



TOWARD A CONCEPTUAL FRAMEWORK FOR BIOLOGY

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ABSTRACT

Science progresses faster when researchers operate within an explicit framework of concepts and theories, but currently biology has no explicit, overarching conceptual framework and few general theories. The single general theory currently recognized is that of evolution, which was put forth by Charles Darwin 150 years ago. Recently, Scheiner and Willig (2008) explicated a similarly general theory of ecology. In this paper, using the theory of evolution as an exemplar, I discuss the nature of theory in biology and put forth an overarching theory, as well as new general theories for cells, organisms, and genetics. Along with the theories of evolution and ecology, these constitute a general conceptual framework for the biological sciences. This framework reveals linkages among the various parts of biology, makes explicit the assumptions behind more narrow theories and models, and provides new insights into the structures of biological theories. This framework can also be used as a teaching tool, moving the teaching of biology beyond the transference of a vast compendium of facts. My hope is that this essay will lead to a vigorous discussion and debate across all of biology about the nature and structure of its theories.

INTRODUCTION

SCIENCE PROGRESSES faster when researchers operate within an explicit framework of concepts and theories. Conceptual frameworks always exist—science is never atheoretic (Suppe 1977)—but often the theories within those frameworks are not well-articulated or explicit. Theory is important because it clarifies thinking. It forces a modicum of formality onto data interpretation, thereby refereeing scientific disputes. It reveals assumptions hidden in specific models or experiments. It shows connections among disciplines, which is especially impor-

tant in guiding interdisciplinary and transdisciplinary work. It defines risky or groundbreaking research. Finally, it clarifies the central questions being addressed by a scientific enterprise.

Despite all of the benefits accrued by having explicit theories, biology appears to be bereft at the widest levels. While there are numerous named theories in biology, nearly all of them pertain to relatively narrow domains (e.g., the theory of island biogeography; MacArthur and Wilson 1967). Currently, there are only two published theories that span wide segments of the

biological landscape. The first is the theory of evolution put forth by Charles Darwin 150 years ago (Darwin 1859). Recently, Michael Willig and I presented a similar broad-level theory for ecology (Scheiner and Willig 2008). The purpose of this paper is to lay out a series of theories that encompass all of biology: an overarching theory and five general theories. In doing so, I will take Dobzhansky's (1964) aphorism that nothing in biology makes sense except in the light of evolution and demonstrate that the complement is also true. Evolution is just one of several general domains within biology. All of those domains intersect and interact, and none holds precedence (Griesemer 2006). The theory of evolution has been given precedence because, until recently, it was the only domain with a well-articulated theory.

The purpose of this paper is to provide well-articulated theories for the rest of biology. I shall accomplish this task by first briefly reviewing the theory of evolution as an example of the nature and structure of theories in biology. With that as an exemplar, I will present a hierarchical structure for theories. I will then outline the overarching theory and the other four general theories. Next, I will discuss how you, the reader, can use this knowledge to frame your own research and make it bolder and riskier. Finally, I will point out aspects of biological theories that only become apparent once they are made explicit, discuss how such theories can change the way that we teach biology, and examine possible next steps in theory development within biology.

This presentation may seem abstract and distant from your day-to-day activities as a scientist, but, as you read this essay, consider how you might use the information revealed. Toward the end, I will discuss some of the immediate, practical uses of this conceptual framework.

THE THEORY OF EVOLUTION AS EXEMPLAR

THE GENERAL THEORY

The theory of evolution should be familiar to all biologists (Table 1). Its funda-

TABLE 1
The domain and fundamental principles of the theory of evolution

Domain
The intergenerational patterns of the characteristics of organisms, including causes and consequences
Principles
1. The characteristics of organisms change over generations.
2. Species give rise to other species.
3. All organisms are linked through common descent.
4. Evolution occurs through gradual processes.
5. Variation among organisms within species in their genotype and phenotype is necessary for evolutionary change.
6. Evolutionary change is caused primarily by natural selection.
7. Evolution depends on contingencies.

mental principles were articulated in Darwin's *On the Origin of Species*, were further refined during the Modern Synthesis, and are still in the process of being debated (e.g., Mayr and Provine 1980; Bowler 1983; Smocovitis 1996; Kutschera and Niklas 2004). The theory of evolution can be encapsulated as seven fundamental principles. (My starting point for the distillation of the theory of evolution was Kutschera and Niklas [2004], with various reorderings and renumberings. Not discussed in their paper is the role of contingency [Table 1, principle 7]. I recognize that others might disagree with the exact number and wording of these principles, but such disagreements over details do not alter the general form of my thesis.) The theory defines a domain: intergenerational patterns of change and stasis of the characteristics of organisms, including causes and consequences. This domain encompasses microevolution, macroevolution, and the origin of species, as well as evolution's tempos and modes.

This formulation of a theory as a set of statements consisting of concepts and confirmed generalization is in line with how many philosophers view theories (van Fraassen 1980; Giere 1988; Beatty 1997; Longino 2002; Pickett et al. 2007; Wimsatt 2007; del Rio 2008; NRC 2008), and is sim-

ilar to the presentation by Darwin. All of the fundamental principles can be found in some form in *On the Origin of Species*, although their meaning and our understanding of them has greatly changed in 150 years. It is a testimony to Darwin's genius that he thought so deeply and broadly about the theory that he was setting forth. However, it in no way denigrates that genius to point out the many things that he got wrong, did not understand, or did not know about (e.g., genetics).

The first three principles—descent with modification, speciation, and single origin—are about the facts of evolution per se. By the 1860s, they were widely accepted by the community of scientists focused on these issues (Ruse 1999), and they have not been seriously questioned within the scientific community since (Bowler 1983, 2004). The other four fundamental principles—gradualism, variation, natural selection, and contingency—are a different story. These principles are about the mechanisms of evolution. They have been, and continue to be, the subject of sometimes vociferous debate. Despite today's general perception, natural selection was not accepted as the primary mechanism of evolution in the late nineteenth and early twentieth centuries (Bowler 1983; Ruse 1999). It was not until the Modern Synthesis that we saw a clear ascendancy of natural selection as the primary mechanism (Smocovitis 1996). The process of the Modern Synthesis can be seen as a pruning away of some mechanisms (e.g., goal directed processes), the refining of others (e.g., genetics), and arguing over the relative importance of yet others (e.g., mutation vs. drift vs. natural selection).

The past 50 years have seen additional debates over those mechanisms and the meaning of the concepts embodied in the fundamental principles. Those debates have been many; I touch on just a few here to illustrate the process of theory change. Gradualism (Table 1, principle 4) in the nineteenth century clearly referred to a very slow process—"Natura non facit saltum [nature does not make a leap]" (Darwin 1859:471). We now recognize that

natural selection can result in substantial change in tens of generations. However, the mean of a trait value or an allelic frequency in a population changes little with each generation and, more importantly, is continuous relative to the total variation within that population. Today's understanding of this principle follows Simpson (1944), who acknowledged that the tempo of evolution can be quite variable. This understanding can be contrasted with the various forms of saltationism that have been proposed over the decades, all of which posit a large change in a single generation, where "large" generally means outside the range of standing variation. One recent example is the theory of punctuated equilibrium, which, in its original version (Eldredge and Gould 1972), claimed that all evolutionary change occurred in a single generation associated with the process of speciation, although this extreme position was later softened (Gould and Eldredge 1977, 1993).

Recent debates about the origin of phenotypic novelties (e.g., West-Eberhard 2003), as well as the emerging discipline of evo-devo (Gilbert and Epel 2009), have focused on the meaning of and the mechanisms underlying fundamental principle 5 (Table 1). The neutralist versus selectionist debates of the 1960s to 1980s were about the relative importance of the mechanisms embodied in fundamental principles 6 and 7. Of course, this is an oversimplification, and often the debates were about several principles simultaneously; however, it clarifies those debates to link specific parts to particular fundamental principles.

One debate demonstrates a definitional resolution. The relative importance of natural and sexual selection was argued in the 1980s (summarized in Michod and Levin 1988) and was, in effect, a debate over whether there should be an additional fundamental principle about sexual selection and a change in fundamental principle 5. The debate was resolved by defining natural selection so that it encompassed all possible forms of selection (Endler 1986). This result subsumed the debate over the relative importance of different mechanisms of selec-

tion within fundamental principle 5, so that the debate was no longer about the principle itself, but about subsidiary theories instead.

As described in Table 1, the theory of evolution provides several clues about the structure of theory. All of the fundamental principles are broad generalizations about evolutionary patterns and processes, and whole subdisciplines are contained within a single principle. The principles are not directly predictive statements, at least not in a quantitative sense. That is the role of subsidiary theories and models.

