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## 50th Anniversary Year Review

## The challenges and scope of theoretical biology

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## ABSTRACT

Scientific theories seek to provide simple explanations for significant empirical regularities based on fundamental physical and mechanistic constraints. Biological theories have rarely reached a level of generality and predictive power comparable to physical theories. This discrepancy is explained through a combination of frozen accidents, environmental heterogeneity, and widespread non-linearities observed in adaptive processes. At the same time, model building has proven to be very successful when it comes to explaining and predicting the behavior of particular biological systems. In this respect biology resembles alternative model-rich frameworks, such as economics and engineering. In this paper we explore the prospects for general theories in biology, and suggest that these take inspiration not only from physics, but also from the information sciences. Future theoretical biology is likely to represent a hybrid of parsimonious reasoning and algorithmic or rule-based explanation. An open question is whether these new frameworks will remain transparent to human reason. In this context, we discuss the role of machine learning in the early stages of scientific discovery. We argue that evolutionary history is not only a source of uncertainty, but also provides the basis, through conserved traits, for very general explanations for biological regularities, and the prospect of unified theories of life.

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## Contents

1. Outline of goals	269
2. Introduction to theory	270
2.1. Case study summary	271
3. The relationship of biological models to theory	271
4. The challenges and character of biological theory	272
4.1. Problems of level separation	273
5. Theoretical biology in relation to evolutionary theory	273
6. Theory and the logic of experimental design	274
7. Theoretical tools and formal languages	274
8. Conclusions	275
References	275

## 1. Outline of goals

Biology has been called “the physics of the twenty-first century”. This remark suggests that biological data have become sufficiently rich and well curated, and biological mechanisms sufficiently wide spread and conserved, that there is a prospect

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for the generation of new effective theories, perhaps even laws, for living systems. The comment also raises important questions about the objectives of theory in the life sciences, whether the grand unified goals of physics serve as the correct prequel to biology, or whether it might not be more fitting to view biology from the perspective of the information and computational sciences, also potent in mathematical and formal reasoning (Keller, 2003). Perhaps biology will be ‘the computer science of the twenty-first century’, seeking to understand the logical structure of life in terms of directed rules of assembly, rather than interactions among fundamental constituents. Others have argued for a grounding in economics or engineering (Jacob, 1977). Both of these areas have proven a rich source of models, from game theory through control theory, but neither have contributed much in the way of general theoretical frameworks. Indeed, in the case of economics, the classical equilibrium theory with an emphasis on individual utility maximization has proven to be both non-empirical and rather easily refuted (Arrow, 1994; Colander, 2000). The recent trend in economics has consequently been to integrate more effectively with biological (Samuelson, 1985; Glimcher and Rustichini, 2004), physical (Farmer and Geanakoplos, 2009) and computational (Tsfatsion, 2001) models and theories. In contrast, the emphasis on practicality in engineering has created very powerful modeling frameworks, but the field has largely neglected synthetic frameworks (see Suh (1990) as an attempt to redress this imbalance). It should be acknowledged that the absence of general theories need not be seen as a weakness, and for some this is probably a strength. In this review we attempt to outline the character of theory – for good or ill – biological theory in particular, where we shall cover some of the following questions:

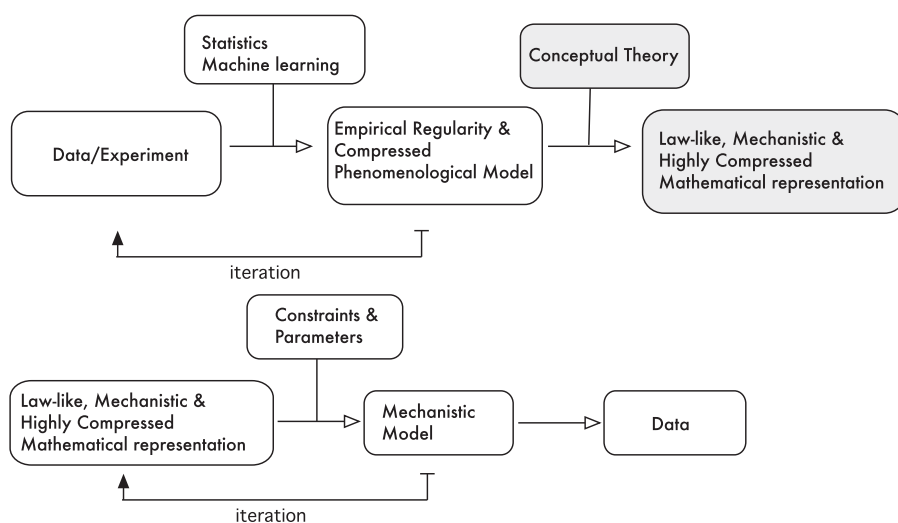
1. What is a scientific theory, and a biological theory in particular?
2. What is the relationship of theory to models?
3. What are the limitations of statistical models, or models based on machine learning?
4. Why have effective biological theories been difficult to construct?

5. In what way is evolutionary history a source of difficulty or a source of solutions in theory construction?
6. Do biological theories require new experimental, mathematical and computational tools?

## 2. Introduction to theory

Science begins by identifying regularities within sets of observations. The challenge of extracting patterns from complex empirical data is the province of statistical inference (Fig. 1A). But even the most parsimonious statistical representations of data do not constitute theories. Before we can look for patterns, we often need to know what kinds of patterns to look for, which requires some fragments of theory to begin with. For the purpose of our argument, we consider an explanatory theory to be a mechanistic-deductive model that applies in a large number of different situations. We might call such a theory a quantitative law if it defines a core set of concepts expressed as universal conditionals from which testable predictions can derive (Nagel, 1979).

