Models and the mosaic of scientific knowledge. The case of immunology

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ABSTRACT

A survey of models in immunology is conducted and distinct kinds of models are characterized based on whether models are material or conceptual, the distinctiveness of their epistemic purpose, and the criteria for evaluating the goodness of a model relative to its intended purpose. I argue that the diversity of models in interdisciplinary fields such as immunology reflects the fact that information about the phenomena of interest is gathered from different sources using multiple methods of investigation. To each model is attached a description specifying how information about a phenomenon of interest has been acquired, highlighting points of commonality and difference between the methodological and epistemic histories of the information encapsulated in different models. These points of commonality and difference allow investigators to integrate findings from different models into more comprehensive explanatory accounts, as well as to troubleshoot anomalies and faulty accounts by going back to the original building blocks.

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1. Introduction

The term ‘model’ is ubiquitous in contemporary biology. But what exactly is a ‘model’? Scientific models are often assimilated to material or theoretical representations (Giere, 1988, 1999; Hesse, 1963), and to mediators between general knowledge and particular phenomena (Morgan, 2003; Morrison & Morgan, 1999). In some cases, general theories are applied, via a model, to a particular phenomenon in order to represent, explain, predict or intervene on certain aspects of the latter (Giere, 1999; Weber, 2005). Models can also mediate a transfer of knowledge in the opposite direction, from a particular object of study, to a more general class of objects. For example, a model organism is said to be ‘exemplary’ or ‘representative of’ a higher taxon to which it belongs (Ankeny & Leonelli, 2011; Bolker, 2009; Fox Keller, 2000; Weber, 2005). Finally, some models are assimilated to instruments used to intervene on the phenomena and models to which these models are attached (Kohler, 1994; Maugeri & Blasimme, 2011; Morrison & Morgan, 1999), while others are treated as idealized or fictional objects (Frigg, 2010; Toon, 2011).

The present paper is motivated by the realization that there are many different kinds of models in contemporary biology (Green, 2013; Leonelli, 2007), doubled by a desire to understand what this diversity can tell us about the structure of scientific knowledge. In the first half of the paper (Section 2), I begin by conducting a survey of models routinely used in immunology using immunology as a source of examples. 1 The survey shows that there are many distinct understandings of the term ‘model’ in immunology, ranging from...
references to experimental setups to mechanistic explanations and theoretical constructs, where some models are used to study specific phenomena, and others are aimed at a more generally applicable knowledge. The results of the survey are systematized as a taxonomy grouping models into distinct kinds demarcated by their material or conceptual nature, their epistemic purpose, and the criteria for evaluating the goodness of a model relative to its intended epistemic purpose.

The survey also reveals that the use of the term ‘model’ in the biological literature has the general syntactic form ‘k model of p’, where k stands for a kind or type of model (e.g., mouse, cell, kinetic) and p stands for a biological phenomenon (e.g., inheritance, T-cell activation, gene regulation) or a physical system, structure, or interaction (e.g., mechanism, protein, binding). This suggests that models can be understood relationally, as mediators between objects of study, on one side, and a particular kind of insight or approach to the study of these objects, on the other. Based on this suggestion, I argue in the second half of the paper (Section 3) that the astonishing variety of models and kinds of models used by researchers reflects the fact that information about the phenomena of interest is gathered from different sources using multiple methods of investigation. Despite its apparent uniformity, the knowledge synthesized in review articles and textbooks is in fact a mosaic in which findings gathered in a multitude of experimental setups and relying on theoretical assumptions borrowed from multiple fields of investigation are pieced together in order to reveal more comprehensive explanatory accounts. Every bit of information, every ‘pixel’ in the ‘big picture’ has its own methodological and epistemic history. Models tell us what this history is. Models anchor the diverse pieces of the mosaic of knowledge to a description of a phenomenon, on the one side, and to the methods and tools, experimental or theoretical, used to obtain each piece of the mosaic, on the other. By specifying how the various bits of information composing scientific knowledge have been acquired, in which experimental setups they have been obtained and on which theoretical commitments they rely, models highlight points of commonality and difference between the methodological and epistemic histories of each bit of information. Understanding what these points of commonality and difference are is necessary for understanding how information acquired from different sources and methods is compared and ultimately integrated in more comprehensive explanatory accounts, what are the assumptions guiding the integration process and the challenges facing this process, as well as provide the means to evaluate and troubleshoot explanatory accounts.

