

Multiple Model Systems and Representation of Biological Phenomena

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Abstract

Biologists often study certain biological systems as models of a phenomenon of interest even if they already know that the phenomenon occurs through diverse mechanisms and hence none of those systems can sufficiently represent it by itself. To understand this modeling practice, the present paper provides an account of how multiple model systems can be used to study a phenomenon whose underlying mechanisms are diverse. Even if generalizability of results from a single model system is significantly limited, generalizations concerning particular 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 one biological system, such as an organism, as a model of a particular phenomenon of interest, where the model is expected to serve as a convenient locus for investigating the phenomenon (Ankeny and Leonelli 2011, 2020). 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 cellular activities underlying certain morphogenetic phenomena differ significantly across taxa or organs. A consequence of such diversity is a limitation on the degree to which a single biological system represents the phenomenon of interest: “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 and Nelson 2014, 2756-2757). In such a case, no single biological system can sufficiently represent the target phenomenon because the phenomenon itself involves diversity of underlying mechanisms.

This might lead one to wonder the following: is it appropriate to regard such a phenomenon, which is known to occur through diverse mechanisms, as a single phenomenon? 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). This view is consistent with what some new mechanistic philosophers argue. For example, Craver and Darden (2013) suggest that 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 actually 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 and Darden 2013, 61, emphasis original). Elsewhere, Craver also writes: “It is a common (but rarely explicit) methodological assumption in neuroscience and elsewhere that discovering a kind to be dissociably realized mandates splitting the kind into as many as there are dissociable realizers” (Craver 2004, 960). Craver and Darden mention research on memory as an example, where discovery of distinct mechanisms led researchers to split several types of memory as distinct phenomena. I do not deny that such phenomenon-splitting is practiced in some cases. However, there are also cases in which researchers do not give up a phenomenon and keep regarding certain biological systems as its models, not as models of its distinct subclasses, even though they already recognize multiple distinct mechanisms that bring about it.¹ Why?

¹ I have to be clear on exactly where I disagree with Craver and Darden. They claim that when distinct mechanisms are identified for a single phenomenon, researchers divide it into distinct phenomena, each of which corresponds to a particular mechanism. This is a claim about a research practice and is based on another, metaphysical view: that natural classification of phenomena is determined by mechanisms. In this paper, I point out that the former claim concerning the research practice is not always true and argue that there are sometimes good epistemological and methodological reasons for not splitting a phenomenon that is known to occur through diverse mechanisms. I do not discuss Craver and Darden’s claim about metaphysics of natural classification of phenomena. Thus, it is beyond the scope of this paper whether collective cell migration (the phenomenon I discuss in my case study) is a natural category or not.

The present paper aims 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 and Glimour 2009; Mayor and Etienne-Manneville 2016; Mishra et al. 2019; Rørth 2009; Scarpa and Mayor 2016). Yet certain biological systems are still regarded as model systems of collective cell migration and this phenomenon remains a legitimate object of research. I argue that there are good epistemological and methodological reasons for this modeling practice. To understand this, I provide an explicit account of how *multiple* model systems are used together to study such a phenomenon. This differs from the existing philosophical discussions of biological model systems, most of which are concerned with how a *single* biological system is chosen and used as a model (with a few exceptions; see below). I argue that even if generalizability from a single model system is significantly limited, local generalizations still can hold, which makes it possible for certain biological systems to jointly represent the target phenomenon. Regarding different biological systems as models of a single phenomenon also facilitates comparisons between them, which help characterization and investigation of individual mechanisms. I also contrast my account with two existing accounts that analyze the use of multiple model systems (Baetu 2014; Fagan 2016). While they both are concerned with how results from different model systems are integrated, such integration is not central in my account; instead, it focuses on how various local generalizations and cross-systems comparisons promote investigations of diverse mechanisms.

This paper is structured in the following way. Section 2 clarifies the notion of model system, which provides a basis for my discussion in the following sections. 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 and 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 and 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

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.

model in biological and biomedical research.³ Although this idea is sometimes mentioned (Ankeny and Leonelli 2020, 28; Bolker 2009, Table 1), philosophical discussions about “living models” usually focus on *organisms* that serve as models, such as the house mouse *Mus musculus* as a model of humans (Ankeny and Leonelli 2011; Burian 1993; Levy and Currie 2015). 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 retinal blood vessels of mice are all regarded as model systems to elucidate how highly branched organs are produced during development (Spurlin and Nelson 2017). 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, such as retinal blood vessels and the mammary gland (within-species, across-component systems comparisons) or with different branched organs of other species, such as the fruit fly respiratory system (across-taxa, across-component systems comparisons). 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 we discuss in the following sections (research on collective cell migration) is one such case.