The progressive refinement of quantitative observables into a suite of variables that are interrelated across temporal and spatial scales is one critical approach to theory building. In a hierarchical refinement, the lowest levels are represented by the most general (sometimes considered as the fundamental) mechanisms and processes, whereas the highest levels refer to “emergent” properties of matter that require new forms of description and explanation (Laughlin et al., 2000). By definition, the highest levels do not capture all of the variation present at the lowest levels. Critical variation at the lowest levels, however, may promote through frozen accidents, diversity at the highest levels of a kind that prevents a theory from attaining the universal character of physical law. We expect this to be the case in biological theories, largely as a result of the enduring role of initial conditions propagated through the evolutionary processes. Bertrand Russell wrote that “All exact science is dominated by the idea of approximation”. This is an insight often missed when criticizing biological theories on the ground of empirical exceptions. We should be more worried if there were none.



**Fig. 1.** The dual logic of model building in theoretical sciences. In Panel A we illustrate the common inductive–deductive flow of information involved in developing theory. Observational data are mined for regularities using inferential statistics that seek to reduce the dimensionality of a phenomenon and filter out uninformative noise. These regularities provide the “effective” degrees of freedom for “effective”, quantitative or logical theories that further compress statistical regularities in terms of verifiable, mechanistic processes. In Panel B we illustrate an alternative means of deriving models through the constraining of a general theory or law of nature. A model of a ballistic trajectory through the parameterization of classical equations of motion or the construction of a population genetics dynamics through the application of Darwinian dynamics are both of this variety. In both cases the models are iteratively improved by means of comparing and reducing discrepancies with compressed, observational data.

Predictive theories that show significant degrees of generality in biology have tended to be based on dynamical properties of biological systems or derived from a logical calculus such as parsimony and its statistical extensions (Hennig, 1965; Felsenstein, 1988). The former category includes a family of theories in population biology (Levins and Lewontin, 1985) (such as ecological theories based on predator–prey interactions), evolutionary biology (such as multilevel selection theory and game theory), and neuroscience (such as learning theories based on neural networks of Dayan and Abbott (2001)). Theories that started out with a logical calculus include cladistics or phylogenetic systematics. Through likelihood-based extensions (Felsenstein, 1988), phylogenetic systematics have become the standard technique for reconstructing the evolutionary history of life and other evolving systems, such as languages.

To ground subsequent discussion, we briefly consider three examples, each of which represents a formal attempt at explaining a key feature of biological systems. These examples span the spectrum from putative theories to simple models. Throughout this review we tend to neglect toy models that make only weak connections to empirical data.

**Scaling:** Despite the diversity and complexity of organisms, key biological processes generate rates  $Y$ , such as basal metabolic rate that scale as simple power laws,  $Y = Y_0 M^b$ , over many orders of magnitude in body mass  $M$  ( $Y_0$  is a normalization constant). The exponents  $b$  are often multiples of  $1/4$ . These scaling laws underlie and constrain many organismal time scales (such as growth rates, gestation times, or lifespans) as well as trophic dynamics. It has been suggested that the relation between basal metabolic rate and body mass is determined by the scaling relation between the volume of a hierarchical space-filling (fractal) vascular network and the number of its endpoints (capillaries) (West et al., 1997). The hypothesis then is that hierarchical, fractal-like branching networks were evolved by natural selection to minimize power loss when delivering resources to the cells of the body.

**Gene regulatory networks:** In many cases, the development of complex phenotypic features is described in terms of gene regulatory networks, or GRNs. Networks of interacting genes provide a causal and partially mechanistic explanation for the temporal and spatial regulations of embryonic differentiation and the development of specific phenotypic characters, such as the skeleton of sea urchin larvae, the heart, or the dorso-ventral patterning of a *Drosophila* embryo (Davidson, 2006; Davidson and Erwin, 2006). Once cell differentiation was recognized as a problem of regulation and molecular mechanisms governing the expression of individual genes were elucidated, logical and conceptual models of ontogenetic patterning became possible. Decades of empirical studies have brought to light dependencies between the expression of genes, revealing the structure of regulatory networks (Britten and Davidson, 1969; Materna and Davidson, 2007). This type of data has enabled conceptual theories that link the structure of GRNs to patterns of phenotypic evolution. Yet, recent data suggest that GRNs are but one element of larger class of regulatory mechanisms that includes RNA based and chromatin-based mechanisms.

**Neural networks:** There is great interest in how architectures of biological systems can be used to solve computational problems. Perhaps the most conspicuous architecture is the brain. In an influential paper, McCullough and Pitts (1943) suggested that the brain be thought of as a distributed computing network with neuronal nodes implementing a boolean logic. Hopfield (1982) neural network builds on this idea providing a simple model of memory by “training” the network to associate input patterns with output patterns using a learning process based on the minimization of an energy-like function.

### 2.1. Case study summary

These examples illustrate that the purpose of both theories and models is to provide unifying frameworks for measurable quantities, capable of generating explanatory and predictive statements about nature. In moving from scaling to GRNs and neural networks, we move from a data rich deductive framework to increasingly engineered models, which provide a proof of principle for developmental or neural function. These models conform to May's (1973) biological model spectrum, ranging from pragmatic or tactical descriptions of specific systems through strategic models aiming to capture widespread regularities. All three examples are broadly applicable, as metabolism, gene regulation and nervous systems are common in nature. However, the genetic and neural examples appeal to contingent structures and functions that are not always observed in biological taxa, and hence depend on a larger set of evolved constraints and parameters (Levins, 1966). These models also illustrate a shift in perspective—from parsimonious systems of relations among macroscopic variables (scaling), towards more detailed algorithmic specifications generating patterns of behavior at a microscopic level (gene and neural regulation). There are in addition numerous models in biology and economics exploring the logical or empirical implications of sets of constraints and interactions without application to carefully curated data sets. Indeed these models – such as game theory – have dominated economic theory. These are often powerful intermediates towards models with a stronger correspondence to data. Due to brevity, we do not consider this class of quantitative “thought experiments” in this review.

