Generalizing While Embracing Differences: Configurations of Representations and Cross-Fertilization

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Abstract

How do biologists pursue generalizations given the heterogeneity of biological systems? This paper addresses this question by examining an aspect of scientific generalization that has received little philosophical attention: how scientists *express* generalizations. Although it is commonly assumed that a scientific generalization takes the form of a representation referring to a property that is shared across a range of things, scientists sometimes express their ideas about generality by displaying multiple representations in certain configurations. Such configurations highlight commonalities between different target systems without eliminating system-specific differences. I analyze visual representations in review articles about collective cell migration as a case study. This illustrates that different types of visualizations, including single diagrams and configurations of multiple representations, function in a complementary way to promote understanding of, and reasoning about, generality, specificity, and diversity of biological mechanisms. I also discuss roles of generalizations in scientific investigations more broadly. I argue that an important role of generalizations in scientific research is to mediate and facilitate cross-fertilization among studies of different target systems. Multiple generalizations in research on collective cell migration together provide perspectives from which different biological systems are characterized and compared. They also provide heuristic hypotheses for studying less-explored systems as well as a basis for comparing developmental, pathological, and regenerative processes. This study sheds new light on how scientists pursue generalizations while embracing system-specific details. It also suggests that philosophical discussions should pay more attention to not only what representations scientists construct, but also how they present such representations.

Keywords: Scientific generalization; modeling; visual representation; diagrams; collective cell migration; developmental biology

1 Introduction

Generality is an important value in biology, as is the case for many other fields of science. Many important achievements in biology, from the development of predator-prey equations to the discovery of the broad conservation of developmental regulatory genes, are celebrated because they revealed regularities that hold across wide ranges of systems or phenomena. At the same time, it is well known that biological systems are heterogeneous. Biological generalizations typically involve many exceptions, which makes it difficult to establish universal laws in biology. This raises the question: how do biologists pursue generalizations given the heterogeneity of biological systems? Philosophers of biology have addressed this question primarily by revising the concept of laws or law-like generalizations. For example, Waters (1998) distinguished biological generalizations about causal regularities and distributions. The former capture exceptionless regularities about how certain kinds of entities behave, while the latter describe contingent distributions of such causal regularities in the biological world. Mitchell (2000) proposed a non-dichotomous view of laws, in which scientific generalizations can exhibit different degrees of "stability" (the scope of application), "strength" (the strength of a conditional relation), and "abstraction" (the extent to which details of a regularity are ignored). Her framework was to capture biological generalizations while at the same time acknowledging irregularities of biological phenomena.

These and other conceptual works have provided useful tools to characterize and categorize generalizations about heterogeneous biological systems and phenomena. However, there is an aspect of scientific generalization that, despite its relevance to the above question, has received very limited philosophical attention: how scientists *express* generalizations. Though

rarely stated explicitly, it is commonly assumed that a scientific generalization is expressed as a representation, such as a statement or model, referring to a feature that applies to a range of things. The statement that "the appendages of endotherms are smaller, relative to body size, in colder climates, in order to reduce heat loss" (Symonds & Tattersall, 2010, p. 188) is a textual representation that describes a pattern in morphological variation that applies to a range of endothermic taxa. The ideal gas law is expressed as $pV = nRT$, which is a mathematical representation that expresses a quantitative relation among the pressure, volume, amount of substance, and temperature that applies to different types of gases. When philosophers discuss scientific generalizations, they consider generalizations like these: textual, mathematical, or other kinds of representations that point to certain features shared across different things. However, scientists express their ideas about generality not always by formulating such a unified representation. Instead, they sometimes *display multiple representations* in one place to highlight commonalities among the target systems. While philosophers rarely discuss this practice explicitly, Yoshida (2021) analyzes it in the context of modeling.[1] According to him, the practice of juxtaposing multiple mechanism diagrams often serves as a strategy to manage a trade-off between generality and mechanistic detail. Although generality and detail are both valued, they

[1] Besides Yoshida (2021), a few historical and philosophical studies of diagrammatic practices point out that juxtaposing multiple diagrams can highlight common features across different target systems (e.g., Wimsatt, 1990; Abrahamsen et al, 2017; Steinert & MacCord, 2018). Outside of history and philosophy of science, the data visualization researcher Edward Tufte (1990) provides a classic discussion of what he calls "small multiples," which is a method of displaying multiple illustrations of the same format to facilitate comparative reasoning.

are often in a trade-off relationship. When multiple biological processes are based on mechanisms that have commonalities but also differ in some important details, it might be impossible to construct a single mechanistic model that satisfies the desiderata of generality and detail at the same time. Yoshida (2021) argues that juxtaposition of multiple mechanism diagrams is often used to manage such a situation. Two diagrams are displayed together in a way that highlights the commonalities between the mechanisms without eliminating differences in details. Such a presentation can express generality in those mechanisms while acknowledging system-specific differences.

The present paper elaborates on Yoshida's (2021) discussion and extends it. Although Yoshida focuses on cases of simple juxtaposition of two mechanistic diagrams, there are more than one way in which multiple representations are displayed together. To characterize such presentational strategies, I focus on a concrete example: the use of different types of visualizations in research on collective cell migration. Collective cell migration is a process in which a group of cells migrate together in a coordinated manner and plays important roles in different developmental, pathological, and regenerative phenomena. Mechanisms of collective cell migration exhibit interesting similarities across systems and processes, but there also are non-negligible differences in their details. I show that there are different ways in which multiple representations are displayed together. My analysis is not intended to be an exhaustive list of how scientific representations are arranged to express generalizations. Instead, it focuses on how the different types of visualizations, some of which display multiple representations together, work in a complementary way to facilitate understanding of, and reasoning about, generality,

specificity, and diversity of biological systems. Through this analysis, I argue for the importance of configurations of multiple representations as a generalization strategy.

My analysis also provides a new insight into roles of generalizations in scientific research. Although philosophers of science have devoted attention to the question of whether and how generalizations enable scientific explanations (e.g., Hempel, 1965; Friedman, 1974; Kitcher, 1989; Woodward, 2001), I focus on another role of generalizations, which has been neglected in previous discussions: generalizations mediate and facilitate cross-fertilization among studies of different target systems. Different biological systems (developmental, pathological, and regenerative systems in different organs of different species) are studied as examples of collective cell migration. Biologists establish generalizations that hold across different ranges of those systems. Such generalizations provide perspectives from which different mechanisms are characterized and compared, heuristic hypotheses for studying less-explored systems, and a basis for comparing different classes of biological systems or processes, such as developing tissues and invasive cancer. I argue that those generalizations together provide an interface where studies of the diverse biological systems mutually inform one another, which leads to new discoveries about, and better characterizations of, individual mechanisms.

