Studies in History and Philosophy of Science xxx (xxxx) 1–11

Contents lists available at ScienceDirect

Studies in History and Philosophy of Science

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

Joint representation: Modeling a phenomenon with multiple biological systems

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ABSTRACT

Biologists often study particular biological systems as models of a phenomenon of interest even if they already know that the phenomenon is produced by diverse mechanisms and hence none of those systems alone can sufficiently represent it. To understand this modeling practice, the present paper provides an account of how multiple model systems can be used to study a phenomenon that is produced by diverse mechanisms. Even if generalizability of results from a single model system is significantly limited, generalizations concerning specific aspects of mechanisms often hold across certain ranges of biological systems, which enables multiple model systems to jointly represent such a phenomenon. Comparing mechanisms that operate in different biological systems as examples of the same phenomenon also facilitates characterization and investigation of individual mechanisms. I also compare my account with two existing accounts of the use of multiple model systems and argue that my account is distinct from and complementary to them.

1. Introduction

Contemporary biology often studies particular biological systems, such as organisms, as models of a phenomenon of interest, where the models are expected to serve as convenient loci for investigating the phenomenon (Ankeny & Leonelli, 2011, 2020; Bolker, 2009; Burian, 1993; Levy and Currie 2015). This paper discusses how such a modeling practice works in a specific type of situation: when the target phenomenon occurs through diverse mechanisms. Some biological phenomena are brought about by very different mechanisms. For example, studies of developmental biology have shown that mechanisms underlying certain developmental phenomena differ significantly across taxa and organs. A consequence of such diversity is a limitation on the degree to which a single biological system represents the phenomenon of interest. This point is exemplified by the following passage from a review article on branching morphogenesis,[1] where the authors point out that responsible mechanisms are so diverse that the phenomenon cannot be modeled by a single biological system: "the differences between [organ systems] are large enough to suggest that no single branching epithelium can be considered as representative of the development of all branching systems" (Varner & Nelson, 2014, pp. 2756–2757). Interestingly, even when it is already known that a phenomenon is produced by diverse mechanisms, biologists often keep regarding certain biological systems as models of that phenomenon. In the above example, although the authors recognize the differences in mechanisms among organ systems, that does not stop them from treating certain organ systems as models of the phenomenon of interest: "The advent of fluorescent reporter strategies, including tissue-specific promoter-driven transgenic expression, and of mosaic reporters has begun to reveal the dynamics and kinematics of branching morphogenesis in a variety of *model organs*" (Varner & Nelson, 2014, p. 2750; emphasis added).

The present paper asks how we should understand such a modeling practice in mechanistic research. In what sense are biological systems regarded as "models" of a phenomenon, when there is not a single mechanism for the phenomenon to be elucidated? A related question is: why do biologists keep treating such a phenomenon as one thing? When an apparent phenomenon is produced by diverse mechanisms, this could be taken to suggest that the apparent phenomenon is actually multiple phenomena, each of which can be represented sufficiently by particular biological system(s) (Craver, 2004; Craver & Darden, 2013). However, there are cases in which researchers do not give up a phe-

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[1] Branching morphogenesis is a phenomenon in which a branched biological organ or structure (such as nerves, blood vessels, lungs, kidneys, and mammary glands) is formed.

https://doi.org/10.1016/j.shpsa.2023.03.002
Received 30 May 2022; Received in revised form 1 March 2023; Accepted 19 March 2023
0039-3681/© 20XX

nomenon and keep regarding certain biological systems as its models, not as models of its distinct subclasses, even after recognizing the diversity of underlying mechanisms. Why?

I aim to explain this modeling practice by focusing on a concrete example: research on collective cell migration. Studies in the last few decades have revealed that diverse cellular and molecular mechanisms bring about the phenomenon of collective cell migration in different organs and taxa (e.g., Friedl & Gilmour, 2009; Mishra et al., 2019; Rørth, 2009; Scarpa & Mayor, 2016). Yet certain biological systems are still regarded as model systems of collective cell migration and this phenomenon remains a single, legitimate object of research. I argue that there are good epistemological and methodological reasons for this practice. To explain this, I focus on how multiple model systems are used together to study this phenomenon. Even if generalizability from a single model system is significantly limited due to the diversity of mechanisms, generalizations concerning specific features of mechanisms still hold in certain ranges of biological systems (which I call "local generalization"; see section 4). Furthermore, which mechanisms are regarded as similar to a given mechanism varies depending on which aspect of mechanisms one focuses on. Consequently, each model system can represent different subclasses of the target phenomenon with respect to different features of the mechanisms. This makes it possible for multiple biological systems to jointly represent the target phenomenon. I also argue that regarding different biological systems as models of a single phenomenon facilitates comparisons between them, which help characterization and investigation of individual mechanisms. These considerations clarify why collective cell migration remains a legitimate object of research that is studied by employing multiple model systems.

This study provides a new contribution to the philosophical literature on how multiple biological model systems are used together. Philosophers of science are aware that biological model systems do not function in isolation; model systems very often work in combination with other models. It has been pointed out that a model organism plays a role in building and maintaining a research community, where various representational practices (such as mathematical and diagrammatic modeling) are integrated through the use of the organism (Ankeny & Leonelli, 2020). Furthermore, some authors have examined how multiple biological model systems are combined to fulfill specific research purposes. Their discussions focus on how findings from different biological systems are integrated, either to develop a single, overarching mechanistic account of a phenomenon (Baetu, 2014) or to elucidate a single, specific target system by using multiple surrogate models complementarily to address practical limitations peculiar to the individual models (Fagan, 2016; Green et al., 2021). I contrast my analysis of research on collective cell migration with these previous accounts. This comparison shows that there is another way in which multiple model systems are studied together. The type of integration of research findings from different model systems, which is central in the previous accounts, is not the major goal in research on collective cell migration as a whole. Instead, my analysis reveals how multiple generalizations (each of which is about a specific feature of mechanisms and holds in a certain range of biological systems) and cross-system comparisons facilitate the elucidation of individual mechanisms operating in different biological systems.

The goal of this paper is to formulate a representational relationship between a phenomenon that occurs through diverse mechanisms and multiple model systems. To do so, I focus on articulated mechanisms and researchers' treatment of them in a concrete example. This is not because I believe that other aspects of biological model systems are irrelevant or less important. As some authors emphasize, whether a biological system is a good or plausible model of the target phenomenon depends on various factors, including the availability of institutional and political resources that facilitate the use of the system (e.g., Ankeny & Leonelli, 2020; Dietrich et al., 2019). But a comprehensive discussion of all such relevant factors is beyond the scope of this paper.

This paper is structured as follows. Section 2 clarifies the notion of biological model system. Section 3 introduces research on collective cell migration with an emphasis on the diversity of mechanisms underlying it. Section 4 analyzes the case. It first shows that accounts of how a single biological system works as a model cannot fully accommodate the case of collective cell migration. Then it provides a new account, which focuses on how multiple biological systems can jointly serve as models of a phenomenon that occurs through diverse mechanisms. Section 5 compares my account with two existing accounts of the use of multiple model systems. I argue that my account is distinct from and complementary to them.

