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# Toward a mechanistic explanation of phenotypic evolution: The need for a theory of theory integration

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## Abstract

Reconciling different underlying ontologies and explanatory contexts has been one of the main challenges and impediments for theory integration in biology. Here, we analyze the challenge of developing an inclusive and integrative theory of phenotypic evolution as an example for the broader challenge of developing a theory of theory integration within the life sciences and suggest a number of necessary formal steps toward the resolution of often incompatible (hidden) assumptions. Theory integration in biology requires a better formal understanding of the structure of biological theories The strategy for integrating theories crucially depends on the relationships of the underlying ontologies.

**KEYWORDS**

ontology, phenotypic evolution, theory integration

## 1 | INTRODUCTION

Explanations of phenotypic evolution focus mainly on the dynamics of change. Mechanisms, such as natural selection or genetic drift, make predictions about the fate of variation within populations at both the phenotypic and genetic level and have been empirically tested in both natural and artificial settings (Coyne & Orr, 2004; Endler, 1986; Fox & Lenski, 2015; Grant & Grant, 2010, 2014; Kawecki et al., 2012; Lenski, 2001; Lenski, Ofria, Pennock, & Adami, 2003; Wilke, Wang, Ofria, Lenski, & Adami, 2001; Wiser, Ribeck, & Lenski, 2013). However, the focus on populations and their variational properties, or on "evolution in action," has overshadowed other evolutionary phenomena, such as the substantial degrees of stability at different evolutionary timescales (Dvorak, Casamatta, Hasler, & Poulickova, 2015; Eldredge et al., 2005; Kerr, 1994). These phenomena feature more prominently in paleontology and comparative biology and often generate their own set of explanatory models disconnected from those rooted in population dynamics (Davidson & Erwin, 2006, 2010; Erwin & Davidson, 2002). For the development of an inclusive evolutionary theory, this situation is highly unsatisfactory. The goal of formal evolutionary theory should be to conceptualize and explain the whole set of evolutionary phenomena, that is both stability and change, from one common explanatory framework (Wagner, Chiu, & Laubichler, 2000a; Krakauer et al., 2011; Laubichler & Renn, 2015; Laubichler, Stadler, Prohaska, & Nowick, 2015).

To accomplish this requires rethinking the formal structure of evolutionary theory. Specifically, developing a more inclusive framework that enables the integration and mapping of different explanatory models relevant for the understanding of phenotypic evolution. These include the population-based models of evolutionary dynamics, the regulatory network and developmental systems based models of the origin of phenotypic variation, and the molecular and cellular-based models of mutations and genomic change (Lynch, 2007; Peter & Davidson, 2015). Each of these models has its own logic, defined objects and

ontologies (see Box 1) that need to be mapped onto the others in order to arrive at a more integrated theory of theory integration. From a formal point of view, this amounts to the development of a theory of theory integration that has both formal and applied or practical dimensions. Another dimension of such a theory of theory integration is the need to pay attention to the appropriate level of coarse graining relative to the desired level of explanation. While this represents a more general problem applicable to all areas of science, in the case of the development of a more inclusive theory of phenotypic evolution these challenges fall into several interrelated categories as follows.

*(1) How can we relate macroscopic pattern to microscopic causes?*

The challenge here is one of srelating macroscopic phenomenology describing patterns of variation at different time scales and levels of analysis to experimental data based on the manipulation of specific elements in molecular and developmental processes (Erwin & Davidson, 2009). The situation is even more challenging due to the fact that we have different conceptual structures, models, vocabularies, and ontologies for each level of description. One important dimension here is the challenge to scale specific mechanisms. For example, we have a detailed understanding of the rates of mutations based on molecular principles, but we have no way to simply scale such a uniform mutation rate to explanations of long-term evolutionary change and stability as this requires us to integrate molecular evolution rates into other explanatory models of developmental regulation and control as well as long-term organism–population–environment interactions (Odling-Smee, Laland, & Feldman, 2003; Odling-Smee, Erwin, Palkovacs, Feldman, & Laland, 2013; Peter & Davidson, 2015).

*(2) How can we relate explanatory models at different scales to each other?*

A more specific problem, and one we will discuss in more detail below, is the issue of how to integrate explanatory models at different scales. The conceptual and technical issues here are related to coarse graining or the challenge to find appropriate levels of description and explanation for phenomena (Daniels, Krakauer, & Flack, 2012; Krakauer et al., 2011). But coarse graining the appropriate level of description is only part of the answer here. We also need to develop a rational and reproducible strategy of how to relate mechanisms at different scales to each other. In the case of phenotypic evolution, these range from molecular to cellular, developmental all the way to environmental causes (Bergstrom & Dugatkin, 2016; Gilbert & Epel, 2015). The traditional approach within evolutionary biology focuses on decomposing measured phenotypic variance into various components. But, even though this exercise generates covariance terms, we do not learn a lot about the specific nature of these interactions, even though they are causally relevant for understanding patterns of phenotypic variation and their evolutionary consequences (Falconer, 1989; Wagner, Laubichler, & Bagheri-Chaichian, 1998; Wagner & Zhang, 2011).

*(3) How can we relate different theoretical contexts?*

The problem becomes even more complicated as soon as we realize that these different levels of biological systems are embedded into different theoretical contexts that (1) define the concepts used to describe the phenomena and (2) also define the epistemological criteria used to assess what explanation means in different contexts (Laubichler & Maienschein, 2013). This challenge is not just a philosophical exercise. In the case of explanations of phenotypic evolution, we are dealing with two explanatory paradigms that operate at different scales and involve different standards of explanation, often referred to as ultimate or evolutionary and proximate or causal-mechanistic explanations (Mayr, 1961). Integration between these paradigms is necessary for any complete explanation of phenotypic evolution, but requires explicit consideration of the specific details and assumptions of these different theoretical and explanatory contexts, especially if the goal is, as we argue here, to develop a mapping between different types of formal models.

*(4) How can we relate different measurements?*

A final problem here is related to measurements. Each theoretical context also defines its own measurement procedures that define the objects and identify the functional properties of entities that are part of explanations (Wagner, Laubichler, & Bagheri-Chaichian, 1998; Laubichler & Wagner, 2000; Wagner, Chiu, & Laubichler, 2000b; Wagner & Laubichler, 2000; Wagner & Zhang, 2011; Zhang & Wagner, 2013; Laubichler, Stadler, Prohaska, & Nowick, 2015). In previous calls for integration across different models not enough attention has been paid to the measurement dimension. It is essential for any formal mapping between models that we define the properties of all involved objects precisely. Integrating models of phenotypic evolution is a good test case for such an exercise as it has been the subject of a lot of previous work as well as confusion, exacerbated by the fact that often the same term, such as “gene” is used in radically different measurement and theoretical contexts.