## 3. The relationship of biological models to theory

We can be more explicit about the relationship of models to theories. When general deductive and logic rule-based frameworks (theories) are modified to fit a specific system by means of the addition of constraints and parameters, or when logic rules are “engineered” to describe a particular phenomenon, we speak of models (Fig. 1B). Models represent the dominant application of mathematics and computation in biology. Theories would ideally support a large number of different models and frame a broad range of nominally different modeling contexts. The more fundamental the theory, the greater its generality. Newton's theory of gravitation can be applied to masses of any scale and configuration, such that a model of a solar system resembles a model of a billiard table.

It is seldom the case in biology that a model is derived deductively from a more fundamental quantitative theory, with the possible exception of population genetics which has its foundations in evolutionary theory. But this need not be a grave weakness. The Hardy–Weinberg principle for alleles at equilibrium is not based on a general theory of inheritance, although this might be a realistic goal. Rather it is a model based on a set of very specific assumptions or constraints. The model is very useful in providing insights into departures from neutral expectations, i.e. the basic conditions for its formulation, and in establishing one desirable end point for a theory. In this way models can be a useful stop-gaps in working toward, or engineering a theory, by suggesting possible experiments and providing a testable and predictive re-description of a complex body of data in lower dimensions.

Models often serve pragmatic purposes. Machine learning approaches and related engineering formalisms, such as neural networks, decision trees and support vector machines are prevalent in bioinformatics and neuroscience (Bishop, 2006). This type of modeling of data seeks to construct computationally

efficient representations of data with the aim of generalizing from given instances and making predictions out of sample. In this goal these approaches have been extremely successful. In most cases, it is neither intended nor possible to extract from these models an insight into what they have learned. One of the vaunted benefits of machine learning is that classification and prediction tasks can be performed without insights into the structure and dynamics of the underlying system. For this reason machine learning is a powerful means of preprocessing data in preparation for mechanistic theory building (Witten and Frank, 2005), but should not be considered the final goal of a scientific inquiry. There is a growing trend to equate the results of machine learning with the kinds of insights generated by algorithmic models like those described above applied to gene regulation. This is to confuse the implicitly algorithmic nature of inferential frameworks used in data mining, with the mechanistically principled, computational frameworks that have arisen over the course of evolution.

A related approach is simulation, where computational power allows for a large number of variables and parameters to be included in the exploration of empirical regularities. Rather than reconstruct properties of the data by dimension reduction as in machine learning, one seeks to fit data based on *a priori* mechanical models. This is somewhat different from the straightforward reductionist approach (Fig. 1A), as it seeks to employ prior principles in order to accommodate ensembles of data (Fig. 1B). The best known examples for this are Monte Carlo (MC) simulations and agent based models (ABM) (Bonabeau, 2002). MC simulation seek to solve problems where there is a lack of statistical power by generating large data sets compatible with model assumptions. ABM seek to increase the degrees of freedom of individual agents and in this way, represent more realistic models of behavior where agent rules are assumed to percolate into collective dynamics (Epstein, 1999). This approach often presupposes that coarse-graining a system is not desirable, as the process of abstraction can eliminate essential details required to fully explain, or reproduce, the system dynamics. A weakness of ABM in practice is that they can too easily be constructed and their underlying rule sets are often poorly tested empirically.

The most recent incarnation of the model-based approach to biology is systems' biology, which seeks to automate, as far as possible, the analysis and reduction of large bodies of – most recently molecular – data present these in terms of parsimonious data structures (Alon, 2007; Hood, 2003; Kirschner, 2005). These structures tend to be selected on the basis of calculational efficiency and generality. However, in system's biology there has also been an effort to reconcile these structures with known mechanism through simulation and rule-based approaches in order to provide a basis for systematic logical analysis of biological pathways and dynamics (Danos et al., 2009).

Thus models can be derived from a general theory – top down – through the application of constraints, or derived from data – bottom up – through the assumption of preferred data structures. In both cases, the model represents a structure of local cognitive and predictive utility. Theory provides the basis for the general synthesis of models, and a means of supporting model comparisons and ideally establishing model equivalence.

#### 4. The challenges and character of biological theory

The current absence of a strong theoretical foundation in biology means that there is weak guidance regarding what quantities or variables need to be understood to best inform a general understanding (an explanatory basis) for biological features of interest. An unfortunate result of the absence of theory is that some researchers confuse just having data with 'understanding'.

For example there is a base for collecting and analyzing the most microscopic data: experimental procedures and measurements in a high-throughput transcriptomics study are built around the assumption that transcripts are the primary data to be explained, and in neuroscience, recording from numerous individual neurons. This bias reflects a rather naive belief that the most fundamental data provide a form of explanation for a system, as if enumerating the fundamental particles were equivalent to the standard model in physics.

With the advent of high-throughput genomics, transcriptomics, proteomics, and metabolomics, and functional imaging we have witnessed a technological revolution in biology that went hand-in-hand with the rise of bioinformatics and the widespread use of machine learning predictions. There has been a lack of complementary conceptual theory that could help us organize the flood of facts. An emphasis on models, rather than theory, has led to an occasional failure to recognize as legitimate conceptual questions that do not yet have associated with them a set of well-defined modeling tools. This lack of conceptual guidance in the practice of technology driven research can also be seen in the problematic and historically derived structure of large scale databases, which are still static and largely sequence-based, whereas recent empirical discoveries strongly suggest that a database structure explicitly representing the multiple dynamic relations between relevant elements (DNA sequence, transcripts, proteins, etc.) would be more desirable.

