Life is Physics: Evolution as a Collective Phenomenon Far From Equilibrium

Nigel Goldenfeld[1] and Carl Woese[1,2]

[1]Department of Physics, Center for the Physics of Living Cells, and Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801; email: nigel@illinois.edu

[2]Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, IL 61801

Annu. Rev. Condens. Matter Phys. 2011. 2:375–99

First published online as a Review in Advance on January 3, 2011

The *Annual Review of Condensed Matter Physics* is online at conmatphys.annualreviews.org

This article's doi:
10.1146/annurev-conmatphys-062910-140509

1947-5454/11/0310-0375$20.00

Keywords

evolution, collective effects, statistical mechanics, genes

Abstract

Evolution is the fundamental physical process that gives rise to biological phenomena. Yet it is widely treated as a subset of population genetics, and thus its scope is artificially limited. As a result, the key issues of how rapidly evolution occurs and its coupling to ecology have not been satisfactorily addressed and formulated. The lack of widespread appreciation for, and understanding of, the evolutionary process has arguably retarded the development of biology as a science, with disastrous consequences for its applications to medicine, ecology, and the global environment. This review focuses on evolution as a problem in nonequilibrium statistical mechanics, where the key dynamical modes are collective, as evidenced by the plethora of mobile genetic elements whose role in shaping evolution has been revealed by modern genomic surveys. We discuss how condensed matter physics concepts might provide a useful perspective in evolutionary biology, the conceptual failings of the modern evolutionary synthesis, the open-ended growth of complexity, and the quintessentially self-referential nature of evolutionary dynamics.

1. INTRODUCTION

Shortly after the publication of the draft of the Human Genome (1), Stephen Jay Gould, the noted evolutionary biologist, penned an extraordinary Op-Ed piece in the *New York Times*. Although the occasion was in some sense the apotheosis of the molecular biology revolution, begun nearly 50 years earlier with the elucidation of the structure of DNA by Watson and Crick at the Cavendish Laboratory, Gould's tone was far from laudatory. For, with the entire genome in hand, the genes could be immediately counted, yielding an initial estimate of between 30,000 and 40,000 genes, half again as many as those in the genome of the tiny roundworm *C. elegans* [we now know that the initial estimate was incorrect, and the correct number of genes is smaller, closer to 21,000 (2)]. Gould commented:

> Homo sapiens possesses between 30,000 and 40,000 genes. . . In other words, our bodies develop under the directing influence of only half again as many genes as the tiny roundworm. . . .The collapse of the doctrine of one gene for one protein, and one direction of causal flow from basic codes to elaborate totality, marks the failure of reductionism for the complex system that we call biology . . . The key to complexity is not more genes, but more combinations and interactions generated by fewer units of code and many of these interactions (as emergent properties, to use the technical jargon) must be explained at the level of their appearance, for they cannot be predicted from the separate underlying parts alone (3, p. A15).

In other words, if we are to understand our biology, we need a statistical mechanics of genes: The fundamental processes that have shaped us are strongly collective in nature, and need to be treated appropriately.

The complexities of the human genome are by no means an isolated example of collective phenomena in biology. The majority of cellular life is microbial, and these organisms also are strongly interacting. Microbes are able to exchange genes (horizontal gene transfer) (4), communicate between cells (quorum sensing) (5), translocate collectively over surfaces (swarming motility) (6, 7), and form biofilms—spatially-extended multicellular colonies with coordinated division of labor, cellular differentiation, and cooperative defense against antagonists (8). Clearly, collective processes abound in biology, but they have been relatively neglected by the biological physics community; most of the biological research being performed in physics departments today is an outgrowth of the tremendous technological advances in molecular biology, single-molecule biophysics, and computational biology.

