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Exploring the Modalities of Combining Biological Models

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Abstract

This article examines how biological models are combined in biomedical research. It analyzes the notion of epistemological space, understood not as an abstract space of epistemic possibilities but as a framework for coordinating heterogeneous models through zones of partial compatibility structured by shared features, biological constraints, and research objectives. It also questions the ways in which models are combined, highlighting the methodological choices and epistemic commitments that guide pluralistic modeling practices. Finally, it proposes a representation of these modalities as a heuristic tool for comparing and reflecting on strategies of model combination.

1. Introduction

Models are essential tools for investigating physiological processes, elucidating underlying mechanisms, screening and selecting compounds based on their potential efficacy, and developing therapeutic strategies for conditions as diverse as cancer and depression. Models serve as mediators between the empirical and the theoretical: They are both representative *of* specific biological phenomena (the target systems under investigation) and representative *for* theoretical frameworks applied to these phenomena (Morgan 2003). This dual representational role allows models to function as epistemic bridges: They render certain aspects of biological systems observable, manipulable, or measurable within a controlled research setting while also serving as test beds for abstract hypotheses and conceptual assumptions. For example, neuronal cell cultures can be used to investigate synaptic dysfunctions in neurodegenerative diseases, and inbred mice may be employed to test predictions derived from the theory of excitotoxicity in Huntington's disease.

Among the wide variety of available models (mathematical, computational, biological, epidemiological, analogical, etc.), in vitro and in vivo models are distinctive in that they involve living matter. In vitro models typically include cell cultures or tissue samples, whereas in vivo models involve organisms chosen for their functional analogy to the biological phenomena in question and their suitability for experimental manipulation (e.g., short life cycles, genetic tractability, or widespread

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use in the scientific community). These models are biological entities that share the same ontological nature as the phenomena they aim to represent. Because of this shared biological nature, in vitro and in vivo models are privileged tools in biomedical research, and specialized animal models are frequently developed for specific human diseases.

These models are often selected or engineered to embody particular biological characteristics, which may be experimentally induced but only partially inferred. As such, they require careful specification of their representational scope (what physiological mechanisms they stand for) and their representational targets (the phenomena under investigation) (Ankeny and Leonelli 2020). These two dimensions of representation are distinct but closely interrelated: A model organism such as the fruit fly may be chosen to stand for a broader category of organisms (e.g., metazoans or mammals in certain genetic studies) while also being used to explore specific target phenomena, such as neurodegeneration or developmental patterning. Then, because the mere fact of sharing a biological nature does not justify why a fruit fly or a mouse can stand in for a human being, clarifying both the scope and the target of a model is essential to establish the relevance and reliability of any extrapolations or translations to other contexts (e.g., Giere 2006; Belzung and Lemoine 2011; Matthewson and Weisberg 2009; Schaffner 1993).

The choice and use of a particular model depend on a variety of factors, including the theoretical context of the research, the accessibility of the model, existing knowledge about its properties, its adaptability to laboratory conditions, cost, and translational potential (Dietrich et al. 2020). The relevance of any single model is negotiated through empirical, methodological, and theoretical considerations, and it can carry different epistemic meanings depending on its use context (Knuuttila 2005). Although the use of a single model needs to be justified, in practice, the complexity of biological phenomena often exceeds the scope of individual models, making it necessary to combine multiple models of different kinds.

The question of model combination arises within a broadly pluralistic approach to scientific inquiry. The use, justification, and outcomes of epistemic pluralism have been extensively discussed in the philosophical literature (Ruphy 2016; Mitchell 2002). Once the epistemic value of pluralism is acknowledged, this raises the question of how to account for the possible convergences and divergences between epistemic strategies, as well as how these strategies may be effectively combined. In this respect, the epistemological implications of model combination remain quite underexplored (Huneman 2018a; Green 2015; Baetu 2014; Leonelli 2007). If model selection is context sensitive, the possibilities for model combination are even more difficult to delimit and formalize. Thus, this article seeks to explore how we might interrogate the modalities of model combination in biomedical research. The aim of this article is to promote an explicit articulation of how model combinations are constructed and justified, thereby shedding light on the argumentative strategies they support.