Two basic accounts of how a biological system works as a model are worth introducing: the accounts of Krogh-principle models and exemplary models.⁴ 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, 202), where the convenience is interpreted most typically in terms of features that make experimental work easier, such as the size, simple anatomical structures, and transparency. 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. 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 because it represented a larger group of biological systems to which it belongs. 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 a Krogh-principle model and exemplary model at the same time. These accounts provide basic ideas of how certain model systems work, which are useful (though not sufficient) to analyze the case that is introduced in the next section.

Finally, I clarify the scope of this paper. The goal of this paper is to formulate a certain kind of representational relationship between a phenomenon that occurs through diverse mechanisms and multiple model systems. To do so, I concentrate on articulated mechanisms and

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, 47). This is *not* the definition adopted in this paper.

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

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 have recently emphasized (Ankeny and Leonelli 2020; Dietrich et al. 2019), whether a biological system is a good or plausible model of the target phenomenon relies on various factors, including availability of institutional and political resources that facilitate the use of the system. But a comprehensive discussion of all such relevant factors is beyond the scope of this paper.

3 An Example: Collective Cell Migration

This section introduces research on collective cell migration with an emphasis on the diversity of mechanisms underlying it. *Collective cell migration* refers to a set of processes through which cells migrate as a group while interacting with each other (Mishra et al. 2019).⁵ It has become an active area of research in developmental biology as well as in related disciplines in the last few decades. The phenomenon has been studied by a range of researchers, including both basic and application-oriented ones. 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 structures (i.e., *morphogenesis*, which is one of the major problems of developmental biology; Love 2014). On the other hand, collective cell migration plays crucial roles in cancer invasion, metastasis, and wound healing. Cancer researchers and regeneration researchers have actively studied the phenomenon. 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 for developing better treatments.

Collective cell migration has been studied by using various biological systems. 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 and Mayor 2016, 143; emphasis added); “A variety of genetic *model systems* are used to examine and define the cellular and molecular mechanisms behind collective cell migration including border cell migration and tracheal branching in *Drosophila melanogaster*, neural crest cell migration in chick and *Xenopus* embryos, and posterior lateral line primordium (pLLP) migration in zebrafish” (Olson and Nechiporuk 2018, 1; emphasis added). While the exact lists of the model systems differ to some extent among authors and papers, the underlying idea is the same; those biological systems are regarded as useful loci for investigating collective cell migration.

⁵ I adopt a broad definition of collective cell migration here. Different, more detailed definitions have been proposed by several authors (e.g., Friedl and Glimour 2009; Rørth 2009; Theveneau and Mayor 2011).

The most common approach to collective cell migration aims to articulate cellular and molecular aspects of mechanisms underlying it.⁶ There are various questions that researchers ask to characterize those mechanisms, for example⁷:

- How is the direction of migration determined?
- What is the spatial configuration of the migrating cohort? Are the migrating cells epithelial, mesenchymal, or a combination of both?⁸
- How do the migrating cells interact with one another? What adhesion molecules are used for the connections?
- How do the migrating cells interact with the environment? How do they exert traction for migration?
- Is there a functional difference among migrating cells? If so, what is it?

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 example of collective cell migration (Montell 2003; Prasad et al. 2011). Border cells are several epithelial cells 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) (Figure 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 during migration and which of them plays this leading role can vary (Figure 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 chemoattractant (some TGF β homologs and PVF1), which are secreted by the egg cell. Border cells are tightly associated with each other by an adhesion molecule (E-cadherin), 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).