Also neglected, but with even less justification, is the process of evolution itself; written off as a solved problem under the catchphrase "natural selection," it was relegated to a peripheral role during the development of molecular biology (9). With the growing recognition of the importance of collective phenomena in evolution especially (10–13), but also in ecology (14–18), immunology (19, 20), microbiology (21–23), and even global climate change (24–26), it is timely to assess the extent to which a condensed matter physics perspective—with its unifying principles of collective behavior arising from interactions—can be illuminating in biology. Equally fascinating is the notion that biology may extend the frontier of nonequilibrium physics, revealing principles of self-organization that seem absent in purely physical processes such as pattern formation. Is the study of biology merely an exercise in reverse-engineering a rich set of extremely complicated chemical reactions, or are deeper principles at work to bring molecules to life?

The purpose of this review is to discuss these questions by providing a necessarily selective survey of evolutionary biology, highlighting the role of collective effects and

thereby the possible connections with condensed matter physics. Thus, no attempt is made here at a complete review of evolution. Instead, we have tried to focus on points of principle, where the shortcomings of present-day understanding seem most acute to us. It would be impossible to review the entire literature of evolution or even the subset of this literature that is potentially engaging for physicists. For a useful and self-contained introduction to the conventional, eukaryote-centric framework of evolutionary theory, accessible to physicists with little biological background, we refer the reader to the standard text by Smith (27); an introduction that also covers physics-related topics especially has been given by Drossel (28). Most of life is microbial, and a modern microbe-centric view of evolution can be found in Sapp (29).

We envisage a readership with a wide range of knowledge and interest in evolutionary biology. To the biologist interested in practical issues, we ask that you do not dismiss the seemingly useless and naïve issues that we necessarily raise. On the one hand, a fundamental understanding of evolution may not seem to offer immediate benefits in terms of finding the next wonder drug; on the other hand, the lack of appreciation for the rapidity and pervasiveness of evolution has, within a lifetime, destroyed the effectiveness of numerous antibiotics (30), and probably is responsible for the limited success in treating cancer (31). The biomedical-industrial complex cannot afford to ignore the need to create a fundamental science of biology. To the physicist, who might be repelled by the seeming lack of structure represented by biology, we ask that you look beyond the currently incomplete state of biological understanding and be open to the possibility that evolution is both a physical phenomenon and the natural framework in which biology is embedded. The lack of structure in the way that biology is traditionally presented reflects the field's unavoidable focus on a single sample path; however, the underlying evolutionary process itself is surely one with deep mathematical structure, capable of expression and elucidation in unifying terms based on emergent physical laws. This is a true frontier of physics, but one that will require a great deal of what has been termed (in another context of nonequilibrium physics) "open-minded spadework" (32) to unearth.

2. EVOLUTION AS A PROBLEM IN CONDENSED MATTER PHYSICS

2.1. Life is Chemistry

Most living organisms are composed of cells. Setting aside, for the moment, the question of what constitutes "life," one might attempt to gain further insight into the nature of life by examining carefully the contents of cells. This enterprise culminated in the advent of molecular biology in the second half of the twentieth century, and it is now firmly established that cells contain a multitude of molecular components to perform the functions of life. These include such examples as phospholipid bilayers to bound the cell; cytosol, containing water and organic molecules that form the fluid matrix of the cell; nucleic acids to record genetic information; proteins comprised of strings of amino acids that *inter alia* structure the cell, pump molecules in and out of the cell, catalyze metabolic processes, perform mechanical functions, participate in the cell cycle, transcribe and translate genetic information, and allow for signaling between cells; and small molecules such as adenosine triphosphate that transport energy within a cell. The study of life must proceed by the study of the machinery within the cell, with additional consideration given to multicellular phenomena where applicable. Moreover, any discussion of the origin of life from early geochemistry should focus on the chemical environments from

which life might have arisen and describe the biochemical pathways through which metabolic and genetic information could arise spontaneously from such a milieu. Indeed, as van Helmont concluded in 1648, and as is even today the rallying cry at conferences on the origin and evolution of life, it seems quite clear that "all life is chemistry" (33).

Or is it?