## 2 | THE CHALLENGE OF THEORY INTEGRATION

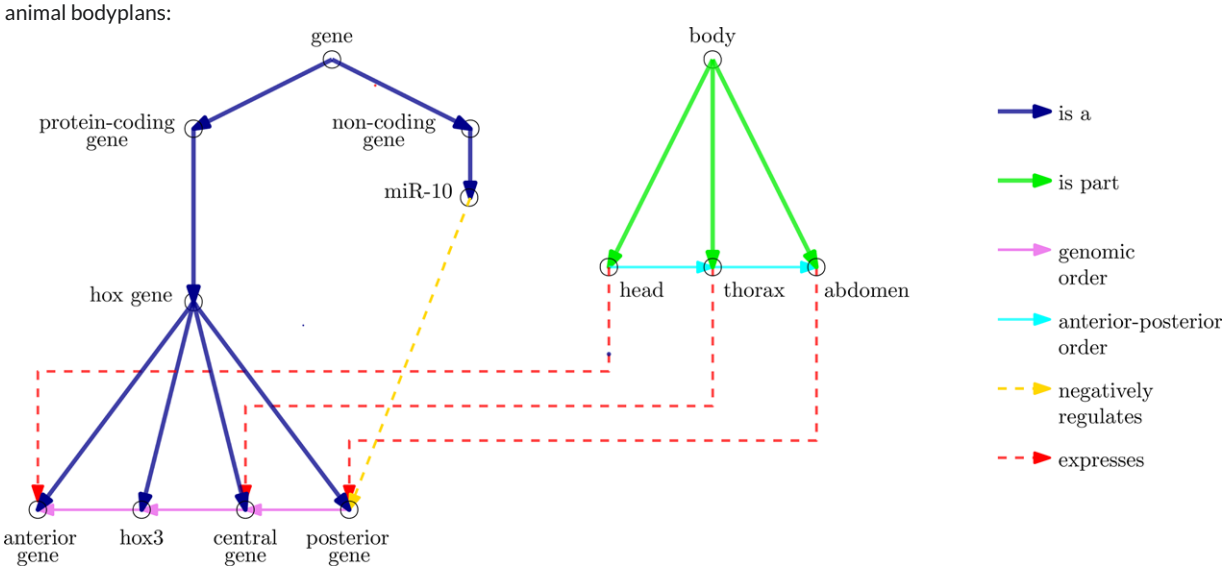
Throughout the history of science theory integration has been a driving force in many disciplines including evolutionary biology (Mayr & Provine, 1980; Smocovitis, 1996). Here, the challenge of theory integration has taken several different forms. On the one hand, there have been continuous attempts to ground explanations of biological phenomena in fundamental principles of physics and chemistry (de Chadarevian, 2002; Morange, 1998; Schrödinger, 1945). Despite challenges related to diversity and complexity of biological systems this approach has been remarkably successful for certain dimensions of biological systems. Scaling laws governing wide domains of life can in many instances be derived from basic physical principles related to the energetics of systems (West, 2017). Similarly, specific aspects of the role of information in biological systems can also be connected to principles of nonequilibrium thermodynamics (Coulon, Chow, Singer, & Larson, 2013; Sengupta, Stemmler, & Friston, 2013; Wolpert, 2016). On the other hand, evolutionary theory has also acted as an integrative force for many properties of living systems. Concepts such as the universal replicator equation (Hofbauer & Sigmund, 1988) or Fisher's Fundamental Theorem of Natural Selection (Fisher, 1930) emphasize universal aspects of evolutionary theory.

However, despite these unquestionable successes many areas of the life sciences have not yet been similarly integrated as challenges

**Box 1. Ontologies as formal systems of knowledge representation**

In information science, an *ontology* is a formal, explicit specification of a shared conceptualization (Gruber, 1993). It provides a flexible, but formally rigorous, framework for the representation of knowledge that aims at capturing our way of thinking in categories and relations. To this end, it provides a controlled, shared vocabulary to specify the objects and concepts, that is, the entities, that exist within a model domain and their relationships. Ontologies comprise individuals (the basic objects), classes (sets, collections, concepts, or kinds of objects), attributes (in particular properties that can be ascribed to objects), and relations (ways in which classes and individuals can be related to each other). To enable formal reasoning, function terms (complex combinations of relations), restrictions (formal statements of conditions that certain objects, classes, relations, or function terms must satisfy), rules (if–then statements that allow inference), and axioms (assertions in the form of formal logic that together describe the basic knowledge about the model domain) can be specified. An ontology is thus a formal way to specify theories. In practice, however, formal theories are usually specified "on top of"—that is, as extensions of—an underlying ontology. Importantly, alternative theories can be formulated by extending the same underlying ontologies with mutually inconsistent sets of assertions.

Ontologies can be visualized as directed (usually acyclic) graphs, with vertices and edges representing the entities and their relationships, respectively, as in the tiny example below, which represents some simple facts about the involvement of hox genes in the formation of animal bodyplans:




In practice, ontologies are usually specified in special ontology languages such as OBO, which is most commonly used in biological and biomedical sciences, and is used for the well-known Gene Ontology GO GO (GO Consortium, 2009). The practical organization of empirical knowledge—that is, data—in a particular domain is strongly influenced by the underlying ontology: the relationships among objects, concepts, and terms explicitly or implicitly informs the data models that guide the design of databases.

related to different measurements, scales, and explanatory frames are still unresolved. This has led to a prolific debate among biologists and philosophers about the role of theory and explanation within the life sciences (Craver & Darden, 2013; Dupré, 1993; Godfrey-Smith, 2003, 2014; Mitchell, 2003; Sarkar, 1998, 2005; Schaffner, 1993; Wimsatt, 2007). One result of this debate has been a conception that sees biology less as an axiomatic science based on first principles, and more as a family of models and theories of varied explanatory scale and reach. A number of philosophers have emphasized explanatory pluralism over the perceived straightjacket of formal reductionism and highlighted the unique nature of the life sciences and their explanatory practices. In many ways, this perspective has accurately described the actual practices of vast domains of the life sciences during the last decades of the 20th century. Another reason that has often been put forward in defense of a pluralistic view of biological sciences is the fact that biological systems are intrinsically complex and therefore resists simple reductionist explanations.