This paper is structured as follows. Section 2 describes different ways in which generalizations are expressed in review articles about collective cell migration. In particular, I analyze how specific configurations of multiple representations serve to highlight commonalities between different mechanisms without eliminating system-specific differences, and thereby facilitate reasoning about generality, specificity, and diversity of biological processes. Section 3 discusses how generalizations facilitate productive interactions among studies of different

biological systems. This discussion illustrates that pursuits of generalizations and studies of different, individual mechanisms contribute to each other. In Section 4, I discuss implications of my discussion for several philosophical issues, such as the conceptualization of scientific generalization, trade-offs in modeling, and different approaches to diagrammatic practices.

2 Generalizing with Different Types of Visualizations

Collective cell migration is a phenomenon in which a group of cells migrate collectively. Cellular and molecular aspects of this phenomenon have been actively studied in the last few decades. Collective cell migration is known to play crucial roles in normal development of various organs in different species, cancer invasion and metastasis, and wound healing. Heterogeneous cellular and molecular mechanisms for this phenomenon have been elucidated in different biological systems. Because of this heterogeneity, one cannot generalize an entire mechanism of collective cell migration across systems. The mechanism of border cell migration in the fruit fly ovary (a model system of collective cell migration), for example, involves peculiarities that make it difficult to generalize it to other examples of collective cell migration. Nevertheless, researchers in this area pursue and establish generalizations in a productive way. How do they do this?

To answer this question, this section examines different types of visualizations used in review articles. I focus on review articles because they are a major locus for generalization in experimental biology. In experimental biology, original research articles typically focus on one or a few biological systems and provide new information about specific mechanisms operating in these systems. It is in review articles where researchers compare mechanisms articulated in

different model systems and discuss commonalities among them. Data obtained by studying specific biological systems are summarized, compared, and processed into general knowledge in review articles. General knowledge produced in this way in turn suggests where further research can or should proceed.[2]

Diagrams and other visualizations play a crucial role for review articles to contribute to the production of general knowledge.[3] Visualizations are often drawn and arranged in ways that draw readers' attention to important commonalities across systems, and thereby promote reasoning about, and understanding of, such commonalities. This is what I mean by saying that visualizations can express generalizations. Importantly, to understand and reason about regularities in heterogeneous biological mechanisms, one often has to study them in relation to system-specific differences. Displaying multiple representations in certain configurations is an important presentational strategy to promote such integrated understanding of generality, specificity, and diversity of mechanisms.

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[2] Textbooks play a role similar to review articles, but there are some differences between them. While textbooks tend to provide systems of knowledge that are more widely accepted by the community, review articles often include recent and less-established findings. Furthermore, whereas textbooks are usually aimed at educating novices, many review articles are often targeted towards researchers working in the same or related areas.

[3] Some authors provide more general philosophical discussions of how diagrams function in mechanistic research (Bechtel and Abrahamsen, 2005; Sheredos et al., 2013; Abrahamsen & Bechtel, 2015; Abrahamsen et al., 2017; Tee, 2018).

Link to the image: https://www.nature.com/articles/nrm.2015.14/figures/1 (panel c of the figure)

Fig. 1 A principle diagram. It abstractly represents the leader-follower distinction, a widely shared feature of collective cell migration (Mayor & Etienne-Manneville, 2016, Fig. 1c).

2.1 Generalizing with Single Representations

Let me begin with discussing how single diagrams are used to express generalizations. Mechanisms of collective cell migration are heterogeneous across systems. A diagram that depicts a detailed mechanism of collective cell migration in a specific model system (say border cell migration in the fruit fly ovary) does not generalize to other examples of collective cell migration. Thus, when a single diagram is used to express a generalization, it focuses on a feature that is shared across different mechanisms while ignoring other features (that differ across systems). There are at least two ways to do this. What I call a *principle diagram* ignores specificity of biological entities (such as kinds of biomolecules and types of cells). It is an abstract representation that focuses on a relation or interaction that is instantiated by different entities in different mechanisms. In contrast, what I call a *component mechanism diagram* focuses on a specific, evolutionarily conserved component mechanism, while ignoring other component mechanisms. Mechanisms of collective cell migration consist of many component mechanisms (which themselves are mechanisms), including those for directional guidance, cell polarity regulation, cell-substrate adhesion, cell-cell adhesion, and so on. A diagram that focuses on one of those component mechanisms provides a partial explanation that applies to a range of examples of collective cell migration. Note that whether a mechanism is regarded as a component mechanism depends on perspectives and contexts. This paper focuses on a specific

context, i.e., review articles about collective cell migration, in which a component mechanism refers to one of those lower-level mechanisms (e.g., that of directional guidance) that is a part of the entire mechanisms of collective cell migration. But this categorization is not universally applicable. For example, in the context of cancer biology, an entire mechanism of collective cell migration might be regarded as a component mechanism, which is a part of higher-level mechanisms of cancer spreading.

Fig. 1 is an example of a principle diagram (Mayor & Etienne-Manneville, 2016). It represents what is called the *leader-follower distinction*, a feature shared across many examples of collective cell migration.[4] It refers to a functional difference among migrating cells. Those cells at the leading edge or migrating front (at the right-hand side in the diagram) actively extend protrusions and sense the extracellular environment surrounding them. Their migration is stimulated by external guidance cues (such as signaling molecules diffusing from certain cells). In this way, these cells lead migration. Other cells in the migrating cohort (at the left-hand side in the diagram) do not play such a role and follow the leader cells (Mayor & Etienne-Manneville, 2016).[5] The leader-follower distinction is instantiated differently in actual mechanisms across

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[4] Throughout this paper, I use expressions like "this diagram represents *x*." Obviously, when a diagram in a scientific publication represents something, there is an agent (i.e., the author(s)) who intends the diagram to represent *x* (Giere, 2010). The above expression must be understood as a shorthand of "this digram is used to represent *x* by the scientist(s) who publish the article."