2. A taxonomy of models in immunology

Two main categories of models can be easily recognized in any field of biological investigation: experimental and conceptual (Leonelli, 2007). The former are physical objects, such as organisms, cells, or in vitro experimental setups in the context of which researchers conduct experimental interventions, usually in order to gain knowledge of the causes and mechanisms underpinning biological phenomena. Conceptual models are a more heterogeneous group encompassing explanations and explanatory hypotheses involving mechanisms (mechanistic models), descriptions of physical structures (structural models), as well as an increasing number of mathematical models of various sorts (kinetic, boolean, biomechanical models).

2.1. Experimental models

2.1.1. Models as suitable experimental setups for studying the phenomena of interest

The philosophical literature on models in biology emphasizes a connection between models and generalizations to a wider array of living organisms (Ankeny & Leonelli, 2011; Steel, 2007; Weber, 2005). It is interesting however to note that researchers talk of ‘models’ even when the potential for generalization is severely restricted, such as in the case of phenomena restricted to one species or even subpopulations within a given species. For example, HIV infection is a phenomenon that occurs naturally only in humans, while resistance to HIV infection is a phenomenon further restricted to certain human subpopulations; nonetheless, uninfected infants born to HIV infected mothers are thought to constitute an ‘experimental model’ for investigating protective immunity to HIV in humans (Rich et al., 2008, p. 576). Even more common are cases when experimental setups are referred to as ‘models’ in the absence of explicitly defined external target systems to which findings are or could be generalized. For instance, an experimental set-up allowing for single-cell identification using monoclonal antibodies recognizing variable regions with the T-Cell Receptor is referred to as being a ‘model system’ for investigating clonal deletion of T-cells responsive to self-antigens (Rich et al., 2008, p. 219).

In these cases, a model refers to an experimental setup well suited for studying a phenomenon. What may justify the term ‘model’ in such situations is the fact that an experimental setup is never just an object, such as an organism, cell or some other physical system, but a labeled object. An experimental setup also includes an operationalized protocol detailing how and from which source the system in question has been obtained, how it has been grown, maintained, and prepared prior to experimentation, and what criteria and experimental controls have been used in order to ensure and demonstrate that the system has been indeed obtained and prepared as described in the protocol (Rheinberger, 1997; Weber, 2005, 2008b). An experimental setup is thus subjected to a process of standardization which ultimately plays a role in ensuring that the setup can be reproduced and identified by different research teams; in turn, findings generated in the context of a standardized experimental setup are more likely to be about ‘the same thing’, and therefore can be directly compared and synthesized into more comprehensive bodies of knowledge (Ankeny, 2001; Bowker & Star, 1999; Clarke & Fujimura, 1992; Müller-Wille, 2007).

Not any experimental setup used to study a phenomenon is indiscriminately said to be an ‘experimental model’ of that phenomenon. As a general rule, the use of the term ‘model’ is used only when the phenomenon of interest can be consistently documented or replicated in the context of an experimental setup that relies on experimental techniques that are known to be reliable. In the above examples, an experimental setup is considered to be a good model for studying a phenomenon because it allows researchers to reproduce the phenomenon of interest with a sufficiently high rate of success (the human model of protective immunity), or to detect and gain experimental control over a particular aspect relevant to the phenomenon of interest (the anti-T-Cell Receptor antibody model of clonal deletion). The fact that the phenomenon can be consistently documented/replicated (reproducibility) increases the likelihood that the experimental setup is circumscribed precisely enough to distinguish correlations related to the phenomenon of interest from the background noise of chance correlations, and that the experimental setup in question contains all or most of the causally relevant factors and components of the mechanisms responsible for the phenomenon (Baetu, 2013). The fact that the techniques associated with the experimental setup (e.g., detection of HIV, induction of blisters, antigen–antibody assays) are known to be reliable makes it possible to distinguish between genuine negative results and experimental errors, as well as to troubleshoot failed and inconclusive experiments (Mayo, 1998; Weber, 2005).

These three methodological virtues—standardization, reproducibility, and reliability—facilitate and guide the discovery process, ultimately translating into pragmatic benefits. The higher cost of...
a methodologically superior experimental model, as compared with less expensive, but methodologically less desirable experimental setups, is likely to be compensated by quicker and more conclusive results; thus, in the long run, the methodologically superior model is also likely to be the most cost-effective alternative.