The focus will be specifically on organic models—that is, models that involve living matter, considering the following:

- The use of biological material in these models implies an ontological continuity to the phenomena under investigation. But this proximity is problematic: A cell line is not a mouse, and a mouse is not a human.

- Even though agencies have tended to encourage alternatives (e.g., in 2023, the US Food and Drug Administration [FDA] canceled the mandatory use of animals in preclinical studies), organic models remain crucial in biomedical research (the European Medicines Agency [EMA] continues to require toxicological and pharmaceutical data from at least two different animal species in preclinical studies).

2. Why epistemic pluralism matters for model combination

The use of a given model only makes sense within the broader context of a research process, shaped by theoretical assumptions, ways of describing phenomena, and specific research goals. Because any scientific inquiry offers a particular perspective on the phenomenon under investigation, the coexistence of multiple and sometimes heterogeneous approaches enables the development of complementary insights into a single phenomenon by capturing the diversity of processes that realize it. Huneman (2018b) illustrates this with the example of a mousetrap: A trap can fulfill its function through poisoning, crushing, or electrocution—each relying on distinct physical principles. The functional identity remains the same, but the underlying mechanisms differ. Analogously, biological phenomena can be realized through materially distinct pathways, and thus they cannot be fully captured by a single explanatory lens. Understanding them often requires a plurality of models, each grounded in different explanatory frameworks and highlighting different realizations of the same phenomenon.

This plurality constitutes a structural condition for model combination: It is precisely because no single model can account for all aspects of a complex phenomenon that multiple models must be articulated together. Pluralism is a necessary condition for constructing robust knowledge through model integration. As Levins (1966) argued, model construction involves trade-offs between three key epistemic values: generality, precision, and realism. Maximizing all three at once is impossible; researchers must choose which to prioritize based on the objectives of the inquiry. As a result, individual models are necessarily partial and idealized. But rather than being a limitation, this partiality opens the possibility for a stronger epistemic strategy: If several models, each shaped by different value trade-offs, lead to the same conclusion (whether a proposition or a prediction), this conclusion is more likely to be true. Epistemic robustness lies in the convergence of distinct partial modeling perspectives.

If a research setup functions as a coherent unit that provides access to a particular perspective on a phenomenon, the plurality of research approaches becomes necessary to overcome the inherent limitations of any single model. It enables a more precise understanding of biological complexity. Model combination in the biomedical sciences should therefore not be understood as a mere accumulation but rather as an articulation of different approaches. This dynamic of complementarity and compromise makes it essential to analyze the epistemological modalities of model combination in order to understand how distinct research perspectives are integrated and how scientific knowledge of a given phenomenon is built.

3. Epistemological spaces for model combination

Understanding how models contribute to the construction of robust scientific knowledge requires examining the conditions under which they interact and complement each other. Sustaining knowledge claims across varying evidential and methodological contexts implies exploring the nature of the epistemological spaces in which such interactions take place.

At first glance, an epistemological space refers to a conceptual environment within which different models can align and contribute to a shared understanding of a phenomenon. As such, an epistemological space is a zone of articulation, where different forms of evidence or modeling strategies can converge without requiring full unification. It involves making explicit the methodological, conceptual, empirical, and ontological conditions that enable model combination. The construction of such spaces involves managing epistemic risk (Hempel 1965; Douglas 2000; Baetu 2014) between two pitfalls: If the space is too broad, it may encompass incoherent data or perspectives; if too narrow, it may exclude compatible data or perspectives, limiting the articulation of other heterogeneous approaches. The spaces for model combination are constrained by partial regularities identified across different biological configurations.