[5] Theveneau and Linker (2017) argue that "leader cells" is not accurate terminology and suggest different terms, such as "front cells" and "steering cells." But I use "leader cells" throughout this paper, which is still commonly used in research on collective cell migration.

Link to the image: https://pubmed.ncbi.nlm.nih.gov/25054920/#&gid=article-figures&pid=captionless-figure-uid-0

Fig. 2 A component mechanism diagram. It depicts how a group of proteins (Cdc42, Rac, Rho, and many others) interact to regulate cell polarization and cytoskeletal dynamics, which are common in some mechanisms of collective cell migration (Zegers and Friedl, 2014, Fig. 1)

systems. There are differences across mechanisms in how leader and follower cells are spatially arranged; what types of cells serve the leader and follower roles; molecular details of the guidance cues; molecular details of interactions between leader cells and the extracellular environment; and so on (Mayor & Etienne-Manneville, 2016). Fig. 1 ignores those differences and abstractly depicts the relation and interaction between cells at the leading edge and those that follow. By doing so, it promotes the reader to move away from molecular and cellular idiosyncrasies in specific mechanisms and focus on a pattern, i.e., the division of labor in a migrating cohort, that applies to a range of examples of collective cell migration. Fig. 1 expresses a generalization by drawing the reader's attention to an abstractly characterized commonality.

Fig. 2 is an example of a component mechanism diagram (Zegers & Friedl, 2014). This diagram depicts how a group of signaling proteins function by mediating between external signals, cell polarity, and dynamics of cytoskeleton.[6] While Rac and Cdc42 regulate protrusion formation at the free edge a cell, RhoA regulates contraction at the rear side of the cell. And their activities influence each other within and between migrating cells via molecular and mechanical interactions. This mechanism is shared across a certain range of examples of collective cell

[6] The cytoskeleton is a network of special kinds of molecules within the cell that influences the shape and mechanical properties of the cell.

migration. In this sense, Fig. 2 expresses a generalization. But unlike Fig. 1, which focuses on an abstractly characterized feature that is instantiated by different types of entities, Fig. 2 generalizes by focusing on a component mechanism consisting of specific types of biomolecules and their activities that is evolutionarily conserved, and hence shared across different mechanisms of collective cell migration.

2.2 Generalizing through Configuring Multiple Representations

Another widely adopted style of visualization in review articles is to juxtapose multiple diagrams, where those diagrams represent mechanisms operating in different biological systems. Examples include Friedl and Gilmour (2009), Khalil and Friedl (2010), Mayor and Etienne-Manneville (2016), Scarpa and Mayor (2016), Mishra et al (2019), Olson and Nechiporuk (2018), Lu and Lu (2021), and Saraiva and Barriga (2021). Such *juxtaposed mechanism diagrams* express generalizations by highlighting common or similar features without eliminating details peculiar to different mechanisms (Yoshida 2021).

Fig. 3 illustrates how mechanism diagrams are often juxtaposed. The three diagrams depict different examples of collective cell migration: (a) epidermal regeneration (a healing skin wound), (b) border cell migration (in fruit fly ovaries), and (c) angiogenesis (blood vessel sprouting in vertebrates). The diagrams are drawn and arranged in a way that guides expert readers to recognize certain shared features. For example, the leader-follower distinction is highlighted in all three diagrams; in each diagram, leader cells (labeled as “tip cell” in diagrams b and c) extend protrusions and express receptor proteins (represented as Y-shaped icons), through which they detect guidance molecules and lead the migration. At the same time, these

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Fig. 3 Juxtaposed mechanism diagrams. The three diagrams represent different mechanisms of collective cell migration operating in different (types of) biological systems: a healing wound of skin (a), border cells in a fruit fly ovary (b), and a sprouting blood vessel of vertebrates (c) (Friedl & Gilmour, 2009, Fig. 2). The three diagrams together express generalizations by highlighting shared features, such as the leader-follower distinction, while containing information about differences among the mechanisms

diagrams provide information about differences among the three mechanisms, such as the spatial arrangements of the migrating cells (flat sheet, detached cluster, or extending tube), substrates on which cells migrate (extracellular matrix or other cells), and types of guidance molecules (EGF and ROS; EGF and PVF1; or VEGF and FGF). Juxtaposition is a way to highlight shared features without abstracting away mechanistic details that differ across systems.

Juxtaposed mechanism diagrams have a distinct set of advantages. An important advantage is that they convey information about *distributions* of shared features. Biologists are not only interested in a causal regularity that is shared across *some* biological systems. They are also interested in *what biological systems* share that causal regularity (Waters, 1998). In research on collective cell migration, the distribution of a general feature is often characterized in terms of specific biological systems that share it. Biological systems, in turn, are characterized in terms of a specific taxon and tissue the system belongs to as well as the condition of the system (i.e., developmental, pathological, or regenerative). Principle diagrams and component mechanism diagrams do not convey information about distributions. They are often detached from any particular biological system (Fig. 1 and 2). In other words, they just represent features shared across *some* examples of collective cell migration without specifying *which* examples. In contrast, juxtaposed mechanism diagrams typically show in what specific examples of collective

cell migration the features of interest are distributed. For example, by looking at Fig. 3, the reader can know that the leader-follower distinction is shared at least across epidermal regeneration, border cell migration (in fruit fly ovaries), and neo-angiogenesis (in vertebrate blood vessels).[7]

Another advantage of juxtaposed mechanism diagrams is that they can present different features and components of mechanisms as integrated wholes. Principle diagrams and component mechanism diagrams usually do not convey this type of information since each of them focuses on a specific feature and ignores everything else (Fig. 1, Fig. 2). In contrast, in juxtaposed mechanism diagrams, shared features are represented as being embedded within specific mechanisms. For example, Fig. 3 shows how the leader-follower distinction is related to, or causally connected with, other features or components (e.g., secretion and sensing of specific types of guidance molecules; molecular interactions between migrating cells and the substrates) in each of the three mechanisms. The general feature is presented not by itself, but as a part of specific mechanisms.

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[7] This is not the full depiction of the distribution of the leader-follower distinction. There are other systems that are known to share this feature. Distributions usually cannot be shown thoroughly in juxtaposed mechanism diagrams; there are so many biological systems that undergo collective cell migration, and many of them have never been studied in detail. Even if one focuses on several well-studied model systems, including all of them in one figure is not always reasonable due to a limited space and for the sake of readability. Nevertheless, even displaying a few representative or well-studied mechanisms is beneficial for the reader to get a rough idea of what biological systems share the feature of interest.

