanism of the dynamic interaction between Aβ40–Aβ42 and other enzymes. *Drosophila* as a simulator provides an avenue for the researcher to learn about the pathological *process* leading to an outcome, instead of focusing on the final outcome of the pathological mechanism. The researcher may identify the temporal point at which the process in the *Drosophila* is similar to that of the human patients, and the temporal point at which the processes are dissimilar. The simulation of the neurodegenerative *process* provides a more comprehensive representation of the target

phenomenon in terms of emergence as compared to the standard non-dynamic view of model organism research.

One might reasonably ask in what sense the Aβ40- and Aβ42-expressed *Drosophila* acts like a simulator. As elaborated in Sect. 2, the definition of **SIMU** accommodates the case in which a simulator is not actually simulating (like a computer simulator) but believed or hoped (based on valid scientific reasons) to simulate the target system. If one insists to identify such a simulation activity in the *Drosophila*, it can be said, without violating **SIMU**, that the experimental activity is the simulation activity.

To see that the experimental activity in *Drosophila* is a simulation of the human patients, it is important to identify, according to **SIMU**, the similar dynamical behaviors in both organisms. In Iijima and colleagues' (2004) experiment, we have seen that transgenic *Drosophila* was used—*Drosophila* carried with human Aβ40 and Aβ42 peptides in their cells. The fact that the human-originated peptides (Aβ40 and Aβ42) and the homologous cellular pathways are found in the *Drosophila* provides a valid scientific basis for the simulation of human Alzheimer's patients using this model organism. The dynamic interaction of Aβ40 and Aβ42 with other enzymes displays a temporal profile of the emergence of the progressive loss of learning ability in the *Drosophila*. This temporal profile can play the role to simulate the emergent phenomenon of the progressive loss of learning ability in human patients. The similarity of the neurodegenerative pathways caused by the accumulation of Aβ40 and Aβ42 in the *Drosophila* and human patients provides a scientific basis for the former to act as a simulator. The microstates and microdynamics in the Aβ40- and Aβ42-expressed *Drosophila* can be mapped to the microstates and microdynamics of Aβ40- and Aβ42-expressed human patients. With the similarity in the neurodegenerative pathways in both species, there is a similarity of the way in which the emergent phenomenon of the progressive loss of learning ability arises. By taking the *Drosophila* as a simulator, one can learn about various pathological conditions in human patients.

5 Conclusion

Traditionally, model organisms are taken as a non-dynamic living model that represents a wide range of target species. This non-dynamic view, according to which the temporal evolution of various emergent phenomena has been excluded in the model organism research, always leads to an inadequate representation of the target species. It is important to learn about the temporal evolution of the emergent phenomena in a model organism in order to learn better about the similar phenomena in the target species. What is important in biological research is to learn about *the process which is leading to an outcome*, instead of focusing on the final outcome of a biological mechanism. I articulate that we may regard model organisms as a dynamic model that simulates the biological process of the target species. One may identify the temporal point at which the process in the model organism is similar to that of the target species, and the temporal point at which the processes are dissimilar. Model

organisms as simulators provide a temporal perspective in which a more comprehensive insight can be gained about the emergent process in the target species.

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