Here, we argue that this philosophical conception of methodological and explanatory pluralism is no longer adequate for several areas of biology because of (1) the data revolution and (2) the computational revolution within the life sciences that have brought the goal of theory integration within reach again. Taken together these two trends, in addition with progress in our understanding of complex systems, enables us to develop appropriately coarse grained explanations of complex phenomena based on the systematic integration of local theories describing specific domains. But theory integration will not happen by itself and requires a number of conceptual and formal advances discussed below. In the age of high-throughput methods and big data, increasingly diverse data sets are brought together in order to address specific biological questions, often related to disease (Gligorijevic et al.,

2016; Rappaport et al., 2017). Each of these data sets is structured according to a specific data model and ontology that reflects the theoretical commitments of a particular domain. As these assumptions are often hidden, without a clear and explicit focus on integration of different data, the promise of big data will remain largely elusive. Furthermore, without an explicit critical assessment of data models used to organize large-scale data sets, any user will be locked into a number of assumptions that might not be adequate for the specific question of interest. The computational revolution and the increased use of complex models to both analyze and simulate biological phenomena is similarly dependent on an explicit understanding of data models, ontologies, and theoretical frameworks. Both of these trends make theory integration more feasible while at the same time also pointing to the need to adequately focus on the challenges related to theory, data, and model integration in the life sciences. And as this kind of integration is happening as part of current practices within the life sciences, we argue that it should be guided by a set of principles and standards that we call a theory of theory integration.

As we have seen, in the life sciences we are confronted with a large number of models and theories with limited scopes. Each of these uses its own terminology and describes relationships between their respective entities in a manner that is informed by an often quite specific set of questions and assumptions. In the emerging age of big data, many of these "local" theories are accompanied by large amounts of empirical data that are stored, indexed, and organized according to the theoretical framework in which they were produced. The integration of such "local" theories into a more global one with a wider scope is desirable not only for both theoretical reasons but also pragmatically, as we increasingly rely on the (re)use of a potentially much larger body of data that were produced for and in specific experimental contexts.

The problems related to the integration of local theories in biology are quite different, and in a sense more difficult, from the physical sciences because in the life sciences different theoretical frameworks rarely can be thought of as simple coarse or fine grainings of each other. The practical problem thus becomes one of finding mappings between entities and relations in distinct local theories in such a way that it becomes possible to reason consistently in both local theories.

The fact that a successful integration of local theories also *implies* a meaningful integration of their associated data makes this endeavor also useful in practice. Practical data integration, however, implies that the maps between local theories have to be precisely defined mathematical objects that can be encoded in computer programs. Theory integration at this level, therefore, goes beyond a pleasing philosophical exercise and calls for a certain minimum level of mathematical formalization of the local theories. Theories associated with large bodies of data, of course, have reached this level of formality, albeit maybe implicitly, by the very data models that are used.

## 3 | EXPLAINING PHENOTYPIC EVOLUTION

In light of these reflections on the need for theory integration, we next turn to one specific explanatory challenge—the problem of phenotypic evolution. Over the last decades, evolutionary biology has made incredible advances in many different domains from molecular evolution to phylogeny and from behavioral to developmental evolution. But these advances have come at a price. Evolutionary biology is today more fragmented than ever before. Some see this as inevitable and argue that a more pluralistic conception of science better reflects the complexity of the world we want to explain (Dupré, 1993; Mitchell, 2003). Indeed, as we discussed this pluralistic conception of science is rapidly gaining acceptance among philosophers of biology. Many of these debates focus on challenges, such as the connections between models and theories or adequate domains of representation that are related to the our position. But these philosophical discussions are mainly reflexive (as good philosophy should be) and are not primarily concerned with the practical challenges of model building and data integration that we focus on here. Another difference between our position and those of many philosophers is that we, as theoretical evolutionary biologists, are guided by the assumption that there is value in striving for theoretical unification and integration, both for explanatory and for practical reasons and that even if we do not reach our theoretical goals yet, the formal clarifications related to ontologies and data models that are necessary to connect different types of data and models at any scale are an important first step toward reaching this goal eventually.

Complete explanations of phenotypic evolution have the following logical structure that also highlights the challenges for model integration as we need to map between objects and properties at each of these levels (Laubichler & Maienschein, 2013). Formulated this way, the logic of phenotypic evolution provides a clear road map for the integration of different models and data sets:

**(1)** All phenotypes are the product of development in multicellular organisms.

**(2)** All phenotypic variants are therefore the product of some corresponding variation in developmental processes.

**(3)** Developmental processes are determined by a complex set of causal mechanisms controlled by regulatory networks ranging from the genome, to cellular signaling, to environmental signaling networks.

**(4)** Variation can be introduced at each level of these complex causal mechanisms and regulatory and signaling networks.

**(5)** All stages of developmental control display redundancy and plasticity, making the mapping from one level to the other nontrivial.

**(6)** All stages of developmental control are structured networks that display their own set of regularities.

**(7)** Causal–mechanistic explanations of development thus have to integrate the actions of these hierarchical regulatory networks with molecular mechanisms of morphogenesis.

**(8)** An integrated model of development and of developmental variation provides a causal understanding of the origin of variation within populations. This was actually Darwin's second question, the origin of variation.

**(9)** Mechanisms of evolutionary dynamics such as selection or drift account for the fate of variants in concrete populations and environmental conditions.

**(10)** A unified explanation of the causal mechanisms of phenotypic evolution has to be based on the integration of all these different causal layers.

We have argued before that one of the challenges of explaining phenotypic evolution is to simultaneously account for patterns of change and stability. From the logic of phenotypic evolution, we can see that explanations of phenotypic stability need to be derived from the properties of regulatory networks and developmental systems that translate variational inputs at different levels (different types of molecular changes, changes in regulatory architecture or changes to various type of signaling input) into heritable phenotypic variation. Clearly, natural selection at different scales plays an important role and can contribute to stability in the form of dynamic equilibria (Fox & Wolf, 2006). However, these are of a different kind than dynamic stability that is a consequence of the variational properties of complex regulatory systems. Given the complexities of these systems, this is not just a simple mapping exercise, commonly referred to as the genotype–phenotype map (Lynch, 2007; Wagner & Zhang, 2011; Zhang & Wagner, 2013). It requires us to find a way to connect local models and their input–output structure to each other. This way it will be possible, for instance, to connect regularities that are the consequence of a specific network topology of a gene regulatory network with observed patterns and constraints of available phenotypic variation in populations. But before doing this, we need to address some fundamental challenges of formal model integration.

## 4 | CHALLENGES IN MODEL INTEGRATION

One of the big challenges in modern (theoretical) biology it to understand and explain the diversity of living organism (Krakauer et al., 2011; Wagner et al., 2000b). With the advent of modern molecular biology, it quickly became clear that the observed phenotypic variation within a population cannot be attributed in a simple manner to genotypic variation. There is orders of magnitude too much genotypic variation under the simplest model assumption, namely that genotypic variance translates directly into phenotypic variance (de Brito, Pletscher, & Cheverud, 2005; Jarvis & Cheverud, 2009; Mitteroecker, Cheverud, & Pavlicev, 2016; Pavlicev, Norgard, Fawcett, & Cheverud, 2011; Porto, Schmelter, VandeBerg, Marroig, & Cheverud, 2016).