A persistent problem in biology is that regularities exist at aggregate levels of description. It is assumed that a qualitatively different theory is required to explain these emergent phenomena than the theory describing the underlying microscopic dynamics (Anderson, 1972). Chemistry, in particular synthetic organic chemistry, serves as a good example. It is taken for granted in the field that chemical reactions can be understood in terms of the underlying quantum mechanics. Higher-level concepts, such as "bonds" or "electronegativity" are used in practice to explain chemical reactivity. In fact, organic chemistry is taught in terms of rules of transformations ("reaction mechanisms" and "named reactions") that are much more akin to the graph grammars of theoretical computer science than to the many-body quantum mechanics alluded to as the theoretical foundation (Benko et al., 2004). Interestingly, although we learn organic chemistry to a large extent as a collection of structured (transformation) rules, this is rarely made explicit, and even more rarely formalized at this level (with the exception of a few enterprises in *Artificial Chemistry* (Fontana and Buss, 1994; Benko et al., 2003; Suzuki and Dittrich, 2009). The rule-based representation of chemistry might serve as an example of a "non-physics"-type theory. Whereas chemical (reaction) equations again describe relationships of sets of observables (in this case the educts and products of a chemical reaction), the algorithmic *transformation rules* provide a means of predicting what novel entities might be produced. The price we have to pay for the convenient high-level description—for not being derailed by details of electron densities and nuclear movements in physical space—is twofold: First, we have to memorize quite a few rules, not just a single, beautiful and fundamental equation. And secondly, the predictive power of the rules is limited: For instance, to decide which of the (potentially many) applicable rules describes the chemical reaction that is going to take place in a certain situation requires recourse to the underlying physics—in this case, to determine activation energies and the energy balance of a reaction.

The same logic applies to biological models in theoretical ecology and population genetics (Bulmer, 1994; May, 2001). Systems of competition equations seek to capture essential interaction rules among individuals and species, without including the energetic, physiological and behavioral bases of the

interactions. It is assumed that these processes, all of which in some fundamental way determine the nature of the competition, can be summarized by means of interaction coefficients. This is admissible if one is simply trying to ascertain the most likely equilibrium outcome of competition in a density regulated population. Historically, the simple formulation of the Lotka–Volterra equation as a system of linked differential equations has not only enabled the description of a wide range of population dynamics, but also allowed for a general analysis of such processes with regard to their stability (Kingsland, 1995). As with ecology, in population genetics the details of the nucleic acid sequences, the molecular biology of cell division and development, as well as those factors determining the aggregate value of fitness are deliberately neglected (Gillespie, 1994; Kimura and Takahata, 1994). The essential transmission rules of Mendelian inheritance are captured through simple recurrence equations (Gillespie, 2004). Once again, the processes of drift and selection acting on heritable traits are considered suitable coarse-grained descriptions in order to grasp the equilibrium behavior of populations of genomes. And within these general dynamics, a family of more specific models has emerged that investigate the consequences of particular types of constraining assumptions, such as specific constraints on the underlying genetic architecture or the interactions between the genome and the environment.

#### 4.1. Problems of level separation

So why has constructing biological theory been such a challenge? In biology, unlike for traditional physical and chemical phenomena, many of the spatial and temporal scales interact. In physics, nuclear forces can be neglected when calculating planetary orbits as these are screened off over large distances. In biology, however, the lowest levels can have a direct impact on the highest levels (and vice versa), as in the case of genes that influence behavior and social structures and behavior that influence gene expression patterns (Young and Hammock, 2007; Abbott et al., 2003). Levin et al. (1997) suggests that one of the central issues for theoretical biology is the better understanding of how detail at one scale makes its signature felt at other scales, and how to relate phenomena across scales. There is no reason to assume that the imperfect separation of levels of description is prohibitive to formulating meaningful theory, although it might place limits on the accuracy of prediction at any given level.

This connects directly with the thorny question of emergence. How much of biological nature can be predicted from basic physical law? This question is simple to answer: effectively zero. We know, in so far as we have tested them, that all of biology is compatible with, or in principle derivable from, physical laws. But this is a different statement. Classical mechanics, quantum mechanics, relativity and condensed matter physics (Einstein et al., 1966; Kragh and Brush, 2001), to name only four classes of physical theory, do not in themselves predict biological evolution or any of its products (Anderson, 1972). This tells us that evolutionary dynamics must be the outcome of a series of frozen accidents in physical dynamics, accidents that somehow have provided the basis for the formation of adaptive bio-molecules. This is called the emergence problem. There are two properties of interest in the emergence discussion. One might be called *endogenous coarse-graining property*. The other might be called the *long history property*. Endogenous coarse-graining is the use of some summary statistic, or aggregate variables, by the system or its components to make decisions. The idea is that the summary statistic, which changes relatively slowly, is a better predictor (or hypothesis) of the system's future state than lower-level, faster timescale fluctuations in component behavior (Crutchfield and

Shalizi, 1999; Krakauer and Zanotto, 2008; Boehm and Flack, 2010). Building these variables is a way to buffer against misleading or erroneous information at lower levels (Boehm and Flack, 2010; Flack and deWaal, 2007). For example in the brain, individual neurons can be unreliable and population averages provide more reliable information through redundancy. And in populations of organisms, individual preferences can be misleading of group trends. Hence system components are a product of and respond to system averages.

Systems with long histories (i.e., mechanisms of long-term memory) allow for the “emergence”, or accumulation of physical properties in a growing space of otherwise highly unpredictable states. This idea has been captured intuitively through a complexity measure – algorithmic depth – which seeks to equate complexity with historical depth (Bennett, 1988; Machta, 2006). Hence complex systems are systems for which a full understanding requires a specification of a historical sequence. Replication and natural selection are themselves endpoints on one or more of many paths along which basic physical symmetries have been broken, leading to sustained preferences for alternative configurations of matter. Finding some principled means of enumerating and bounding these trajectories presents a great challenge for theoretical biology.