2.2. Life is Physics

From a condensed matter physicist's perspective, we have been led to a rather strange conclusion. To see why this is the case, and why it is important to dwell on this point, let us reflect on the modern way in which many readers of *Annual Review of Condensed Matter Physics* view their field. We contrast that with an explicitly reductionist perspective, one which typifies most (but certainly not all) reasoning in biology. To begin, suppose that we were to apply this "biological" perspective to study the phenomenon of superconductivity. The first step might be the construction of a catalog of the known superconductors, a list that might include elements such as Niobium or Tin, the cuprate oxides such as $La_{2-x}Sr_xCuO_4$, the alkali-doped fullerenes such as Cs_2RbC_{60}, and the heavy-fermion materials such as URu_2Si_2. From consideration of the structure of the electronic band structure of these materials, the biologist might try to argue, quite reasonably, that the transfer of electrons between outer atomic orbitals is somehow the cause of the interesting transport, thermodynamic and electrodynamic response of these materials. Even though we would not be able to actually construct a predictive theory of superconductivity, we might still conclude that "all superconductivity is chemistry." Although we have referred to this hypothetical line of reasoning as a "biological perspective," it was actually a failed approach tried originally by physicists. In fact, such a line of reasoning was attempted by Einstein in 1922 (34) (see also Reference 35 for historical context) prior to the development of quantum theory in its mature form. From the manifest failure of his effort, Einstein concluded (correctly) that not only was superconductivity of quantum mechanical origin, but that it must involve electrons transported between closed chains of orbitals, an uncanny precursor of Feynman's theory for macroscopic quantum order in superfluid helium (36). We learn from all this that reductionism is a natural, intuitive step in the construction of theory, and that its failure mode can be an instructive pointer to the necessary ingredients of a successful theory.

The fallacy of "superconductivity is chemistry" is more evident than the fallacy in the logic leading to the conclusion that "life is chemistry." We know now, starting with the work of Ginzburg and Landau, that superconductivity has, in fact, little to do with the quantum chemistry of the atoms in the material. Instead, superconductivity is best understood as arising from the breaking of the global U(1) gauge symmetry in the effective field theory that describes the interaction between off-diagonal long-range order and the electromagnetic field. Any microscopic Hamiltonian whose effective field theory is Ginzburg-Landau theory will give rise to the phenomena associated with superconductivity. There is nothing fundamental about the atoms or molecules. Indeed, our putative biologist would be astonished to learn of color superconductivity in deconfined quark matter (37), likely to be realized in the neutron star remnants of core-collapse supernovae. Such high temperature superconductivity would be inconceivable from a narrow perspective based purely upon atomic chemistry; moreover, the conceptual relationship between the astrophysical and condensed matter versions of superconductivity would appear obscure.

To summarize, the phenomenon of superconductivity as a process is captured by the universal, symmetry-based Ginzburg-Landau theory, but that process can have many different

realizations or instantiations from matter at a variety of energy and length scales. This level of understanding is one that crucially informs the modus operandi of condensed matter physics. Typically, we regard a phenomenon as essentially understood when two conditions have been met. The first is that the reasons for the very existence of the phenomenon are known, usually from some form of symmetry or topological consideration. The second is that we have a way to determine under what circumstances a particular system (atomic, molecular, nuclear, etc.) represents an instantiation or realization of the phenomenon. Thus, the mantra of condensed matter physics, sometimes attributed to Murray Gell-Mann but surely anticipated in spirit by Lev Landau, becomes a recipe for discovery: "That which is not forbidden is mandatory." By this is meant that any allowable process can occur, and therefore it behooves one to try and identify the universality classes (i.e., categories) of interesting phenomena, and then to try and identify the likely realizations of them. This pattern of discovery is a relatively recent one, arising during the emergence and maturation of condensed matter physics as a scientific discipline during the past 25 years of the twentieth century, and exemplified, for example, by the new and important condensed matter subfield of topological insulators, where the theoretical understanding has led to a concerted and successful search for experimental realizations. This example is by no means an isolated one: Other examples of major significance include the Aharonov-Bohm effect, the quantum spin hall effect, localization, and the renaissance in atomic, molecular, and optical physics provided by the experimental realization of atomic Bose-Einstein condensates.