Link to the image: https://www.nature.com/articles/nrm.2015.14/figures/5

Fig. 4 Juxtaposed diagrams presenting an abstract principle. The three diagrams illustrate different ways in which a gradient of a signaling molecule is generated by an activity of the migrating cell cluster itself (Mayor & Etienne-Manneville, 2016, Fig. 5). a: Zebrafish lateral line primordium. b: Melanoma cells. c: Frog neural crest cells. See the text for more details

Juxtaposition is also effective for indicating a range of processes through which an abstract principle is instantiated. Fig. 4 illustrates the principle of self-generation of a chemoattractant gradient (Mayor & Etienne-Manneville, 2016). According to this principle, migrating cells are not guided by a preexisting gradient of a signaling molecule. Instead, the migrating cell cluster itself generates a gradient, which then guides directional migration of the cluster. Fig. 4 depicts three examples instantiating this principle: zebrafish lateral line primordium, melanoma cells, and frog neural crest cells. How the principle is instantiated differs among them. In zebrafish lateral line primordium (Fig. 4a), cells at the rear-side of the migrating cohort express a "scavenger" receptor protein (red, Y-shaped icons) that binds the signaling molecule that originally exists uniformly in the extracellular environment (gray). Because of this receptor, the rear-side of the migrating cluster functions as a "sink" of the signaling molecule and a gradient of the signaling molecule is generated. In the case of melanoma cells, the signaling molecule also exists uniformly in the extracellular environment in the initial state (Fig. 4b). Melanoma cells break down this signaling molecule, which reduces its concentration around the melanoma cell cluster. The gradient produced in this way drives melanoma cells to leave the cluster and spread into the surrounding tissue. Finally, frog neural crest cells (white) are attracted by a signaling molecule (gray) secreted by a group of cells called placodes (pink) (Fig. 4c). When neural crest cells reach and contact the placode cells, the latter migrate away, and this

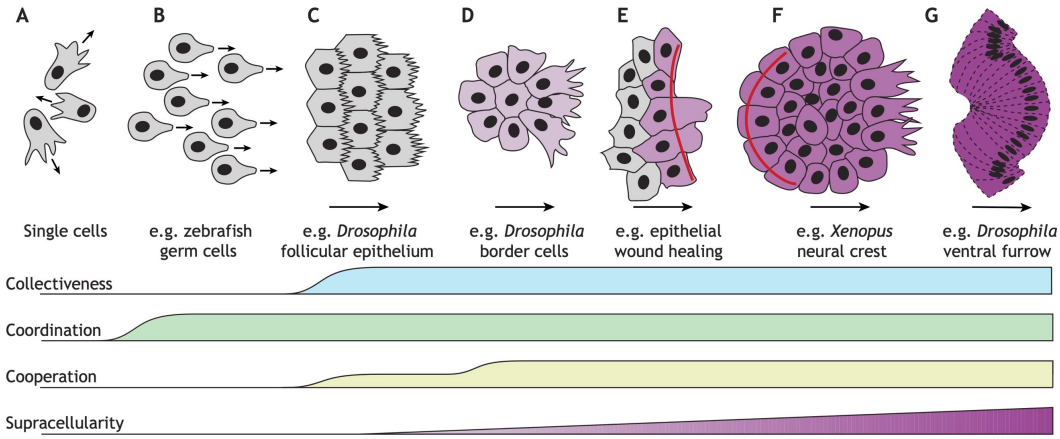

Fig. 5 A spectrum presentation. It orders different cell behaviors according to different degrees of coordination, cooperation, collectiveness, and supracellularity (Shellard & Mayor, 2019, Fig. 4). Reprinted under a CC BY 4.0 license

"chase and run" process produces collective cell migration. By displaying the diagrams of the three mechanisms together, Fig. 4 effectively presents the abstract feature shared by them (i.e., that the migrating cell group itself generates a gradient of the signaling molecule), while showing the variability in how this principle is instantiated.

Another version of juxtaposed diagrams is what I call a *spectrum presentation*. In this type of visualization, diagrams are not simply juxtaposed, but ordered. In review articles about collective cell migration, spectrum presentations are often used for a specific purpose: to characterize different degrees of collectiveness (e.g., Friedl, 2004; Gray et al., 2010; Mayor & Carmona-Fontaine, 2010; Theveneau & Mayor, 2011; Friedl et al., 2012; Campbell & Casanova, 2016; Ferrari & Giampietro, 2019; Shellard & Mayor, 2019). In Fig. 5, diagrams of different biological systems are ordered according to a set of features that define collective behaviors of cells: coordination, cooperation, collectiveness, and supracellularity (Shellard & Mayor, 2019). When migration of a group of cells is both *coordinated* (i.e., moving in parallel directions) and *cooperative* (i.e., interacting with each other), it is *collective*. *Supracellularity* refers to a

Link to the table: https://rupress.org/view-large/7951393

Table 1 A table that summarizes different mechanisms of collective cell migration (Scarpa & Mayor, 2016, Table 1). The rows correspond to different (types of) mechanisms, while the columns correspond to different variables that characterize these mechanisms

situation where a group of cells behave as if a single cell (Shellard & Mayor, 2019). Like Figs. 3 and 4, Fig. 5 provides a generalization by highlighting shared features. It draws the reader's attention to what the examples of collective cell migration (fruit fly *Drosophila*'s follicle cells, *Drosophila* border cells, epithelial wound healing, and the clawed frog *Xenopus*'s neural crest; Fig. 5C–F) have in common: coordination, cooperation, and (hence) collectiveness. At the same time, this figure shows that examples of collective cell migration exhibit different degrees of supracellularity. Importantly, Fig. 5 includes diagrams of individual cell migration (Fig. 5A, B) and a highly integrated morphogenetic movement of a cell collective without migration (Fig. 5G). By including these processes at the ends of the spectrum, Fig. 5 characterizes collective cell migration (Fig. 5C–F) in contrast to them. Spectrum presentations highlight general characteristics that distinguish collective cell migration from other cell behaviors, while showing the variation in collectiveness and supracellularity within the category of collective cell migration. Put more generally, spectrum presentations present a more systematized perspective for characterizing different biological systems or processes than simple juxtaposition. They not only present shared features; they also guide the reader to arrange different examples of a phenomenon of interest based on the degrees of certain parameters, as well as make the reader recognize the boundaries of the phenomenon.