#### 5. Theoretical biology in relation to evolutionary theory

The evolutionary history characteristic of biological systems is most frequently adduced – as above – as an argument against theory. Evolution has been called a tinkerer (Jacob, 1977), improving on existing biological adaptations by incremental modification over generations. Should we expect tinkering to generate structures and functions comparable to those observed in abiotic systems, a regularity permitting the development of theories of great generality and predictive power (Avisé and Ayala, 2007)? The pervasive distribution of contingencies, or accidents of history across the tree of life, suggests that this is not likely to be the case. In response, some have argued for theories of “contingent generality”-models of adaptive regularities restricted to specific clades and guilds.

The idea of a contingent generality also alludes to the power of a shared history and the opportunities afforded by historically grounded generalities. The observation that all of life shares an evolutionary history, imposes enormous regularity on biology in the form of conserved traits amenable to general description and explanation (Krakauer, 2002). For example, many of the mechanisms of inheritance and of development are effectively universal (Carroll, 2000). This also extends to the level of individual sequences and proteins. The conserved structure of life opens up a huge space for general theory that could not be developed if life where the outcome of multiple independent origins.

The common phylogenetic structure of living systems forms the basis for a large range of powerful theoretical frameworks that seek to explore the ancestor–descendant relationships among species (Hillis et al., 1997). Cladistics, numerical taxonomy, phylogenetic inference, coalescent theory and all provide useful generalizations that apply across many different species, and can claim to form a quantitative theoretical framework for much of biology (Hennig, 1965; Felsenstein, 1988). The foundation of these fields is the common recognition that lineages undergoing evolutionary diversification can be grouped into monophyletic groups based on shared characters or synapomorphies and that the nested hierarchy of these lineages is characterized by a similarly nested hierarchy of characters. Phylogenetic reasoning is thus a universally applicable calculus

for the reconstruction of branching patterns in genealogical systems.

At the level of the genome, models of gene regulation, drawing heavily on insights from engineering, developed in relation to a model system, such as the fly or sea urchin, are by virtue of the conserved structure of developmental regulation, likely to apply to most forms of multicellular life (Davidson, 2006). In this way, a general theory of regulation in biology becomes possible, even though life itself has clearly evolved as a result of a huge number of frozen accidents. Such a universal theory has to incorporate multiple competing basic mechanisms (transcriptional regulation, post-transcriptional silencing, chromatin modifications, DNA amplifications) (Materna and Davidson, 2007). Clades evolve in ways that emphasize different traits; some are reduced while others are elaborated in great detail. Is this variability really “just” a frozen accidents or is there a way to understand physical and/or logical constraints on these historical contingencies?

The field of social evolution is another area that has had success in developing theories based on mid-level generalities. Complex social systems have evolved several times, with primates (including humans) and eusocial insects being the most prominent examples. Important features of these systems include the full or partial division of labor, heterogeneity, learned strategies sets, novel transmission mechanisms, and the prominent role of ontogenetic in addition to evolutionary dynamics. These features have highlighted fundamental problems, such as explaining altruism within a framework of individual-based selection (Hamilton et al., 2001; Hamilton, 1971). Recently, progress has been made through the development of theories that have either expanded fundamental selection dynamics in a hierarchical fashion, such as multilevel selection theory (Lehmann et al., 2007a), demonstrating a mathematical isomorphism between kin selection and group selection (Hamilton, 1975; Traulsen and Nowak, 2006; Lehmann et al., 2007b; Frank, 1998), or how individual-based strategies in game theory might account for the evolution of behavior. This last case is particularly interesting, as we have subsequently seen an expansion of this concept to account for dynamical interactions at lower levels of complexity such as viral dynamics (Nowak, 2006). Hence game theory, and population dynamical models, has contributed to the common organization of a large range of materially disparate phenomena, and might eventually assume the status of “theory” in the sense of providing a quantitative demonstration of principle that applies to dynamics at very different biological levels (Levin et al., 1997).

## 6. Theory and the logic of experimental design

Many natural sciences make progress through a careful choice of model system. Model systems in physics seek to isolate the crucial, causal components in system dynamics, and render them amenable to observation and quantification. Galileo's inclined plane and Newton's experiments with a prism are of this sort. The analysis of the giant squid axon by Hodgkin and Huxley was also in this tradition, as it sought to bring the properties of excitable cells into the purview of a controlled, laboratory experiment.

A qualitatively different model system in physics, and one that is closer to traditional biological model systems, is the hydrogen atom. The hydrogen atom is simple enough in structure and properties to offer itself up as a test case for fundamental theory – from quantum mechanics through to chemistry. An ability to predict many, if not all, of the chemical properties of the hydrogen atom is thought to provide strong support for fundamental theory, and justify the extension of the theory to more complex atoms, and perhaps even molecules.

The most common biological “hydrogen atoms” are the standard model organisms, such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, etc. These are all species that represent nominally tractable and representative forms of life. The discovery of genetic and molecular machinery in any one of these is assumed to represent a reasonably plausible prior for the discovery of a related mechanism in an untested species. This is often the case, but calls for a very careful choice of model system in terms of our basic knowledge of phylogenetic relationships and identification of representative features. A uniform, or at least principled, distribution of species for analysis over the tree of life might be weighted as heavily as the more typical economic factors when selecting model species. There is otherwise a risk of providing detailed insights into idiosyncratic species. Social evolution is a good example in so far as there will be no compelling theory of social evolution if it is built on data on social processes at a single level. We require a set of model systems – from biofilms to *volvox* to the primates – that span a space of problems encountered in the evolution of aggregates. In this way, theoretical approaches might provide a justification and procedure for the choice of model species or genera. Furthermore, adopting a *comparative model systems approach* offers the prospect of testing the generality of theories as they pertain to life on earth.