SUBSIDIARY THEORIES AND MODELS

Within the general theory of evolution are nested a large variety of more specific theories. As an exemplar, consider the theory of natural selection. That theory consists of the following syllogism (Darwin 1859; Endler 1986):

If individuals within a population vary in their characteristics, and
if that phenotypic variation causes differences in reproductive success, and
if that phenotypic variation is heritable, then the population will change its characteristics over generations.

Like the more general theory, this theory also generates many specific subtheories that are often labeled “models” when they have a mathematical formulation. For example, one instantiation of the theory is the familiar breeder’s equation: $\Delta\bar{z} = sV_G/V_P$, in which the change in the mean phenotype of a trait ($\Delta\bar{z}$) is a function of the strength of selection (s), the genetic variance of that trait (V_G), and the phenotypic variance (V_P). (Typically the ratio of genetic to phenotypic variance is shown as the heritability, h^2). This is a quantitative genetics model in which each of the four terms corresponds to one of the four components of the syllogism. One function of subtheories is to provide guidelines for model construction.

A completely different instantiation is a genic, single-locus model: $\Delta p = \frac{sp(1-p)^2}{(1-s(1-p)^2)}$, in which the change in the frequency of an allele (p) is a function of the strength of selection and the current

allele frequency. Both equations are valid, both contain a long list of overlapping but different background assumptions, and they can both be linked if additional assumptions are made (Price 1970; Lynch and Walsh 1998).

THEORY, IN GENERAL

THE STRUCTURE AND ROLE OF THEORY

Now that we have looked at one general theory, let us consider theory and its structure (Tables 2 and 3). I recognize that theories can take many forms, and I do not mean to imply that the structure presented here is the only possible one. However, this structure appears capable of embodying a wide variety of theories within biology.

In my structure, theories are hierarchical frameworks that connect broad general principles to highly specific models. For heuristic purposes, I present this hierarchy as having three tiers—a general theory, constitutive theories, and models. Scheiner and Willig (2008) coined “constitutive theory” as a neutral term that simply indicates that a particular theory is one constituent of a larger framework.

In the example presented above, the theory of evolution is the general theory, the theory of natural selection is a constitutive theory within that general theory, and the breeder’s equation is a specific model derived from that constitutive theory. This view of theories as families of subtheories, including models, is consistent with how theories are treated across all of biology and in other sciences as well (van Fraassen 1980; Giere 1988; Beatty 1997; Longino 2002; Pickett et al. 2007; Wimsatt 2007; del Rio 2008; NRC 2008).

Theories do not necessarily fit neatly into these categories. Rather, the framework will often stretch continuously from the general to the specific. The three tiers merely illustrate that continuum, and provide a useful way of viewing that hierarchy. This paper focuses on general theories and presents an overarching theory of biology, plus five narrower, but still general, theories. I also give an example of an even narrower general theory (multicellular or-

TABLE 2
A hierarchical structure of theories and its components

General theory
Background: domain, assumptions, framework, definitions
Fundamental principles: concepts, confirmed generalizations
Outputs: constitutive theories
Constitutive theory
Background: domain, assumptions, framework, definition
Propositions: concepts, confirmed generalizations, laws
Outputs: models
Model
Background: domain, assumptions, framework, definitions, propositions
Construction: translation modes
Outputs: hypotheses
Tests: facts
See Table 3 for definitions of terms (from Scheiner and Willig 2011a).

ganisms) nested within a broader one (all organisms). For a discussion of the nature of constitutive theories, see Scheiner and Willig (2008, 2011a).

A theory defines a domain—the scope of that theory. For the theory of evolution, the domain is intergenerational patterns of organismal change. For the theory of natural selection, the domain is those aspects of that change that are caused by differential fitness. The breeder’s equation applies

specifically to changes in quantitative characters.

For general and constitutive theories, the domain delimits the boundaries within which constituent theories or models may be connected to form coherent entities. The theory of natural selection tells us that we should be able to link quantitative and single-locus models, but it also limits those models to ones where change is driven by fitness differences. Without such boundaries, we would be faced with continually trying to create a theory of everything. We need to keep in mind, however, that domains are conceptual constructs and that theories may have overlapping domains. Therefore, it is possible to build models that combine processes of selection and genetic drift, but such a model is then contained within a constitutive theory that is broader than the theory of natural selection.

When asked to describe a theory, we often list a set of broad statements describing empirical patterns and processes that operate within a domain, as we saw with the theory of evolution. These broad statements form a set of fundamental principles consisting of concepts and confirmed generalizations (see Table 3 for definitions). Fundamental principles are meant to be broad in scope, often encompassing multiple interrelated patterns and mechanisms.

Laws, in contrast, reside within constitu-

TABLE 3
Definitions of the theory components in Table 2

Component	Description
Assumptions	Conditions or structures needed to build a theory or model
Concepts	Labeled regularities in phenomena
Confirmed generalizations	Condensations and abstractions from a body of facts that have been tested
Definitions	Conventions and prescriptions necessary for a theory or model to work with clarity
Domain	The scope in space, time, and phenomena addressed by a theory or model
Facts	Confirmable records of phenomena
Framework	Nested causal or logical structure of a theory or model
Hypotheses	Tested statements derived from or representing various components of the theory or model
Laws	Conditional statements of relationship or causation, or statements of process that hold within a universe of discourse
Model	Conceptual construct that represents or simplifies the natural world
Translation modes	Procedures and concepts needed to move from the abstractions of a theory to the specifics of a model, application, or test

Modified from Pickett et al. 2007.

tive theories. They are not part of the general theories of biology, because no single law is ever required for the construction of all models within the domain of a given theory. A brisk debate has occurred over whether biology even has any laws (e.g., Beatty 1997; Brandon 1997; Mitchell 1997; Sober 1997; Fox Keller 2007), and the continuing search for such laws is an important impetus of theory change.

The fundamental principles need not embody all assumptions, as some assumptions derive from other domains. If an assumption is taken unchanged from another domain, it may be unspecified within a theory. For example, all theories in biology take as given the conservation of matter and energy, fundamental principles in the domain of physics. By taking as given the fundamental principles of any other general theory, we recognize the general tenet of consilience—i.e., that the entire set of scientific theories must be consistent with each other (Whewell 1858). The decision to explicitly include particular assumptions as fundamental principles within a theory depends on whether those assumptions are subject to test within that theory. Since no theory in biology would ever test the conservation of matter, that principle lies outside of biology's theories.

At the lowest level of the theory hierarchy are models. The term "model" is used for theories at this level because of their particular role. Models are where the theoretical rubber meets the empirical road. Scientific theories can encompass a wide variety of types of models, including physical models (e.g., Watson and Crick's ball and wire model of a DNA molecule), as well as abstract or conceptual models, which may be analytic, statistical, or simulations. Models are where predictions are made and hypotheses are tested. Theories at this level have the hypothetico-deductive structure that we are more familiar with, as compared to the semantic structure evinced at other levels. Because general theories consist of families of models, they very rarely rise or fall based on tests of any one model.

Theories play three roles (R. Creath, un-

published research). First, theories serve as generalizations that go beyond the scope of the specific data upon which those generalizations are based. Second, theories provide concepts that go beyond what can be expressed in observational terms. Both of these roles involve theories as descriptors of the world. Third, theories provide a framework for guiding and evaluating research—what Kuhn (1962) called a "paradigm" and Laudan (1977) called a "research tradition." The theories presented in this paper play all of these roles.

The most common role of a general theory is to serve as a reminder of the implicit assumptions built into models, hypotheses, and experiments. For an extensive discussion and numerous examples of how such reminders can improve models and experiments, see Scheiner and Willig (2011b), as to discuss this here would substantially expand an already extensive essay. I urge the reader to investigate this further for herself or himself, however, as the various general theories are presented.

RULES FOR THEORY CONSTRUCTION

Before we can examine biology's general theories, we must consider the rules that will be followed in their construction. First, a general theory must potentially apply to all species. That is not to say that the patterns and processes embodied in those theories apply to all organisms at all times. However, the theories should not be about just a limited set of species. I will return to this point when discussing the theory of organisms.

Second, a fundamental principle must apply to all or most of the constitutive theories within the domain of the general theory. The components of a constitutive theory need not refer back to all of the fundamental principles; however, those principles should act as basic assumptions behind all of the constitutive theories and models, and act as links among constitutive theories.

Third, the first fundamental principle of a theory should encompass the basic object of interest, and all of the other parts of the theory should serve to either explain this central observation or to explore its consequences. Thus, the first fundamental princi-

ple serves as a guide for the rest of the theory.

Fourth, a fundamental principle must potentially be up for falsification within the domain of consideration. If it is not, then the principle belongs to another domain and is applicable in the domain of consideration through consilience. Falsification comes about through the constitutive theories within that domain.