The application of the strategy of juxtaposition and ordering is not limited within the context of diagrammatic representation. Textual representations also can be juxtaposed to

generalize about mechanisms, although it is less common compared to juxtaposition of diagrams. Table 1 is an example. In this table, rows correspond to specific model systems of collective cell migration, while columns correspond to variables that characterize its mechanisms (Scarpa & Mayor, 2016). This table indicates features shared across different examples of collective cell migration while conveying information about details that differ across them. In this sense, the table works similarly to juxtaposed diagrams[8]; it invites the reader to pay close attention to commonalities, while at the same time acknowledge differences in mechanistic details. There are important differences between juxtaposed diagrams and tables, of course. For example, the most important benefit of representing mechanisms diagrammatically—visual depiction of spatial and temporal relations among mechanism components—is not available in tables. Instead, tables use textual representations to tell the reader explicitly where to break down mechanisms into variables to make effective comparisons. Despite these differences, one crucial advantage of juxtaposition applies to both: generalizations can be formulated by configuring representations (whether diagrammatic or textual) of multiple target systems, which highlights features shared across them without eliminating interesting differences.

2.3 Complementary Relations between Different Types of Visualizations

I have introduced several types of visualizations that are used to express generalizations about mechanisms of collective cell migration. How are the different types of visualizations related to one another? One possibility is that juxtaposition of multiple representations is used only at early

[8] Tables are visual representations because they function by exploiting their visual nature: two dimensional, ordered display of textual representations (Perini, 2005).

stages of research, when researchers have not yet developed a single, unified representation that captures shared features (e.g., a principle diagram or component mechanism diagram). According to this view, juxtaposition is a transient generalization practice that will be replaced by more unified representations when research progresses. I doubt this is the case. In this subsection, I argue that the different types of visualizations are in a complementary relationship. They have different advantages in expressing generalizations and work in a complementary way.

I have already suggested that the different types of visualizations have different advantages. For example, principle diagrams are simple and relatively easy to understand, even to novices. Component mechanism diagrams are often complex and harder to grasp, but they provide detailed mechanistic depiction of specific parts or components of mechanisms. Unlike these two types of diagrams, juxtaposed mechanism diagrams convey information about how certain features are distributed across different mechanisms. They also indicate how different features and components are organized together to constitute individual, integrated mechanisms. Spectrum presentations provide a more systematic picture of variation within the category of collective cell migration and characterize its examples in contrast to other cellular behaviors. And so on.

The idea that multiple representational approaches work in a complementary way has been actively discussed by philosophers and scientists, especially in the last two decades (e.g., Green, 2013; Levins, 1966; Leonelli 2007; Matthewson & Weisberg, 2009; Morrison, 2011; Weisberg, 2007, 2013). For example, Weisberg (2007, 2013) observes that scientists often formulate multiple models for a single phenomenon, especially when the target phenomenon is highly complex. A high degree of complexity makes it difficult to construct a single tractable

model that exhibits or maximizes all desiderata of modeling (such as generality, precision, and realism). Instead, researchers construct multiple models based on different idealization assumptions that exhibit or maximize different modeling desiderata. Weisberg names this modeling strategy multiple-models idealization (MMI). The basic idea of MMI applies to the different types of visualizations that we have seen. Each of the mechanisms of collective cell migration is complex, and they also exhibit diversity in cellular and molecular details. Because of the complexity and diversity, it would be impossible to formulate a single diagram that effectively depicts all relevant details of all of the mechanisms. Instead, researchers formulate multiple, different types of visualizations that provide different information about the mechanisms or provide the same information in different ways.[9] In particular, juxtaposed or ordered representations (such as Fig. 3—5 and Table 1) play an important role in bridging between unified representations focusing on shared features (such as principle diagrams and component mechanism diagrams) and detailed representations focusing on individual mechanisms (such as detailed diagrams of fruit fly border cell migration or zebrafish lateral line primordium migration). Scientist can switch between the different focuses and acquire more integrated understanding of generality, specificity, and diversity of the mechanisms of interest.

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[9] There is an important feature of the case of collective cell migration that Weisberg's account does not capture. In Weisberg's framework, a modeling desideratum is attributed to a single model or a set of models. In contrast, I argue that certain desiderata, such as generality, are attributed not always to a single model or a set of models; they can be attributed to a *configuration of models in a physical space*. I discuss epistemological implications of this idea in Section 4.

Scarpa and Mayor (2016) provide a good example. They review findings about mechanisms of collective cell migration in different developmental systems. This article includes one table and five figures, including juxtaposed mechanism diagrams, juxtaposed principle diagrams, and component mechanism diagrams. This article first presents a table and juxtaposed mechanism diagrams that summarize different mechanisms of collective cell migration in such a way that highlights shared features. Although the table and the juxtaposed mechanism diagrams have much in common in terms of their content, they aid different reasoning because of the difference in the representational formats. Then it proceeds to more focused visual representations (juxtaposed principle diagrams and component mechanism diagrams) to discuss some of those shared features in more detail, such as cell-substrate and cell-cell interactions, generation of gradients of signaling molecules, and interactions between leader and follower cells. In these visualizations, the same feature of mechanisms is presented repeatedly, in isolation in one figure, while together with other features in another. The reader can connect and relate these visualizations, and sometimes move back and forth among them, to acquire understanding of how individual mechanisms are structured, what features they share, and in what interesting ways they differ from each other. Combining the different types of visualizations works effectively to promote understanding of, and reasoning about, generality, specificity, and diversity of mechanisms of collective cell migration.