It has become part of the program of modern molecular and development biology to explain this apparent contradiction. There is broad consensus that phenotypic variation is the causal consequence of genotypic variation. However, this connection is not direct but mediated by several layers of explanatory theory.

The simplest model sets phenotypic variation in a direct causal relation to genomic sequence variation. The problem here is that individual mutations can only explain a petit fraction of phenotypic changes. Nevertheless, this crude model has been the basis for mutation tests, a measurement technique that artificially introduced sequence changes into the genome, that was used to study the effect of single mutations on the phenotype. In early days, this resulted in an effort to catalog pairs of genomic and phenotypic changes (Griffiths, Wessler, Carroll, & Doebley, 2012), still an active endeavor, for example, in the context of monogenic diseases (Lahiry, Torkamani, Schork, & Hegele, 2010).

Further understanding of the underlying logic in the mapping resulted from the pooling of genomic mutations with the same phenotypic effect into entities, forming the concept of a "gene." This coarse graining is to the cost of resolution but in favor of a higher level of description. As a consequence, the model is refined and variation within genes is now set in a causal relation with phenotypic variation. This, however, has to be understood as an approximation.

With a theory of gene expression built around the central dogma, not only variation in gene expression products but variation in their amounts was considered to be of central importance for phenotypic variation. Today, high-throughput techniques allow measurement of gene expression profiles (Kwon & Ricke, 2011). While aiming to measure protein abundance, measurement techniques only facilitate the observation of abundances at the level of transcripts. The theoretical model therefore requires to set the transcript level into relation with the amount of gene product. A handy model assumption is to propose a correlation between the level of transcription and the amount of protein. As a consequence, transcript levels serve as an approximation for protein abundance. Measurement techniques such as Affymetrix GeneChips and RNA-seq are used to measure gene expression levels (Gohlmann & Talloen, 2009; Kwon & Ricke, 2011). The measurement theory behind chip technology relies on hybridization and assumes that the gene structure is known and unique probes hybridize to individual (coding) exons equally well. An average over a set of matching probes finally approximates the amount of transcript of the corresponding gene. Only very thoughtful chip layouts allow identification of splicing variants and absolute instead of relative quantities. In contrast, measurement of transcript abundance with RNA-seq is based on the assumption that transcripts can be reverse transcribed from random primers with equal rates and efficiency.

This example highlights the importance of the theoretical conceptions behind measurements—and it points to the sometimes subtle but important differences arising from different measurement technologies: in the case of gene chips, transcript structures are known *a priori*, while for RNA-seq data it becomes the experimenters' choice whether they are reconstructed from data or taken for granted in the data analysis pipeline. The very same experiment therefore may yield different quantitative and even qualitative results depending on the theoretical model used to extract a representation of gene expression from the raw measurement data. The choice which representation is most suitable or useful will depend on the theoretical framework employed to integrate gene expression with other data or knowledge.

The observation that variation in gene expression level can cause phenotypic variation raises a further question: where does this variation come from? The answer lies in the organization of gene regulatory networks: A specific subset of proteins, so-called transcription factors, interacts with genomic elements associated with a particular genes, and regulate their expression (Alberts, 2015; Arendt et al., 2016). In

addition, controlled integration of environmental signals adds an additional source for phenotypic variation that is not based on genomic sequence variation at all (epigenetics) (Feil & Fraga, 2012; Marsit, 2015). These interactions are manifold and involve molecules of different type that together form an interaction network. After abstraction, the units at this level of description are eventually nested within intersecting subnetworks with particular features, such as pathways, feedback loops, and elementary regulatory systems (Peter & Davidson, 2015). We can add further layers of description as, for example, tissue formation that has groups of cells as its entities, or mechanisms of organogenesis.

In all cases, the levels of description we pick are a consequence of our theoretical assumptions and their corresponding measurement techniques, and not necessarily the levels of nature's ontology. Therefore, in this theoretical framework certain features, like neutrality, might be independent from the particular nature of the entities and appear on multiple levels.

Summarizing these observations, we can conclude that a mechanistic understanding of the processes leading to the transformation of genomic into phenotypic variation has to be built "bottom-up" starting with the molecular level. The many intermediate levels we pass on the way to the top are characterized by specific measurement techniques. The connections between these levels and their respective measured entities are provided by specific local theories. What is needed for an integrated causal understanding of phenotypic evolution is a systematic way to connect these local descriptions and models into a common explanatory framework.

## 5 | TOWARD A THEORY OF THEORY INTEGRATION

Let us now investigate the implications of these theoretical considerations in more detail. First, we notice that we have introduced distinctive "levels" of description (genetic variation, transcription and translation, transcriptional and posttranscriptional gene regulation, tissue organization, etc.). It is important to notice that these levels are constructs of our choice of a specific representation of the biological system at hand. Whether we integrate posttranscriptional regulation of mRNAs by microRNAs (Djuranovic, Nahvi, & Green, 2011) or the manifold influences of chromatin structure into a model of gene regulation, or whether we treat them as separate layers or components of a description of the biological system is a matter of our choice, not a property of biology itself.

Even if, for the sake of argument, we adopt the point of view that there is a unique or optimal ontology of biological objects, and this is very much a point of view that can be contested as well, this does not in any way imply that there is a unique or optimal level of description and thus of formulating theories in or of biology. Distinct theories, therefore, will be formulated using different slices of an ontology. In the case of coarse graining, the situation is shown in Figure 1. In general, the more fine-grained theory will populate lower, that is, more resolved parts of the ontology. The very nature of biological systems necessitates are trade-off between detail and generality. Hence, we

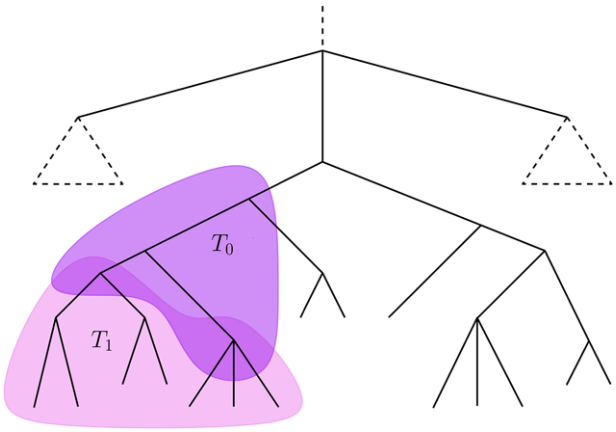



**FIGURE 1** Theories that are coarse grainings of each other "live" in different regions of the same ontology. Here, $T_0$ is a coarse graining of $T_1$. For simplicity, we sketch ontologies, which in general are directed acyclic graphs, see Box 1, as trees [Color figure can be viewed at wileyonlinelibrary.com]

argue that there is no "privileged" position at which theories are inherently superior to others levels of description. Instead, biological theories are formulated relative to the questions that they supposed to answer and relative to the measurements (data) that they are meant to explain (Laubichler et al., 2015).