Fifth, the set of fundamental principles of a subsidiary theory should not simply repeat those of a more general theory, but must be consequences of them for that particular domain. Otherwise, all of the fundamental principles of the more general theory are assumed to hold.

Sixth, the number of fundamental principles should be as few as necessary, but no fewer. This simplicity is achieved if each fundamental principle encompasses a single concept, although that concept can itself contain a multitude of subconcepts, processes, or patterns. By striving toward simplicity in theory structure, we are forced to consider which concepts are most central.

THE THEORY OF BIOLOGY

The theory of biology is encapsulated in ten fundamental principles (Table 4). These principles are phrased in terms of living systems because they apply, to one degree or another, to the entire biological hierarchy (Figure 1). The fundamental principles define a domain—the diversity and complexity of living systems, including causes and consequences. Those causes and consequences relate to six attributes of living systems defined by the fundamental principles of persistence, boundedness, information, variation, complexity, and continuity. Those attributes cause or are the result of four processes: interaction, emergence, change, and contingency. Within this overarching theory are five general theories, and, of these, two are about hierarchical units (cells and organisms = individuals), one is about an attribute (genetics = information), and two are about particular aspects of processes (ecology = interactions of individ-

TABLE 4
The domain and fundamental principles of the theory of biology

Domain
The diversity and complexity of living systems, including causes and consequences
Principles
1. Life consists of open, non-equilibrium systems that are persistent.
2. The cell is the fundamental unit of life.
3. Life requires a system to store, use, and transmit information.
4. Living systems vary in their composition and structure at all levels.
5. Living systems consist of complex sets of interacting parts.
6. The complexity of living systems leads to emergent properties.
7. The complexity of living systems creates a role for contingency.
8. The persistence of living systems requires that they are capable of change over time.
9. Living systems come from other living systems.
10. Life originated from non-life.

uals and populations, and evolution = change over generations).

The first fundamental principle—persistence—as with all of the theories, defines the central observation to be explained: that living systems are open and non-equilibrium (von Bertalanffy 1950) and yet manage to persist, both over the course of a single lifetime and over aeons. “Open” means that living systems take in and release matter and energy. “Non-equilibrium” means that living systems consist of ordered structures in a universe that otherwise tends toward disorder. For life to persist, order must be actively maintained. Thus, the persistence is surprising and in need of explanation.

The second fundamental principle—boundedness—describes the foundation of living systems, the cell that maintains a pocket of order in a disordered universe (Dutrochet 1824). The cell holds together the complex machinery of life along with the energy needed to power that machinery. Life, if it could exist at all, would have a very different character if it was not bounded in this way. An alternative expres-

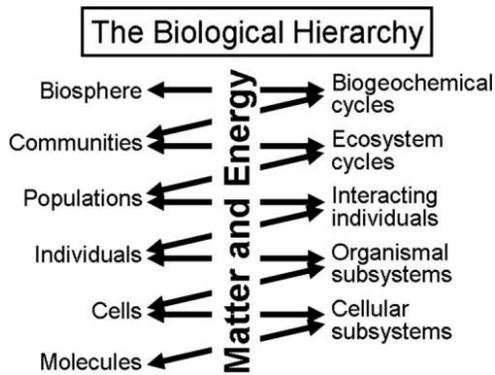


FIGURE 1. A BIOLOGICAL HIERARCHY

One biological hierarchy extends from biomolecules to the entire biosphere. At each level, interactions among the units of that level, including the flow of matter, energy, and information, result in subsystems that are the components of the next level. All of the attributes (persistence, boundedness, information, variation, complexity, and continuity) and processes (interaction, emergence, change, and contingency) of living systems can be found at each level.

sion of this idea is that life, at its foundation, consists of bounded units. While some organisms are acellular, they still exist as bounded individuals.

The third fundamental principle—information—recognizes that life is ordered complexity and that order contains information (Quastler 1953). For living organisms to maintain themselves, they must have a way to capture and use the information contained in that order.

The fourth fundamental property—variation—recognizes that living systems vary in space and time at all levels of the biological hierarchy (Mayr 1982). This ubiquity of variation separates the science of biology from many others. For example, physics deals with a limited number of types of particles (e.g., protons, neutrinos, quarks) that are the same everywhere in the universe.

The fifth fundamental principle—complexity—acknowledges that a hallmark of living systems is that they are made up of many different kinds of parts, arranged in a complicated fashion and interacting with each other in many different ways (Kolasa and Pickett 1989). This interacting struc-

ture results in non-additive and non-linear outcomes (Lorenz 1963). Complexity is a direct result of life's dynamic variation (von Bertalanffy 1951).

The sixth fundamental principle—emergence—is a result of the complexity of living systems (Reason and Goodwin 1999). An emergent property is one that is found at a certain level of organization due to properties, structures, and processes that are unique to that level. Emergent properties can be contrasted with those that are merely aggregates of properties at a lower hierarchical level. Consider locomotion. A human's ability to walk down the street requires the existence of many different parts—bones, muscles, connective tissues, nerves, and so forth—arranged in a specific three-dimensional configuration, and all operating together in a particular way. The separate parts cannot move on their own, thus movement is an emergent property of the whole organism. Such emergent properties can be found at all levels of living systems. The function of a protein depends on the sequence of amino acids and how that chain is folded together into a precise three-dimensional shape. Cells function by separating and concentrating molecules into particular subsections. Emergent properties are the result of feedbacks within living systems.

The seventh fundamental principle—contingency—is again a result of life's complexity. Contingency is the combined effects of two processes: randomness and a sensitivity to initial conditions (Lorenz 1963; Reason and Goodwin 1999). The dynamic nature of living systems is one factor that allows randomness to play a role, while its complexity creates the sensitivity to initial conditions.

The eighth fundamental principle—change—is the recognition that the dynamic nature of living systems is necessary for their persistence (von Bertalanffy 1950). An individual has to continually change to survive. Change in one part of the system creates stability in other parts. For example, mammals and birds tend to maintain a constant body temperature by having an active system for converting

chemical energy into heat. Over much longer periods of time, evolution is important for the survival of a lineage. Because the world keeps changing, a species would go extinct if it did not evolve. Change does not guarantee persistence, but a lack of change guarantees eventual death or extinction.

The ninth fundamental principle—continuity—recognizes that for change to occur from one generation to the next, there has to be continuity of living systems. That continuity embodies two principles—that living systems come from other living systems and that, on the whole, these new living systems are extremely similar to the ones that they came from. This principle is a generalization of one of the two basic tenets of the old cell theory, which stated that new cells come from old ones (Dutrochet 1824).

The tenth fundamental principle—origins—arose during the emergence of biology as a scientific discipline in the nineteenth century (Ruse 1999). The organic origins question was hotly disputed, with one extreme position relying on the action of miracles and the other on processes governed by natural laws. This principle does not require that all life on Earth have a single origin; that claim is left to the theory of evolution (Table 1, principle 3).

BIOLOGY'S CONCEPTUAL FRAMEWORK

THE GENERAL THEORIES

Within the theory of biology are five general theories that span its domain: cells, organisms, genetics, ecology, and evolution. Here, I briefly consider the first four and look at their implications for the fifth. For the sake of brevity, I do not examine each fundamental principle; for those details, please see the Appendix.

One view of life is that it consists of a set of controlled chemical reactions. Life exists only because it is possible to maintain highly ordered systems against the decay of entropy. The cell provides the wall between order and disorder. Thus, cells are the foundational units of life (Table 4, principle 2). The domain of the theory of

cells is the properties and causes of the structure, function, and variation of cells. The theory consists of ten fundamental principles (Table 5). The first three principles are about the molecular constituents, internal structures, and functions of cells, and they provide links between this theory and the theory of genetics. The next three are about how cells interact with their external environment. These principles provide links with the theories of organisms and ecology. The next principle is about energy use. The final three are about where cells and their properties come from, and these provide links with the theories of genetics and evolution. The properties of cells embodied in this theory can be found in any textbook on cell biology (e.g., Lodish et al. 2008).

If cells are the foundational units of living systems, then organisms are its integrative units. For single-celled organisms, they are one and the same. Multicellular organisms separate the foundational and the integrative, which is why I include a separate subtheory dealing specifically with multicellularity. The domain of the theory of organisms consists of individuals and the causes of their structure, function, and variation. What constitutes an individual is a key concept within this theory (Pepper and Herron 2008). The theory of organisms consists of ten fundamental principles (Table 6A). The first four principles deal with the internal structure and function of organisms. They provide links with the theories of cells and genetics. The next four principles deal with interactions with the external environment and provide links to the theories of cells and ecology. The last two principles are about the causes of organismal properties, and these link to the theory of evolution. The theory of organisms was developed with my colleague, William Zamer. We are currently working on a manuscript that will provide a detailed exploration of this theory, including the sources of its principles, although most can be found in any introductory biology textbook (e.g., Sadava et al. 2008; Campbell et al. 2009).