2.3. The Need for a Physics of Living Systems

The point of this lengthy discourse should now be clear. It is as limiting to view life as chemistry as it is to view condensed matter collective states as being primarily about the atoms. The physics of living systems would have at its core a generalized description of evolutionary processes, reflecting allowable dynamical symmetries, not merely static configurational ones. Such a description would, in a very crude sense, be a counterpart to the description of emergent states of matter embodied by effective theories such as the Ginzburg-Landau theory alluded to above. A genuine physics of living systems would encompass different limits of the evolutionary process, each recognized as, and described by different effective theories.

A biological example of a universality class and the corresponding effective theory is classical population genetics, itself subdivided into two universality classes: one for sexual organisms and one for asexual organisms. Taken at face value, population genetics contains phenomenological parameters, such as effective population size, fitness and growth rate, and attempts to model generic aspects of populations and their genes. It certainly is not a microscopic theory, because it lacks a biochemical level of description, and it is certainly an effective theory, valid only when there is a separation of scales between ecosystem dynamics and gene mutation dynamics. Condensed matter physics was liberated from the hegemony of Fermi liquid theory by the recognition that there are many other universality classes describing the behavior of electrons in solids, representing different types of collective behavior and interactions between (e.g.) spin and charge degrees of freedom. Similarly, we anticipate that evolutionary biology can be liberated from the hegemony of classical population genetics by the recognition that other universality classes must exist and will be manifest under the appropriate conditions. We say more below about the ways we see that the discoveries of modern biology are positioning it to take the next step beyond the paradigm of classical population genetics.

This perspective redefines what we demand of biological understanding in two additional ways. First, the very existence of the phenomenon of life needs to be understood. Second, the realization or instantiation of it, on Earth, for example, needs to be understood. For the most part, it is fair to say that the discipline of biology has neglected the first condition, and in pursuit of the second, has confused understanding of the realization with understanding of the phenomenon. This has had a number of unfortunate consequences, which arguably have hindered both the conceptual development of biology and the proper application of foundational understanding to societal applications.

Let us begin with the conceptual difficulties. A unified view of a phenomenon, such as that which we have alluded to in superconductivity, has the benefit that further instances of it do not come as a surprise and do not require further ad hoc explanation. With a proper understanding of superconductivity as a symmetry-breaking process, for example, one does not find it surprising to learn of superconductivity in nuclear or astrophysical contexts. With a proper understanding of the phenomenon of life as a dynamical process, for example, one would not find it surprising to learn of life in so-called extreme environments (such as deep beneath the ocean floor) or even on other planets. Among the surprises that biology has encountered recently are several of major significance, including the discovery of horizontal gene transfer in multicellular eukaryotes (38–42) and the discovery of a fully anoxic multicellular life form (43). In short, a unified view prevents the unnecessary multiplication of hypotheses, which is the sure sign of a lack of fundamental understanding (think epicycles!).

The second consequence of a lack of fundamental understanding in biology is the failure to recognize that biology is a manifestation of evolution—not the other way round. Interventions in biological systems inevitably provoke an evolutionary response that is rapidly emerging and spatially-distributed. Examples of the ability of biological systems to defeat human attempts at mitigation include (*a*) the world-wide spread of antibiotic resistance genes across distantly related bacteria, crossing species, and phylum boundaries and physical locations (30); (*b*) the rapid evolution of cancer tumors in the face of chemical attack (31, 44, 45); (*c*) the ability of HIV to out-adapt treatment (46, 47); and (*d*) the ability of life to adapt to the massive poisoning of the Precambrian atmosphere by cyanobacteria-released oxygen 2.4 billion years ago [i.e., changing from a reducing to an oxidizing atmosphere (48)] with a remarkable subsequent flowering of life. With the exception of example (*d*), these examples indicate a fundamental limitation to medical science, akin to trying to design integrated circuits without a fundamental knowledge of quantum electronics and semiconductor physics.