2.1.2. Surrogate models

Surrogate models are by far the most commonly cited type of experimental models in clinical immunology. A surrogate model can be defined as a more manageable experimental setup for studying a phenomenon, where this experimental setup serves as a substitute for another, experimentally less manageable, but physiologically more relevant target setup. It is hoped that the findings yielded by the investigation of the surrogate model can be safely extrapolated to the target experimental setup despite the differences between the two (Bolker, 2009; LaFollette & Shanks, 1996; Piotrowska, 2012; Steel, 2007).

For example, extensive knowledge about HIV infection and AIDS in humans was generated by studying SIV infection in rhesus macaques and HIV infection in humanized rodents; these same models are also used to test treatments, such as vaccines and retroviral inhibitor drugs. In order to extrapolate findings to the target system, the surrogate model must be validated (Cardiff et al., 2004; Steel, 2007). That is, evidence must be provided that the phenomenon of interest, as documented in the surrogate experimental setup, forms a better exemplary model of the target phenomenon, as it occurs in the target experimental setup (e.g., AIDS in humans). These attributes include descriptive features of the phenomenon (e.g., symptoms of AIDS) and, if known, causally relevant factors, or partially elucidated mechanisms (e.g., immunodeficiency symptoms caused by retroviral infection).

Fundamental research routinely relies on surrogate models as well. For example, immortalized cell-lines, such as Jurkat T-cells (originally derived from a patient with T-cell leukemia) are used as substitutes for primary T-cells (normal cells extracted from healthy individuals) in order to investigate phenomena such as T-cell signaling and HIV infection (Abraham & Weiss, 2004). Since the former are a cancerous derivative of the latter, the two kinds of cells are identical in many relevant respects: both express the same range of cell surface receptors, both respond to antigens by producing the same cytokines, both can be infected by the same viruses. The differences are thought to lie in one or more unidentified mutations, presumably affecting oncogenes and tumor suppressor genes, that allow immortalized cells to continue to replicate indefinitely; by contrast, primary cells undergo a limited number of divisions, after which they die. There are many advantages in using cell-lines, the immediately obvious one being that these cells can be cultured indefinitely in vitro, thus making it possible to conduct experiments and manipulations requiring longer periods of time and large quantities of cells, such as genetic manipulations. Cell-lines are also highly standardized, in the sense that they constitute a population of stable clones with well characterized morphological features that can be stored and obtained from cell culture banks, such as the American Type Culture Collection. Genetic and phenotypic homogeneity reduces experimental variation, thus making it possible to amplify, identify and purify mechanistic components, and to generate control and comparison markers for a variety of experimental designs.

2.1.3. Exemplary models

In principle, knowledge gained by studying a phenomenon in any experimental setup can be extrapolated with various degrees of confidence as probable, but fallible generalizations about a group of target systems similar in some relevant way, such as developmentally related cells or phylogenetically related organisms (Ankeny, 2001; Ankeny & Leonelli, 2011; Leonelli, 2007; Weber, 2005, 2007). In the case of organism models, the general intuition is that the strength of the generalization decreases with phylogenetic distance. The main challenge is standardizing phylogenetic relationships in order to allow for meaningful comparisons. In as much as all terminals within a clade of extant species are equally related to their last common ancestor, this ancestor constitutes a phylogenetically equidistant exemplar from which one could extrapolate findings with an equal degree of confidence to all the extant species in the clade. Since the vast majority of common ancestors are extinct, living surrogates must be used instead. Many argue that extant species belonging to basal lineages within the target clade are more likely to have retained ancestral traits (Bolker, 2009; Raff, 2000). Thus, relative to a given taxon, a species belonging to a basal group within the taxon is thought to be a better exemplar than species belonging to crown groups because it is likely to be a better surrogate model for the last common ancestor of the targeted taxon, and therefore allow for equally probable extrapolations to all the extant species in the taxon.