The principles of the general theory apply to

TABLE 5
The domain and fundamental principles of the theory of cells

Domain
Cells and the causes of their structure, function, and variation
Principles
<ol style="list-style-type: none"> 1. Cells are highly ordered, bounded systems. 2. Cells are composed of heterogeneous parts consisting of subsystems that act to localize resources and processes. 3. Cells are regulated by a network of biochemical and supermolecular interactions. 4. Cells interact with their external environment, including with other cells. 5. Cells exchange matter through boundaries consisting of semipermeable membranes. 6. Cells require an external energy source, either chemical or electromagnetic. 7. Cells use energy to create concentration gradients of ions and molecules. 8. New cells are formed from other existing cells. 9. Cells contain all of the information necessary for their own construction, operation, and replication. 10. The properties of cells are the result of evolution.

all organisms. Additional fundamental principles are necessary in order to account for the special properties of multicellular organisms (Table 6B). The theory of multicellularity consists of six fundamental principles. The first principle captures the essential feature of multicellular organisms—that is, cell specialization. The next two principles deal with the processes necessary for specialization to occur, and the final three principles deal with the consequences of specialization.

This subtheory of the theory of organisms is an example of how theory hierarchy can be stretched to fit one general theory inside another. It becomes a matter of convention whether one wants to call the theory of multicellularity a general theory or a constitutive theory. I consider it more than a constitutive theory because it does not lead directly to model building, one of the hallmarks of a constitutive theory. However, neither is it a general theory at the level of the others because it only applies to a specific subset of species. I present it here because so much of the science of

biology focuses on multicellular organisms.

The order within living systems can be described as information that is addressed by the theory of genetics (Table 7). The persistence of living systems means that its information is maintained. Because the theory of organisms states that all organisms die, that maintenance must include transmission across generations. Thus, the domain of the theory of genetics is about the patterns and processes of the use, storage, and transmittal of information in organisms. The theory consists of nine fundamental principles and derives from principle 3 of the theory of biology (Table 4). The general properties of genetic systems embodied in this theory can be found in any genetics textbook (Pierce 2007; Brooker 2008; Lewin 2008).

The theory of ecology (Table 8) addresses the abundance and distribution of organisms, and it consists of eight fundamental principles that were recently codified as the components of a general theory (Scheiner and Willig 2008; see Scheiner

TABLE 6A
The domain and fundamental principles of the theory of organisms

Domain
Individuals and the causes of their structure, function, and variation
Principles
<ol style="list-style-type: none"> 1. An individual organism actively maintains its structural and functional integrity. 2. All organisms are composed of cells at some point in their life cycle. 3. Organismal maintenance at one level requires change at other levels. 4. Organismal functions trade-off against each other. 5. Organismal maintenance is a function of interactions with the abiotic and biotic environment. 6. Organisms require external sources of materials and energy for maintenance, growth, and reproduction. 7. Because organisms are changeable, external influences can force change. 8. Heterogeneity of resources in space and time leads to variation in ontogeny and life history patterns. 9. Organismal reproduction is both a cause and consequence of evolutionary processes. 10. The properties of organisms are the result of evolution.

TABLE 6B
The fundamental principles of the subtheory of multicellular organisms

Principles
1. Multicellularity allows for specialization of cells.
2. Cell-cell interactions are necessary for cell specialization.
3. Specialization of cells requires their spatial or temporal localization at some point in the life cycle.
4. Specialization of cells leads to emergent organismal properties.
5. Specialization of cells allows for modularity.
6. Development requires heterogeneity in cellular or organismal composition.

and Willig 2011a for a more detailed exploration of this theory). The theory as presented here is the result of numerous conversations that we had with our colleagues in producing the predecessor paper and the subsequent book. See those sources for a detailed exploration of the sources of these principles.

During the process of developing these theories, various principles were reformulated or swapped between theories, so as to make them consistent with each other and with the rules for theory construction that I put forth earlier in this paper. This process is one reason for the differences in the theory of ecology as put forth in Scheiner and Willig (2008) and Scheiner and Willig (2011a).

I make no claim that these fundamental principles are entirely novel. Quite the contrary, all of them can be found in many biology textbooks. What is new here is the extraction of these principles into clear, simple statements that constitute the core set of concepts in biology.

THE THEORY OF EVOLUTION, REDUX

Returning to the theory of evolution in light of the other general theories, we see that the fundamental principles dealing with the mechanisms of evolution (Table 1, principles 4–7) are dependent on the other theories for their meaning. Fundamental principles 4 and 5—gradualism and variation—link to the theories of genetics, cells, and organisms to provide the mechanisms for generating variation and

change. Fundamental principle 6—natural selection—links to the theories of organisms, ecology, and genetics. Fundamental principle 7—contingency—links to the theories of genetics (genetic drift) and ecology (historical contingency). Thus, everything in evolution makes sense only in light of the rest of the biology of the organism. In my framework, the theory of evolution no longer holds center stage.

In my explication of the other theories, I have moved some of the issues previously considered to be part of the theory of evolution—notably, the role of inheritance—out of that theory. Another way of saying this, rather than viewing the Modern Synthesis as the incorporation of Mendelian genetics into evolution, is that this process was the development of a parallel theory of genetics that linked to and informed evolutionary theory.

Recently there have been calls for the replacement of the theory of evolution, as articulated by the Modern Synthesis, with a version in which development is given central stage (Hull 2006). In the context of the

TABLE 7
The domain and fundamental principles of the theory of genetics

Domain
The patterns and processes of the use, storage, and transmittal of information in organisms
Principles
1. Offspring resemble their parents.
2. The fidelity of information transmittal requires an error correction system.
3. Because life is the product of natural selection, the information system must be capable of producing new information.
4. The imperfections of error correction create new information.
5. The exchange and recombination of information among individuals create new information.
6. Random processes play an important role in information transmittal, error correction, and the exchange of information among individuals.
7. The system of information usage must be robust to errors.
8. Information usage is context dependent.
9. The properties of information systems are the result of evolution.

TABLE 8
*The domain and fundamental principles of the
 theory of ecology*

Domain
The spatial and temporal patterns of the distribution and abundance of organisms, including causes and consequences
Principles
1. Organisms are distributed unevenly in space and time.
2. Organisms interact with their abiotic and biotic environments.
3. Variation in the characteristics of organisms results in heterogeneity of ecological patterns and processes.
4. The distributions of organisms and their interactions depend on contingencies.
5. Environmental conditions are heterogeneous in space and time.
6. Resources are finite and heterogeneous in space and time.
7. Birth rates and death rates are a consequence of interactions with the abiotic and biotic environment.
8. The ecological properties of species are the result of evolution.

theory presented here, this change could involve the addition of a fundamental principle about the role of development in determining phenotype and the pathways of evolutionary change. However, because development is a process confined to multicellular organisms, such an evolutionary theory would not be general. Instead, that new principle would have to be a more general statement about the link between genotype and phenotype. Such a principle would have to encompass processes other than those contained in principle 8 of the theory of genetics (Table 7), which states that information usage is context dependent. Another way to state the issue is that the insights provided by evo-devo do not overturn the theory of evolution; rather, they add to our understanding of its fundamental principles, as well as to how that theory links to the other general theories.

UNIFIED THEORIES IN BIOLOGY

There is extensive precedence in biology for the development of unified theories. For example, at the turn of the twentieth century, Wilson (1896) put forth a theory of cells and organisms grounded in what

he saw as the two general theories of biology—cell theory and evolutionary theory. The architects of the Modern Synthesis sought to unify biology through evolution (Huxley 1942; Dobzhansky 1964; Smocovitis 1996), and, more recently, metabolic theory has been touted as a general explanation for the properties of living systems (West et al. 1997; Allen et al. 2002; Brown et al. 2004).

Often the goal in developing such theories is to produce a single explanation for living systems. My goal is quite different. In my hierarchical framework, each theory encompasses a family of subtheories, so that explanation is embedded throughout. There is no single explanation. This pluralistic view of theories is similar to that of Longino (2002).

HOW TO BE AN ICONOCLAST

The conceptual framework just outlined provides a context for our research enterprise. First, it allows us to define what is meant by bold research. A bolder study addresses a broader domain or a more general theory. I urge you to consider your own research within the framework just outlined, and to use that framework to make your work bolder by attempting to directly address fundamental principles.