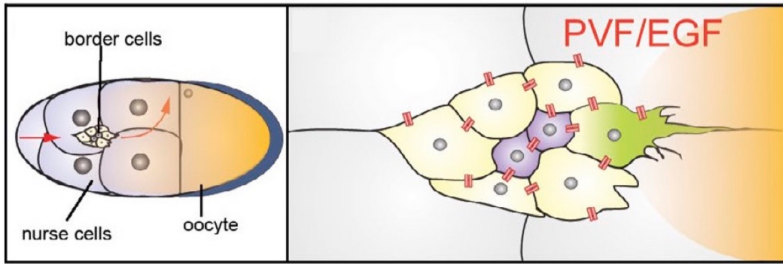
3.2 Zebrafish lateral line primordium

⁶ This paper focuses on studies of collective cell migration that seek to elucidate cellular and molecular mechanisms underlying it. There also are studies that aim at overarching principles of collective cell migration. Developmental biologists sometimes discuss general and abstract rules of collective migration of interacting entities, even beyond collective *cell* migration (e.g., Davies 2013, chapter 13; Shellard and Mayor 2020). Another approach is to construct a theory that focuses on the liquid-like behavior of cell collectives (e.g., Newman 2014). It will be interesting to explore how the cellular and molecular studies are related to those different approaches, but that will require a separate paper.

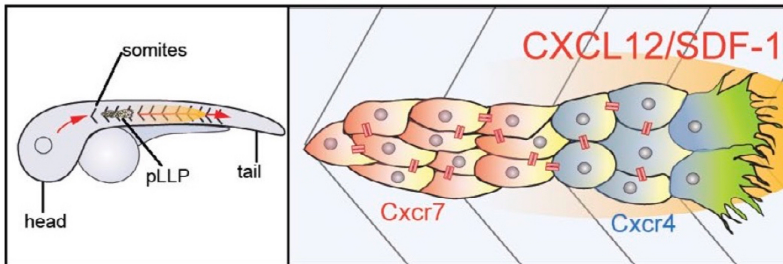
⁷ In other words, the problem of collective cell migration consists in part of the specific questions about the details of the underlying mechanisms. For a more general discussion of how problems and questions are organized in developmental biology, see Love (2014).

⁸ Epithelial cells are tightly connected with each other by specific types of molecular junctions and typically constitute a sheet-like structure. Mesenchymal cells are more loosely associated and contact with each other only at focal points.

A



B



C

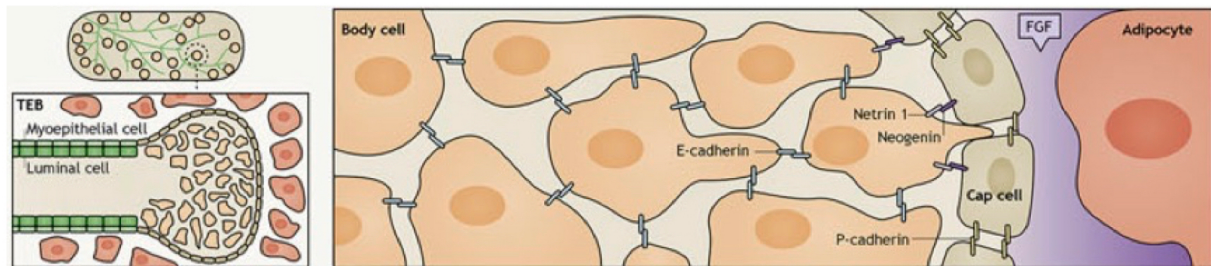


Figure 1. Three different mechanisms of collective cell migration that operate in different biological systems. A: Fruit fly border cells. Left: Several border cells migrate together towards an egg cell (oocyte) among other cells (nurse cells). Right: An enlarged view of the migrating border cells. They are tightly associated with each other. 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. Left: The posterior lateral line primordium (pLLP) migrates on a side 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. 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 are taken from Scarpa and Mayor (2016), Figure 2; C is taken from Mishra et al. (2019).

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 (Figure 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 configuration of the migrating lateral line primordium is different (Figure 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 and Nechiporuk 2018). The lateral line primordium is made an organized cohort by two types of adhesion molecules (E-cadherin and N-cadherin), 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 (CXCL12) that serves as chemoattractant. Unlike the case of border cell migration, there is no preexisting gradient of the chemoattractant in the environment that the lateral line primordium can use for guided migration; the chemoattractant is uniformly expressed by the tissue on which it migrates. Instead, the lateral line primordium itself produces a gradient and this is crucial for its directed migration. Follower cells express a receptor (CXCR7), 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 (CXCR4), 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 (Figure 1C, left). Although body cells are categorized as epithelial cells, they exhibit epithelial features only incompletely (Huebner and Ewald 2014). It is a feature distinct from border cell migration and lateral line primordium migration that the migrating body cells are confined within the terminal end bud. 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 (mediated by E-cadherin) and compete for the front position of the terminal end bud (Figure 1C, right). This leads to extension and bifurcation of the branch. Unlike fruit fly border cells and zebrafish lateral line primordium, there is no leader/follower distinction. A secreted protein (FGF) is known to guide and regulate body cell migration (Mishra et al. 2019).