While most of the philosophical literature on model organisms tends to place the emphasis on the overall exemplarity of particular species, it is also possible to define exemplarity in a piecemeal fashion (Jenner & Wills, 2007). For example, adaptive immunity is thought to have evolved in jawed vertebrates shortly after their divergence from jawless vertebrates. Little is known about the ancestor of jawed vertebrates. Placoderms, the earliest known descendants, are now extinct; this leaves us with even more distant surrogates for studying the ancestral adaptive immunity mechanisms, namely extant elasmobranchs (sharks, rays). It is hoped that comparisons between adaptive immunity mechanisms in elasmobranchs and their counterparts in mice, humans and other vertebrates will lead to the identification of conserved mechanistic features likely to be shared by most vertebrates, as well as a better understanding of the evolution of these mechanisms (e.g., Bartl, Baltimore, & Weissman, 1994). By assessing the degree of similarity between actual and conserved mechanisms, it becomes possible to evaluate whether any given species within the group is a better or worse exemplary organism model of adaptive immunity: a better exemplary model is one that offers a closer instantiation of the conserved mechanism. On this account, the organism that constitutes a better exemplary model varies with the mechanisms of interest, and may or may not coincide with the ancestral surrogate model.

2.2. Conceptual models

2.2.1. Mechanistic models

Models involving descriptions of actual or putative mechanisms are by far the most commonly cited type of conceptual models in immunology. Mechanistic models can be easily recognized as being the sort of explanations discussed in the philosophical literature on mechanisms in molecular biology (Darden, 2006), cell biology (Bechtel, 2006) and neuroscience (Craver, 2007). While browsing an immunology textbook, introductory or advanced, one invariably encounters terms, section titles and diagram labels such as ‘models of the HLA–disease associations’, the ‘idiotype network model of immune regulation’, or ‘the two-signal model for immunologic tolerance’ (e.g., Rich et al., 2008, pp. 840, 892, 1211; Shetty, 2005, pp. 85, 144, 147). In these contexts, the term ‘model’ is used interchangeably with ‘theory’, ‘explanation’, or ‘mechanism’, where these terms invariably refer to descriptions of mechanisms—that is, of entities and activities, interactions, or operations organized such that they are productive of phenomena
These descriptions are sometimes fairly detailed and well supported by empirical findings, and at other times incomplete or hypothetical mechanistic sketches.² The term ‘model’ seems to be preferentially used in relation to the latter, in order to emphasize the fact that the proposed mechanistic explanation is hypothetical or incomplete [e.g., proposed ‘models of the HLA–disease association’ (Rich et al., 2008, p. 840; Shetty, 2005, p. 85)]. In contrast, when there is little doubt about the explanation of a phenomenon, the terms ‘mechanism’ or ‘explanation’ tend to be used instead [as in ‘the mechanism of genetic recombination generating antibody diversity’ (Rich et al., 2008, chap. 4; Shetty, 2005, chap. 6)].

2.2.2. Structural models

Structural models refer to confirmed or hypothesized chemical structures, shapes, spatial arrangements and wiring of cells, cellular and molecular components. In immunology, common examples are chemical and 3D structure models of antibodies and cell-surface receptors, organizational features and sequences of genes and loci associated with immunity, as well as histological, morphological and cellular arrangements (e.g., Rich et al., 2008, pp. 54, 58, 60, 18). In the past, structural models were often instantiated as material scale/analogical models (Hesse, 1962) – the practice fell into desuetude, and has been recently replaced by computer-based visualizations (Weisberg, 2013; Winsberg, 2010). Irrespective of the nature of the material they are made of, structural models in biology are meant to be abstract and partial representations highlighting certain structural/organizational features of physical entities that are explanatorily relevant to the properties of the objects whose structure/organization they represent and the role these features may play in the larger contexts of biological systems.

Structural models are often linked to mechanistic models, in which case they amount to ‘zoomed-in’ bits of more comprehensive molecular, cellular, or physiological mechanisms (Baetu, 2012a). For example, structural models provide more detailed explanations of how molecular parts interact with each other, or how structure enables these parts to play a certain role in the context of the mechanism. Most famously, the chemical structure of DNA both explained chemical and physical properties of DNA and suggested a semiconservative mechanism of DNA replication. Likewise, models of the antibody played a crucial role in understanding how certain defense mechanisms related to humoral immunity work (e.g., activation of complement).