2. Model systems in the life sciences

In this paper, "model system" refers to a biological system, such as a type of cell, tissue, organ, organism, etc. that is studied to learn about a phenomenon of interest. Model systems' representational roles can be characterized in terms of *representational scope* and *representational target* (Ankeny & Leonelli, 2011, 2020).[2] Representational scope of a model system refers to the range of biological systems to which findings from the model system might be projected. Representational target of a model system refers to the specific phenomenon to be explored by employing that model system. A classic example of a model system is the squid giant axon in neurophysiological research (e.g., Hodgkin & Huxley, 1952). The squid giant axon (model system) was studied to articulate the phenomenon of nerve conduction (representational target), and this led to the discovery of the process of action potential, which turned out to underlie nerve conduction in different nerves of different species (representational scope).

I use the term "model system" to highlight the idea that not only an organism, but also a *component system* of an organism, such as a cell, tissue, organ, etc., can and often do serve as a model in biological and biomedical research.[3] Although this idea is not novel (see, for example, Ankeny & Leonelli, 2020; Bolker, 2009), most philosophical discussions about "living models" focus on *organisms* that serve as models, such as the house mouse *Mus musculus* as a model of humans. Making it explicit that a component system can serve as a model is important because extrapolations, generalizations, and inter-model comparisons are made not always across taxa, but also across component systems. For example, the lung, mammary gland, kidney, and blood vessels of mice are all regarded as model systems to elucidate how branched organs are formed during development (Varner & Nelson, 2014). In this context of research, the intended representational scope of these model systems might include any biological systems with branched structures. Specific findings from the mouse lung might be extrapolated to the corresponding organ of other vertebrates, e.g., the human lung (across-taxa extrapolation); but the mouse lung might also be compared with other branched organs of mice, e.g., retinal blood vessels (a within-species, across-component systems comparison) or with different branched organs of other species, e.g., the fruit fly respiratory system (an across-taxa, across-component systems comparison). Note that I am *not* arguing for replacing the idea of organisms as models with the notion of model systems altogether. Organism-based analyses of biological modeling have their own advantages. However, when we analyze cases that involve across-component systems extrapolations, generalizations, or comparisons, the notion of model system serves as a better conceptual tool. The example that I discuss in the following sections (research on collective cell migration) is one such case.

[2] Although these notions are formulated originally to analyze how organisms, not biological systems more broadly, function as models, their basic ideas can be applied to analyze how model systems work.

[3] Another use of the term "model system" is to use it to refer to a system that "encompasses not only the organism, but also the techniques and experimental methodologies surrounding the organism itself" (Ankeny, 2007, p. 47). This is *not* the definition adopted in this paper.

Two accounts of how a biological system works as a model are worth introducing: the accounts of exemplary models and Krogh-principle models.[4] Exemplary models are those biological systems that serve as models of a larger group of biological systems (Bolker, 2009). The process of action potential discovered in the squid giant axon turned out to be shared across different nerves and different animals. Hence, the squid giant axon served as an exemplary model by representing a larger group of biological systems to which it belongs.[5] Krogh-principle models are those biological systems that are chosen and studied to articulate a particular biological phenomenon (Love, 2010). It is based on the idea that there will be a system, or a few systems, on which the phenomenon of interest "can be most conveniently studied" (Krogh 1929, p. 202). Convenience here is interpreted typically in terms of features that make experimental work easier, or that provide useful insights into the target phenomenon that other biological systems cannot provide. The squid giant axon can be seen as a Krogh-principle model for the study of nerve conduction because it was particularly convenient for physiological experimentation in the mid-20th century due to its size (Green et al. (2018) defend a more sophisticated interpretation of the Krogh principle, which emphasizes its heuristic nature and the importance of the comparative method. I discuss this in section 4.). As illustrated by the example of the squid giant axon, these two accounts are not mutually exclusive; the same biological system might serve as both an exemplary model and Krogh-principle model simultaneously. These accounts provide basic ideas of how model systems work, which are useful (though not sufficient) to analyze the case that is introduced in the next section.

3. Collective cell migration

Collective cell migration refers to a set of processes through which cells migrate as a group in a cohesive manner (Mishra et al., 2019).[6] While observational studies existed as early as in the mid-20th century, collective cell migration has become an active area of research in the last few decades. The phenomenon has been studied by a range of researchers. On the one hand, collective cell migration is involved in development of different organs. Elucidating causal interactions underlying it is an important part of explaining biological development, and in particular, the formation of various biological forms (i.e., *morphogenesis*, which is one of the major problem agendas of developmental biology; Love, 2014). On the other hand, collective cell migration plays crucial roles in cancer invasion, metastasis, and wound healing, and hence has been studied for clinical interests. Therefore, research on collective cell migration as a whole has multiple related goals, including explaining development of various biological forms and elucidating pathological and regenerative processes in humans.

Various biological systems are used to study collective cell migration. Those systems are often called model systems, or simply models, of the phenomenon: "The molecular and biomechanical mechanisms underlying collective migration of developing tissues have been investigated in a variety of *models*, including border cell migration, tracheal branching, blood vessel sprouting, and the migration of the lateral line primordium, neural crest cells, or head mesendoderm" (Scarpa & Mayor, 2016, p. 143; emphasis added). Those biological systems, each of which is identified in terms of a specific component part of an organism in a specific taxon, are regarded as useful loci for investigating the phenomenon.

The choice of model systems of collective cell migration has reflected various factors, including the availability of technological, institutional, and social resources as well as anatomical and developmental characteristics preferrable for experimental investigations (just as the choice of experimental organisms does; see Dietrich et al., 2019). Many model systems of collective cell migration are component systems of standard model organisms, such as the fruit fly, mouse, zebrafish, and *Xenopus* (the African clawed frog).[7] Such systems were chosen as models of collective cell migration not only because they undergo this phenomenon and are experimentally tractable, but also they belong to standard model organisms, which were already widely studied beyond the context of cell migration research. Detailed information about development, genetics, and genomics, experimental techniques, and infrastructures that were available in studies of standard model organisms have often motivated researchers to use component systems of such organisms to articulate collective cell migration.

A major approach to collective cell migration aims to articulate cellular and molecular mechanisms underlying it.[8] Researchers ask various questions to articulate those mechanisms, for example.[9]

- How is the balance between cohesion between cells and their relocation maintained?
- How is the direction of migration determined?
- How do the migrating cells interact with one another?
- How do the migrating cells interact with the microenvironment (e.g., surrounding tissues)?
- Is there a functional difference among migrating cells?

Experimental work has shown that answers to these questions vary across biological systems. To illustrate this diversity, I introduce three mechanisms that operate in different model systems: fruit fly border cells, zebrafish lateral line primordium, and mouse mammary gland.