Even when in possession of a suitable set of model systems, there is a problem of establishing causality in highly interconnected systems. There is rarely a single, dominant force at a given scale in biology. This requires novel combinatorial, experimental procedures that allow for multiple fixed or knock-out, interventions, with their consequences monitored in a range of contexts and variety of timescales. Different contexts and time-scale assessments are required for establishing different kinds of causal relations. This is becoming practical with increasing automation of experiment, and in this way comes to resemble large projects in high energy physics. In addition to informing experimental methods to get at complex causal interactions in many biological systems, the exercise of designing knock-out protocols in such systems, particularly when coupled to a comparative model systems approach, promises to provide powerful insight into the problems that the system overcame over its own evolutionary history.

## 7. Theoretical tools and formal languages

Having identified phylogenetically widespread regularities, we might ask what form biological theory might take that best captures the essential phylogenetic sub-structure: natural language narrative (as in the humanities), compressed transformation rules capturing physical interactions (as in organic chemistry), traditional dynamical systems (as in physics), or new forms of computer based logic and simulation?

It is widely agreed that natural language plays a very powerful role in concept formation and in concept dissemination. However, in the middle stages of science, more formal approaches, such as mathematics and computer models, tend to provide a significant advantage over natural language. The reasons for this have been long debated in the philosophy literature.

Wigner (1960) writes of “The Unreasonable Effectiveness of Mathematics in the Natural Sciences”, referring to the existence of empirical regularities of great generality that are often physically continuous properties of a natural system. However, the uncertain nature of initial conditions provides an ultimate limit to law-like theories. In such cases we might be required to generate a variety of theories, each conditioned on the initial conditions. In this way, in a biological setting, each species might require a

different theory as each was originated in slightly different circumstances. This is obviously undesirable, and in all likelihood, unnecessary.

There is, however, another problem discussed by Wigner: there is no *a priori* reason to believe that all phenomena will be unified by mathematics. Speaking of the laws of physics and heredity, Wigner wrote that, '*it is quite possible that an abstract argument can be found which shows that there is a conflict between such a theory [heredity] and the accepted principles of physics*'. Wigner had in mind when writing this, the rather more "modest" difficulty of unifying relativity and quantum mechanics.

If there are few standard, mathematical frameworks of compelling power for biology, might there be alternative frameworks that are better suited to exposing general properties of adaptive nature? It is frequently claimed that – like Newton's invention of calculus – biological theory will require 'new mathematics'. Cohen (2004b) has reviewed many intriguing cases where biological problems have led to the development or refinement of areas of mathematics, from non-linear dynamics through to stochastic processes. There are, however, many areas of mathematics that have been neglected by theoretical biology that could prove to be of great value. Einstein's work on general relativity, for instance, made good use of mathematical ideas, in particular differential geometry that had previously been developed with completely different motivation. More likely than not, the formal structures have been set forth in some context, and await their discovery and subsequent development in representing biological theory.

The analysis of regular features of natural language using formal grammars in linguistics is a powerful example of a formal theory that seeks to explain regularities in nature without adopting the traditional mathematical approaches found in physics (Chomsky, 1990, 1965). This is an approach based on computational rule systems (such as *L*-systems) capable of generating, hierarchical or recursive, tree-like outputs. In a biological context such as development, formal grammars seek to describe transformation rules capable of generating a set of complex phenotypes, such as branching morphologies, or nested sets of cell types.

To-date, the problem with these algorithmic approaches has been their weakness in generating predictions and their limited ability to fit quantitative data. Unlike Newton's laws that can help us place a robot on the surface of Mars, formal grammars have not yet predicted, say, the specific details of the ras cascade. Perhaps this kind of detailed prediction is not the goal in biological examples, in which case we need to be very explicit about the goals of biological theory in the face of a demonstrable absence of fine-grained predictive power.

## 8. Conclusions

Theory in physics has succeeded in identifying effective degrees of freedom at multiple scales of physical organization, and used corresponding effective theories to both predict and intervene, in natural processes. Biology has achieved comparable success, at more modest scales, in only a few domains: best known of which are population biology, population genetics, and the theory of scaling. In each case, the relatively simple nature of the measured variables (population density, allele frequencies, and mass) has allowed that coarse-grained theory achieves a high level of predictive and explanatory power. When we turn to finer grained details, such as gene expression, or components of physiology and behavior, then general theories have proven more elusive, and system-specific or engineering or economic style models have dominated (Keller, 2003). As the volume of

biological data has increased, we have observed a corresponding shift in model preferences, towards those frameworks that provide increasing predictive power and a loss of compressed, explanatory insight. These are often computational models, and suggest a future in which informational and algorithmic concepts will come to dominate our understanding of adaptive processes. The great challenge will be to synthesize these high dimensional predictive frameworks with the kind of low dimensional effective theories that have proved so successful in the physical sciences. If this objective proves to be impossible, we shall find ourselves in a world not unlike that of statistical inference, where we are able to predict and control the biological world, but for reasons unknown.

At this point there are reasons to be more optimistic. There are many properties of biology, including its common phylogenetic structure that seem to offer a powerful organizing framework for mathematical theories of the more traditional variety, even when this history imposes contingency on biology, militating against regularities at the most detailed levels. In this sense biology has a prospect of turning what would be pure modeling approaches in economics or sociology (restricted to a single lineage of primate), into more general principles by virtue of their phyletic generality. This is not a criticism of social science models, merely a limitation of their disciplinary application.

There are also conceptual possibilities that have gone largely unexplored. Physics has grown conceptually by accommodating a diversity of mathematical disciplines, from dynamics through to group theory (Courant and Hilbert, 1962). Einstein was able to develop new physical theory by recognizing the crucial value of differential geometry in describing space time. Theoretical biology has been mathematically somewhat more restricted, focusing largely on dynamics, stochastic processes and more recently, on discrete mathematics (Cohen, 2004a). It will likely prove very profitable to explore a wider range of mathematical ideas (Cowan and Society, 1974), especially those connected with formalizations of logic rules and a variety of frameworks supporting concepts related to information-processing, such as info-max assumptions, and forms of distributed decision-making.