2.2.3. Mathematical models

In immunology, as well as many other experimental branches of biology, mathematical models are a recent addition motivated by advances in systems biology and bioinformatics. Mathematical models can be distinguished from mechanistic and structural models because of the mathematical formalism associated with the former, but not the latter (Westerhoff & Alberghina, 2005). The former are also deemed to be ‘theoretical’ in the sense that they rely on theoretical assumptions and idealizations about quantitative and dynamic aspects of the modeled target. Since these assumptions are often borrowed from mathematically formalized sciences and fields of investigation, mathematical models are sometimes treated as applications of these sciences and fields of investigation in biology (Braillard, 2010; Weber, 2005). Mathematical models of molecular mechanisms and systems of mechanisms revealed a number of unsuspected properties such as robustness, adaptability and hysteresis, all of which are potentially significant from a physiological point of view. Mathematical models have also been used to account for quantitative-dynamics aspects of the phenomenon under investigation (Baetu, 2014; Bechtel, 2012; Bechtel & Abrahamsen, 2010; Brigandt, 2013), to guide the design of synthetic mechanisms that behave in quantitatively precise ways (Morange, 2009), and to evaluate the completeness of mechanistic explanations (Baetu, 2014).

Mathematical models constitute a diverse group both in respect to their theoretical foundations, as well as relative to the targets they model. Any phenomenon (e.g., epidemiology of HIV infection), mechanism (e.g., of T-cell activation), interaction (e.g., host–pathogen, antigen–antibody binding), process (e.g., evolution, adaptation) or physical system (e.g., hematopoietic stem cell, T-cell receptor) can be mathematically modeled in order to generate predictions, or simulate some aspects of the behavior of the modeled target and the phenomena produced by it.

In immunology, most theoretical models are divided among epidemiological models aimed at generating predictions about the incidence of disease in a given population, bioinformatics algorithms for predicting antigenicity/immunogenicity from peptide sequence, and mathematical models of molecular components, their interactions, molecular mechanisms or systems of connected mechanisms associated with immunity; examples from each category can be found in Flower and Timmis (2007). Models falling in the first two categories are usually closer to instrumental constructs in respect to the way they are designed and used, and many can be viewed as models of phenomena (Bogen & Woodward, 1988). Models falling in the last category tend to reflect structural and mechanistic details of the modeled physical systems. As a general rule, models of physical systems explicitly aim to provide low-cost, realistic yet computationally efficient in silico surrogates for investigating properties of the systems they model (Winsberg, 2010).

3. Models and the mosaic of scientific knowledge

The above survey and the resulting taxonomy indicates that the general use of the term ‘model’ in the biological literature has the general syntactic form ‘k model of p’, where k stands for a kind or type of model and p stands for a biological phenomenon, physical system, structure, or interaction. This syntactic form is consistent with the views that models can be understood relationally, as representations, mediators or instruments. This form of usage also suggests that models play a role in contextualizing and anchoring the diverse pieces of information entering the composition of the sum total of scientific knowledge within a certain domain of investigation to a description of a phenomenon, on one side, and to a particular approach to the study of these objects, on the other. In this last section I want to elaborate this suggestion, focusing on the epistemic role models play as a purposively diverse family of epistemic entities.

3.1. Experimental models: local points of reference and cross-model extrapolations

In immunology, like in many other biological sciences with a strong experimental component, the discovery process proceeds in part bottom-up, from experimental data towards mechanistic explanations (Bechtel, 2006; Craver, 2007; Darden, 2006). Bits of information about the causal-mechanistic basis of a phenomenon of interest are first gathered from data generated by several experiments, conducted in the context of distinct experimental models,

² A mechanism sketch “is an abstraction for which bottom out entities and activities cannot (yet) be supplied or which contains gaps in its stages” (Machamer et al., 2000, p. 18).
each designed to overcome a particular experimental difficulty (Baetu, 2012b). Piecing together data gathered in different models comports a non-negligible epistemic risk: despite many similarities, subtle differences can make it such that what is true of one experimental model is not automatically true of another, closely related model. An extreme example would be the straightforward summation of findings generated by the sum total of available experimental models. The ‘big picture’ resulting from such a summation is likely to be both incoherent, because of differences between models, and without a real referent, as there is no such thing as a ‘generic mammal’, ‘animal cell’, or ‘life in general’, but only a multitude of individual biological systems. Differences between taxa are, however, just the tip of the iceberg. Before dealing with this quite obvious obstacle to a naive integrative approach, experimental research in biology has to routinely deal with myriad other, more subtle, yet just as troublesome sources of diversity. To give just a few examples: the overall pattern of gene expression measured by analyzing a large population of genetically and developmentally identical cells may fail to describe the pattern of gene expression of any of the individual cells within that population; genetically engineered organisms may differ from their non-engineered counterparts in more respects than the intended genetic changes; cell-lines do not always behave the same way as the primary cells from which the cell-line was originally derived; and what happens in vitro does not always reflect what happens in vivo. While steps are taken to minimize unwanted sources of variation, it is not clear to what extent these measures are successful, thus leaving the door open to the possibility that the same, or highly similar phenomena may in fact be generated by means of significantly different mechanisms in slightly different experimental models.