3.4 The diversity of mechanisms

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 “What is the spatial configuration of the migrating cohort?” In the case of fruit fly border cell migration, the migrating cohort consists of about four to six epithelial cells that are tightly connected with each other. Zebrafish lateral line primordium is a collection of about 100 cells, which include loosely associated leader cells and tightly associated

follower cells. In the developing mouse mammary gland, each migrating cohort consists of a large number of body cells, which exhibit incomplete epithelial characteristics; they make transient connections with each other and dynamically rearrange themselves. Similarly, questions such as “how is the direction of migration determined?” and “how do the migrating cells interact with the environment?” are answered differently. Collective cell migration occurs through different cellular and molecular mechanisms in different biological systems.

This diversity is recognized by researchers, and also reflected in a presentational practice that is common in this area. Review articles about collective cell migration often display diagrams of distinct mechanisms together in one place (e.g., Friedl and Glimour 2009; Khalil and Friedl 2010; Mayor and Etienne-Manneville 2016; Mishra et al. 2019; Scarpa and Mayor 2016). Figure 2 and 3 give just two examples. In each of them, the authors present within one figure a number of diagrams depicting distinct mechanisms of collective cell migration operating in different biological systems. An extreme case of this form of presentation is Mishra et al. (2019). This review article presents a single figure that juxtaposes eleven different mechanism diagrams, which shows how collective cell migration occurs in different model systems. One might think that this presentational practice (displaying distinct mechanism diagrams together) suggests that research on collective cell migration is motivated only by an interest in individual mechanisms and not by an interest in general features of the phenomenon. I disagree with this interpretation for at least two reasons. First, as I have mentioned earlier, certain biological systems—such as fruit fly border cells, zebrafish lateral line primordium, and mouse mammary gland—are called model systems (or simply models) of collective cell migration. This suggests that those systems are expected to provide broader insights into collective cell migration beyond themselves. Second, review articles of collective cell migration very often seek common features across different examples of the phenomenon, even though scope of such generalizations are limited. (I give a more detailed characterization of such local generalizations in the next section.) A more plausible interpretation of this presentational practice is that it reflects researchers’ dual interest in generality and in mechanistic details. Displaying multiple mechanism diagrams together can both highlight general features shared across those mechanisms and present information about nonnegligible details peculiar to individual mechanisms (Yoshida 2021).

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 explicitly discusses the use of multiple model systems.

4.1 Insufficiency of existing accounts

How can we characterize representational roles of model systems of collective cell migration? Consider the accounts of Krogh-principle models and exemplary models. As I explained in section 2, Krogh-principle models are a few biological systems that are the most convenient for elucidating a particular phenomenon of interest, while 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. 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 idea of convenience emphasized by the Krogh principle no doubt plays some role 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 (due to the fact that zebrafish embryos are transparent and lateral line primordia migrate close to the surface of the