Perhaps the primary shortcoming of the biological enterprise is the manifest failure to account for the phenomenon of the existence of life. Without doubt, this failure reflects not only on biologists, but also on physicists. We say this because the majority of biologists would probably regard their primary role as being, in one sense or another, to reverse engineer the myriad-specific realizations of organic life on Earth—the reductionist exercise that has been notably successful within its own terms of reference. However, the existence of the phenomenon of life, if it can be understood at all in generic terms, is surely an emergent phenomenon, arising somehow as an inevitable consequence of the laws of nonequilibrium statistical physics. How is it that matter self-organizes into hierarchies that are capable of generating feedback loops that connect multiple levels of organization and are evolvable? When life emerged from early geochemistry, the process must have been driven by irreversible thermodynamics, but the extension of that process into the emergence of evolvable structures remains mysterious to us. The physical laws that govern far-from-equilibrium dynamics are still not known.

2.4. Are there New Physical Laws in Biology?

In 1949, Delbrück, inspired by Bohr, famously expressed the view that biology might exhibit phenomena that are beyond quantum mechanics:

> Just as we find features of the atom, its stability, for instance, which are not reducible to mechanics, we may find features of the living cell which are not reducible to atomic physics, but whose appearance stands in a complementary relationship to those of atomic physics. — M. Delbrück, A Physicist Looks at Biology (1949) (49).

Today, few seriously expect that such features or physical laws will be found. However, in the same essay, in a less-celebrated passage, Delbrück drew attention to the problem of spontaneous generation of life. Surprisingly, to him the interesting issue was how statistical fluctuations in the kinetics of the emergence of life would lead to a possible lack of determinacy in the biochemistry of living organisms: The organism might not precisely reflect the geochemistry from which it arose. Delbrück was writing at a time when phase transitions were only beginning to be understood, and the notions of emergence and spontaneous symmetry breaking were in their infancy. Thus, he probably had no precise notion of a "law" of physics being a description of an effective theory, one that is valid on an intermediate asymptotic scale of length, time, or energy, and systematically related to a deeper level of description. Whereas Delbrück looked to biology to extend quantum mechanics, we look to it as a source of insight into nonequilibrium statistical mechanics of the evolutionary process.

Thus, the study of biology should be more than simply cataloguing the wonders of biological organization. We see no reason why the mantra attributed to Gell-Mann should not apply with equal force and predictive power in biology and become part of its methodology. Today a condensed matter physicist envisages a new class of collective processes and finds realizations in the world of materials, or for that matter, optical lattices. What would biology look like as a science if we sought to anticipate the types of evolutionary processes available to the suite of genetic operators now known? What realizations of such processes could we find, if we simply looked?

Maybe this sounds far-fetched, but in fact this methodology has already been used to good effect in biology. One example we have in mind is the groundbreaking discovery of the class of molecules known as topoisomerases, whose existence was first recognized theoretically, leading to their eventual discovery [50, 51 (see p. 40, second column)]. The topoisomerases are a class of enzymes that are able to perform the miracle of passing one strand of DNA through another, by breaking and then reforming them. The end result of this process is that DNA can be uncoiled through a process of successive topological changes, allowing transcription and replication to occur. Without the topoisomerases, this would be essentially impossible on the timescale relevant to cellular processes.

3. BEYOND THE MODERN SYNTHESIS

The classical and widely-accepted framework of evolution is the so-called "Modern Synthesis" or "neo-Darwinism," which is based on the fusion of Mendelian genetics with Wallace's (52) and Darwin's (53) ideas about "natural selection" (or the"survival of the fittest," the terminology preferred by Wallace) (27, 54). This theory and additions to it, primarily those due to Kimura (55), account for very simple genetic processes, such as point mutation and sexual recombination, leading to random single-nucleotide polymorphisms. A characteristic of these

classical theories of evolution is that their genome dynamics is linear, diffusive in nature, and the population sizes of communities are typically sufficiently large that fixation times are long. This union of evolution and genetics that developed in the 1930s and 1940s presumed that evolution proceeded through the simple mechanism of heritable mutation and survival of the fittest. Organisms have offspring that survive and propagate based on the quality of the inevitably mutated genome they inherited from their parents (vertical gene transfer). New positive traits spread through the population because the individuals with those traits were more successful in surviving and breeding than other members of the population. A variety of possible niches in the physical environment enable the multiplication of species, which then interact to create new niches. Thus, in this picture, evolution is essentially synonymous with population genetics. Genes are assumed to be the only dynamical variables that are tracked and are associated with a fitness benefit that is difficult to define or measure precisely but is quantified by a fitness landscape that describes how the population fitness depends on the genotype (56–59). Traits are simply associated with genes, and gene interactions are often ignored, or at best handled through the fitness landscape (59, 60).