One common failsafe strategy for addressing this problem is to reference findings to the particular experimental model in which these findings were obtained. This practice is amply documented in the scientific literature: experimental results are invariably attached to a particular experimental setup which is either fully characterized in Section 2 of the paper presenting the results, or for which a full characterization is cited elsewhere in the scientific literature. Each model acts as a point of reference defined by a common experimental setup and associated investigative methods. Relative to each such point of reference, findings are expected to be reproducible; that is, in order to be trusted, experimental results are expected to be reproducible at the very least in the same experimental model in which they have been originally documented, even though they may fail to be replicated in other models. Furthermore, findings that are known to refer to the same object of investigation studied under the same experimental conditions can be directly compared and integrated into more comprehensive knowledge.

By the same token, model contextualization also makes it explicitly clear when findings are extrapolated across different models in order to gain access to a more complete knowledge of a phenomenon. By defining points of reference to which different pieces of knowledge are attached, experimental models highlight the epistemic relationships between the various bits of information composing what, at first sight, may seem a uniform picture of the sum total experimentally-gained knowledge. Model referencing ensures that there is an awareness of the fact that, unless further steps are taken to validate cross-model extrapolations, knowledge obtained by summing up findings generated in the same model is less likely to be problematic than a more ambitious ‘big picture’ account obtained by summing up of findings generated across many distinct models. This is where surrogate and exemplary models step in, justifying certain extrapolations and thus providing the basis for a wider integration of experimental findings and the possibility of acquiring a more general knowledge.

Alternatively, when extrapolations turn out to have been misguided—as, for example, it is sometimes the case when treatments for human disease designed on the basis on knowledge acquired in cell and animal models ultimately fail in clinical trials—, researchers can always rely on a failsafe alternative: return to the less integrated, but more certain basis of a model-relative knowledge, and try to figure out which extrapolations were ungranted, and why.

3.2. Conceptual models: unification and interdisciplinary theoretical grounding

The composite nature of scientific knowledge is not only a consequence of its many experimental sources. In interdisciplinary fields of investigation such as immunology, the theoretical foundations underpinning structural, mechanistic and mathematical models are equally diverse. On the one hand, explanatory models play an important role in unifying larger segments of experimental knowledge and justifying extrapolations across multiple experimental models. On the other hand, however, they can also fragment knowledge by introducing model-specific theoretical assumptions borrowed from a variety of distinct sources. I will begin by discussing first the unifying role of conceptual models, and then the limits of this unification.

Experimental models anchor various bits of information about of a phenomenon to a specific referent, namely the experimental setup in which that information has been obtained or a group of experimental setups across which that information can be justifiably extrapolated. In contrast, mechanistic and structural models recombine those experimental findings which, in conjunction with theoretical assumptions specific to each model, play an explanatory role by showing how a phenomenon is produced by a mechanism, or how the structure of a biological or biochemical object can account for its observed properties. The same is true of detailed and realistic mathematical models aiming to account for quantitative-dynamics aspects of phenomena or properties of the structures, mechanisms or systems of mechanisms under investigation.