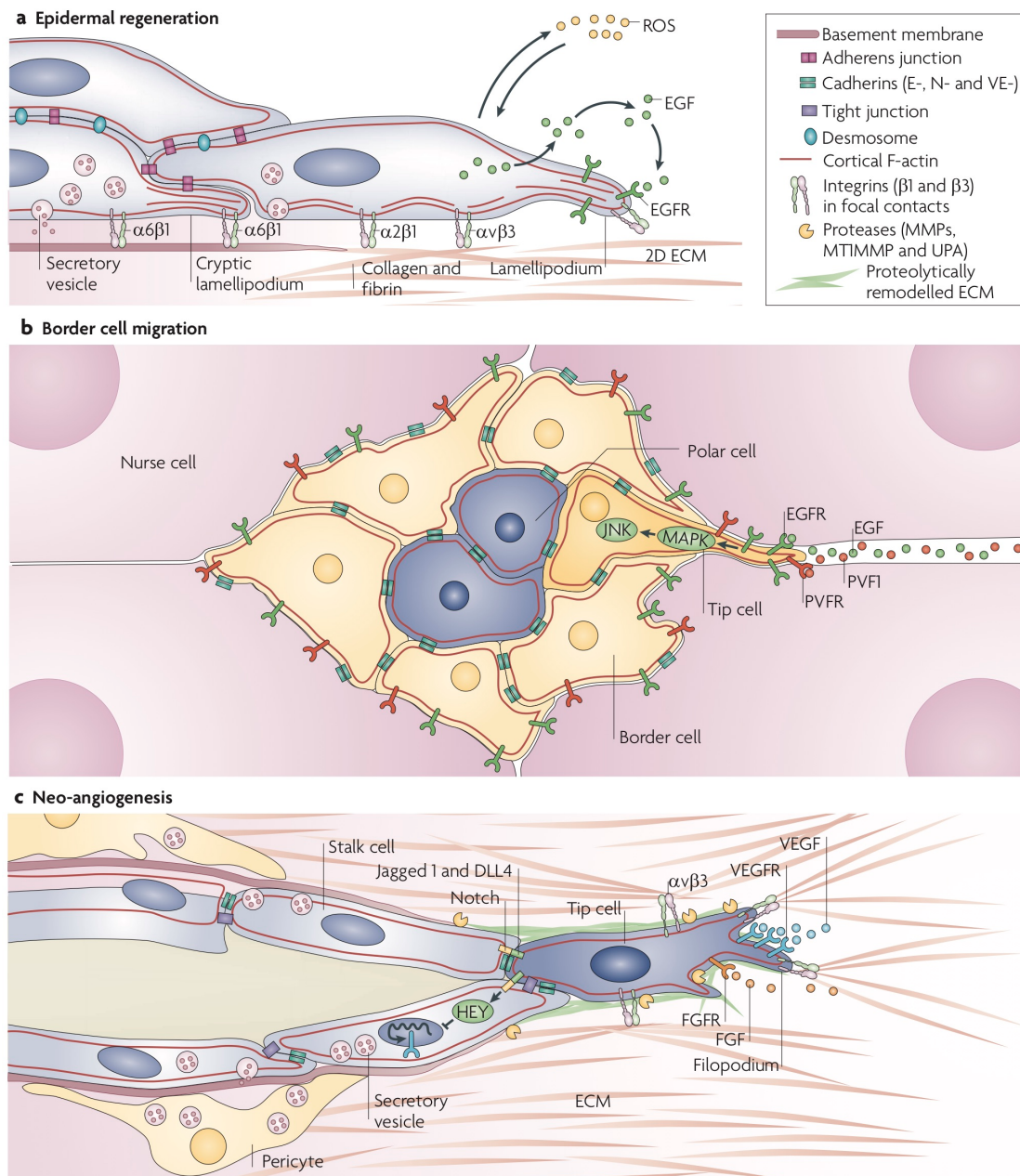


Figure 2. Diagrams of three distinct mechanisms of collective cell migration are juxtaposed within a single figure of a review article (Friedl and Glimour 2009, Figure 2, 451).