Interesting and useful theories of biological phenomena will often tie together unrelated parts of an ontology. We need to be able, for example, to formulate models of the influence of microRNAs on proteins that are involved in the developmental formation of muscle tissue and the consequence of their mis-regulation on the severity of certain diseases (Appasani, 2008; Sayed & Abdellatif, 2011). It is important to note that theories are formulated in terms of particular ontologies, but are not determined by them. For example, a good theory will have a certain level of generality and thus apply to all instances of a particular type. A model that involves a certain level in an ontology presumably should be general enough, therefore, not only to apply to a particular item, but also to its sisters or children. That is, if we model the effect of microRNAs on STAT3 (Löffler et al., 2007), we would expect that the same descriptive level, and thus the same type of modeling, that is, the same theory, can be used to model the effect of microRNAs on other (subclasses of) transcription factors as well as of microRNAs other than those playing a role for STAT3.

The view of models and theories as determined by essentially arbitrary levels of description immediately begs the question of the mutual relations between different theories, and thus of a principled way of integrating theories.

One mode of integration is the "concatenation" of models that overlap substantially in their coverage of an underlying ontology (Figure 2). The description of gene expression may serve as an example. Here, transcription factor networks and models of microRNA-based posttranscriptional regulation can be combined in a rather straightforward manner. However, the combined picture is rarely, if ever, just the union of the models. While a transcription factor networks lumps together A, B, and C, these concepts need to be separated. In particular, the processes of transcription and translation must be disentangled

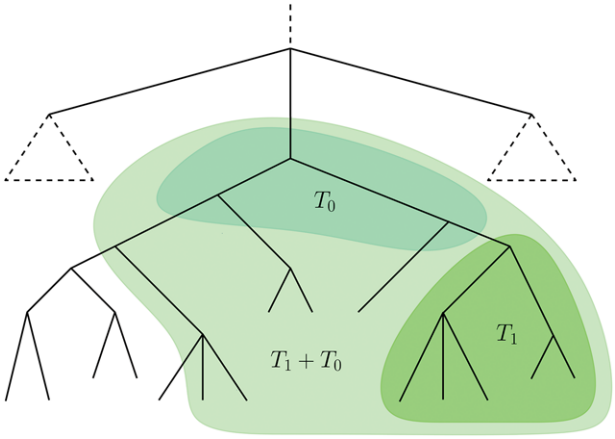



**FIGURE 2** Different theories may describe different aspects of reality that, nevertheless, can be captured within a single consistent ontology. Theory integration then amounts to finding a theory $T_0 + T_1$ that includes (coarse grainings of) both constituent theories $T_0$ and $T_1$. The ontology also might need to be refined in part to accommodate a more fine-grained theory [Color figure can be viewed at wileyonlinelibrary.com]

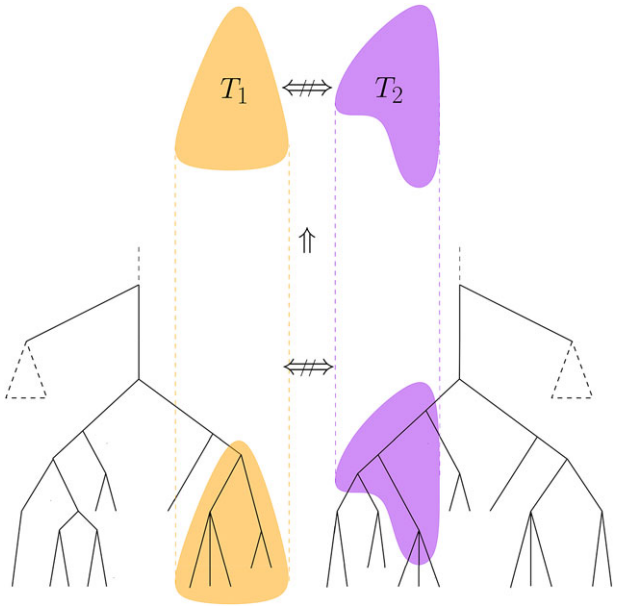



**FIGURE 3** Integration of theories formulated over inconsistent ontologies presumes polyvalent concepts. In so far as these might lead to inherent contradiction, this provides an obstacle to further theory integration [Color figure can be viewed at wileyonlinelibrary.com]

to make it possible to incorporate the negative regulation of translation exerted by microRNAs as well as the transcriptional regulation of miRNA expression.

This simple example highlights that the integration of models, in general, requires an appropriate coarse graining or fine graining of the component models. This process is conceptually guided by the need to map theories onto each other in such a manner that they share the same ontological vocabulary. In the example at hand, "gene expression," for instance, needs to be replaced by more specific terms "transcription" and "translation." Of course, in the case of modeling gene expression an overarching model is already available and we already have an ontology that can be navigated and a consistent terminology can be extracted from various levels of description.

However, in most cases we do not have the same resolution. The concept of a "gene," for instance, is defined and used in very different ways in population genetics, genomics, or developmental biology and the ontologies used in these fields are not integrated with each other in the sense that we would know of a single ontology from which the ontologies of the subfields could be extracted. The disparate definitions of concepts in different subdisciplines preclude a simple matching of terms and thus already makes ontology matching a hard problem because the relationships between terms/concepts appearing in both ontologies are not at all obvious (Euzenat & Shvaiko, 2013; Otero-Cerdeira, Rodríguez-Martínez, & Gómez-Rodríguez, 2015). As a consequence, a theoretical framework needs to be developed that provides these relationships in an explicit form. In the case of the "gene" for example, there is ample literature showing the incompatibilities of different conceptions (Gerstein et al., 2007; Jia et al., 2015; Prohaska & Stadler, 2008; Stadler, Prohaska, Forst, & Krakauer, 2009). The integration of genomics and developmental biology, thus, seems to require a rather detailed description of both the mechanics of "gene expression" and of different notions of biological function used. To reconcile the population genetics notions of a "gene" as locus that contributes to fitness with the use of the term by the genomics community, on the other hand, a broad description of functional DNA elements seems to be necessary.