3.1. Fruit fly border cells

Fruit fly border cell migration is one of the best-studied examples of collective cell migration (Prasad et al., 2011). Border cells are several epithelial cells[10] that undergo collective migration in the developing ovary of the fruit fly *Drosophila*. They migrate between other cells (called nurse cells) towards an egg cell (called oocyte) (Fig. 1a, left). At any given moment, there is typically only one border cell that extends protrusions in between the surrounding cells and leads migration, although border cells are dynamically rearranged and which one plays this leading role can vary (Fig. 1a, right). The cell that is playing this leading role (leader cell) at the moment suppresses protrusions of the other border cells that follow it (follower cells). The leader cell detects and is guided by graded concentrations of several kinds of chemoattractants, which are secreted near the destination. Border cells are tightly

[4] Like the notions of representational scope and representational target, the notions of exemplary models and Krogh-principle models are typically used to refer to *organisms* that serve as models. But I apply their basic ideas to model systems more broadly.

[5] Other examples of exemplary models include fruit flies as a model of animals in genetics research, yeasts as a model of eukaryotes in research on gene regulation, and cultured stem cell lineages as an example of stem cells in general in differentiation research (Bolker, 2009).

[6] I adopt a simple definition of collective cell migration here. More detailed definitions have been proposed by several authors (e.g., Friedl & Gilmour, 2009; Rørth, 2009; Theveneau & Mayor, 2011).

[7] However, not all model systems are component systems of standard model organism. For example, although the slime mold *Dictyostelium discoideum* is not a standard model organism, it has been studied as an important model of collective cell migration.

[8] Another approach is to formulate mathematical models of collective cell migration at different scales (reviewed, for example, by Buttenschön & Edelstein-Keshet, 2020). Articulating how the mechanistic approach is related to such a formal approach requires a separate paper.

[9] In other words, the problem of collective cell migration consists of the specific questions about the details of the underlying mechanisms. For a more general discussion of how problems and questions are organized in developmental biology, see Love (2014).

[10] *Epithelial cells* are tightly connected with each other and constitute a sheet-like structure, while *mesenchymal cells* are more loosely associated.

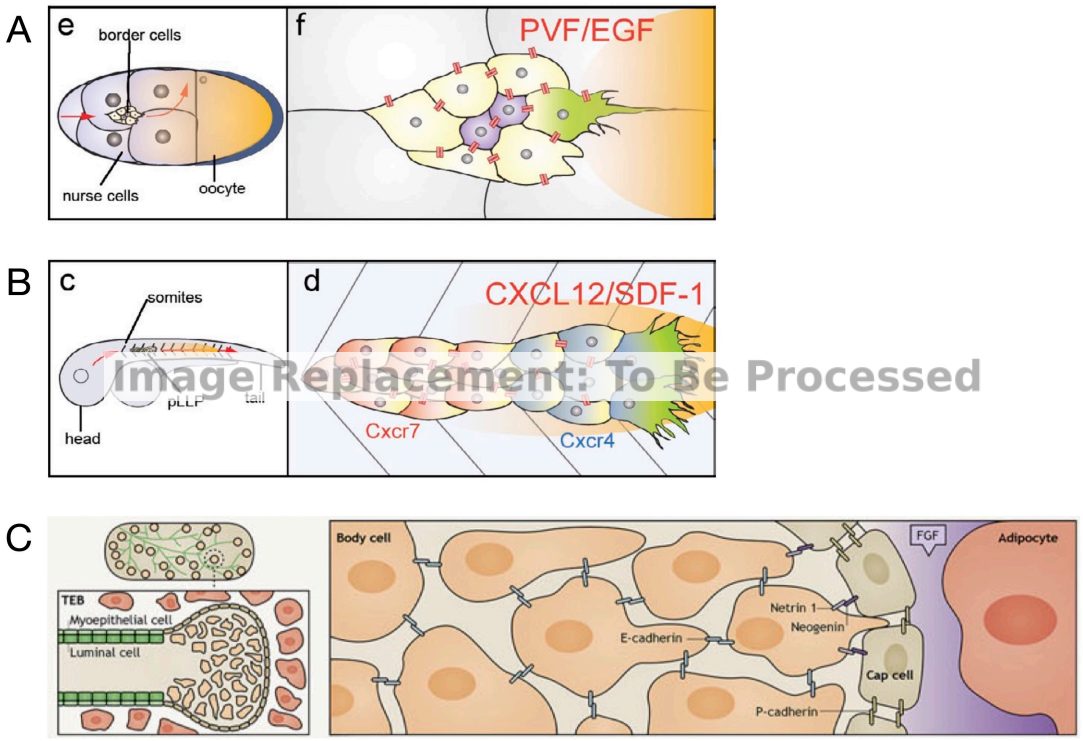

Fig. 1. Three different mechanisms of collective cell migration that operate in different biological systems. A: Fruit fly border cells (Scarpa & Mayor, 2016). Left: Several border cells migrate together towards an egg cell (oocyte) among other cells (nurse cells). Right: An enlarged view of the migrating border cells. One of them is serving as the leader cell, which extends protrusions to the environment and leads migration towards the source of chemoattractant (PVF/EGF). B: Zebrafish lateral line primordium (Scarpa & Mayor, 2016). Left: The posterior lateral line primordium (pLLP) migrates on the sides of the zebrafish embryo from head to tail. Right: An enlarged view of the migrating lateral line primordium. The migrating cohort consists of leader cells and follower cells and is guided by chemoattractant (CXCL12/SDF-1), the gradient of which is produced by the migrating cohort itself (see text). C: Mouse mammary gland (Mishra et al., 2019). Left: Mammary gland forms a branched structure. Collective cell migration occurs at the end of each branch, within the terminal end bud (TEB). Right: An enlarged view of migrating cells at the end of a branch. The cells filling the interior of the bud (body cells) compete for the front position of the bud. A secreted protein (FGF) regulates their migration. A, B: ©2016 SCARPA et al. Originally published in Journal of Cell Biology. https://10.1083/jcb.201508047. C is reprinted with permission of the Company of Biologists.

associated with each other by an adhesion molecule, which enables them to move coherently as a cluster. The same molecule is used for dynamic interaction between border cells and the surrounding cells, which provides traction for migration (Mishra et al., 2019).