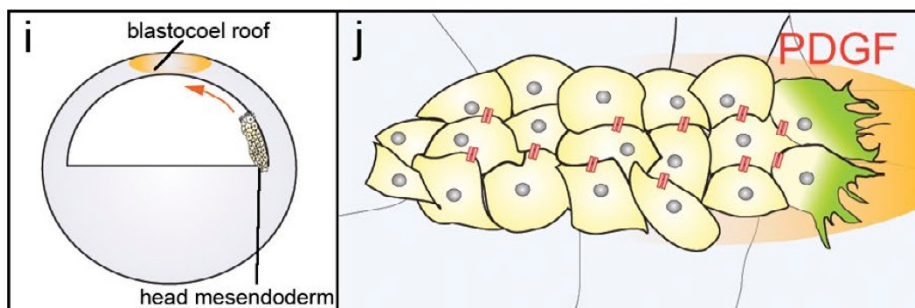
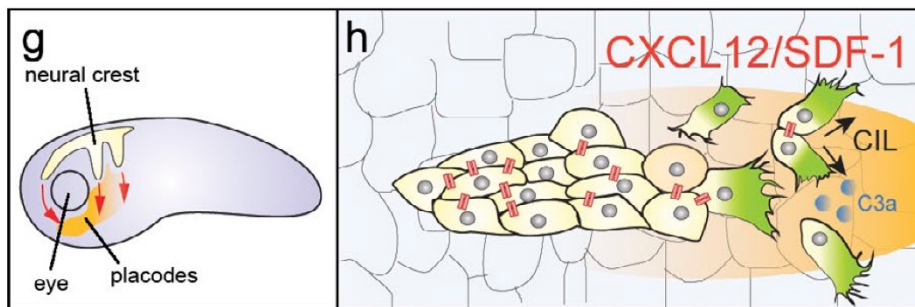
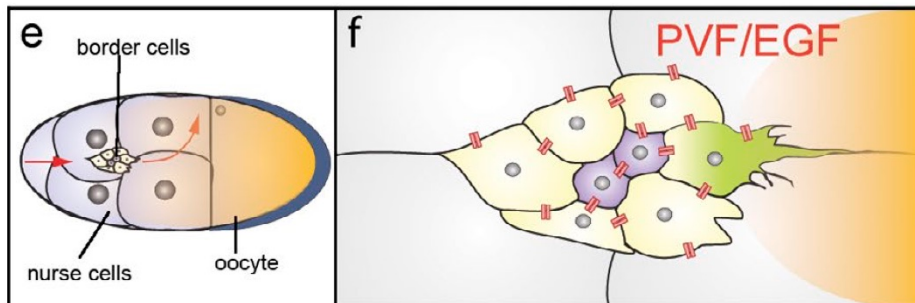
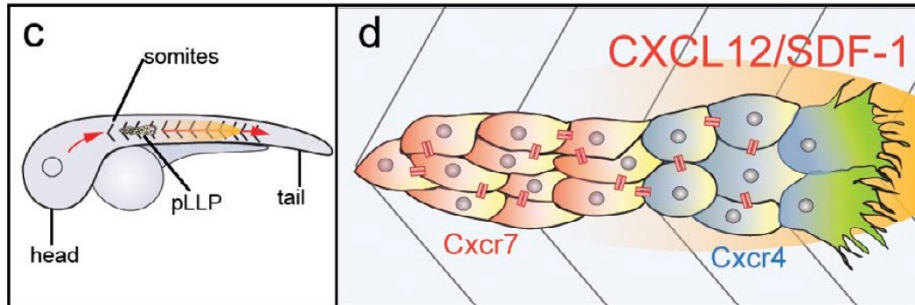
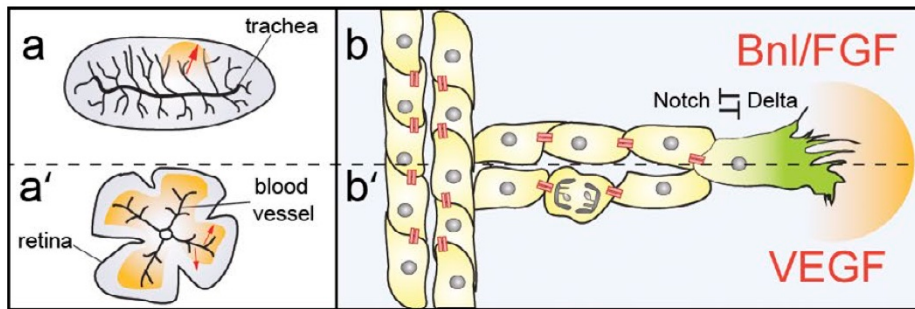


Figure 3. Diagrams of five distinct mechanisms of collective cell migration are juxtaposed within a single figure of a review article (Scarpa and Mayor 2016, Figure 2, 145).

skin), as well as the availability of various resources (such as materials, experimental techniques, and information about zebrafish genetics and genomics) (e.g., Olson and 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.⁹ What we need is an explicit account that characterizes representational relations between such a phenomenon and multiple model systems.

Nor does the account of the exemplary model 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 ideas of Krogh-principle model and exemplary model do not tell us much about how multiple model systems can be used together. In what follows, I provide an account that focuses on the use of multiple model systems within an area of research. It explains why the phenomenon of collective cell migration remains a legitimate object of research and why certain biological systems are still regarded as models of it even though the diversity of underlying mechanisms has been recognized. Even if no single explanatory account can cover diverse mechanisms, local generalizations can be and are 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 certain 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 is local in the sense that it does not apply to all or almost all cases 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 migration mechanisms are characterized by the same answer, or similar answers, to that question (for a related discussion, see Bechtel and 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

⁹ This question remains unanswered even if we appeal to Dietrich et al. (2019)'s more sophisticated account, which considers various criteria relevant to organism choice beyond "convenience." Although they briefly discuss comparative potential, their primary focus is still on the choice of a *single* research organism.