Yoshida (2023) develops the concept of "local generalization" to account for how multiple biological systems can model the same phenomenon despite differences in underlying mechanisms. By "local generalization," Yoshida refers to a generalization that targets a specific feature of a mechanism—one that does not apply universally or even quasi-universally but only across a limited range of biological systems that exhibit the target phenomenon. A local generalization concerns only one aspect of the target phenomenon that is found in various biological systems (whether cellular or organic). He further specifies that a local generalization is "local" in two senses: (1) It holds only across a limited range of biological systems, and (2) what is generalized is not the entire mechanism but a specific characteristic or aspect of it. Among patients with Huntington's disease, the reduced ability to recognize emotion, particularly anger, can be considered a local generalization because it concerns a particular, nonuniversal feature of cognitive symptoms, and it does not apply to the vast majority of patients. Consequently, if one study investigates the recognition of emotional body language through patient surveys (de Gelder et al. 2008), another examines the relationship between anger recognition and striatal lesions using functional imaging (Calder et al. 2004), and yet another explores how brain lesions in monkeys affect aggressive behaviors, their combination can account for several partial aspects of a single phenomenon.

Although local generalization delineates an epistemic space by identifying shared features across studies, such spaces can also be shaped "from the outside," based on constraints shared across the biological systems under investigation. Green (2015) captures this idea with the notion of "constraint-based generality." Unlike generalizations derived from observed regularities across systems, *constraint-based generality* refers to generalization grounded in structural, functional, or evolutionary constraints that limit the range of biologically possible variations. These constraints act as structuring principles: Rather than being inferred from multiple systems, they delimit what can or cannot occur across systems, thereby enabling certain forms of

generalization. For example, gravity and bone structure impose a structural constraint on the ratio between size and shape in organisms. Similarly, genetic regulation mechanisms often require the stabilization of specific gene-expression patterns (as in the case of segment development in *Drosophila*), representing both functional and evolutionary constraints that restrict the range of possible variations in genetic mechanisms. Biological configurations entail constraints that are shared by multiple organisms or biological systems, thereby creating a space of possible generalization. Shared constraints inherent to certain biological features set boundaries on the range of possible variation within a given biological domain; these boundaries delineate generalizable spaces shaped by external necessity.

Although they are shaped by constraint principles, these spaces are not isolated from one another. Instead, they constitute the fabric of current scientific knowledge and its prospective directions. To put it differently, the necessity of establishing favorable conditions for model combination does not produce isolated local spaces but rather "hubs" within potential networks. This echoes the metaphor developed by Baetu (2014), who proposes viewing the structure of scientific knowledge not as a homogeneous and unified representation but as a mosaic. According to this metaphor, scientific models resemble mosaic tiles—each distinct, yet capable of forming a larger (yet still fragmented) picture when assembled. Because of the specific configuration of each tile (that is, the methodological and epistemic constraints of each model), articulating them requires attention to the configurations of adjacent tiles—thus identifying zones of coherence, compatibility, or tension between models. Extending this metaphor, each tile is heterogeneous and has its own shape, which gives it a certain autonomy but also makes it impossible to place it just anywhere in the overall mosaic. Furthermore, a tile only acquires its full meaning within the broader mosaic context. Yet its configuration may allow it to serve multiple functional roles depending on how it is assembled. While a close-up view may focus on the internal coherence of each tile, only their interrelations allow us to assess their placement, function, and limits. In short, although the mosaic may first appear as a set of isolated pieces, its significance lies in the networked interplay among its parts.

Baetu's mosaic metaphor emphasizes the rejection of a unified conception of scientific knowledge. Like the notion of epistemological space, it underscores the heterogeneous and fragmentary nature of science. However, whereas Baetu's account highlights the structure of the assemblage and the epistemic origin of its components, it does not elaborate on the dynamic processes involved in model combination—processes brought to the fore by the notion of epistemological space because it functions as a conceptual tool for organizing model interactions. In this sense, epistemological spaces are not merely the outcome of past modeling practices but actively shaped zones of compatibility that respond to evolving research questions and constraints.