3.2. Zebrafish lateral line primordium

Lateral lines are sensory organs that extend along the sides of aquatic vertebrates to detect changes in water current and pressure. In zebrafish, they are formed as a result of head-to-tail migration of posterior lateral line primordia, each of which consists of about 100 cells, during embryonic development (Fig. 1b, left; "pLLP" is the abbreviation for "posterior lateral line primordium"). Like fruit fly border cells, there is a distinction between leader and follower cells, but the overall arrangement of the migrating cohort is different (Fig. 1b, right). There is a group of leader cells that exhibit mesenchymal character, which extend protrusions and lead the cohort. Follower cells are epithelial; they form rosette-like structures, which are deposited serially during migration and will differentiate into mechanosensory structures (Olson & Nechiporuk, 2018). The lateral line primordium is made an organized cohort by two types of adhesion molecules, which mediate homotypic (between leader cells; between follower cells) as well as heterotypic connections (between leader cells and follower cells). The lateral line primordium migrates on a particular tissue, which secretes a protein that serves as a chemoattractant. Unlike the case of border cell migration, there is no preexisting gradient of the chemoattractant in the microenvironment that guides migration; the chemoattractant is uniformly expressed by the tissue. Instead, the lateral line primordium itself produces a gradient. Follower cells express a specific receptor, which acts as a "sink" of the chemoattractant and reduces its concentration in the rear side of the migrating cohort, while leader cells do not express that receptor. This results in a local gradient of the chemoattractant from the front to the rear of the lateral line primordium. Leader cells express at a high level another receptor, by which they detect the local gradient and lead directed migration (Mishra et al., 2019).

3.3. Mouse mammary gland

Mammary gland consists of branched epithelial tubes. Although the rudimentary structure of the gland is formed during embryonic development, further growth and branching occur during puberty. The tip at each growing branch forms a structure called terminal end bud. Each terminal end bud contains cap cells, which constitute the outer layer of the bud, and body cells, which fill the interior of the bud (Fig. 1c, left). Although body cells are categorized as epithelial cells, they exhibit epithelial features only incompletely (Huebner & Ewald, 2014). The migrating body cells are confined within the terminal end bud, which is a feature distinct from border cell migration and lateral line primordium migration. Since they are surrounded by the layer of cap cells, they cannot extend protrusions to the outside tissue. Instead, body cells migrate

over one another by using cell-cell adhesion and compete for the front position of the terminal end bud (Fig. 1c, right). This leads to extension and bifurcation of the branch. Unlike fruit fly border cells and zebrafish lateral line primordium, there is no functional distinction between leader and follower cells. A secreted protein is known to guide and regulate body cell migration (Mishra et al., 2019).

3.4. Collective cell migration as a phenomenon

Although these are just three examples, they show the diversity of mechanisms underlying collective cell migration. This diversity is illustrated by a variety of answers to the questions that characterize mechanisms of the phenomenon. For example, different answers are given to the question "How is the direction of migration determined?" In the case of fruit fly border cell migration, the migrating cohort is guided by gradients of secreted chemoattractant preexisting in the microenvironment. The migration of body cells of the mouse mammary gland is also regulated by a secreted signaling molecule, but a different molecule plays the role and body cell migration is heavily restricted within the terminal end bud. In the case of zebrafish lateral line primordium migration, there is no preexisting gradient of a signaling molecule; the migrating cohort itself produces a gradient of the chemoattractant that guides its own migration. Similarly, questions such as "is there a functional difference among migrating cells?" and "how do the migrating cells interact with the microenvironment?" are answered differently. The same applies to many other systems that undergo collective cell migration; collective cell migration is produced by different cellular and molecular mechanisms in different biological systems.

The existence of different mechanisms has been recognized by researchers for more than a decade (e.g., Montell, 2008; Rørth, 2009). The diversity of mechanisms also has been reflected in explanatory and representational practices in this area. Review articles about collective cell migration rarely present *the* mechanism of this phenomenon. Instead, they often discuss distinct mechanisms that operate in several major model systems. How diagrammatic representations are used in those articles also illustrates this point. Review articles often display multiple mechanism diagrams together, which operate in different biological systems, to explain collective cell migration. Fig. 2 is an example; here, the authors display within one figure several diagrams representing distinct mechanisms of collective cell migration. Different mechanisms are depicted in a way that highlights certain common features, such as the functional distinction between leader and follower cells, while differences in cellular arrangements and signaling molecules are also indicated. This form of presentation suggests that whereas the researchers are interested in common features among those mechanisms, differences between them are also noteworthy and non-negligible (see Yoshida, 2021). One might expect that the diversity of mechanisms can be understood simply in terms of molecular details differing across mechanisms, and that all mechanisms of collective cell migration still share the same set of abstract principles. This is not the case, at least at the current state of knowledge. Whereas researchers often appeal to abstract features to characterize similarities among certain mechanisms, such abstract features are not universally applicable too. For instance, the leader-follower distinction, an abstract feature mentioned above, is not shared by all mechanisms of collective cell migration. Shifting our attention from molecular details to abstract features does not erase the diversity of mechanisms.

Even though it has been recognized that mechanisms of collective cell migration are diverse, biological systems studied in this area (such as fruit fly border cells, zebrafish lateral line primordium, and mouse mammary gland) are commonly treated as *models of collective cell migration.* (See the quote in the second paragraph of this section.) How should we understand this modeling practice? How can a biological system be a good model of a phenomenon when the phenomenon is produced by diverse mechanisms?

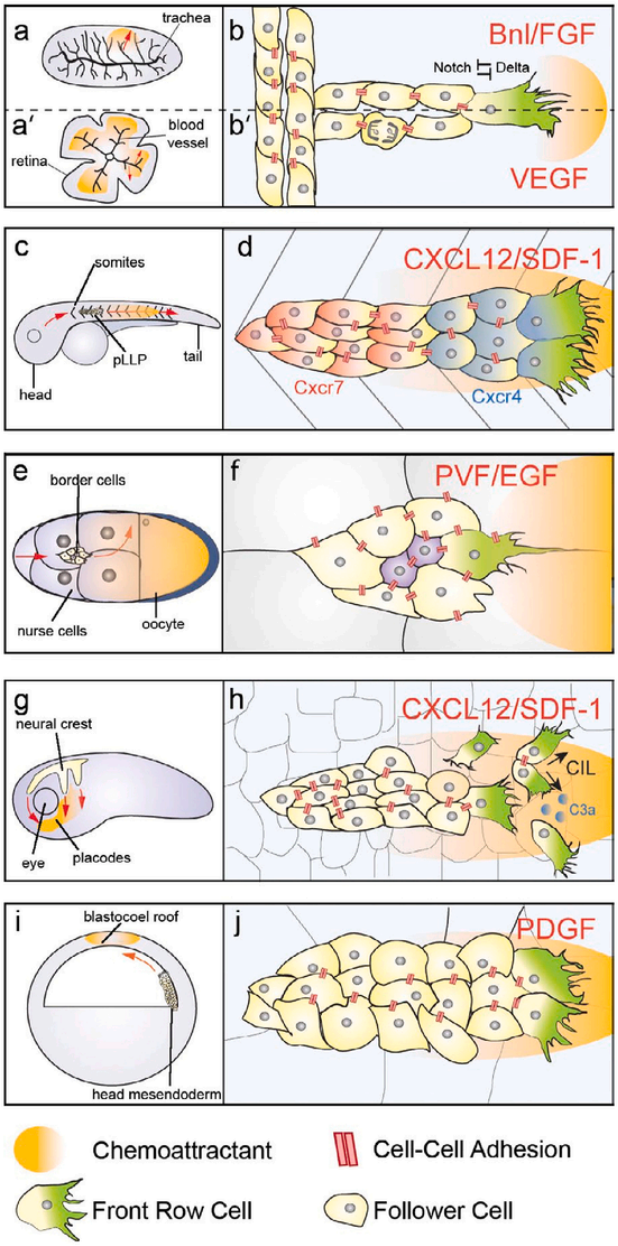

Fig. 2. Diagrams of five distinct mechanisms of collective cell migration are juxtaposed within a single figure of a review article (Scarpa & Mayor, 2016, Fig. 2). ©2016 SCARPA et al. Originally published in Journal of Cell Biology. https://10.1083/jcb.201508047.