this question between zebrafish lateral line primordium and *Xenopus* neural crest cells.¹⁰ The two systems both use the same type of protein (CXCL12) as chemoattractant. Furthermore, they both self-generate directional guidance, instead of being guided by a gradient of the chemoattractant already existing in the environment. 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).¹¹ 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 certain model systems and systems that are sufficiently similar to them. In other biological systems, some other molecules serve as chemoattractant, migration is guided by preexisting gradients of chemoattractant in the environment, 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 and Etienne-Manneville 2016; Scarpa and 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. Leader cells actively extend and retract protrusions to sense environmental cues (e.g., chemoattractant) and guide migration, while follower cells, which are attached to and interact with the leader cells, follow them. Like the first example, this generalization 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 difference and compare those model systems that share it, which suggests the importance of the generalization (e.g., Mayor and Etienne-Manneville 2016; Norden and Lecaudey 2019; Scarpa and Mayor 2016).

Some local generalizations are consequences of evolutionary conservation. Mechanisms of collective cell migration sometimes share homologous components across taxa and/or across organs, even if the entire mechanisms are not likely to be homologous. But evolutionary conservation is not necessary for local generalizations. A local generalization might concern a certain role that different cells play in various migration mechanisms. The above-mentioned generalization concerning the leader/follower distinction focuses not on a conserved molecular signaling pathway, but on a specific kind of functional distinction that contributes to the organized migration of a group of cells. A local generalization could also concern organization

¹⁰ Neural crest cells migrate to different places in the body during embryonic development.

¹¹ I am presenting simplified pictures here; there are other factors that influence directional guidance of these model systems, which I abstract away for simplicity of my discussion (see, for example, Shellard and Mayor 2019).

or a “pattern of causal connectivity” of some mechanisms, which can be represented and analyzed abstractly, often by applying mathematical tools (Levy and Bechtel 2013).

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 (Figure 4). In this table, rows correspond to several model systems, while columns indicate different features that characterize mechanisms of collective cell migration. Depending on which column (i.e., which feature of migration mechanisms) one focuses on, different model systems are regarded as similar. 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 (Figure 4, the second column from the left).¹² However, if one focuses on what types of molecular interactions are used to exert tractive force, fruit fly border cells and zebrafish prechordal mesendoderm can be grouped together, on the one hand, and sprouting blood vessels of mouse and *Xenopus* head mesendoderm can be grouped together, on the other (Figure 4, 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, researchers can elucidate diverse mechanisms underlying the phenomenon. The multiple biological systems jointly represent collective cell migration.

This provides an explanation of why recharacterization or “splitting” of the phenomenon in the sense formulated by some new mechanists (Craver 2004; Craver and Darden 2013) has not occurred in the case of collective cell migration. For the purpose of elucidating diverse mechanisms of collective cell migration, it is fruitful to treat it as a single phenomenon and regard certain biological systems as models of it, not as models of particular subclasses of it. Since there are different ways to divide collective cell migration into groups of similarity, if the phenomenon were recharacterized or split in a single, particular way, then researchers would not be able to benefit from local generalizations supported by other ways of division. 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 and the phenomenon will be split into separate phenomena. Collective cell migration might turn out to be a tentative object of research 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.

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 briefly discuss broader benefits of

¹² 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 <i>Krn</i> and <i>Spi</i> 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	<i>Drosophila</i> Trachea: Branchless (20–22) Mouse retina: VEGF (23)	Yes Specified by Btl/VEGF signaling levels (22–25), dynamic rearrangements may occur (26–29)	Yes <i>Drosophila</i> trachea (24,30) Mouse retina: not yet elucidated	Mouse retina: FN ECM (31)	<i>Drosophila</i> trachea: E-cadherin (32,33) Mouse retina: VE-cadherin (29)	Yes Observations of contact-dependent cell polarity and Rac1 polarization (24)	Yes <i>Drosophila</i> trachea: O-sulfotransferases <i>sulfateless</i> and <i>sugarless</i> genetically interact with <i>branchless</i> (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)	<i>Xenopus</i> : 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)