Most science is centered at the level of constitutive theories and models, and does not often address general theories directly. This is not to say that these efforts do not have implications for general theories; however, most of the time, they take the fundamental principles as fixed assumptions and examine how they play out within narrower domains. In doing so, they help to solidify the generalizations represented by those fundamental assumptions.

Sometimes the purpose of a study is to help establish an unconfirmed principle. Such work is often viewed as exploratory because its purpose is to find enough instances of a phenomenon to either show that it is widespread or to establish the generality from its many instances. It is often claimed that such exploratory work is theory- or hypothesis-free. A conceptual framework makes clear the way in which

theory drives such exploration. By being able to explicate the scope of the domain being explored, the potential importance of the work becomes more evident.

Less frequently, a study aims to put forth a new fundamental principle. Sometimes these come only after the accumulation of sufficient examples to suggest a general principle, but sometimes they arrive as bold new ideas (e.g., the neutral theory of evolution; Kimura 1954). The riskiest and most iconoclastic research is that aimed at disconfirming an established principle. Having a clearly articulated theory makes it easier to identify principles that might be vulnerable, and makes being an iconoclast a conscious decision. Eldredge and Gould (1972) were very aware of what they were doing when they attempted to disconfirm evolution's principle of gradualism. Because fundamental principles are generalizations rather than laws, overturning a fundamental principle can rarely be accomplished by a single observation; generalization allows for exceptions. Being aware of the structure and nature of theory can help an iconoclast plan her attack.

NEW INSIGHTS

THE VALUE OF A FRAMEWORK AND PRINCIPLES

At this point you may be asking yourself, "So what have I learned? Didn't I know all of this already?" Well, yes and no. Often the sorts of generalizations embodied in fundamental principles are obvious only after their explication. Fundamental principles should appear to be obvious once explicated because they are supposed to be statements about confirmed generalizations and, as thus, well-accepted concepts. It is only during the process of proposing new fundamental principles that they will seem unfamiliar.

Generalizations serve as reminders about assumptions contained in lower-level theories. The problem with many assumptions is that they are unstated, even subconscious, in nature, and sometimes such unstated assumptions can turn around and bite us. For example, most models of life history evolu-

tion assume that organisms can always adopt the optimal phenotype, instantaneously reallocating resources from growth to reproduction, and so ignoring evolutionary and developmental constraints. Ignoring these assumptions leads to predictions that are biologically improbable—e.g., that an organism should allocate 100% of its resources to reproduction one day after it devoted 100% of its resources to growth (Schaffer 1983), or that an annual plant should switch multiple times between growth and reproduction (King and Roughgarden 1982).

Making such assumptions explicit may change the focus of a theory. For example, a fundamental principle in ecology is that ecological processes depend on contingencies. Yet many ecological theories and models are deterministic, ignoring the role of contingency or stochasticity in molding patterns and processes in nature. Deterministic models are not wrong, just potentially incomplete. Sometimes ignoring contingencies has no effect on model predictions, but, at other times, the consequences can be profound. As the statistician George E. P. Box is reputed to have said, "Essentially, all models are wrong, but some are useful."

We should not underestimate the simple value of a fully articulated conceptual framework for biology. By itself, it provides a structure within which we can organize our ideas and frame debates. By revealing the scope of theories (Figure 2), it both indicates linkages among theories and possible gaps. Those linkages occur both at the level of fundamental principles (e.g., the evolution principles that appear in the other theories) and at the level of constitutive theories (e.g., the roles of development, ecology, and genetics in the theory of natural selection).

Articulating a theory forces us to provide clear definitions of concepts that have often been in dispute. Theories can evolve through a change in our understanding of a principle, without changing the way the principle is worded (e.g., our understanding of the concept of mutation was recently broadened to include epigenetic changes; Gonzalzo and Jones 1997; Scheid et al. 1998; Laird and Jaenisch 1996). Because

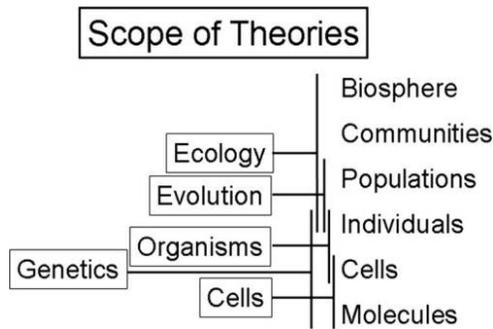


FIGURE 2. SCOPE OF THE THEORIES

The scopes of the five general theories of biology in relation to a biological hierarchy based on the flow of matter and energy. Four of the five theories encompass the level of individuals, thus emphasizing the organism-centeredness of the science of biology.

concepts evolve, they must always be clearly defined so as to prevent scientists from talking past each other. Such misunderstandings are less likely if we have formalized definitions to which we can point. Nearly all of the general domains contain a foundational concept that has been debated over decades and whose meaning continues to be the subject of discussion. Evolution has “species” (e.g., Hey 2001; Reydon 2005), ecology has “community” (Gleason 1926; Clements 1937; Fauth et al. 1996), genetics has “gene” (Portin 1993; Beurton et al. 2000), and organismal biology has “individual” (Pepper and Herron, 2008). Interestingly, I have not been able to identify a similar debate over the meaning of a foundational concept in the realm of cell or molecular biology, although those realms certainly have seen plenty of other types of debates over concepts and theories.

BIOLOGY’S FUNDAMENTAL QUESTIONS

The theory of biology and its five component general theories define six questions that make up the core of the science of biology:

1. Why does life manage to persist? (Biology)
2. What is the cause of organismal change and diversity? (Evolution)

3. Why do offspring resemble their parents? (Genetics)
4. How does a cell maintain its structure and function? (Cells)
5. How does an individual maintain its integrity? (Organisms)
6. What explains the distribution of organisms? (Ecology)

These questions are restatements of the first fundamental principles of each theory. All research within biology eventually leads back to these questions in one form or another. Recognizing that biology has such fundamental questions, and that they have not changed since the origins of the discipline, can help to ground our science at a time of unprecedented growth and change driven by large technological advances (NRC 2009).

COMPARISONS AMONG THEORIES

Some interesting observations come from comparisons among the theories. First, evolution appears as an explicit fundamental principle in all of the other theories, but the reverse is not true. The other theories link to evolution only through the constitutive theories that derive from the principles that deal with evolutionary mechanisms.

Second, contingency does not appear as an explicit fundamental principle in the theories of cells or organisms, whereas it does in the theories of evolution, genetics, and ecology. In the former theories, although contingency may play a central role in particular constitutive theories or models, its importance does not rise to the level of a fundamental principle. Most constitutive theories within those domains need not reference contingent processes, and their models can assume a lack of contingency without compromising their predictive or explanatory accuracy. Recognizing this difference among the theoretical domains helps explain why statistics is used and appreciated very differently by scientists working in different fields. It also explains the dominance of model organisms in molecular, cell, and organismal biology but not elsewhere, as well as possible differences in attitudes concerning the extent

of competition and collaboration among scientists working in different fields.

Third, the theory of genetics never mentions genes or DNA. It is different from the others in that it is the least tied to specifics of living systems on Earth. Its first principle is the only one to directly tie it to biological entities: parents and offspring. Most of its fundamental principles are couched in terms of information systems and properties that can apply equally to non-DNA based systems and even non-living systems. Frank (2009) provides an example of how treating genetics as an information system abstracted from its biology can lead to new insights about evolution.

Recognizing the potential non-biological nature of the theory of genetics leads to new questions about its potential similarity to theories of other information systems, such as cybernetic or cultural (e.g., Wilson 2002; Mesoudi 2007). The answers to those questions will depend on what aspects of the information system are necessary properties of biology and nucleic acids—properties that are not shared by other types of information systems. Such a comparison would highlight the unique properties of those other systems. The formalization of a theory of genetics will help to bring those similarities and differences into sharp relief.

Fourth, the individual is the level within the biological hierarchy where four of the five theories overlap in scope (Figure 2), thereby justifying an organism-centric approach to biology and its general theories. For example, ecologists have disagreed about whether organisms are the central object of study in ecology. In the realms of molecular, cellular, and organismal biology, this organism centrality affirms the new synthetic approaches that are attempting to reconstruct whole systems following many decades of reductionism (Kitano 2002; Ideker et al. 2001).

TEACHING BIOLOGY

Unfortunately, we have a strong tendency to teach biology as a very long list of facts, rather than as a set of theories. Just take a look at any of the current introduc-

tory biology textbooks; nor are upper-level textbooks much better, and I will not except myself from this criticism (Gurevitch et al. 2006). Sometimes those facts are called “concepts,” but they still come across as an extensive laundry list of details. This approach contrasts markedly with the other natural sciences, all of which start with theory and then work toward the facts. In part, this tendency is a natural outcome of the domain of biology. Living systems are diverse and complex. We biologists tend to be fascinated with that diversity and complexity and want to convey our excitement to our students.