It appears that many biologists and some philosophers of science perceive a polyvalent interpretation of key concepts, including gene, species, homology, innovation, etc. as an advantage (Dupré, 1993). While this may be the case in early stages of conceptualization, we argue that polyvalency is one, albeit by no means the only, impediment to theory integration. The reason is that an overlapping but incongruent terminology aggravates in practice the identification of inconsistencies of the ontologies of different subfields (Figure 3). These ontologies, even if they are not formalized or even reflected by practitioners, translate to the data models used to store and disseminate the flood of high-throughput data. Polyvalent terminologies thus are prone to become a practical problem for integrative approaches in computational biology that attempt to transcend boundaries of traditional subfields of the life sciences.

The "alignment" of ontologies is of course only a first, presumably necessary, step in theory integration (Figure 4). Thinking of theories as formal systems of data, measurement procedure, and abstract rules and relationships between them holds the promise to transform theory integration into a problem that can be addressed at a formal level. At least for sufficiently formalized theories such as the ones encapsulated in *reasoning systems*, this is possible and is an active area of research in computer science, in particular in the field of knowledge representation (Brachman & Levesque, 2004; Hunter & Liu, 2010). We propose that less completely formalized theories are also amenable to integration provided (1) they are specified in sufficient detail to allow at least an approximate matching of their underlying ontologies and (2) they do not contradict each other. It would appear that the development of such a more formal *theory of theory integration* is a worthwhile

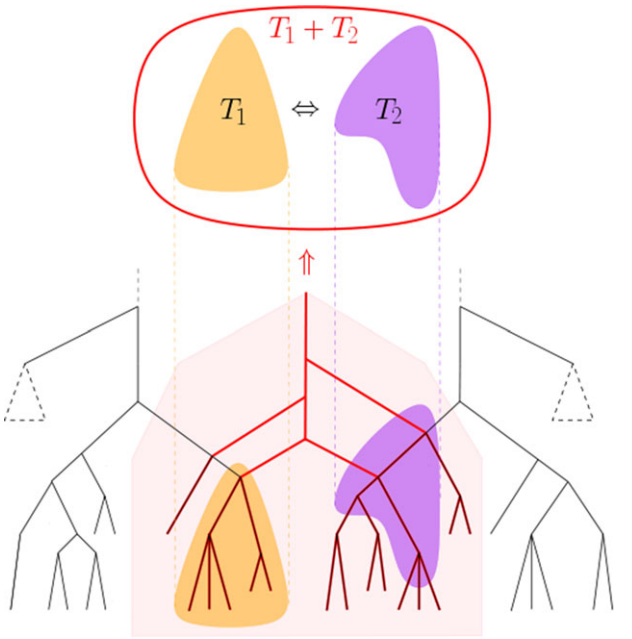



**FIGURE 4** Integration of theories $T_1$ and $T_2$ formulated in unrelated ontologies requires the construction of a consistent common ontology (shown as red tree) capturing the relevant concepts of both domains. Only then a unified theory $T_1 + T_2$ can be formulated [Color figure can be viewed at wileyonlinelibrary.com]

endeavor. As an ultimate goal, we envision a predictive computational model that, for example, is capable of subsuming all of present-day systems biology.

A natural starting point for developing such a theory of theory integration is to consider whether there are already formal frameworks that provide useful tools. The most promising candidate seems to be category theory, a branch of mathematics concerned with the formalization of mathematical structures and their underlying concepts. Focused on mappings between formal structures, category theory already plays an important role in computer science. There already have been interesting attempts to employ it in a systematic manner for knowledge representation (Spivak & Kent, 2012) and the integration of ontologies (Hu & Wang, 2010; Zimmermann, Krötzsch, Euzenat, & Hitzler, 2006). While this is a first step, it is unlikely to be sufficient, given emergent new concepts and thus extensions of underlying ontologies should be expected as a side effect of theory integration.

## 6 | CONCLUSION

In this paper, we have mostly identified serious problems and impediments for developing an integrated theory of phenotypic evolution and provided both conceptual and methodological suggestions for addressing them. We see this as a first step in a long process. We see the role of theoretical biology as providing these kind of solutions and not simply developing models of very narrowly defined biological problems. What we have demonstrated here illustrated by the problem of explaining phenotypic evolution is that:

- explanations of complex biological phenomena require the integration of different theories and models,
- different theories and models generally use different ontologies and operate at different scales,
- therefore, a theoretically guided practice of theory integration is part of developing any form of inclusive integration,
- this requires a degree of formal awareness that is often lacking in attempts of providing synthetic or integrative explanations.

Our initial reflections on how to go about developing a theory of theory integration and our example of how to resolve the integration of different models and their objects in the case of gene expression demonstrate that such an approach is both possible and desirable. Furthermore, in the realm of biological data integration, it even becomes a technical necessity.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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## REFERENCES

Alberts, B. (2015). *Molecular biology of the cell*. New York, NY: Garland Science, Taylor and Francis Group.

Appasani, K. (Ed.). (2008). *MicroRNAs: From basic science to disease biology*. Cambridge, England: Cambridge University Press.

Arendt, D., Musser, J. M., Baker, C. V., Bergman, A., Cepko, C., Erwin, D. H., … Wagner, G. P. (2016). The origin and evolution of cell types. *Nature Reviews Genetics*, *17*, 744–757.

Bergstrom, C. T., & Dugatkin, L. A. (2016). *Evolution*. New York, NY: W. W. Norton & Co.

Brachman, R. J., & Levesque, H. J. (2004). *Knowledge representation and reasoning*. Amsterdam, The Netherlands: Elsevier.

Coulon, A., Chow, C. C., Singer, R. H., & Larson, D. R. (2013). Eukaryotic transcriptional dynamics: From single molecules to cell populations. *Nature Reviews Genetics*, *14*, 572–584.

Coyne, J. A., & Orr, H. A. (2004). *Speciation*. Sunderland, MA: Sinauer Associates.

Craver, C. F., & Darden, L. (2013). *In search of mechanisms: Discoveries across the life sciences*. Chicago, IL: The University of Chicago Press.

Daniels, B. C., Krakauer, D. C., & Flack, J. C. (2012). Sparse code of conflict in a primate society. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 14259–14264.

Davidson, E. H., & Erwin, D. H. (2006). Gene regulatory networks and the evolution of animal body plans. *Science*, *311*, 796–800.

Davidson, E. H., & Erwin, D. H. (2010). Evolutionary innovation and stability in animal gene networks. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *314b*, 182–186.

de Brito, R. A., Pletscher, L. S., & Cheverud, J. M. (2005). The evolution of genetic architecture. I. Diversification of genetic backgrounds by genetic drift. *Evolution*, *59*, 2333–2342.

de Chadarevian, S. (2002). *Designs for life: molecular biology after World War II*. Cambridge, England: Cambridge University Press.