(1) Duchek and Rørth, 2001; (2) Duchek et al., 2001; (3) McDonald et al., 2006; (4) McDonald et al., 2003; (5) Prasad and Montell, 2007; (6) Bianco et al., 2007; (7) Cai et al., 2014; (8) Ramel et al., 2013; (9) Wang et al., 2010; (10) Fernández-Espartero et al., 2013; (11) Niewiadomska et al., 1999; (12) Lucas et al., 2013; (13) Donà et al., 2013; (14) Haas and Gilmour, 2006; (15) Valentin et al., 2007; (16) Matsuda and Chitnis, 2010; (17) Revenu et al., 2014; (18) Lecaudey et al., 2008; (19) Dalle Nogare et al., 2014; (20) Sutherland et al., 1996; (21) Klämbt et al., 1992; (22) Ghabrial and Krasnow, 2006; (23) Gerhardt et al., 2003; (24) Lebreton and Casanova, 2014; (25) Hellström et al., 2007; (26) Arima et al., 2011; (27) Jakobsson et al., 2010; (28) Caussinus et al., 2008; (29) Bentley et al., 2014; (30) Chihara et al., 2003; (31) Stenzel et al., 2011b; (32) Cela and Llimargas, 2006; (33) Shaye et al., 2008; (34) Lin et al., 1999; (35) Ruhrberg et al., 2002; (36) Theveneau et al., 2010; (37) Theveneau et al., 2013; (38) Belmadani et al., 2005; (39) Olesnicki Killian et al., 2009; (40) Carmona-Fontaine et al., 2008; (41) Scarpa et al., 2015; (42) Kuriyama et al., 2014; (43) Carmona-Fontaine et al., 2011; (44) Moore et al., 2013; (45) Alfandari et al., 2003; (46) Kil et al., 1996; (47) Lallier et al., 1992; (48) Montero et al., 2003; (49) Damm and Winklbauer, 2011; (50) Nagel et al., 2004; (51) Davidson et al., 2002; (52) Dumortier et al., 2012; (53) Boucalt and Darribere, 1983; (54) Montero et al., 2005; (55) McLennan and Kulesa, 2010; (56) Weber et al., 2012.

Figure 4. A table that characterizes several mechanisms of collective cell migration (Scarpa and Mayor 2016, Table 1, 144). It compares important features of migration mechanisms (the seven columns) across different model systems (the five rows).

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)'s focus is on the mechanism of collective cell migration of zebrafish lateral line primordium and to do so, they compare it 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 (Figure 4). Each mechanism is characterized more precisely by recognizing not only similarities to, but also differences from, other mechanisms. The display of diagrams of different migration mechanisms in one place, which I have discussed in subsection 3.4, is another example of characterization through comparisons (Figure 2 and 3).

Comparisons of different model systems also can promote investigations of 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 (Figure 4). 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 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 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 likely to be compared with one another (e.g., in review articles or 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 of diverse mechanisms of collective cell migration.

5 Joint Representation and Integration-Based Accounts

In section 2, I emphasized that most philosophical discussions about biological model systems have focused on how a single biological system works (or does not work) as a model. There are a few exceptions to this tendency. In this section, I introduce two accounts that discuss

the use of multiple model systems in detail (Baetu 2014; Fagan 2016) and contrast my account with them. I argue that 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 investigation of 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, 52-53).¹³ For example, a single mechanistic diagram to explain a particular immunological phenomenon very often consists of contributions of 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 as models in stem cell biology. A central goal of stem cell biology is to learn about 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, 128).¹⁴

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 serves to explain the target phenomenon; in Fagan’s case, integration leads to explanations of a specific target (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, it characterizes how investigations proceed and diverse mechanisms are elucidated through various local generalizations and cross-systems comparisons.

My account is not a rival of, but rather complementary to, Baetu (2014)’s and Fagan (2016)’s accounts. The three accounts characterize different ways that multiple model systems are used in combination within an area of research. Indeed, Baetu’s and Fagan’s accounts seem to be useful to analyze the use of multiple model systems *in some local contexts* of research on

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, 50). However, my interest here is in what Baetu says about the use of multiple models, and the above difference is not problematic for this purpose.

¹⁴ Another important idea of Fagan (2016)’s is that different stem cell models have material overlap and are “generatively-related.”

collective cell migration. Baetu's idea of mosaic nature of mechanistic knowledge can be appealed to in order to understand 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 and 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 (Figure 2 and 3). Fagan's account also seems effective to analyze certain aspects of this area. Some researchers who study collective cell migration are interested primarily in 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, research on collective cell migration 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 relations between the multiple model systems and the phenomenon of collective cell migration as a whole, my account is more suitable; it explains how the 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.

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 model systems are used together within an area of research.

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