Structural, mechanistic and mathematical models generate a new set of units organizing the overall knowledge in the field, distinct from those generated by experimental models. Findings from multiple experimental models used to investigate a phenomenon guide the elaboration of structural, mechanistic and mathematical models by circumscribing putative mechanisms/structures within the physical boundaries of a well characterized experimental setup (Baetu, 2013); specifying ways in which these setups can be decomposed (Betchel & Richardson, 2010); by imposing constraints on the space of possible mechanisms (Craver, 2007; Darden, 2006) and structures (Weber, 2009); by identifying correlating factors providing an initial pool of explanatorily relevant factors (Baetu, 2012b); by demonstrating the causal relevance of the entities, activities, and organizational features of a hypothesized mechanism (Baetu, 2012b; Craver, 2007; Woodward, 2002); by providing clues about the causal roles of mechanistic components relative to the operation of the mechanism (Craver, 2001) and structural features molecules relative to the properties of these molecules (Baetu, 2012a). Because conceptual models are expected to be compatible with available experimental findings about a phenomenon—unless incompatibilities can be attributed to mechanistic or structural differences between experimental models—they unify larger segments of experimental information about a phenomenon by showing how bits and pieces of information gathered in distinct experimental setups are jointly contributing to one and the same explanatory account.

In the early stages of a research project, especially when available data is too scarce to impose stringent constraints, it is not uncommon that more than one mechanism or structure is
compatible with available experimental findings; thus, different explanatory models can coexist. Furthermore, it is also not uncommon that, as new findings accumulate, they fail to unambiguously favor a unique candidate. Rather, each candidate model is compatible with some findings, while having trouble accounting for other findings. This forces researchers to develop more and more detailed models explaining how the proposed mechanism or structure can account for the phenomenon of interest despite the problems raised by incompatible findings. These elaborations often rely on additional theoretical assumptions and conjectures going beyond available experimental data, with the resulting models subjected to experimental confirmation at various points in time during their development, until an accepted explanation, or sometimes a set of explanations emerge. The eventual success of the proposed explanatory accounts, especially in light of subsequent confirmation of predictions and technological applications, plays an important part in retrospectively justifying cross-model extrapolations and, ultimately, the widespread scientific practice of studying any given phenomenon from the perspective of a multitude of distinct experimental models.

An important feature of conceptual models is that they anchor experimental findings to broader theoretical frameworks (Blasimme, Maugeri, & Germain, 2013). In addition to constraints imposed by experimental findings, the construction of structural models is stringently regimented by the principles of chemistry, biochemistry and physical chemistry, and in this sense structural models are deeply indebted to the theoretical achievements of chemistry and physics. Mechanistic models too have a theoretical basis, albeit much less constraining, namely the view that the behavior of complex systems is a consequence of the properties, actions, interactions and organization of their parts. In biology, immunology included, this general theoretical basis takes the more specific form of a commitment to the cellular and the chemical-molecular basis of biological activity, and to the evolutionary origin of living organisms and their parts. Finally, at least some mathematical models can be viewed as applications of theories, such as the laws governing the kinetics of biochemical reactions, motion of ions, or thermodynamic processes (Weber, 2005, 2008a), or again as applications of the principles of cybernetics and systems theory (Brallard, 2010). Famously, the Hodgkin–Huxley model of the action potential, the Michaelis–Menten model of enzyme kinetics, and Knudson’s two-hit model of cancer development made use of theoretical tools in order to demonstrate that biological and biochemical phenomena can be accounted for as consequences of the laws or rules governing the behavior of certain systems. These same models played an important role in guiding the subsequent elucidation of molecular mechanisms, thus anchoring some structural and mechanistic models in biology to the theoretical foundations of chemistry and physics.