A related puzzle concerns the fact that collective cell migration is still treated as a single phenomenon. Although distinctions are sometimes made between its subtypes (such as epithelial collective cell migration and mesenchymal collective cell migration), collective cell migration as a general phenomenon remains the major category in this area. "Collective cell migration is *a widely observed phenomenon* during animal development, tissue repair, and cancer metastasis" (Qin et al., 2021, p. 1267; emphasis added). This is contrasting with what some new mechanists claim, according to which, when multiple distinct mechanisms are identified for a single phenomenon, scientists recharacterize the phenomenon into multiple phenomena according to the underlying mechanisms. "If the goal is to provide a mechanistic explanation, the phenomena should be chunked in such a way that they correspond to distinct underlying mechanisms. […] For example, in a *lumping* error, one might assume that several distinct phenomena are actu-

ally one, leading one to seek out a single underlying mechanism when one should in fact be looking for several more or less distinct mechanisms." (Craver & Darden, 2013, p. 61, emphasis original). This picture does not accommodate the case of collective cell migration, where the recognition of diverse mechanisms has not led to splitting the phenomenon. A major criticism of Craver and Darden (2013)'s view is provided by Colaço (2020). According to Colaço, identifying distinct mechanisms does not necessarily lead to splitting a phenomenon into multiple phenomena. Rather, such splitting is warranted when a discovery is made that is inconsistent with the accepted *description* or *characterization* of the phenomenon in question. I agree with Colaço that discovering distinct mechanisms itself does not warrant splitting a phenomenon. I also agree that evidence about features of a phenomenon plays an important role in recharacterization of the phenomenon. Unlike Colaço, however, I focus on another reason for why retaining a phenomenon category is justified even after distinct mechanisms are identified for it: keeping such a phenomenon category can facilitate inquiries into and comparisons among individual mechanisms (see the next section).

In the next section, I present an account of how certain biological systems serve as models of collective cell migration despite the diversity of the underlying mechanisms. This account also shows that there are sometimes good epistemological and methodological reasons for not splitting a phenomenon that is known to occur through different mechanisms.

4. Modeling a phenomenon with multiple biological systems

In this section, I first show that the two basic accounts of model systems that we have seen in section 2 are not sufficient to analyze the case of collective cell migration. Then I provide my account, which discusses the use of multiple model systems.

4.1. Insufficiency of the basic accounts

How can we characterize representational roles of model systems of collective cell migration? Consider the accounts of exemplary models and Krogh-principle models. As I explained in section 2, exemplary models are those biological systems that are studied for the purpose of generalization, i.e., to learn about a larger group of biological systems to which they belong, while Krogh-principle models are biological systems that are the most convenient for elucidating a particular phenomenon of interest. Although these accounts provide useful, basic conceptual resources, they both are insufficient for analyzing the use of model systems in research on collective cell migration.

The account of the exemplary model does not fully capture the situation. It is true that model systems of collective cell migration are exemplary models since their supposed representational scope is a larger group of biological systems (i.e., those systems that undergo collective cell migration). However, exemplary models are typically associated with the idea of wide generalizability of research findings, which in turn is based on the assumption of broad conservation of traits and mechanisms across taxa (Bolker, 2009). We cannot rely on this idea of wide generalizability because what we are asking here is how, *despite the diversity of underlying mechanisms*, a phenomenon can be studied by using model systems.

The famous idea of convenience emphasized by the Krogh principle no doubt plays important roles in the choice of model systems. For example, zebrafish lateral line primordium has been studied as a model system in part because of the ease of observation and manipulation (since zebrafish embryos are transparent and lateral line primordia migrate close to the surface of the skin), as well as the availability of various resources (such as materials, experimental techniques, and information about zebrafish development, genetics, and genomics) (e.g., Olson & Nechiporuk, 2018). However, the fact that a particular biological system is useful for research does not provide a satisfactory answer to the question of how it serves as a model of a phenomenon, together with other biological systems, when it is known that the phenomenon's underlying mechanisms are diverse.

Green et al. (2018) argue for a more sophisticated interpretation of the Krogh principle. According to them, the Krogh principle should be understood as a heuristic of studying an organism with an "extreme" trait to obtain generalizable insights into an underlying mechanism. Importantly, this heuristic works in combination with the comparative method. How widely and to what species findings from a "Krogh organism" can be extrapolated is not assumed in advance; rather, it is to be empirically investigated. Furthermore, even when a finding from the organism turns out not to be widely generalizable, it can provide various useful insights into mechanisms through comparisons with other species. This emphasis on the heuristic nature and the importance of the comparative method is useful to analyze the case of collective cell migration as well (see section 4.3). However, representational practice of research on collective cell migration is not limited to this specific heuristic strategy. Moreover, even though it highlights the importance of the comparative method, the Krogh principle's focus is on how a single biological system can be a useful research tool because of its distinct physiological or morphological feature. In contrast, my goal in the remaining of this section is to articulate how multiple biological systems serve as models of a diversely-produced phenomenon. Thus, although Green et al. (2018) and the present paper both focus on how studies of biological variation produce generalizable findings concerning mechanisms, they make distinct contributions.

In what follows, I provide an account that focuses on the use of multiple model systems. Even if no single explanatory account can cover diverse mechanisms, generalizations concerning specific aspects of mechanisms are often formulated across certain ranges of biological systems, which makes it possible for those systems to jointly represent the phenomenon. Furthermore, there is utility for characterization and investigation of individual mechanisms in comparing different biological systems as models of the same phenomenon. We can appeal to these facts to understand how multiple biological systems can represent collective cell migration.

4.2. Local generalizations

By local generalization, I mean a generalization concerning a particular feature of mechanisms that holds not universally or even nearly universally, but across a certain range of biological systems that undergo the phenomenon of interest. A local generalization is local in two senses. First, it does not apply to all or almost all examples of the phenomenon. Second, it is local because what is generalized is not the entire mechanism description but a specific feature or aspect of it. Recall that in section 3, I listed several questions that are typically asked to characterize each mechanism of collective cell migration. No two migration mechanisms that operate in different model systems are so similar that the same answers are given to all of those questions. However, if one focuses on a particular question, one can often find that multiple mechanisms are characterized by the same answer, or similar answers, to that question (for a related discussion, see Bechtel & Abrahamsen, 2005; Halina, 2018).