Teaching from a well-articulated set of theories can change the way we approach that task (NRC 2003). Instead of assuming that students will induce generalizations from the welter of detail, we should give them the big ideas up front. The theories would prioritize those big ideas, so that students would know where to focus and what they need to remember. It would help students see the connections among the parts of biology, in both introductory and upper-level courses. Those links would be explicit both by constant reference back to the overarching attributes and processes (e.g., complexity and change), and through explicit use of fundamental principles from other parts of biology (e.g., principles about the dynamic nature of cells and individuals when discussing ecological interactions). In short, theory gives unity to that diversity.

Taking a theoretical approach to teaching makes it easier to show how knowledge comes about. A general theoretical framework will encourage all of us to make reference to and use the constitutive theories within each domain. This, thus, makes biological knowledge more dynamic and tentative, not the received wisdom that our students typically assume. Such a change will not be easy for our students. I know from experience that they often have little use for the history of science and where our knowledge came from. It is the Joe Friday method of learning—“Just the facts, ma’am.”

Recently, there have been numerous

calls for pedagogical reform across all of the sciences, especially in order to make classes more dynamic and interactive (e.g., Ebert-May et al. 1997; NRC 2003; Allen and Tanner 2005; Smith et al. 2005). The dynamic of science is theory generation and hypothesis testing, and having an explicit theoretical framework will enhance the students' appreciation of that dynamic.

NEXT STEPS

I make no claims that the theories presented here are complete, that all of the fundamental principles are correct in whole or in part, or that the fundamental principles are necessary and sufficient to account for all of the constitutive theories within each domain. My level of uncertainty is greatest for the theory of cells, the area of biology that I know the least about. For an example of how a theory can evolve or vary, compare the theory of ecology as presented in Scheiner and Willig (2008) with Scheiner and Willig (2011a) and with this essay.

Are these the right theories? Have I carved up the discipline of biology properly? Although theories and their domains are to some extent arbitrary, they divide along what appear to be natural fault lines. But not all attributes, processes, or hierarchical levels are represented by a separate theory, suggesting the potential for additions or substitutions, particularly the latter if the theories are supposed to avoid redundancy.

Among the various attributes of living systems in the overarching theory (Table 4), only information has its own theory. What about other attributes? One often hears reference to complexity theory and systems theory. Are these possible alternatives? I argue that they are not.

A theory works best when it has a clear central question or observation that it addresses. The observation can be very general (e.g., the resemblance of parents and offspring), in which case the theory will be general and will contain numerous constitutive theories and models aimed at subsidiary questions. Complexity theory (Reason and Goodwin 1999) and systems theory

(von Bertalanffy 1951) do not have such central questions within the domain of biology. Instead, they are collections of tools used to address questions about interaction structures raised by various biological theories (Wolkenhauer 2001). Complexity theory and systems theory reside within the domain of mathematics, where they address questions about the behavior of abstracted networks.

On the other hand, recognizing that complexity and interactions are ubiquitous across all of biology encourages us to examine models developed in one biological domain for possible application in other domains. Complexity theory and systems theory tell us how to translate those models across domains. An important type of interdisciplinarity is the importation of tools from across disciplinary boundaries.

What about a theory dealing with other processes? None of the theories address a single process in all its manifestations. The process of change is represented only by evolution—change across generations. Other types of change (e.g., developmental change of organisms, successional change of communities) are addressed by more specific constitutive theories. Again, I argue that what is being explained by each of those constitutive theories is so different that a single general theory of change could not be devised. But I am quite willing to be proven wrong.

What about seemingly missing theories? Where are the theories of the origin of sex, island biogeography, development, reproduction, individuality, cell-cell signaling, or the endothelial origin of stem cells? All of these are constitutive theories within the general theories. The list of such constitutive theories is legion. My neglect of them here is not to discount them; rather, my hope is that this paper will encourage others to draw those theories into coherent frameworks. That is no simple task. Even an entire book (Scheiner and Willig 2011b) fails to capture the entire domain of ecology.

My theoretical framework cries out for historical analyses. The history of the theory of evolution has been examined much

more extensively than theories in other parts of biology. An articulated conceptual framework can help guide such historical analyses. Philosophical analyses are equally needed and would put this current list of fundamental principles in context, possibly revealing other overarching aspects of living systems.

CONCLUSIONS

It is appropriate that these general biological theories be explicated during the sesquicentennial of *On the Origin of Species*. This project reveals that biology is a theory-rich discipline, a fact that is often not recognized and sometimes denied. For example, within organismal biology, the word “theory” is rarely used to describe ideas, despite the fact that it contains a large number of well-developed constitutive theories. Conversely, ecology is awash with a welter of seemingly contradictory theories. The development of theory frameworks can tame this debate by organizing theories into coherent structures (e.g., Scheiner and Willig 2011b).

This process of theory explication is evolutionary rather than revolutionary, a direct continuation of the process that occurred during the Modern Synthesis (Smocovitis 1996). Much of this process is the formalization of ideas that have been around for a long time, but some are new, resulting from being forced to confront all aspects of biology when developing general theories. For example, our explication of a theory of organisms led William Zamer and me to consider why individuals die and reproduce (Table 6A, principles 7 and 9).

A recent attempt to look at theory broadly across all of biology resulted in a document by the National Research Council (2008) that was rich in models but deficient in general theories. My efforts here are, in part, a direct reaction to that exercise. It is clear to me that the structure and function of general theories are not well understood by most biologists. This paper should advance that understanding.

My hope is that this essay will lead to a vigorous discussion and debate across all of biology, and past history gives us some

hints about the possible nature of that debate. The hardest decision concerning the content of a general theory is not whether a fundamental principle is true, although that can lead to a vociferous debate, but whether it is general enough to rise to the level of a fundamental principle. For example, in the theory of evolution, the debate over the role of contingency (Table 1, principle 7) was not about contingency, per se, but about whether the process was important enough to be a fundamental principle.

I emphasize that these debates should be over meaning, not wording. I have a preference for simple, jargon-free language, and I tried to express the fundamental principles in that way, but I would not go to battle over word choices. On the other hand, I have and will argue over their content.

In honor of Darwin’s bicentenary, I end with this thought. There is grandeur in this view of life, with its entangled bank of theories both general and specific. From so simple a beginning, endless models most wonderful have been, and are being, evolved.

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reflect those of the National Science Foundation or the United States Government.

APPENDIX: FUNDAMENTAL PRINCIPLES

TABLE 5. THE THEORY OF CELLS

The first fundamental principle—boundedness—recognizes that a cell is defined by its lipid membrane (Lintilhac 1999). That membrane allows a cell to maintain an internal environment that differs from its external environment—in particular, it concentrates and organizes chemical processes. A membrane sets the stage for two types of feedback systems: those internal to the cell, and those between the cell and its exterior. The internal feedback system keeps the chemical reactions in balance. A cell also needs to maintain itself in the face of a changing external environment, and it is able to do so because its membrane is selectively permeable. A cell is not at equilibrium with its surroundings, and maintaining that non-equilibrium state requires energy. If a cell is part of a multicellular organism, the membrane is a critical component of the signaling system among the cells. Many of the other fundamental principles relate to these consequences of membrane properties.

The second fundamental principle—heterogeneous subsystems—recognizes that cells are highly structured in ways that increase the efficiency of cellular functions. Rather than watery bags of chemicals, they are viscous solutions—more Jell-O™ than Kool-aid™. The efficient functioning of a cell is, thus, an emergent property of this structure. This cellular sub-structuring was recognized in the nineteenth century (Wilson 1896), although the details of that structure are still being elucidated today. This principle is the cellular manifestation of variation and emergence in complex systems (Table 4; principles 4, 5, and 6).

The third fundamental principle—regulated networks—represents the dynamic consequences of the physical complexity embodied in the previous principle (Proulx et al. 2005; Costanzo et al. 2010). A cell is a dynamic entity; parts are continually being assembled, disassembled, and reassembled for other functions. The chemical reactions must be controlled. Complex physical structures support the intricate network of chemical reactions that undergird living systems. This principle is at the heart of the newly emerging field of systems biology and is the cellular manifestation of the interaction principle (Table 4, principle 5).

The fourth fundamental principle—external interactions—indicates that cells are open

rather than closed systems. The cell membrane is the gateway that regulates these interactions. These gateways can be passive or active and can involve the movement of energy, materials, and information across the membrane (Lodish et al. 2008).