A few uniquely biological problems that might benefit from an infusion of new mathematics include unraveling the intimate relationship between energy and information, the origins of heterogeneous, hierarchical structures, the development of principled explanations for individuality (Krakauer and Zanotto, 2006), the emergence of learning mechanisms, how social systems and multicellular organisms arise from simple adaptive agents, and when persistence mechanisms, as opposed to replication mechanisms, play the organizing role in evolutionary dynamics. In each of these cases, new ideas will be required to realize the ultimate goal of theory, as articulated by Mach, "the completest possible presentation of the facts with the least expenditure of thought". The least expenditure of thought, to imply comprehension, not the minimal representation of the data *in silico*.

## References

- Abbott, D., Keverne, E., Bercovitch, F., Shively, C.A., Mendoza, S.P., Saltzman, W., Snowdon, C.T., Ziegler, T., Banjevic, M., Garland, T., Sapolsky, R.M., 2003. Are subordinates always stressed? a comparative analysis of rank differences in cortisol levels among primates. *Hormones and Behavior* 43, 67–82.
- Alon, U., 2007. An introduction to systems biology: design principles of biological circuits. An Introduction to Design Principles of Biological Circuits URI Alon. Chapman & Hall/CRC, Taylor Francis Group Computational, CRC Press.
- Anderson, P., 1972. More is different. *Science* 177, 393–396.
- Arrow, K., 1994. Methodological individualism and social knowledge. *The American Economic Review* 84, 1–9.
- Avise, J., Ayala, F., 2007. In the light of evolution i: adaptation and complex design. *Proceedings of the National Academy of Sciences USA* 104, 8563–8566.