Let us consider some examples. An important question for characterizing a migration mechanism is what determines the direction of migration. There is some similarity concerning this question between zebrafish lateral line primordium and *Xenopus* neural crest cells. The two systems both use the same type of protein as chemoattractant. Furthermore, they both self-generate directional guidance, instead of being guided by a gradient of the chemoattractant already existing in the microenvironment. As I described in subsection 3.2, zebrafish lateral line primordium produces a local gradient of the chemoattractant by reducing its concentration in the rear side of the migrating cohort. It has been

suggested that *Xenopus* neural crest migration also involves self-generation of directional guidance, although the way that it is done is not exactly the same (Theveneau et al., 2013). Therefore, these two mechanisms are similar in this specific feature. This generalization concerning the chemoattractant and self-generation of directional guidance is local in the two senses I specified above. It applies only to some examples of collective cell migration; in other examples, other molecules serve as chemoattractant, migration is guided by preexisting gradients of chemoattractant in the microenvironment, or the direction of migration is determined in a totally different manner. The generalization also concerns only a specific feature of the migration mechanisms, namely, the kind of chemoattractant and self-generation of directional guidance. Not all features of the mechanisms of zebrafish lateral line primordium migration and *Xenopus* neural crest migration are similar. Despite this locality, these two migration mechanisms are sometimes discussed together to highlight the similarity between them (Mayor & Etienne-Manneville, 2016; Scarpa & Mayor, 2016).

Another example of a local generalization concerns a functional difference among the cells constituting a migrating cohort. Leader cells and follower cells play distinct functions in many migrating systems, such as fruit fly border cells and zebrafish lateral line primordium. Like the example of self-generated directional guidance, this generalization about the leader-follower distinction is local. Although the functional difference between leader and follower cells is observed in several model systems, it is by no means a universal feature of collective cell migration; there are migration mechanisms that do not exhibit this functional difference, such as mouse mammary gland development (section 3.3). This generalization is also about a specific feature of the migration mechanisms and not about the entire mechanisms. But researchers often discuss this functional distinction and compare those model systems that share it, which suggests the importance of the generalization (e.g., Mayor & Etienne-Manneville, 2016; Norden & Lecaudey, 2019; Scarpa & Mayor, 2016).

Some local generalizations are consequences of evolutionary conservation. Mechanisms of collective cell migration sometimes share homologous components across taxa and/or organs, even if the entire mechanisms are not likely to be homologous. But evolutionary conservation is not necessary for local generalizations. Some local generalizations concern specific roles that certain types of cells play in various migration mechanisms. The above-mentioned generalization concerning the leader-follower distinction focuses not on a conserved molecular signaling, but on a specific kind of functional distinction that contributes to the organized migration of a group of cells. Local generalizations are also sometimes instantiations of highly abstract principles, such as organizational features or "design principles" (Green, 2015; Levy & Bechtel, 2013). Note that design principles and local generalizations are distinct categories. While design principles are characterized and studied as highly abstract principles concerning how systems behave under a similar set of constraints (Green, 2015), local generalizations are characterized more concretely as interactions between cells and/or molecules. However, local generalizations can instantiate such highly abstract principles, and hence can mediate between mechanistic and formal approaches.

Importantly, which mechanisms are regarded as similar to the given mechanism varies depending on which feature of them one focuses on. This point is illustrated by a table that Scarpa and Mayor (2016) present (Fig. 3). In this table, rows correspond to several model systems, while columns indicate different variables that characterize mechanisms of collective cell migration. Depending on which column (i.e., which feature of migration mechanisms) one focuses on, different sets of model systems are grouped together as similar systems. For example, the generalization concerning the leader-follower distinction applies to fruit fly border cells and sprouting blood vessels of mice, whereas mesendoderm of zebrafish and *Xenopus* is excluded from its scope (Fig. 3, the second column from the left).[11] However, if one focuses on what types of molecular interactions are used to exert tractive force, fruit fly border cells and zebrafish mesendoderm can be grouped together, on the one hand, and sprouting blood vessels of mouse and *Xenopus* mesendoderm can be grouped together, on the other (Fig. 3, the fourth column from the left). The point I am making here is this: there are different possible and useful ways to divide the diverse mechanisms into groups of similarity. This means that each model system can represent different subclasses of collective cell migration depending on which specific feature of the mechanisms one focuses on. Therefore, by studying those model systems, the community of researchers can elucidate diverse mechanisms underlying the phenomenon. The multiple biological systems jointly represent collective cell migration.

This consideration also highlights an important aspect of the comparative method in mechanistic research. Biologists are often interested in how and why similar morphological or physiological features result from distinct mechanisms across biological systems. (In research on collective cell migration, developmental biologists and cell biologists often have this type of interest.) Answering such a question requires characterizing, comparing, and mapping diverse mechanisms. My account shows how local generalizations serve as a crucial basis for such inquiries of mechanistic diversity. Formulating local generalizations is a strategy to identify and study regularities without ignoring differences in mechanisms across biological systems.

We can now answer the question of why recharacterization or "splitting" of a phenomenon in the sense formulated by some new mechanists (Craver, 2004; Craver & Darden, 2013) has not occurred in the case of collective cell migration. For the purpose of elucidating diverse mechanisms, it is fruitful to treat collective cell migration as a single phenomenon and regard certain biological systems as models of it, not as models of particular subclasses of it. If the phenomenon were recharacterized or split in a single, particular way, then researchers would not benefit from local generalizations that crosscut the recharacterized phenomena. This consideration also suggests that if, for a given phenomenon, certain biological systems were always grouped together no matter which feature of the mechanisms one focuses on, then the phenomenon would be more likely to be split into multiple phenomena corresponding to that grouping. Another possibility is that if the community of researchers were interested in a particular feature of the mechanisms much more than in other features, then the phenomenon might be split according to a grouping based on that feature, no matter what other groupings are supported concerning other features. I do not deny the possibility that either of these might become the case in the future in research on collective cell migration. Collective cell migration might turn out to be a tentative category that is eventually be replaced by some other categories. However, at least so far, the phenomenon has not experienced such splitting, and the idea of joint representation formulated above helps us understand why.

Before proceeding to the next subsection, I clarify where I disagree with Craver and Darden (2013). Craver and Darden claim that when distinct mechanisms are identified for a single phenomenon, scientists should divide it into distinct phenomena, each of which corresponds to a particular mechanism, and that indeed this is what scientists do. This is both a descriptive and normative claim: it describes scientific practice, as well as providing a normative guide regarding what scientists seeking mechanistic explanation should do. In contrast, I have shown that scientists sometimes retain a general phenomenon (rather than split it according to distinct mechanisms underlying it) and this is epistemologically beneficial. (I discuss more epistemological benefits in the next subsection.) However, I am not denying that in some (possibly many) cases, scientists do engage in phenomenon-splitting described and prescribed by Craver and Darden. My position is a pluralism about

[11] Mesendoderm (an embryonic tissue) migrates from the surface to the inside of the embryo during early embryogenesis of vertebrates.