Implicit in this approach is the assumption that the evolutionary timescale is different from the timescale of the ecosystem. The crucial question of the timescale of the evolutionary process, even taking at face value the perspective of the Modern Synthesis (which we do not) remains a thorny issue (61), and indeed it is fair to say that the theory's conceptual framework is so poorly quantified that one cannot confidently make sensible and realistic estimates of timescales (for an excellent pedagogical discussion of this point, see Reference 62).

3.1. Epistasis

Even within the framework of the Modern Synthesis, one can begin to make model calculations of how evolution rates vary with population size and the nature of the fitness landscape (59, 63–66) and probe the role of collective effects—epistasis—between genes. For example, phenotypic variance is generally thought to be the result of many-gene interactions (67), as documented in a tour de force analysis of the yeast metabolic network, for example (68). In yeast, a single-cell eukaryote, any positive selection that accrues from many interacting genes with small but positive contributions to fitness must contend with recombination that mixes up and randomizes the genotype. This competition can lead to collective states, more or less by analogy to phase transitions: a high recombination rate (analogous to high temperature) where genes are weakly correlated and genotypes are short-lived, and a low recombination rate (analogous to low temperature) regime where favorable genotypes are stable and compete essentially clonally (60). In bacteria, which reproduce clonally, recombination is a stabilizing factor and can compete in a similar way with point mutations, leading to two phases: one that contains a narrow distribution of genotypes and one that is genomically diverse, with global genome sequence divergence arising through the propagation along the genome in evolutionary time of diversification fronts triggered by horizontal gene transfer events (69), or perhaps even by indels (70). How these dynamics play out when the spatial structure of microbial populations is included is a fascinating question, bringing together genome dynamics, ecosystem dynamics, and population dynamics in a way that has not yet been explored.

3.2. Mobile Genetic Elements

The difficulties in making detailed and quantitative theories of the rate of evolution become vastly more acute as a result of discoveries from the emerging science of genomics (13). Building

on the seminal work of Barbara McClintock (69), the past decade or so has witnessed the discovery of a plethora of what one might term "classically-forbidden" processes that radically transform our understanding of dynamics at the level of the genome (72). Of particular importance is the discovery of mobile genetic elements in many forms, ranging from transposons to horizontal gene transfer agents (4, 73–78), whose levels of activity and evolutionary impact have almost surely been severely underestimated (79). Horizontal transfer means that genes or other genetic materials are transmitted through a variety of nonhereditary mechanisms from one organism to another, and subsequently expressed, thus altering the behavior (phenotype) of the recipient. Long known to be present in Bacteria and Archaea, horizontal gene transfer is now known to be present in multicellular Eukaryotes as well, as a result of genome-wide surveys published in the past year or so (37–41, 80). Although the horizontal transfer of genes is widely recognized to be a major evolutionary force in Archaea and Bacteria, it is still too early to be precise about its role in Eukaryotes.

However, it is not only genes that can be transferred: In Eukaryotes, genes are a small fraction of the total genome, with noncoding DNA and transposable elements making up the majority of the genome in some cases. Transposable elements, sometimes inaccurately but colorfully known as "jumping genes," can easily move around and between chromosomes, and through the disruption that they potentially inflict upon a genome, cause deleterious mutations and illness. In humans, it is estimated that approximately 45% of the genome is composed of transposable elements (1). Horizontal transfer of transposable elements can be a major driver of eukaryotic genome evolution and a source of genetic innovation (81–83). Indeed, the textbook picture of a static genome composed of genes and junk DNA has now been superseded by recent findings, and it is arguably more appropriate to think of the genome as a set of one-dimensional ecosystems, coupled together by horizontal transfer and containing numerous genetic elements interacting with each other, creating niches for themselves, and evolving stochastically to create a community ecology (84).