3 Generalizations Facilitate Cross-Fertilization

I have shown that generalizations are expressed through different types of visualizations, which work in a complementary way to promote understanding of, and reasoning about, generality,

specificity, and diversity of biological mechanisms. Identifying patterns in the world and thereby promoting scientific understanding and reasoning is an important role of generalizations. But we can still ask what roles generalizations play in further research. Philosophers of science have been particularly interested in roles of generalizations in scientific explanations. Two influential accounts—deductive-nomological account and unificationist account—conceptualize explaining as subsuming phenomena under a general pattern or regularity (Hempel, 1965; Friedman, 1974; Kitcher, 1989). And the development of causal and mechanistic accounts has led to an active debate on the status of generalizations in causal-mechanistic explanations (e.g., Woodward, 2001; Hitchcock & Woodward, 2003; Craver & Kaiser, 2010; Leuridan, 2010; Andersen, 2011). Philosophical discussions about generalizations have been dominated by the strong interest in scientific explanation. But generalizations play various roles in scientific research beyond explanations. Bogen (2005) points out a number of roles in mechanistic research, such as to "describe facts to be explained, suggest and sharpen questions about causal mechanisms, suggest constraints on acceptable explanations, measure or calculate crucial quantities, and support inductive inferences without which mechanisms could not be successfully studied, and the results of their study could not be applied to new instances of causal productivity" (p. 401). Waters (1998) also discusses several non-explanatory roles of generalizations, such as providing insights into structure, mechanism, or ecological relations of interest, as well as serving as tools for various kinds of investigations.

Although I do not deny that generalizations play the explanatory and non-explanatory roles mentioned above, I argue that they play another important role that has been neglected in previous discussions: generalizations mediate and facilitate cross-fertilization among studies of

different target systems. By cross-fertilization, I mean mutual contributions of insights that promote better characterizations of, and further inquiries into, different target systems. Generalizations play this role in a number of ways. I discuss the following, partially overlapping functions, by examining research on collective cell migration again. First, each generalization provides a specific perspective from which scientists can characterize and compare different target systems. Individual target systems are characterized and understood more precisely by comparing or contrasting them with other systems from such a perspective. Second, generalizations established through studying certain systems guide inquiries into new or less-understood target systems. Here, generalizations provide default assumptions about how the phenomenon of interest is produced, which serve as heuristic hypotheses that guide new investigations. Finally, generalizations sometimes promote large-scale comparisons between different classes of target systems or processes, such as developing tissues and invasive cancer. In such a case, a higher-order generalization concerning similar patterns of regularity and variability provides a basis of comparisons and "mutual informing" across fields. These functions are not limited to generalizations expressed in a specific representational format. However, in research on collective cell migration, visual representations (and in particular, configurations of multiple representations) often contribute to generalizations playing these functions (as shown below).

3.1 Promoting Better Characterizations of Individual Target Systems

Generalizations help scientists characterize individual target systems more precisely. For instance, the generalization about the leader-follower distinction, which is actively discussed in

review articles, invites researchers to see mechanisms of collective cell migration in a specific way. Juxtaposed mechanism diagrams, such as Fig. 3, are illustrative, where each mechanism is depicted in a way that highlights this feature. The generalization about the leader-follower distinction makes researchers pay close attention to the division of labor in a migrating cell cohort. By doing so, it leads to a new research question and points to an object that requires further inquiry: "[d]espite [the leader cells'] crucial role in controlling collective migration, and therefore their involvement in tumour spreading, the mechanisms leading to the emergence of leader cells and the molecular specificities of these cells remain unclear" (Mayor & Etienne-Manneville, 2016, p. 106). A generalization also guides scientists to examine why it has the distribution that it has. For example, vertebrate blood vessel sprouting and fruit fly tracheal development are both examples of collective cell migration with the leader-follower distinction, and they are known to be particularly similar; they share a specific type of molecular interaction between leader and follower cells. The recognition of this resemblance has led some researchers to an evolutionary hypothesis that the two mechanisms have evolved by adopting the same, conserved component mechanism for sensing and responding to hypoxia (Muñoz-Chápuli, 2011). In such a way, a generalization sometimes points to a shared feature that requires an explanation, which becomes a target of new inquiries.

3.2 Guiding Investigations into Less-Understood Systems

Generalizations also guide investigations into less-understood biological systems. Once a generalization is established (that is, once it is confirmed that a feature is shared across a certain range of target systems), it starts providing a default assumption about how mechanisms of

collective cell migration operate. For example, the leader-follower distinction has been observed and studied in many model systems and highlighted as one of the paradigmatic features of collective cell migration since the 2000s (Friedl, 2004). Because of this recognition, when researchers study a new or less-explored example of collective cell migration, it is natural to expect that the system also exhibits the leader-follower distinction. This can lead to confirming the hypothesis and expanding the scope of the generalization. Or it can lead to a discovery of an exception to the generalization.[10]

For example, Ewald et al. (2008) examined three-dimensional culture of mouse mammary gland and reported that collective cell migration in this system does not exhibit the active extension of protrusions, which is characteristic of leader cells in many other systems. The leader-follower distinction provided a typical image of collective cell migration against which the authors investigated and characterized the mechanism operating in mouse mammary gland.

> Recent time-lapse imaging studies have established models for the collective movement of groups of cells, including neuronal precursors in the zebrafish lateral line, epithelial cells during *Drosophila* dorsal closure, and border cell migration in *Drosophila*. In each of these examples, cells at the front of the migrating group extended cellular extensions

[10] My argument here is similar to Bechtel's (2009). He argues that biologists' assumptions about shared or similar mechanisms serve as a heuristic for new discoveries. However, although Bechtel focuses on evolutionary conservation as the basis of such assumptions, I emphasize that biologists' assumptions about shared or similar mechanisms do not have to be based on the idea of evolutionary conservation.

Link to the image: https://pubmed.ncbi.nlm.nih.gov/24747369/#&gid=article-figures&pid=fig-3-uid-2

Fig. 6 A figure illustrating that collective cell migration in mouse mammary gland does not involve the leader-follower distinction (Huebner & Ewald, 2014, Fig. 3). It contrasts photomicrographs of mouse mammary gland (C, C', D, D') with a diagram representing a common image of the leader-follower distinction (B)

> or protrusions in the direction of movement. By contrast, cells at the front of elongating mammary ducts did not have leading cellular extensions or actin-rich protrusions. As protrusive activity can function to guide cells, how elongating mammary ducts move directionally remains an open question. (Ewald et al., 2008, p. 577)

In review articles, this exceptional feature of mouse mammary gland is sometimes highlighted by contrasting an image of collective cell migration in this system with an abstract diagram that depicts the leader-follower distinction (Huebner & Ewald, 2014; Uechi & Kuranaga, 2017) (Fig. 6). The discovery of the lack of the leader-follower distinction opened up a new research question of how a group of cells lacking the leader-follower distinction moves directionally. In this example, the generalization about the leader-follower distinction, which was established through studies of other model systems, provided an image of what a mechanism of collective cell migration typically looks like. This image has guided the investigation into, and characterization of, collective cell migration in mouse mammary gland by providing a heuristic hypothesis and promoting the comparison between the mechanism operating in this system and those in other model systems.