The fifth fundamental principle—semipermeable membranes—establishes one of the primary mechanisms by which the cell exchanges matter and interacts with its external environment. The semipermeability of the membrane is a key property that helps to maintain the non-equilibrium state of the cell (Philippson 1921).

The sixth fundamental principle—external energy—establishes one of the other primary external interactions. Living systems maintain themselves in an ordered state by using energy which must come from an external source (Lodish et al. 2008).

The seventh fundamental principle—concentration gradients—embodies a central use for that energy, one of the primary mechanisms that cells use both to maintain order through boundary membranes, and to organize chemical reactions on internal membranes (Griffiths 2007).

The eighth fundamental principle—new cells from old—is one of the two central tenets of the original cell theory from the nineteenth century (Dutrochet 1824), the other being that all organisms are composed of cells. Here, I separate these two components into one part that concerns cells and another part that concerns organisms. The promulgation of the old theory of cells was part of the general development of biology as a discipline in the nineteenth century. This principle is the cellular version of principle 9 of the theory of biology (Table 4).

The ninth fundamental principle—information location—indicates that cells, as fundamental units, are also the places where the information described in the theory of genetics resides (Morgan 1917). To say that cells contain all of the necessary information does not conflict with the notion that the use of that information is at least partially dependent on external factors (see below). Rather, it is a statement that that information, at the very least, consists of DNA sequences arranged into chromosomes. The development of the chromosomal theory of inheritance in the early twentieth century was an important step toward the emergence of molecular biology.

The tenth fundamental principle—properties through evolution—is the result of processes that derive from the theory of evolution. Evolution is often touted as the central organiz-

ing theory of biology. Rather, the theory of biology is a set of general theories that consist of overlapping and interacting domains, all of which inform each other.

TABLE 6A. THE THEORY OF ORGANISMS

The first fundamental principle—integrity—captures the central observation that individuals actively maintain their structure and function. Such integrity serves to separate self from non-self, both from the abiotic environment as well as from other individuals. This principle parallels the first fundamental principle of cells (boundedness), but differs in that the boundaries of individuals are not always as easily characterized (Pepper and Herron 2008). This principle is the organismal version of persistence (Table 4, principle 1).

The second fundamental principle—cells—recognizes that all organisms are composed of cells at some point in their life cycle (Dutrochet 1824). Indeed, most organisms consist of cells all of the time, some being unicellular and others multicellular. Other organisms (e.g., slime molds, many fungi) are acellular, consisting of a single entity with multiple nuclei; however, at some point in their life cycle, usually as part of the reproductive process, individual cells are produced. This principle is the other central tenet of the old cell theory.

The third fundamental principle—change—encapsulates the primary mechanism by which organismal integrity is maintained. Organisms are dynamic entities (Sadava et al. 2008; Campbell et al. 2009). They vary in their biochemical composition from second to second as they react to environmental stimuli. From year to year, they vary in their morphological structure as they grow and develop. This dynamic results from a complex web of positive and negative feedbacks that creates a role for contingency in organismal structure and function. This principle is the organismal manifestation of the change over time principle (Table 4, principle 8).

The fourth fundamental principle—trade-offs—recognizes that no organism is able to do everything. This principle forms the basis of many constitutive theories (e.g., Roff 1992). The existence of trade-offs drives phenotypic variation through niche differentiation—an instance of the intersection of the theory of organisms with the theories of ecology and evolution. This intersection demonstrates how some constitutive theories straddle the domains of general theories. For example, models of the evolution of phenotypic plasticity depend equally on trade-offs in organismal function, the ecological

structure of metapopulations, and evolutionary dynamics (for reviews see Scheiner 1993; Berri-gan and Scheiner 2004). This is the organismal manifestation of the interaction principle (Table 4, principle 5).

The fifth fundamental principle—external interactions—is the organismal equivalent of the fifth principle of the theory of cells. Organisms interact with their external environments in a variety of ways (Sadava et al. 2008; Campbell et al. 2009). Electromagnetic energy (light and heat) flows in and out of organisms. Organisms obtain information from the environment through a variety of types of sensors that respond to many different kinds of stimuli, such as electromagnetic energy (e.g., sight), chemicals (e.g., taste and smell), and gravity (e.g., root geotropism). Information exchange can include signals among conspecifics or with other species. Individuals also have physical interactions, and these can be both positive and negative and both within and between species. This principle, thus, forms the basis for large swaths of the constitutive theories that make up organismal biology.

The sixth fundamental principle—materials and energy—highlights a key interaction between an organism and its environment (Sadava et al. 2008; Campbell et al. 2009), again paralleling the principles of the theory of cells. The second law of thermodynamics requires that organisms lose energy when they use it to perform functions—functions that are required because organisms are dynamic (principle 3). That energy often comes packaged in organic molecules. Even autotrophs must build structures to capture energy in the form of light or heat. When organisms reproduce, they must build new structures.

The seventh fundamental principle—forced change—deals with a central property of living systems: they are mortal. That is, no organism is invulnerable; any organism might die as the result of predation, stress, trauma, or starvation. Death comes about through environmental interactions. Obviously, principle 6 implies that any organism can be starved of materials and energy. Not as obviously, principle 3 implies that the dynamics of an organism can be disrupted. Only an inert object can potentially avoid external change. This vulnerability appears to be inherent in the carbon-based life found on Earth and may be true of any living system, whatever its chemical or energy basis. This principle does not mean that all organisms senesce. There is evidence that some animals do not, nor has senescence been demonstrated

in plants (Roach and Gampe 2004). The senescence of organisms is a narrower version of this principle that applies to particular constituent theories.

The eighth fundamental principle—ontogeny—accounts for the vast diversity that we see in the tempo and mode of organismal growth, reproduction, and mortality (Roff 1992). The development of multicellular organisms is a subset of these processes. This principle is another manifestation of the change over time principle (Table 4, principle 8).

The ninth fundamental principle—reproduction—addresses a fundamental characteristic of all organisms: they reproduce sexually or asexually at some point in their life cycle. But why shouldn't organisms simply grow indefinitely? If all organisms are the result of evolution (principle 10), they must reproduce. The primary driving process of evolution is natural selection (Table 1, principle 6), and natural selection acts on heritable variation among individuals. The generation of heritable variation occurs through a combination of mutation and recombination (see the theory of genetics, below). Even organisms that reproduce strictly asexually generate variation through the accumulation of mutations. If organisms did not reproduce, variation would not be generated, and the processes of evolution and natural selection would grind to a halt. Thus, evolution implies reproduction. This is the organismal version of principle 9 of the theory of biology (Table 4).

As with the theory of cells, the tenth fundamental principle—evolution—is the result of processes that derive from the theory of evolution. It forms the basis for disciplines such as comparative physiology. This principle may seem obvious, but even today many organismal studies are not comparative, and even those that are do not necessarily use a phylogenetic framework. The need to use a phylogeny is an example of how a fundamental principle can continually prod the assumptions that may lie hidden within a study.

TABLE 6B. MULTICELLULAR ORGANISMS

The first fundamental principle—cell specialization—highlights a feature of nearly all multicellular organisms—i.e., that they consist of more than one cell type. Such specialization allows us to distinguish a multicellular individual from a mere collection of cells. Specialization leads to increased functionality and efficiency because it breaks the trade-offs (principle 4 of the theory of organisms) caused by having to perform multiple

functions simultaneously or with the same set of structures. For example, Solari et al. (2006) postulated that within volvocine algae, the evolution of multicellularity was due to a trade-off between flagellated cells necessary for colony buoyancy and non-flagellated, reproductive cells. The evolution of animals and plants can be modeled as an increase in the number of cell types (Hedges et al. 2004). This principle derives from the variation principle of the theory of biology (Table 4, principle 4).

The second fundamental principle—cell-cell interactions—addresses the first mechanism necessary for cell specialization. In order for cells to specialize in an orderly fashion, they must be able to communicate (Lodish et al. 2008). This principle provides a link with the theory of cells and derives from the interaction principle (Table 4, principle 5).

The third fundamental principle—localization—addresses the second specialization mechanism (Gilbert 2006). If multicellular organisms consist of specialized cells, those cells either exist at particular points in a life cycle (e.g., spores) or are spatially separated (e.g., tissues and organs). This principle is another example of biology's variation principle (Table 4, principle 4).

The fourth fundamental principle—emergence—addresses the new properties that come from cell specialization. The existence of multiple cell types and their spatial or temporal localization allow for emergent properties (Gilbert 2006). This principle is the organismal manifestation of the emergence principle (Table 4, principle 6).