Table 1. **Comparing collective cell migration across different models**

Model	Chemoattractant	Leader/ follower	Rac activation at leader cell	Traction substrate	Cadherin subtype	CIL/contact-dependent polarity	Gradient of chemoattractant
Border cell	PVF/EGF (1–4) Gurken(2)	Yes (5) Dynamically rearranged (5,6)	Yes (7–10)	E-cadherin (7,11)	E-cadherin (7,11)	Yes Observations of contact-dependent cell polarity (5) Active suppression of internal protrusions (12) and Rac1 polarization (7)	Not yet elucidated PVF-1 protein is expressed in the oocyte (2), and *Krn* and *Spi* mRNAs are also detected in the oocyte (3)
Lateral line	CXCL12/SDF-1 (13–15)	Yes (14) Dynamic rearrangements not yet elucidated	Not yet elucidated	Not yet elucidated	E-cadherin (16) N-cadherin (17)	Yes Observations of contact-dependent cell polarity (14,18)	Yes Self-generated SDF-1 gradient (13) Moving source of FGF: anterior lateral line (19)
Branching morphogenesis	*Drosophila* Trachea: Branchless (20–22) Mouse retina: VEGF (23)	Yes Specified by Btl/VEGF signaling levels (22–25), dynamic rearrangements may occur (26–29)	Yes *Drosophila* trachea (24,30) Mouse retina: not yet elucidated	Mouse retina: FN ECM (31)	*Drosophila* trachea: E-cadherin (32,33) Mouse retina: VE-cadherin (29)	Yes Observations of contact-dependent cell polarity and Rac1 polarization (24)	Yes *Drosophila* trachea: *O*-sulfotransferases *sulfateless* and *sugarless* genetically interact with *branchless* (34), although gradient not yet elucidated Mouse hindbrain: VEGF isoforms binding to ECM create a gradient of VEGF protein (35)
Neural crest	CXCL12/SDF-1 (36–39) VEGF (55)	Yes (40,41) Dynamically rearranged (42)	Yes (36,41,43,44)	Fibronectin ECM (45–47)	N-cadherin (36, 37,41,42)	Yes Mediated by N-cadherin and Wnt/PCP (36,37,40) Rac1 polarization and suppression of protrusions at internal contacts (36,40,41)	Yes Moving source of SDF-1: epibranchial placodes (37) VEGF gradient suggested (55)
Mesendoderm	PDGF (48–50)	No All cells in the collective form oriented unipolar protrusions (48,51)	Yes Rac required for protrusion formation in zebrafish (52)	*Xenopus*: FN ECM (51,53) Zebrafish: E-cadherin (52,54)	E-cadherin (52,54), C-cadherin (56)	Yes Mediated by E-cadherin and Wnt/PCP via Rac1 (52) Tension-dependent polarization mediated by C-cadherin (56)	Not yet elucidated. PDGF mRNA expressed in roof plate but protein localization not yet investigated (49,50)

Fig. 3. A table that characterizes several mechanisms of collective cell migration (Scarpa & Mayor, 2016, Tabled 1). It compares important features of migration mechanisms (the seven columns) across different model systems (the five rows). ©2016 SCARPA et al. Originally published in Journal of Cell Biology. https://10.1083/jcb.201508047.

recharacterization of scientific phenomena. Scientists might *often* recharacterize phenomena according to underlying mechanisms, but they do not do so *when retaining a general phenomenon has epistemological benefits*.[12]

4.3. Utility for characterization and investigation of individual mechanisms

The previous subsection focused on how certain biological systems can serve as models of a diversely produced phenomenon in a narrow sense, namely, how findings from those systems can be projected to other systems. In this subsection, I discuss broader benefits in regarding certain biological systems as examples of the same phenomenon. Comparing mechanisms that operate in different biological systems as models of the same phenomenon can promote research by facilitating characterization and investigation of individual mechanisms.

Let us start with a benefit for characterization. Even when the migration mechanisms being compared are not similar with respect to the feature one is interested in, contrasting those mechanisms often helps to characterize them more precisely. This is commonly done in review articles. In some cases, the purpose of a review article is to characterize a particular mechanism in detail, and to do so, the authors compare that mechanism with other ones. For instance, Olson and Nechiporuk (2018) aim at clarifying what is known about the mechanism of collective cell migration of zebrafish lateral line primordium. To do so, they compare this mechanism with mechanisms that operate in several other model systems. In other cases, an article aims at a more comprehensive review of diverse mechanisms, where comparisons are an effective way of doing it. Scarpa and Mayor (2016)'s table is a good example, which compares different migration mechanisms in terms of several features (Fig. 3). Each mechanism is characterized more precisely by recognizing not only similarities to, but also differences from, other mechanisms. Displaying diagrams of different migration mechanisms in one place is another example of characterization through comparisons (Fig. 2).

Comparisons of different model systems also can promote investigations into individual mechanisms. For example, Scarpa and Mayor (2016)'s table indicates that some features of migration mechanisms are "[n]ot yet elucidated" for certain model systems (Fig. 3). Features that require further studies are effectively identified and highlighted by comparing a given mechanism with what are known about other mechanisms. Comparisons also have heuristic value. When biologists investigate a less-explored system, they often assume as a working hypothesis that system employs a similar mechanism to those that operate in certain other (better-understood) model systems. For example, a molecular signaling that is known to play a crucial role in some model systems might play the same role in the new system under study. Such a working hypothesis might be confirmed by experimentation, which leads to

[12] Craver and Darden (2013)'s account also has a metaphysical component: natural classification of phenomena is determined by underlying mechanisms, which provides the basis for the descriptive and prescriptive aspects of their account. In contrast, the present paper focuses on description and epistemology of scientific practice; metaphysics of phenomena classification is beyond its scope. Thus, I do not discuss whether collective cell migration is a natural category. I argue that no matter whether it is a natural category or not, collective cell migration has been treated as a single phenomenon, and there are good epistemological reasons for it.

the formulation of a new local generalization. Even if it is disconfirmed, i.e., even if it turns out that the system under study does not employ a similar mechanism, that discovery itself is an achievement because the researchers learned something new about the system and can utilize that finding to proceed to the next step (Bechtel, 2009). It is *not a necessary condition* for this heuristic that different biological systems are regarded as models of a single phenomenon. But the heuristic is *facilitated* by such a situation, because if certain biological systems are seen as models of the same phenomenon, they are more actively compared with one another in review articles, collected volumes, and conference sessions.

In summary, there are good epistemological and methodological reasons to keep regarding collective cell migration as a single phenomenon and certain biological systems as models of it, not as particular subclasses of it. A crucial point is that doing so facilitates research activities. Local generalizations about different features of mechanisms that hold across different ranges of biological systems make it possible for multiple model systems to jointly represent the phenomenon. Comparisons of different model systems also have benefits for characterization and investigation of individual mechanisms. In these ways, multiple model systems enable efficient inquiries into different mechanisms of collective cell migration.