These genetic mechanisms permit the spread of genetic novelty much faster than vertical or hereditary transmission of genes, essentially amounting to a Lamarckian (85) dynamic of evolution (12, 86). If this was not enough, it is now incontrovertible that the inheritance of acquired characteristics, long discredited, but violating no known law of nature, can sometimes occur, not only through horizontal gene transfer (e.g., in microbes), but also through so-called epigenetic mechanisms that bypass the usual modes of inheritance (87, 88) [especially in ciliates (89)].

Not only is the Modern Synthesis afflicted by strong interactions, but its very foundation is questionable. The evident tautology embodied by "survival of the fittest" serves to highlight the backward-looking character of the fitness landscape: Not only is it unmeasurable a priori, but it carries with it no means of expressing the growth of open-ended complexity (90) and the generation of genetic novelty. Thus, the Modern Synthesis is, at best, a partial representation of population genetics; but, this on its own is a limited subset of the evolutionary process itself, and arguably the least interesting one.

3.3. Coupling Between Evolution and Ecology

It is not only the microscopic basis for current evolutionary theory that has been challenged by recent advances in biology. There is now a substantial and growing literature that documents a surprisingly rapid rate of evolution in numerous systems (91–98), ranging from cancer tumors and the immune system to ecosystem-driven adaptations in all three domains of life. Moreover, detailed observations document the coupling between evolutionary and ecological timescales (92, 99–105). In a predator-prey system realized in rotifer-algae interactions, the rapid

evolutionary dynamics is responsible for the unusual phase-lag characteristics of the observed population oscillations (106).

Evolutionary and ecological timescales can also become coupled if the ecological timescale becomes very long: An important example of this is provided by the ecology of the translation apparatus in the cell. The genetic code—the map between triplet codons and amino acids is degenerate: There can be several synonomous codons that code for the same amino acid. It is well-established that the synonomous codons are not used with equal frequency, and this codon usage bias reflects selection for speed or accuracy of translation of highly-expressed genes (107, 108). The translation process is a highly-complex one, but relies essentially on the availability of resources, in particular tRNA molecules. Evolution of the genome can of course also lead to a coevolution of the abundance of tRNA in the cell, leading to a nonlinear dynamics of the genome and its tRNA abundance distribution (109). By going beyond the classical mutation-drift-selection framework into the regime of nonlinear evolutionary dynamics, the theory predicts multistability of the genome and an explanation of the pattern of observed microbial genome biases, not only in translation, but also in transcription and replication.

The coupling between environmental and ecological timescales has also been argued to lead to another generic feature of biology: the prevalence of modularity (110–113). Modularity refers to the relative independence of a biological component or network—relative, because everything is connected, of course, but the intramodule connections are more important than intermodule connections. Modularity carries with it the connotation of reuse of motifs, simple building blocks from which complex systems can be built (110). One might think that such networks could be generically obtained from simulations of the evolutionary process, for example using genetic algorithms and digital life simulations (114), but remarkably this is not the case (112). The reason is that typically such simulations emulate the assumed process of "natural selection": Networks are evolved by mutations, recombination, and other genetic operators, and only those that perform a defined goal well enough are permitted to enter the next generation. The key to modularity seems to be the coupling to the environment, as evidenced by two rather different calculations. In the first, the network was evolved in an environment of goals that changed in a modular fashion (112); moreover, a follow-up study (113) showed clearly that environmental fluctuations do indeed accelerate the rate of evolution. In the second study (115, 116), modularity emerged spontaneously as an outcome of horizontal gene transfer in the presence of environmental fluctuations. This result, admittedly obtained in a rather specific model, nevertheless highlights the importance of collective interactions and the interplay between environmental fluctuations and evolution, which are neglected in the Modern Synthesis.