- Benko, G., Flamm, C., Stadler, P.F., 2003. A graph-based toy model of chemistry. *Journal of Chemical Information and Computer Science* 43, 1085–1093.
- Benko, G., Flamm, C., Stadler, P., 2004. Multi-phase artificial chemistry. In: *The Logic of Artificial Life: Abstracting and Synthesizing the Principles of Living Systems*, vol. 1, pp. 10–20.
- Bennett, C., 1988. Logical depth and physical complexity. *The Universal Turing Machine A Half Century Survey*, The Universal Turing Machine: A Half-Century Survey. Springer.
- Bishop, C.M., 2006. *Pattern Recognition and Machine Learning*. Springer, NY.
- Boehm, C., Flack, J.C., 2010. The emergence of simple and complex power structures through social niche construction. In: Guinote, A., Vescio, T.K. (Eds.), *The Social Psychology of Power*. The Guilford Press.
- Bonabeau, E., 2002. Agent-based modeling: methods and techniques for simulating human systems. *Proceedings of the National Academy of Sciences USA* 99, 7280–7287.
- Britten, R., Davidson, E., 1969. Gene regulation for higher cells: a theory. *Science* 165, 349–357.
- Bulmer, M., 1994. *Theoretical Evolutionary Ecology*. Sinauer Associates.
- Carroll, S.B., 2000. Endless forms: the evolution of gene regulation and morphological diversity. *Cell* 101, 577–580.
- Chomsky, N., 1965. Aspects of the theory of syntax. Special Technical Report of the Research Laboratory of Electronics of the Massachusetts Institute of Technology, vol. 11.
- Chomsky, N., 1990. On formalization and formal linguistics. *Natural Language Linguistic Theory* 8, 143–147.
- Cohen, J., 2004a. Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better. *PLoS Biology* 12, e439–e440.
- Cohen, J.E., 2004b. Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better. *PLoS Biology* 2 (12), e439. doi:10.1371/journal.pbio.0020439.
- Colander, D., 2000. The death of neoclassical economics. *Journal of the History of Economic Thought* 22, 127–143.
- Courant, R., Hilbert, D., 1962. *Methods of Mathematical Physics*, vol. 11. Interscience.
- Cowan, J.D., Society, A.M., 1974. Some mathematical questions in biology. *Lectures on Mathematics in the Life Sciences*, vols. 6, AMS Bookstore, p. 141.
- Crutchfield, J.P., Shalizi, C.R., 1999. Thermodynamic depth of causal states: objective complexity via minimal representations. *Physics Review E* 59, 275–283.
- Danos, V., Feret, J., Fontana, W., Harmer, R., Krivine, J., 2009. The middle way. *Transactions on Computational Systems Biology* 11, 116–137.
- Davidson, E., 2006. *The Regulatory Genome: Gene Regulatory Networks in Development and Evolution*. Associated Press.
- Davidson, E., Erwin, D., 2006. Gene regulatory networks and the evolution of animal body plans. *Science* 311, 796–800.
- Dayan, P., Abbott, L., 2001. *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*. The MIT Press, Cambridge, MA.
- Einstein, A., Infeld, L., Infeld, L., 1966. *The Evolution of Physics: From Early Concepts to Relativity and Quanta*. Simon and Schuster.
- Epstein, J., 1999. Agent-based computational models and generative social science. *Complexity* 4, 41–60.
- Farmer, J.D., Geanakoplos, J., 2009. The virtues and vices of equilibrium and the future of financial economics. *Complexity* 14, 11–38.
- Felsenstein, J., 1988. Phylogenies from molecular sequences: inference and reliability. *Annual Review of Genetics* 22, 521–565.
- Flack, J.C., deWaal, F., 2007. Context modulates signal meaning in primate communication. *Proceedings of National Academy of Science USA* 104, 1581–1586.
- Fontana, W., Buss, L.W., 1994. What would be conserved if 'the tape were played twice'? *Proceedings of National Academy of Science USA* 91, 757–761.
- Frank, S., 1998. *Foundations of Social Evolution*. Princeton University Press, Princeton.
- Gillespie, J., 1994. *The Causes of Molecular Evolution*. Oxford University Press, USA.
- Gillespie, J., 2004. *Population Genetics: A Concise Guide*. JHU Press.
- Glimcher, P.W., Rustichini, A., 2004. Neuroeconomics: the consilience of brain and decision. *Science* 5695, 447–452.
- Hamilton, W., 1971. Geometry for the selfish herd. *Journal of theoretical Biology* 31, 295–311.
- Hamilton, W., 1975. In: Fox, R. (Ed.), *Biosocial Anthropology*. Malaby Press, London.
- Hamilton, W., Ridley, M., Dawkins, R., Bunney, S., 2001. *Narrow Roads of Gene Land: The Collected Papers of wd Hamilton*. Oxford University Press.
- Hennig, W., 1965. Phylogenetic systematics. *Annual Review of Entomology* 10, 97–116.
- Hillis, D., Moritz, C., Mable, B., Sperling, F., 1997. Molecular systematics. *Annals of the Entomological Society of America* 85, 536–537.
- Hood, L., 2003. Systems biology: integrating technology, biology, and computation. *Mechanisms of Ageing and Development* 124, 9–16.
- Hopfield, J., 1982. Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the National Academy of Sciences USA* 79, 2554–2558.
- Jacob, F., 1977. Evolution and tinkering. *Science* 196, 1161–1166.
- Keller, E., 2003. *Making Sense of Life: Explaining Biological Development with Models, Metaphors and Machines*. Harvard University Press, Boston.
- Kimura, M., Takahata, N., 1994. *Population Genetics, Molecular Evolution, and the Neutral Theory: Selected Papers*. University of Chicago Press.
- Kingsland, S.E., 1995. Modeling nature: Episodes in the History of Population Ecology. University of Chicago Press, p. 306.
- Kirschner, M., 2005. The meaning of systems biology. *Cell* 121, 503–504.
- Kragh, H., Brush, S., 2001. Quantum generations: a history of physics in the twentieth century. *American Journal of Physics* 69, 524–525.
- Krakauer, D., 2002. From physics to phenomenology. Levels of description and levels of selection. 'In silico' simulation of biological processes, *Novartis Foundation symposium*, vol. 247. John Wiley and Sons.
- Krakauer, D.C., Zanotto, A.P., 2008. *Transitions From Non-Living to Living Matter*. MIT Press, Boston.
- Krakauer, D., Zanotto, P., 2006. Viral individuality and limitations of the life concept. In: *Protocells: Bridging Nonliving and Living Matter*, vol. 1, pp. 513–536.
- Laughlin, R., Pines, P., Schmalian, J., Stojkovic, B., Wolynes, P., 2000. The middle way. *Proceedings of the National Academy of Sciences USA* 97, 32–37.
- Lehmann, L., Keller, L., West, S., Roze, D., 2007a. Group selection and kin selection: two concepts but one process. *Proceedings of the National Academy of Sciences USA* 104, 6736–6739.
- Lehmann, L., Keller, L., West, S., Roze, D., 2007b. Group selection and kin selection: two concepts but one process. *Proceedings of National Academy of Science USA* 104, 6736–6739.
- Levin, S.A., Grenfell, B., Hastings, A., Perelson, A.S., 1997. Mathematical and computational challenges in population biology and ecosystems science. *Science* 275, 334–343.
- Levins, R., 1966. The strategy of model building in population biology. *American Scientist* 54, 421–431.
- Levins, R., Lewontin, R.C., 1985. *The Dialectical Biologist*. Harvard University Press, p. 303.
- Machta, J., 2006. Complexity, parallel computation and statistical physics. *Complexity (New York)* 5, 46–64.
- Materna, S.C., Davidson, E.H., 2007. Logic of gene regulatory networks. *Current Opinion in Biotechnology* 18, 351–354.
- May, R., 1973. *Stability and Complexity in Model Ecosystems*. Princeton University Press, Princeton.
- May, R., 2001. *Stability and Complexity in Model Ecosystems*. Princeton University Press, Princeton, NJ.
- McCullough, W., Pitts, W., 1943. A logical calculus of ideas immanent in nervous tissue. *Bulletin of Mathematical Biophysics* 5, 115–133.
- Nagel, E., 1979. *The Structure of Science: Problems in the Logic of Scientific Explanation*. Hackett Publishing Company, Cambridge, USA.
- Nowak, M., 2006. *Evolutionary Dynamics: Exploring the Equations of Life*. Harvard University Press, Boston.
- Samuelson, P.A., 1985. Modes of thought in economics and biology. *The American Economic Review* 75, 166–172.
- Suh, N.P., 1990. *The Principles of Design*. Oxford University Press, USA.
- Suzuki, H., Dittrich, P., 2009. Artificial chemistry. *Artificial Life* 15, 1–3.
- Tesfatsion, L., 2001. Introduction to the special issue on agent-based computational economics. *Journal of Economic Dynamics and Control* 28, 281–293.
- Traulsen, A., Nowak, M., 2006. Evolution of cooperation by multilevel selection. *Proceedings of National Academy of Science USA* 103, 10952–10955.
- West, G., Brown, J., Enquist, B., 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276, 122–126.
- Wigner, E., 1960. The unreasonable effectiveness of mathematics in the natural sciences. *Communications in Pure and Applied Mathematics* 13 (1), February.
- Witten, I., Frank, E., 2005. Data mining: practical machine learning tools and techniques. <books.google.com>.
- Young, L.J., Hammock, E.A.D., 2007. On switches and knobs, microsatellites and monogamy. *Trends in Genetics* 23, 209–212.