If theoretical grounding contributes to the unification of experimental knowledge, it also imposes limitations on how far unification can go. Even though structural and mechanistic models share some core tenets—a commitment to the cellular and molecular basis of all biological activity in the case of mechanistic models, and a commitment to the principles of chemistry for structural models—a, this does not mean that these tenets constitute a mono- lithic theoretical foundation. Different models may rely on different theoretical assumptions within the same broad general approach, and it is not necessarily clear how these assumptions fit together, or even if they are compatible with one another. For example, there is an ongoing debate in molecular biology about whether the specificity of chemical interactions generates cellular structures (Monod, 1972) or whether cellular structures ensure specificity [e.g., via molecular crowding (Ellis, 2001)]; figuring out the causal order is crucial for understanding how molecular mechanisms produce biological phenomena (Kupiec, 2009). Likewise, structural and mathematical models can and often diverge depending on what is taken to be the right physical/chemical principles governing the behavior of the entities or systems under investigation. For example, the Michaelis–Menten model notoriously relies on the assumption of free diffusion, which is thought to accurately describe a test-tube environment, but not the cytoplasm; for this reason alone, there are several variations of the model aiming to describe more accurately in vivo enzyme kinetics. The problem of diverse, and potentially incompatible theoretical commitments is exacerbated in interdisciplinary sciences, where a mosaic of theoretical tools are directly and indirectly borrowed from many other fields of investigation. For example, discrete modeling in systems biology has its roots in cybernetics, computer science and engineering, and has been formalized under the general framework of network theory; continuous models, on the other hand, rely on laws and mathematical models from chemistry and biochemistry (e.g., law of mass action), many of which are themselves applications of statistical mechanics and thermodynamics to chemistry (Shmulevich & Aitchison, 2009). Any given molecular network can be modeled in more than one way, and, as it turns out, depending on the modeling strategy and associated assumptions, the same network may or may not be shown to possess certain properties. The absence of a unified theoretical background makes it particularly difficult to elucidate the relationship between the various models of the same physical system. It is not clear, for example, if one model can be treated as a limit case of another, more general type of model, or whether, in some respects or circumstances, the modeled systems can behave as described by both types of models despite contradictory predictions.

Structural models derived from biochemistry and cell biology, mechanistic models from molecular biology, and mathematical models from systems biology anchor immunology to a very diverse mosaic of theoretical approaches. In this respect, immunology is more akin to an interdisciplinary rendezvous point where many theoretical approaches coexist than a thoroughly unified science built on unique theoretical foundation. What is theoretically assumed under one conceptual model is not necessarily shared by other conceptual models, and it is not in any way obvious or easy to establish whether what is assumed across the sum total of models in immunology—or any other interdisciplinary field of investigation for that matter—amounts to a coherent set of tenets, let alone a logically consistent theory. A careful contextualization of explanatory accounts to specific theoretical assumptions is needed for reasons similar to those driving the referencing of experimental findings to the particular experimental model in which those findings were obtained. It is only after a more thorough evaluation of the relationships between the theoretical assumptions underpinning each model, and of the relationship of the theories from which these assumptions are borrowed, that attempts to integrate the explanatory store of the discipline in a unified theoretical framework may be conducted.

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3 Examples abound in biology. Perhaps the most famous historical example in immunology is the series of theories aiming to account for the exponential generation of antibodies triggered by the primary exposure to antigens. This historical episode begins with a phenomenon first observed by Paul Ehrlich in the 1900s and culminates with the currently accepted clonal selection theory elaborated by Frank Macfarlane Burnet, David Talmage and Niles Jerne in the 1950s, and the experiments confirming it in the following years. A similar point applies to structural models—e.g., models of antibodies, from the initial lock-and-key model hypothesized by Ehrlich and Pauling, to the classical Y-shaped model developed by Rodney Porter and Gerald Edelman, to present day software for predicting the structure of the variable domains of antibodies. For a brief review of these models and related confirmatory/disconfirmatory experimental findings, see Silverstein (2002) or Brownlee (2007).

4 See, for example, the premises of the reasoning used to infer the Y-shaped model of the antibody (Edelman & Gally, 1964).

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4. Conclusion

A survey reveals an unsuspected diversity of distinct uses of the term ‘model’ in immunology, ranging from references to experimental setups to mechanistic explanations and theoretical constructs. The same degree of diversity can be easily documented in other specialized branches of biology, such as virology, oncology, developmental biology. More comprehensive fields of biology, such as biochemistry, molecular biology and evolutionary biology are also characterized by a variety of models, although in these fields some kinds of models tend to be much more common than others. I argue that model diversity reflects the often neglected fact that knowledge in biology is a mottled entity, whereby pieces of information that have been obtained according to different methodologies are put next to each other even though they are not all directly comparable, equally supported by empirical data or based on the same theoretical foundations. Based on the observation that findings in the scientific literature are typically attached to a particular experimental or conceptual model, I propose that models organize the sum total of findings about any given phenomenon into units according to the experimental setups in which those findings have been obtained, in the case of experimental models, or to the theoretical assumptions and frameworks involved in the construction of conceptual models. This partitioning of findings plays an important role for knowledge integration, most notably by allowing investigators to discriminate between situations where findings can be compared, extrapolated and integrated with a minimal risk of going astray, and situations where integration compports substantial epistemic risks.

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