The fifth fundamental principle—modularity—addresses another property of multicellular organisms. One difference between unicellular and multicellular organisms is that the latter have the potential for modularity (e.g., leaves, limbs, body segments). Modularity allows for more extensive differentiation and the spatial separation of cell functions. It also permits greater evolutionary independence of the parts by breaking pleiotropic and epistatic correlations among genes (Wagner 1989; West-Eberhard 2003; Hansen and Houle 2008). Again, this principle derives from the variation and interaction principles (Table 4, principles 4 and 5).

The sixth fundamental principle—development—addresses another consequence of multicellularity. Development is the determination of cell fate, cell differentiation, and morphogenesis. By definition, development can occur only in multicellular organisms. Some unicellular organisms undergo ontogenetic change,

such as *Bacillus subtilis* that can switch between a metabolically active state and a resting or spore state. While that process is often referred to as development (e.g., Losick and Stragier 1992), I distinguish it from true development.

All development requires the existence of some sort of asymmetry (Gilbert 2006), either within a single cell (e.g., a fertilized egg) or an organism (e.g., gradients of morphogens in a *Drosophila* larva). These asymmetries are what allow for cell differentiation to occur in an ordered fashion.

Evolutionary theory treats the source of phenotypic variation and the genotype-phenotype link as a black box. This principle shows that the explanation for phenotypic variation in multicellular organisms comes from a theory of development embedded within a theory of organisms, which, in turn, exists as a complement to the theory of evolution (Gilbert and Epel 2009).

TABLE 7. THE THEORY OF GENETICS

The first fundamental principle—resemblance of relatives—establishes the fact that relatives are similar to each other. However, resemblance is not identity, and the theory of genetics is as much about why relatives do not resemble each other as why they do. This principle subsumes within it all of Mendel's laws (1865), the models of quantitative genetics (Fisher 1930), and the Watson-Crick model of DNA (Watson and Crick 1953).

The second and third fundamental principles—fidelity of transmission and new information—are about complementary properties. On the one hand, an information system must be able to correct errors in order for its information to persist (Pierce 2007; Brooker 2008; Lewin 2008), but, because the environment is always changing (see the theory of ecology) and natural selection requires genotypic and phenotypic variation (see the theory of evolution), the information content of the system must also be able to produce new information. Thus, the error correction system cannot be perfect. The actual error rate (i.e., the mutation rate) is shaped by evolution (Lynch 2008) and is higher than the theoretical minimum. These principles derive from the variation and change over time principles (Table 4, principles 4 and 8).

The fourth and fifth fundamental principles—mutation and recombination—embody all of the ways in which new information can be created (Morgan 1911, 1917). In using the term “errors,” I am including all types of changes to DNA, including base-pair changes, deletions, insertions, transpo-

sitions, and polyploidy, as well as epigenetic changes such as DNA methylation. In Bacteria and Archaea, recombination occurs in a hapazard fashion. The evolution of meiosis in Eukaryotes can be seen as a process through which DNA exchange and recombination became regularized (Wilkins and Holliday 2009). This is again a manifestation of the change over time principle (Table 4, principle 8).

The sixth fundamental principle—random processes—describes one of the major ways that contingency plays a role in living systems (Table 4, principle 7). Mutations occur randomly. This is not to say that all mutations are equally likely; rather, mutations are never goal directed (Pierce 2007; Brooker 2008; Lewin 2008). The independent assortment of genes on different chromosomes is the best example in biology of a truly random process. If this were not so—if an allele could favor its transmittal over its homolog—even a very small advantage would quickly fix that allele in a population. Linked alleles would also be quickly fixed, while alleles linked with the disfavored variant would quickly become much rarer. Thus, the entire meiotic machinery is geared toward suppressing the possibility of such skewing of gene segregation. Although we know of skewing processes (e.g., meiotic drive and transposable elements), they are exceptions rather than the rule.

The seventh and eighth fundamental principles—robustness and context dependency—deal with information usage. They encompass the entire machinery of transcription and translation, and link to cellular networks (Table 5, principle 3) and the ontogeny of organisms (Table 6A, principle 8; Table 6B, principle 6), as well as to the external interactions described by both of those theories (Pierce 2007; Brooker 2008; Lewin 2008). These two principles are complementary. On the one hand, a persistent information system needs to be robust to errors. The processes that allow for some mutations without phenotypic change (e.g., the degeneracy of the genetic code) enhance the error correction system. On the other hand, those silent mutations can act as a hidden pool of variation for evolution to act upon if they suddenly are no longer silent.

Such a change in expression is the context dependency of information usage. That context includes the other DNA sequences on the same chromosome, the DNA sequences of other alleles at that locus, the rest of the genome, and, most notably, the environment outside the cell. That environment can include other cells within the same organism or in other organisms, as well as

the individual's physical surroundings. That is, context dependency includes the concepts of dominance, epistasis, genotype-environment interactions, and maternal effects. It also includes cultural and other such forms of non-genetic inheritance. Context dependency is a type of emergent property (Table 4, principle 6).

The ninth fundamental principle—evolution—parallels those of the other theories. Not only mutation and recombination rates are shaped by evolution. Phenotypic plasticity—the ability of the system to respond to environmental context dependency—is heritable and selectable (Scheiner 1993). Evolution establishes a relationship between the quantity of information and its usefulness (Frank 2009).

TABLE 8. THE THEORY OF ECOLOGY

The first fundamental principle—heterogeneous distributions—is one of the most striking features of nature: all species have a heterogeneous distribution at some, if not most, spatial scales. Arguably, the origins of ecology as a discipline and the first ecological theories can be traced to its recognition (Forster 1778; von Humboldt 1808). This heterogeneous distribution is both caused by and a cause of other ecological patterns and processes. This is the ecological manifestation of the variation principle (Table 4, principle 4).

The second fundamental principle—interactions—includes within it the vast majority of ecological processes responsible for heterogeneity in time and space. They include both intraspecific and interspecific interactions such as competition, predation, and mutualism, as well as feedbacks between biotic and abiotic components. Many definitions of “ecology” are restatements of this principle (Scheiner and Willig 2008). This principle links to the interaction principle (Table 4, principle 5).

The third fundamental principle—variation—is the result of processes that derive from the theory of organisms. It is notable that many constitutive theories and models within ecology assume invariance, and, in some cases, relaxing this assumption has led to substantial changes in predictions (Scheiner and Willig 2011b). For example, if the actual chance of survival varies among individuals within a population, treating all individuals as identical can substantially over- or underestimate the risk of local extinction from demographic stochasticity (Kendall and Fox 2003). This principle links to both the variation and interaction principles (Table 4, principles 4 and 5).

The fourth fundamental principle—contin-

gency—has grown in importance in ecological theory and now appears in a wide variety of constituent theories and models. Contingency is an important cause of the heterogeneous distribution of organisms (Gleason 1926), both at very small and very large extents of time and space (e.g., a seed lands in one spot and not another; a particular species arises on a particular continent). This principle links to the theories of genetics and evolution. It also exemplifies the dynamic nature of a theory. The consensus that contingency was a fundamental process emerged from a debate among ecologists during the 1960s through the 1980s. This principle is the ecological manifestation of the contingency principle (Table 4, principle 7).

The fifth fundamental principle—environmental heterogeneity—is a consequence of processes from the theories of earth and space sciences, as well as from other biological principles when those environmental factors are biotic (Gurevitch et al. 2006). For example, seasonal variation in temperature is the result of orbital properties of the Earth, whereas a variety of geophysical processes create heterogeneity in environmental stressors such as salt (e.g., wave action near shores) or heavy metals (e.g., geologic processes that create differences in bedrocks). This principle contains a broad class of underlying mechanisms for the heterogeneous distribution of organisms.

The sixth principle—finite resources—is again a consequence of processes from the theories of earth and space sciences as well as other biological principles (Gurevitch et al. 2006). Although variation in resources is similar to variation in environmental conditions, a fundamental distinction is the finite, and thus limiting, nature of these resources. Unlike an environmental condition, a resource is subject to competition. For example, seasonal variation in light and temperature are caused by the same orbital mechanisms, but light is subject to competition (e.g., one plant shades another) whereas temperature is a condition and not subject to competition.

The seventh fundamental principle—birth and death—is a consequence of the processes that derive from the theories of cells and organisms. While birth and death come about through cellular and organismal processes, their rates depend on the interactions of an organism with its environment (Hasting, 2011; Holt 2011). This principle derives from biology's principles 5 and 9 (Table 4).

The eighth principle—evolution—is the result of processes that derive from the theory of evolution. The inclusion of evolution within

ecological thinking was an important outcome of the Modern Synthesis. Although evolutionary thinking about ecological processes goes back at least to Darwin (1859), only since the 1920s

has ecology embraced its principles (Collins 1986; Mitman 1992), and its widespread acceptance occurred primarily in the latter half of the twentieth century.

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