Left panel is not available online

Link to the right panel: https://www.nature.com/articles/ncb2548/figures/2 (panel a)

Fig. 7 Spectrum presentations of developmental and cancer systems. Left: A spectrum presentation that orders different cellular behaviors according to molecular features associated with different degrees of collectiveness (Friedl, 2004, Fig. 1). Right: A spectrum presentation that orders invasive behaviors of cancer cells according to some characteristics associated with degrees of collectiveness (Friedl et al., 2012, Fig. 2a)

3.3 Promoting Comparisons between Different Classes of Systems

Generalizations also have promoted comparisons between two classes of biological systems that undergo collective cell migration: developmental and pathological systems. Researchers of collective cell migration have been interested in the similarity between collective cell migration in development and cancer invasion (e.g., Friedl, 2004). This interest originated in part from the observation that these two classes of systems exhibit similar morphological variations. Fig. 7 shows two spectrum presentations from two review articles. One orders different forms of (primarily developmental, but also pathological) cell migration according to different degrees of collectivity (Fig. 7, left; Friedl, 2004). The other adopts a very similar format to order, specifically, different forms of cancer cell invasion (Fig. 7, right; Friedl et al, 2012). Characteristic forms of cell behaviors are observed in both development and cancer invasion, such as chain migration, detached clusters, sheets or strands, and hollow tubes. This morphological similarity is often explicitly discussed:

> *Similar to morphogenesis*, the phenotypic and junctional organization of moving cancer cell groups varies greatly ("collective plasticity"). *In experimental live-cell models, all types of collective movements can be adopted by tumor cells* including (1) cohesive

> sheets or strands, typically detected in epithelial cancers; (2) isolated clusters detached from the primary/metastatic lesion such as epithelial tumors and melanoma; (3) neuronal-like networks of connected cells, detected in neuroectodermal tumors, such as glioblastoma; or (4) as "jammed" collective cohorts induced by spatially narrow tissue boundaries (confinement) of otherwise transiently/loosely connected (single) cells in experimental melanoma and sarcoma models. (Friedl & Mayor, 2017, p. 11; emphasis added)

A higher-order generalization is going on here. Each of the two spectrum presentations generalizes about collectivity across different cellular behaviors of a class of biological systems (primarily developing tissues and invasive cancers, respectively). Then, researchers generalize across the two spectra, identifying the similarity in the patterns of variability of collective cellular behaviors across developing tissues and invasive cancers. (For instance, both developing tissues and invasive cancers exhibit a range of collective behaviors, such as chain migration, cluster migration, multicellular sheets, branching of a tube, etc.) This higher-order generalization draws researchers' attention to overall similarities and differences between development and cancer invasion. It thereby promotes further comparisons and exchanges of insights between developmental biology and cancer biology.

These examples illustrate how generalizations mediate and facilitate cross-fertilization between studies of different biological systems in a number of ways. Each mechanism of collective cell migration is efficiently investigated, and better characterized, by comparing and contrasting it with other mechanisms operating in different biological systems. By "different

biological systems," I do not just mean different species. It also refers to different organs (or component parts of an organism) and different conditions of those systems (i.e., developmental, pathological, and regenerative). Studies of apparently distantly related biological processes (for example, fruit fly ovary development, sprouting of zebrafish blood vessels, streaming migration of the slime mold *Dictyostelium*, and human breast cancer invasion) inform each other when they are compared from specific perspectives. Indeed, an important rationale for having the category of collective cell migration is that it promotes researchers to compare different biological systems, which they would otherwise not compare, in a productive manner. This cross-fertilization is mediated and facilitated by generalizations.

3.4 Multiplicity of Generalizations as a Resource

Multiple generalizations have been formulated about mechanisms of collective cell migration. This is different from my earlier claim that research on collective cell migration employs multiple different types of visualizations to express generalizations. Here, I am talking about the fact that there are *multiple features* that are shared across different examples of collective cell migration, about which researchers generalize. For example, Schumacher (2019) discusses eight important generalizations concerning collective cell migration that have been formulated. (Schumacher calls them "principles" in the article.)

- Heterogeneity of cell states (equal to what I have called the leader-follower distinction)
- Substrate-free migration
- Contact-inhibition of locomotion
- Confinement and repulsive cues

- Self-generated gradients
- Stochastic group decisions
- Cell migration and substrate mechanics
- Reprogramming

Most of these generalizations are not universally applicable even to known examples of collective cell migration; they have limited distributions. And their distributions only partially overlap. In other words, although a single example of collective cell migration can and often does exemplify multiple "principles" listed above, it is not the case that two principles always coincide. Although Schumacher's is not the only possible list of generalizations in research on collective cell migration, it provides a useful insight: there are multiple generalizations about mechanisms of collective cell migration, whose distributions only partially overlap. And different model systems serve as useful sources of information about different features of mechanisms of collective cell migration.

The multiplicity of generalizations has an important implication. That different generalizations have different distributions means that one model system can contribute to articulating different subsets of examples of collective cell migration, depending on which feature of the mechanisms one focuses on (Yoshida, 2023). Furthermore, contributions are often mutual. Studies of one model system can both inform and be informed by studies of other model systems. Multiple generalizations together provide a platform on which studies of different biological systems mutually inform.

Whereas the discussion of this section has focused on how generalizations mediate and facilitate productive interactions among studies of different biological systems, generalizations

also mediate between experimental studies of living model systems and theoretical studies of mathematical models. Mathematical modeling of collective cell migration has recently become an active area of research (e.g., Méhes & Vicsek, 2014; Schumacher et al., 2016; Alert & Trepat, 2020). Sometimes, generalizations are proposed on the basis of experimental observations and then mathematical models are employed to formulate and analyze them. Other times, novel hypotheses are proposed on the basis of theories of general physical phenomena and then tested in experimental studies that employ specific model systems.