Djuranovic, S., Nahvi, A., & Green, R. (2011). A parsimonious model for gene regulation by miRNAs. *Science*, *331*, 550–553.

Dupré, J., (1993). *The disorder of things: metaphysical foundations of the disunity of science*. Cambridge, MA: Harvard University Press.

Dvorak, P., Casamatta, D. A., Hasler, P., & Poulickova, A. (2015). Putative extremely long evolutionary stasis in bacteria might be explained by serial convergence. *Proceedings of the National Academy of Sciences of the United States of America*, *112*, E2559–E2559.

Eldredge, N., Thompson, J. N., Brakefield, P. M., Gavrilets, S., Jablonski, D., Jackson, J. B. C., … Miller, W. (2005). The dynamics of evolutionary stasis. *Paleobiology*, *31*, 133–145.

Endler, J. A. (1986). *Natural selection in the wild*. Princeton, NJ: Princeton University Press.

Erwin, D. H., & Davidson, E. H. (2002). The last common bilaterian ancestor. *Development*, *129*, 3021–3032.

Erwin, D. H., & Davidson, E. H. (2009). The evolution of hierarchical gene regulatory networks. *Nature Reviews Genetics*, *10*, 141–148.

Euzenat, J., & Shvaiko, P. (2013). *Ontology matching* (2nd ed.). Berlin, Germany: Springer-Verlag.

Falconer, D. S. (1989). *Introduction to quantitative genetics*. Essex, England: Burnt Mill.

Feil, R., & Fraga, M. F. (2012). Epigenetics and the environment: emerging patterns and implications. *Nature Reviews Genetics*, *13*, 97–109.

Fisher, R. A. (1930). *The genetical theory of natural selection*. Oxford, England: Clarendon Press.

Fox, C. W., & Wolf, J. B. (2006). *Evolutionary genetics: concepts and case studies*. Oxford, New York: Oxford University Press.

Fox, J. W., & Lenski, R. E. (2015). From here to eternity—The theory and practice of a really long experiment. *PLoS Biology*, *13*, e1002185.

Gerstein, M. B., Bruce, C., Rozowsky, J. S., Zheng, D., Du, J., Korbel, J. O., … Snyder, M. (2007). What is a gene, post-ENCODE? history and updated definition. *Genome Research*, *17*, 669–681.

Gilbert, S. F., & Epel, D. (2015). *Ecological developmental biology: The environmental regulation of development, health, and evolution*. Sunderland, MA: Sinauer Associates, Inc. Publishers.

Gligorijevic, D., Stojanovic, J., Djuric, N., Radosavljevic, V., Grbovic, M., Kulathinal, R. J., & Obradovic, Z. (2016). Large-scale discovery of disease-disease and disease-gene associations. *Scientific Reports*, *6*, 32404.

GO Consortium. (2009). Gene ontology in 2010: Extensions and refinements. *Nucleic Acids Research*, *38*, D331–D335.

Godfrey-Smith, P. (2003). *Theory and reality: An introduction to the philosophy of science*. Chicago, IL: University of Chicago Press.

Godfrey-Smith, P. (2014). *Philosophy of biology*. Princeton, NJ: Princeton University Press.

Gohlmann, H., & Talloen, W. (2009). *Gene expression studies using affymetrix microarrays*. Boca Raton, FL: Taylor & Francis.

Grant, P. R., & Grant, B. R. (2010). *In search of the causes of evolution: From field observations to mechanisms*. Princeton, NJ: Princeton University Press.

Grant, P. R., & Grant, B. R. (2014). *Forty years of evolution: Darwin's finches on Daphne Major island*. Princeton, NJ: Princeton University Press.

Griffiths, A. J. F., Wessler, S. R., Carroll, S. B., & Doebley, J. (2012). *Introduction to genetic analysis* (10th ed.). New York, NY: W. H. Freeman.

Gruber, T. R. (1993). A translation approach to portable ontology specifications. *Knowledge Acquisition*, *5*, 199–220.

Hofbauer, J., & Sigmund, K. (1988). *The theory of evolution and dynamical systems: Mathematical aspects of selection*. Cambridge, England: Cambridge University Press.

Hu, L., & Wang, J. (2010). Geo-ontology integration based on category theory. Computer design and applications (ICCDA). IEEE, Piscataway, NJ. V1.5–V1.8.

Hunter, A., & Liu, W. (2010). A survey of formalisms for representing and reasoning with scientific knowledge. *The Knowledge Engineering Review*, *25*, 199–222.

Jarvis, J. P., & Cheverud, J. M. (2009). Epistasis and the evolutionary dynamics of measured genotypic values during simulated serial bottlenecks. *Journal of Evolutionary Biology*, *22*, 1658–1668.

Jia, Y., Chen, L., Ma, Y., Zhang, J., Xu, N., & Liao, D. J. (2015). To know how a gene works, we need to redefine it first but then, more importantly, to let the cell itself decide how to transcribe and process its RNAs. *International Journal of Biological Sciences*, *11*, 1413–1423.

Kawecki, T. J., Lenski, R. E., Ebert, D., Hollis, B., Olivieri, I., & Whitlock, M. C. (2012). Experimental evolution. *Trends in Ecology & Evolution*, *27*, 547–560.

Kerr, R. A. (1994). Between extinctions, evolutionary stasis. *Science*, *266*, 29–29.

Krakauer, D. C., Collins, J. P., Erwin, D., Flack, J. C., Fontana, W., Laubichler, M. D., … Stadler, P. F. (2011). The challenges and scope of theoretical biology. *Journal of Theoretical Biology*, *276*, 269–276.

Kwon, Y. M., & Ricke, S. C., editors. (2011). *High-throughput next generation sequencing: Methods and applications*. Berlin, Germany: Springer.

Lahiry, P., Torkamani, A., Schork, N. J., & Hegele, R. A. (2010). Kinase mutations in human disease: interpreting genotype phenotype relationships. *Nature Reviews Genetics*, *11*, 60–74.

Laubichler, M. D., & Maienschein, J. (2013). Developmental evolution. In M. Ruse (Ed.), *The Cambridge encyclopedia of Darwin and evolutionary thought* (pp. 375–382). Cambridge, England: Cambridge University Press.

Laubichler, M. D., & Renn, J. (2015). Extended evolution: A conceptual framework for integrating regulatory networks and niche construction. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *324*, 565–577.

Laubichler, M. D., Stadler, P. F., Prohaska, S. J., & Nowick, K. (2015). The relativity of biological function. *Theory Bioscience*, *143*, 143–147.

Laubichler, M. D., & Wagner, G. P. (2000). Organism and character decomposition: Steps towards an integrative theory of biology. *Philosophy of Science*, *67*, S289–S300.