In sum, epistemological spaces are local and situated. They are structured as sites for coordinating inquiry into a phenomenon, a class of biological systems, or a specific scientific objective. These epistemological spaces are zones of partial compatibility between models, within which heterogeneity is managed but not erased. Within such a space, models are brought into relation without being merged, despite differences in their ontological commitments and methodological approaches. Epistemological spaces act as structuring frameworks that make robust knowledge possible. By intersecting partial yet convergent models within a shared epistemological space, the

robustness of conclusions is strengthened despite the absence of direct evidence or a fully specified mechanism. The locality of these spaces may be defined either by shared and limited features (see Yoshida 2023) or by constraints common to particular biological systems (see Green 2015). Their boundaries can be reconfigured depending on the models involved, the evolving state of knowledge about the target phenomenon, or the redefinition of the scientific goal. In this way, epistemological spaces respond to contingent research contexts and foreground the explicit formulation of the conditions under which models can be (at least partially) aligned.

Although the notion of epistemological space is rooted in the coordination of heterogeneous models, it bears a conceptual affinity with Chalmers's notion of epistemic space (Chalmers 2011). Both function as frameworks for organizing possibilities—whether concerning belief and knowledge or model interaction and alignment. Yet they differ in focus, structure, and temporality: Epistemic space primarily operates at a formal level, concerned with the logical structure of belief and the delineation of epistemically possible scenarios. Epistemological space, by contrast, is oriented toward organizing model combinations in the pursuit of robust scientific understanding. Whereas epistemic space comprises maximally specific ways things might be, epistemological space is delineated by feature conditions and empirical, methodological, or ontological constraints. Moreover, epistemic space is often treated as a static snapshot of what is knowable at a given time, whereas epistemological spaces are dynamically restructured in response to contextual needs. Nevertheless, the two notions remain complementary: Epistemological spaces can be viewed as situated, practice-driven zones within the broader landscape of epistemic space.

Developing the notion of an epistemological space enables the articulation of diverse models without reducing them to a single explanatory framework. The epistemological space becomes a conceptual tool for understanding robustness as a collective outcome rather than a property of any single model. It also makes visible the points of interaction between different research approaches by making explicit the modalities of their articulation (see the following section), thus, by contrast, highlighting what is excluded—encouraging reflection on the potential biases introduced by the chosen framework.

4. Making the modalities of combination explicit

If epistemological spaces define the conceptual environment in which models can be brought together, what remains to be examined are the modalities through which such combinations occur. The history of philosophy offers a rich tradition of thinking about the ways in which properties can be ascribed to an object. Aristotle's *Categories*, for instance, explore the various modes by which something can be affirmed of a substance. Although the list of categories differs between the *Categories* and the *Metaphysics*, the overarching aim remains consistent: To identify the types of attributes that can be predicated of being, along with their logical and ontological implications. My intention is not to engage with the general structures of thought. Rather, drawing inspiration from this Aristotelian tradition, my aim is to encourage a more explicit analysis of how models are combined in scientific practice. To open up a line of inquiry into this issue, I propose to distinguish several (nonexclusive) modalities of combination.

4.1. Differences in model natures

One can first observe the difference in nature between the models being used. Diverse model types are frequently brought together to address different aspects of a research question, precisely because of their divergent representational scopes and experimental possibilities. Mégret et al. (2021), for example, combine multiple in vivo mouse models, cell-type-specific transcriptomic data, and computational shape deformation analysis to map molecular responses to mutant huntingtin in Huntington's disease. Using different kinds of models is not a matter of redundancy (reproducing the same result across multiple systems to increase confidence in a finding) or of triangulation (multiple models are expected to converge on a single representation of a phenomenon). Rather, it reflects a division of epistemic labor, where each model, by virtue of its nature, offers access to different dimensions or aspects of the target phenomenon.

4.2. Complementary quality of models

Differences in model natures can lead to a mutual enrichment of partial insights if the qualitative question of how models complement each other is explicitly raised. Complementary robustness (Wimsatt 1981) involves assessing the extent to which different models (whether of the same or different natures) allow for a unified understanding of various aspects of a shared problem. This qualitative perspective helps clarify the shared objectives, the complementary perspectives, and the ways in which results can be integrated. In Mégret et al. (2021), the mouse models provide physiological substrates for disease progression, the cell-type-specific RNA sequencing elucidates molecular specificities, and the computational framework enables pattern extraction across high-dimensional datasets. The complementary quality of these models lies in how they distribute epistemic tasks across levels of analysis and experimental conditions. This combination clarifies the shared research objectives, highlights synergies between experimental strategies, and enables a richer understanding of results.