These considerations suggest how generalizations facilitate cross-fertilization among different approaches. Collective cell migration is studied by researchers with different interests: developmental biologists who are interested in explaining development of various tissues and organs; cancer biologists who are trying to elucidate mechanisms of cancer invasion and metastasis for inventing better treatments; regeneration biologists who are hoping to better understand regeneration processes; and physicists who aim at generating new physical theories by studying physical properties of biological systems. None of these interests can be regarded as *the* goal of this area. A better characterization is that research on collective cell migration involves multiple aims and interests. These different aims and interests contribute to each other, and such mutual contributions are (at least in part) mediated by generalizations. Developmental biology, cancer biology, and regeneration biology contribute to each other by exchanging insights into general principles and conserved component mechanisms; experimental research contributes to theoretical research by providing informal generalizations to be formalized as well as specific model systems for testing general theoretical ideas, while theoretical research contributes to experimental research by offering formalized general models that can be used in

hypothesis generation and confirmation in experimentation. Generalizations mediate productive interactions between studies motivated by different interests.

4 Implications

My account regards configurations of multiple representations as a form of generalization. A skeptical reader might think that this is too much of an expansion of the notion of generalization. Whether this conceptual move is appropriate or not depends on what kinds of questions we want to answer by studying generalizations. For example, much of the philosophical debate on laws of nature has aimed at understanding the nature of universal generalizations that distinguishes them from merely accidental generalizations (Carroll, 2016). For this purpose, it seems appropriate to characterize generalizations as universally quantified propositions since this formulation captures the idea of an exceptionless regularity. My goal is different. I am interested in elucidating how scientists pursue generalizations in heterogeneous biological systems by employing various investigative and representational resources. The focus on configurations of multiple representations contributes to this project because it helps us explain how scientists explore, reason about, and communicate regularities without ignoring specificity and diversity of their target systems. Adopting such a picture will enable us to analyze new aspects of scientific generalizations and conduct more inquiries into generalization practices. This will supplement the existing philosophical literature.

The emphasis on configurations also provides the philosophy of modeling with new insights. In previous discussions about trade-offs among modeling desiderata, each desideratum has typically been attributed to individual models or a set of models. This is understandable,

given a primary focus of the discussion has been on mathematical modeling. A classic, influential paper on trade-offs among modeling desiderata was written by the ecologist Richard Levins (1966). This paper addressed the problem of trade-off in mathematical modeling of ecological processes. Since then, the trade-off literature has debated the nature of mathematical representation—more specifically, how different qualities, such as generality, precision, and realism, are related with each other in mathematical models (Levins, 1993; Orzack & Sober, 1993; Odenbaugh, 2003, 2006; Orzack 2005; Matthewson & Weisberg, 2009; Evans et al., 2013; Gelfert, 2013).[11] However, when we analyze diagrams and tables as visual representations, we should consider not only how representations are constituted (e.g., what abstractions and idealizations are involved), but also how those representations are configured in a physical, two-dimensional space in journal articles, textbooks, conference slides, etc. This is because visual representation consists in presenting information two-dimensionally. This consideration opens up new philosophical questions. For example, in the context of visual representation, do we have to consider any modeling desiderata in addition to the standard set of desiderata that have been discussed in the literature (such as generality, precision, and realism)? Do we need a new conceptual framework for analyzing the nature of, and relations between, modeling desiderata in visual representations? We may ask similar questions about other forms of representations, such as three-dimensional physical models.

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[11] There are exceptions, such as Matthewson (2020) and Yoshida (2021), who discuss configurations of mechanistic models, and Inkpen (2016), who discusses trade-offs in experimental design.

Another related implication concerns how we study scientific diagrams. My account accords with an integrated approach to diagrammatic representations defended by Ambrosio (2020). Ambrosio observes that there has been a divide in studies of diagrams. Whereas most of philosophical discussion about diagrams concentrates on analyzing their representational nature, historians and scholars of visual culture have criticized such a representation-centered view. They have argued that diagrams must be understood not as representations of something else, but as objects that exist in the world and are a target of inquiry in their own right. Ambrosio calls this the "object-based view" of diagrams, which is contrasted with the "representational view" common in philosophy. But as Ambrosio rightly points out, studying diagrams as representations and treating them as objects of inquiry in their own right are not incompatible. The present paper provides an example that supports this idea. Although my analysis was based mainly on the representational view, it focused on diagrams and tables that exist in a specific context (review articles) and examined what influences they exert on interactions in the research community (cross-fertilization). Furthermore, my discussion of how scientists generalize was dependent crucially on an analysis of not only how individual diagrams represent target systems, but also how they are configured in a physical space.

Finally, how and to what extent is my account generalizable to other cases in science? This paper is based on a single, very specific example, and so certain aspects of my account might be peculiar to research on collective cell migration. Nevertheless, I believe that attention to configurations of multiple representations will provide useful insights for analyzing generalization practices in other fields of science. It seems likely that displaying multiple representations in certain configurations is a generic strategy to highlight features shared across

the systems being represented, and hence employed in many different fields of science. Although I discussed only four variations of this strategy (juxtaposed mechanism diagrams, juxtaposed principle diagrams, spectrum presentation, and tables), there will be more ways to configure multiple representations. I also expect that in many other areas of research, generalizations mediate and facilitate cross-fertilization among studies of different target systems. This perspective might be particularly useful for studying a field whose subcommunities specialize in specific systems or objects of research. (Developmental biology is an example, where each researcher or laboratory often specializes in one or a few model organisms.) Like the case of collective cell migration, generalizations might be promoting cross-system comparisons in such fields.

5 Conclusion

This paper addressed the question of how biologists pursue generalizations despite the heterogeneity of biological systems by focusing on the epistemic importance of configurations of multiple representations. My analysis of review articles about collective cell migration showed that researchers in this area often generalize by employing different types of visualizations, many of which juxtapose or order representations of different mechanisms. This example illustrates that formulating a representation referring to a widely shared feature is not the only way to generalize; scientists sometimes generalize by configuring multiple representations. This is a strategy to highlight shared features without eliminating differences between systems. The different types of visualizations are used in a complementary way to promote understanding of, and reasoning about, generality, specificity, and diversity of mechanisms in an integrated manner.

I also argued that generalizations mediate and facilitate cross-fertilization among studies of different target systems by providing perspectives from which different systems are characterized and compared; providing heuristic hypotheses for inquiries into new or less-explored systems; and promoting comparisons between the regularity and variability of different classes of target systems. Multiple generalizations together provide a platform where studies of different biological systems can inform and contribute to each other. Through this analysis, this study provides new conceptual resources for philosophical discussions about scientific generalization, modeling, and diagrammatic practices.

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