5. Joint representation and integration-based accounts

Some philosophers of science have discussed how multiple biological model systems are combined to fulfill specific research goals (Baetu, 2014; Fagan, 2016; Green et al., 2021). But the case of collective cell migration exemplifies a different way multiple model systems are used together. In this section, I introduce two accounts that discuss the use of multiple model systems (Baetu, 2014; Fagan, 2016) and contrast my account with them. While these accounts are concerned with how results from different model systems are integrated, such integration is not a central element of my account; rather, the focus of my account is on efficient investigations into diverse mechanisms.

Baetu (2014) points out the "mosaic" nature of mechanistic knowledge through his detailed discussion of immunological research. He argues that in immunology, mechanistic accounts are often constructed by combining data acquired in studies of different model systems. "Bits of information about the causal-mechanistic basis of a phenomenon of interest are first gathered from data generated by several experiments, conducted in the context of distinct experimental models, each designed to overcome a particular experimental difficulty" (Baetu, 2014, pp. 52–53).[13] For example, a single mechanistic diagram to explain a particular immunological phenomenon is very often produced by integrating contributions from studies conducted in different experimental models, such as human primary cells, genetically engineered human cells, and murine models (also see Baetu, 2016). Fagan (2016)'s focus is on the use of human embryonic stem cells (hESC) and other kinds of stem cells studied as models in stem cell biology. A central goal of stem cell biology is to understand early human cell development. This is a taxonomically narrow, but mechanistically complex target, and this complexity requires researchers to rely on different kinds of stem cells, including hESC and induced pluripotent stem cells (iPSC). Researchers integrate pieces of information acquired from different stem cell models in order to develop mechanistic explanations for this specific target. "This complex phenomenon [early human cell development] is represented by an ever-expanding family of related models, each narrowly targeting a different aspect of this complex phenomenon of interest. hESC is one of many stem cell model organisms, interrelated in their construction and use" (Fagan, 2016, p. 128).

In discussing how multiple model systems are used together, Baetu (2014) and Fagan (2016) both emphasize integration of results acquired from different model systems. In Baetu's case, integration results in a generalized, "mosaic" mechanistic account that explains the target phenomenon; in Fagan's case, integration leads to explanations of a single, specific target system (i.e., early human cell development). My account of joint representation is not concerned with such integration. Its point is neither to develop a single, overarching mechanistic account by combining data from studies of different model systems, nor to utilize information from different model systems in order to elucidate a single, specific target system. Instead, my account characterizes how individual mechanisms are investigated through various local generalizations and cross-system comparisons. I also highlighted that local generalizations allow researchers to identify and study regularities without ignoring differences in mechanisms among biological systems. By doing so, they serve as a crucial basis for inquiries into why and how similar morphological or physiological features result from distinct mechanisms. Here, the diversity of mechanisms is neither problematic complexity to be abstracted away, nor a mere means, to achieve an integrated mechanistic explanation. Rather, the diversity itself interests researchers and motivates investigations into and comparisons among different mechanisms.

My account is not a rival of, but rather complementary to, the existing accounts. It characterizes a different way that multiple model systems are used in combination within an area of research. Indeed, the accounts of Baetu and Fagan seem to be useful to analyze the use of multiple model systems *in some local contexts* of research on collective cell migration. Baetu's idea of mosaic nature of mechanistic knowledge is useful for understanding how each migration mechanism has been elucidated. For example, although the mechanism of collective cell migration in sprouting blood vessels is often treated as one thing, it is informed by studies of different types of blood vessels, such as mouse retinal blood vessels and zebrafish intersegmental arteries (Gerhardt et al., 2003; Siekmann & Lawson, 2007). However, such integration to construct a single, generalized mechanistic account is not the dominant approach to the phenomenon of collective cell migration *as a whole*. This point is illustrated by the common presentational practice of displaying diagrams of multiple distinct mechanisms together (Fig. 2). Fagan's account also seems effective to analyze certain aspects of this area. Some researchers studying collective cell migration are interested primarily in medical application. To them, collective cell migration in a particular biological system (e.g., human breast cancer) is *the* target, and knowledge of other migration mechanisms is a means to it. Fagan's account fits such situations, where researchers try to explain a particular target by utilizing pieces of information from studies of different model systems (e.g., Stuelten et al., 2018). However, no interest in a single, particular biological system dominates the entire research on collective cell migration. As I explained in section 3, this area involves researchers from different disciplines and is motivated by a range of interests, including those in explaining development of various biological forms and in better understanding pathological and regenerative processes in humans. Therefore, to understand representational relationships between multiple model systems and the phenomenon of collective cell migration as a whole, my account is more suitable; it explains how multiple model systems are studied as loci for investigation and jointly promote elucidation of diverse mechanisms in order to pursue different goals in this area of research.

[13] Baetu's notion of "experimental model" is not exactly the same as the notion of "model system" adopted in this paper. In his terminology, an experimental model refers to "an experimental setup well suited for studying a phenomenon," where the experimental setup is characterized in terms not only of the biological system (e.g., an organism or cell) but also of an operationalized protocol and information about various aspects of the system, such as its source and the process of its standardization (2014, p. 50). However, my interest here is in what Baetu says about the use of multiple models, and the above difference is irrelevant given this purpose.

6. Conclusion

There are biological phenomena whose underlying mechanisms are so diverse that single model systems cannot sufficiently represent them. Despite such diversity, biologists often keep regarding certain biological systems as models of those phenomena. I proposed that to account for this modeling practice, we should examine how multiple model systems are used together within an area of research. The case study from research on collective cell migration showed that despite the mechanistic diversity, local generalizations concerning specific features of the mechanisms hold across certain ranges of biological systems. Such local generalizations enable the multiple model systems to jointly represent the target phenomenon. Furthermore, comparisons of different model systems facilitate the research in a number of ways: they enable more precise characterization of individual mechanisms; help to identify and highlight issues that require more studies; and provide a basis for a heuristic to study less-explored systems. These considerations provide further explanations of the use of multiple model systems in research on a phenomenon that occurs through diverse mechanisms. Finally, I compared my account of joint representation with two existing accounts of the use of multiple model systems and argued that they are distinct and complementary. This comparison suggests that more philosophical inquiry is needed to understand different ways that multiple biological model systems are combined to fulfill specific research goals.

Acknowledgements

I am grateful to Alan Love, Max Dresow, Katherine Liu, Lauren Wilson, Kelle Dhein, and Amanda Corris for their useful comments on earlier drafts. Discussions with Melinda Bonnie Fagan and David Colaço helped me revise the paper. I also thank the two anonymous reviewers as well as the two editors of the journal, Rachel Ankeny and Sara Green, whose comments greatly contributed to improvement of the paper. Previous versions of this manuscript were presented at the Philosophy Online Seminars in Japan, Philosophy of Science Association, and European Philosophy of Science Association, where I received helpful feedback. Financial support for the research and writing of this article came from the Philosophy of Science Association and the Department of Philosophy at the University of Minnesota.

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