A special case of this complementarity arises when different models share the same phenomenal extension (i.e., they target the same phenomenon), yet they approach it from different perspectives in order to enhance epistemic robustness. Marshall et al. (2002), for instance, investigated contrasting behavioral responses to alcohol withdrawal in two strains of mice, and they used public genomic databases to conduct in silico analyses. These analyses sought correlations between behavioral responses and genetic variations in chromosomal regions known to influence withdrawal symptoms. In other words, the study mobilized two types of models (behavioral and genetic) that targeted the same set of phenomena but from distinct standpoints.

4.3. Spatial level and temporal stage of combination

Drawing from Aristotle's category of place, another key consideration is the biological level at which models are situated and combined: genomic, proteomic, cellular, organ level, and so on. Similarly, inspired by the category of time, is the stage at which models are brought together—whether at the outset of inquiry (as a way to define the problem), during intermediate experimental phases (as cross-validation or constraint

sources), or toward the end (as an integrative synthesis of earlier findings). Mégret et al. (2021) exemplify this by combining whole-striatum and cell-type-specific transcriptomic data across multiple time points in Huntington's disease model mice. The alignment across spatial (cell type vs. whole tissue) and temporal (early vs. late disease stage) axes is key to interpreting the dynamic nature of compensatory and pathogenic responses. This approach underscores the significance of synchronic and diachronic alignment when interpreting how multiple models map a dynamic biological system.

4.4. Modalities of inclusion or embedding

When model combination does not take the form of distinct models operating in parallel or juxtaposition but rather of nested architectures, one model is embedded within another. Framed in terms of Aristotle's category of possession (the condition or status in which something is held), a model may serve as a component, substrate, or input layer of another model, without being fully reducible to it. This nesting relation defines an epistemic structure wherein each model retains its own representational constraints while contributing to the function of a larger composite system (Green 2013).

In Mégret et al. (2021), the biological models are not replaced by the computational one; rather, they become epistemic components embedded within a larger model that integrates and interprets their outputs. This embedding enables the emergence of higher-level insights—such as the detection of temporal inversions in gene function—that are not accessible through any one model alone. The way models are embedded within one another helps to understand the epistemic scope and limits of their nesting. This raises questions about coherence, compatibility of formal structures, and the loss or transformation of meaning between levels. As Green (2013) argues, the embedding of one model within another should not be viewed as a hierarchical inclusion but as a mode of epistemic resonance, where the representational constraints of each component model contribute to the intelligibility of the whole. What matters is that one model becomes a structural element of another.

4.5. Relational modality

In addition to experimental integration, models can also be related discursively, through the narrative and argumentative structures of research articles. These structures shape how different models are positioned, compared, or coordinated, even in the absence of material, computational, or direct methodological combination. The relational modality refers to the way models are connected through the rhetorical and conceptual scaffolding of a study, especially in literature reviews or synthetic research. For instance, van Duijn et al. (2007) conducted a review of studies on the psychopathology of Huntington's disease gene carriers. The relational modality thus captures how the conceptual interrelations between models are made visible through the organization of discourse, the framing of research problems, and the interpretive narratives that emerge in the review. The relational modality highlights how field-specific expectations influence the way in which these models are associated in scientific discourse, depending not only on epistemic goals

but also on disciplinary norms of coherence and compatibility. In this sense, the relational modality reflects both the logic of research and the epistemic culture in which it is embedded (Knorr Cetina 1999).

4.6. Positional modality

Closely related to the relational modality, but focused more narrowly on citation practices, the positional modality concerns the status and function of referenced models within scientific texts. In this view, models are tools situated in complex scientific practices, and the way a model is cited (whether in a footnote, as an experimental precedent, as a source of data, or as a theoretical background) reflects its epistemic positioning within a broader network of inquiry. As an example, Lobbé et al. (2021) analyze the citation networks in COVID-19-related scientific publications. By examining how certain models and studies are cited across a vast corpus of articles, they show how citation practices contribute to the construction of epistemic authority and the establishment of dominant narratives within the scientific community. Their work highlights the role of citation dynamics in shaping the perceived relevance and credibility of models. In this sense, the positional modality shapes the epistemic authority granted to certain models, as well as the network of models implicitly brought into dialogue within the text.