Lenski, R. E. (2001). Genetics and evolution: Come fly, and leave the baggage behind. *Science*, *294*, 533–534.

Lenski, R. E., Ofria, C., Pennock, R. T., & Adami, C. (2003). The evolutionary origin of complex features. *Nature*, *423*, 139–144.

Löffler, D., Brocke-Heidrich, K., Pfeifer, G., Stocsits, C., Hackermüller, J., Kretzschmar, A., … Horn, F. (2007). Interleukin-6 dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer. *Blood*, *110*, 1330–1333.

Lynch, M. (2007). *The origins of genome architecture*. Sunderland, MA: Sinauer Associates.

Marsit, C. J. (2015). Influence of environmental exposure on human epigenetic regulation. *The Journal of Experimental Biology*, *218*, 71–79.

Mayr, E. (1961). Cause and effect in biology. *Science*, *134*, 1501–1506.

Mayr, E., & Provine, W. B. (1980). *The evolutionary synthesis: Perspectives on the unification of biology*. Cambridge, MA: Harvard University Press.

Mitchell, S. D. (2003). *Biological complexity and integrative pluralism*. Cambridge, UK, New York, NY: Cambridge University Press.

Mitteroecker, P., Cheverud, J. M., & Pavlicev, M. (2016). Multivariate analysis of genotype-phenotype association. *Genetics*, *202*, 1345–1363.

Morange, M. (1998). *A history of molecular biology*. Cambridge, MA: Harvard University Press.

Odling-Smee, F. J., Laland, K. N., & Feldman, M. W. (2003). *Niche construction: The neglected process in evolution*. Princeton, NJ: Princeton University Press.

Odling-Smee, J., Erwin, D. H., Palkovacs, E. P., Feldman, M. W., & Laland, K. N. (2013). Niche construction theory: a practical guide for ecologists. *The Quarterly Review of Biology*, *88*, 4–28.

Otero-Cerdeira, L., Rodríguez-Martínez F. J., Gómez-Rodríguez, A. (2015). Ontology matching: A literature review. *Expert Systems With Applications*, *42*, 949–971.

Pavlicev, M., Norgard, E. A., Fawcett, G. L., & Cheverud, J. M. (2011). Evolution of pleiotropy: Epistatic interaction pattern supports a mechanistic model underlying variation in genotype-phenotype map. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, *316*, 371–385.

Peter, I. S., & Davidson, E. H. (2015). *Genomic control process: Development and evolution*. London, England: Academic Press/Elsevier.

Porto, A., Schmelter, R., VandeBerg, J. L., Marroig, G., & Cheverud, J. M. (2016). Evolution of the genotype-to-phenotype map and the cost of pleiotropy in mammals. *Genetics*, *204*, 1601–1612.

Prohaska, S. J., & Stadler, P. F. (2008). "Genes". *Theory Bioscience*, *127*, 215–221.

Rappaport, N., Twik, M., Plaschkes, I., Nudel, R., Stein, T. I., Levitt, J., … Lancet, D. (2017). MalaCards: An amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. *Nucleic Acids Research*, *45*, D877–D887.

Sarkar, S. (1998). *Genetics and reductionism*. Cambridge, UK: Cambridge University Press.

Sarkar, S. (2005). *Molecular models of life: Philosophical papers on molecular biology*. Cambridge, MA: MIT Press.

Sayed, D., & Abdellatif, M. (2011). MicroRNAs in development and disease. *Physiological Reviews*, *91*, 827–887.

Schaffner, K. F. (1993). *Discovery and explanation in biology and medicine*. Chicago, IL: University of Chicago Press.

Schrödinger, E. (1945). *What is life? The physical aspect of the living cell*. Cambridge, England: Cambridge University Press.

Sengupta, B., Stemmler, M. B., & Friston, K. J. (2013). Information and efficiency in the nervous system: A synthesis. *PLOS Computational Biology*, 9, e1003157.

Smocovitis, V. B. (1996). *Unifying biology: The evolutionary synthesis and evolutionary biology*. Princeton, NJ: Princeton University Press.

Spivak, D. I., & Kent, R. E. (2012). Ologs: A categorical framework for knowledge representation. *PLoS One*, *7*, e24274.

Stadler, P. F., Prohaska, S. J., Forst, C. V., & Krakauer, D. C. (2009). Defining genes: A computational framework. *Theory Bioscience*, *128*, 165–170.

Wagner, G. P., Chiu, C. H., & Laubichler, M. (2000a). Developmental evolution as a mechanistic science: The inference from developmental mechanisms to evolutionary processes. *American Zoologist*, *40*, 819–831.

Wagner, G. P., Chiu, C. H., & Laubichler, M. D. (2000b). Developmental evolution as a mechanistic science: The inference from developmental mechanisms to evolutionary processes. *American Zoologist*, *40*, 819–831.

Wagner, G. P., & Laubichler, M. D. (2000). Character identification in evolutionary biology: The role of the organism. *Theory Bioscience*, *119*, 20–40.

Wagner, G. P., Laubichler, M. D., & Bagheri-Chaichian, H. (1998). Genetic measurement of theory of epistatic effects. *Genetica*, *102–103*, 569–580.

Wagner, G. P., & Zhang, J. (2011). The pleiotropic structure of the genotype-phenotype map: The evolvability of complex organisms. *Nature Reviews Genetics*, *12*, 204–213.

West, G. B. (2017). *Scale: The universal laws of growth, innovation, sustainability, and the pace of life in organisms, cities, economies, and companies*. New York, NY: Penguin Press.

Wilke, C. O., Wang, J. L., Ofria, C., Lenski, R. E., & Adami, C. (2001). Evolution of digital organisms at high mutation rates leads to survival of the flattest. *Nature*, *412*, 331–333.

Wimsatt, W. C. (2007). *Re-engineering philosophy for limited beings: Piecewise approximations to reality*. Cambridge, MA: Harvard University Press.

Wiser, M. J., Ribeck, N., & Lenski, R. E. (2013). Long-term dynamics of adaptation in asexual populations. *Science*, *342*, 1364–1367.

Wolpert, D. H. (2016). The free energy requirements of biological organisms; implications for evolution. *Entropy*, *18*, 138.

Zhang, J., & Wagner, G. P. (2013). On the definition and measurement of pleiotropy. *Trends in Genetics*, *29*, 383–384.

Zimmermann, A., Krötzsch, M., Euzenat, J., & Hitzler, P. (2006). *Formalizing ontology alignment and its operations with category theory. Proceedings of the Fourth International Conference (FOIS 2006)*. Amsterdam, NL: IOS Press, 277–288.

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