4.7. Picturing the modalities of combination

Taken together, these modalities help to make explicit how model combinations operate within a given study. But beyond individual analyses, they also offer a comparative framework to reflect on how different studies combine models. The modalities can be understood as a set of conceptual axes or dimensions, each capturing a distinct way in which models relate to one another—through their natures, functions, spatiotemporal coordination, discursive positioning, and so on.

By considering these modalities jointly, one can begin to sketch a multidimensional epistemological space, where each case of model combination occupies a specific position defined by the characteristics and roles of the models involved.

As such, Figure 1 illustrates how, regarding a given topic (X), three different studies (A, B, and C) mobilize distinct modalities of model combination across six conceptual dimensions. Each study occupies a distinct shape within this space, reflecting a specific configuration of epistemic strategies and relationships between models.

This geometric metaphor does not in itself define the epistemological space in any strict sense: It does not specify the conditions of realization under which such spaces are realized, nor does it account for the external constraints that bound the space from the outside. Rather, it serves to organize its internal dimensions, describing the kinds of epistemic relationships that can exist between models once such a space has been established. This figure functions as a heuristic device for visualizing the reflective process through which we question how pluralism in modeling is implemented, negotiated, and coordinated.

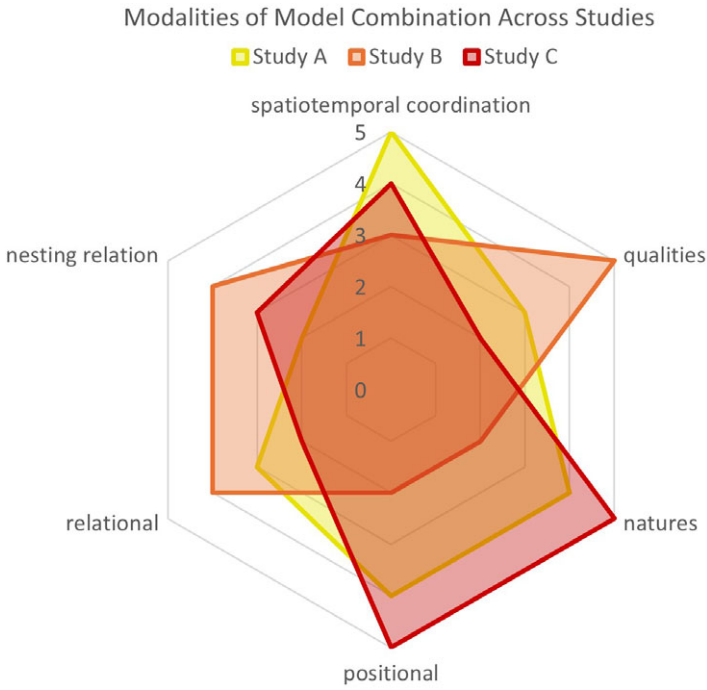


Figure 1. Schematic illustration of the epistemological space across different studies.

5. Conclusion

The pluralism of biomedical sciences provides a powerful means of clarifying the complexity of biological phenomena. Because a single biological phenomenon can be represented in different ways, addressing its complexity often requires the use of complementary models—each shedding light on distinct facets of the same phenomenon. Within such a pluralistic framework, epistemological spaces emerge as the conditions that make it possible to articulate models with one another. These spaces are defined by partial regularities or shared features among the models involved, as well as by external constraints grounded in the biological phenomena under investigation. Within these epistemological spaces, it becomes crucial to make explicit the modalities through which models are combined—questioning their nature, complementarity, position, temporality, degree of nesting, and so forth. Such an examination contributes to a clear identification of the methodological choices, the argumentative strategies employed, and their implications for the kinds of knowledge that are ultimately produced.

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