How does horizontal gene transfer influence the architecture of actual biological networks? Comparative genomics, coupled with the flux balance analysis of the metabolic network of *Escherichia coli* has demonstrated that the network grows by acquiring genes individually and in groups (typically operons governing coupled reactions), which are attached preferentially at the edges of the existing network (117). This form of network organization does not necessarily imply modularity, but it suggests one way that modularity can arise. Although there is no unique measure of modularity, the available analyses indicate that modularity is an increasing function of the variability of the environment (118) and that modularity also reflects the number of niches available and is associated with horizontal gene transfer (119).

An example of the nontrivial coupling between evolution and ecology has been obtained by recent metagenomic surveys of marine microbial environments, which sample and analyze environmental DNA collected from the Sargasso Sea and the Red Sea. Thirty percent of global carbon fixation occurs through the photosynthetic pathways of two cyanobacteria,

Prochlorococcus and *Synechococcus*. Remarkably, the phages of these organisms also contain photosystem II genes, presumably to maintain the host as a functioning phage factory, thereby increasing the production of phages during the lysis process as the host cell is destroyed. From analyzing the molecular sequences of these genes, and reconstructing their evolutionary history, Chisholm's group at MIT has documented the transfer of photosystem II genes back and forth between these marine cyanobacteria and their phages (120). Moreover, these genes underwent evolution and sequence shuffling while residing in the phages. Thus, rather than supporting the traditional view of the relationship between microbes and viruses as being a predator-prey relationship, the new findings suggest that there are collective interactions between microbes and viruses through gene exchange, with the creation of an effective global reservoir of genetic diversity that profoundly influences the dynamics of the major marine ecosystems. These findings had been anticipated many years earlier by numerous investigators (73, 75, 121–123), who appreciated and rediscovered the collective outcome of horizontal gene transfer.

During the past few years, an even more astonishing example has come to light, prompted in part by the attempt to find the cause of colony collapse disorder—the dramatic reduction in the honey bee population (in the United States, losses of adult workers were 23% during 2006-2007 and 36% during 2007–2008) (124). One of the potential pathogenic causes, the Israeli acute paralysis virus, was found to be able to integrate harmlessly its genome into that of the bee host, and thus confer immunity on the host to further infection. The surprise is that this virus is not a retrovirus: It does not need to integrate itself into the host genome in order to replicate, and so it lacks the genetic machinery for reverse transcription of its RNA into the host DNA. It is not currently known, therefore, how the Israeli acute paralysis virus was able to work its way into the host genome. This is not an isolated example: It is now known that a similar process has occurred in at least 19 vertebrate species, the relevant viruses that have conferred immunity being the lethal Bornavirus and Ebolavirus (125, 126). It seems that this mechanism is a eukaryotic analog to lysogeny in microbes. These findings support the notion that there are collective interactions between viruses and their hosts.

Evolution and ecology couple not only through time but also through space. Wallace was the first to emphasize that speciation is a phenomenon localized in both space and time (127): Evolution proceeds through a process of front propagation in space that couples to population genetics in ways that are conceptually simple but are only now beginning to be understood in a quantitative way (128–131). As fronts expand, the pioneer organisms at the leading edge experience large demographic fluctuations that are known to play a significant role in temporal oscillations (132) and spatial patterns (133) in ecosystems. It is important to stress that horizontal gene transfer is also strongly influenced by spatial structure. For example, it was recently established that the frequency of conjugation events between bacteria is dependent on the local density, being essentially one per generation in closely-packed biofilms, and an order of magnitude smaller in planktonic culture (77). How the interplay between evolutionary dynamics, ecosystem dynamics, and species distribution is reflected in patterns of species abundance distributions, diversity measures, and community structure is a frontier topic in ecology, and relevant to the emerging conceptual framework of niche construction (134, 135).

4. THE DYNAMICS OF EVOLUTION

Most existing approaches to formulating evolutionary dynamics mathematically, as Drossel (28) explicitly points out, share the limitation that the space in which evolution takes place is fixed. For example, some models consider the dynamics of genomes of fixed length in a specified

fitness landscape; others consider the interplay between agents who are using specified strategies of behavior in their repeated encounters with other agents.

Such approaches to evolution miss what is to us the central aspect of evolution: It is a process that continually expands the space in which it operates through a dynamic that is essentially self-referential. Self-reference should be an integral part of a proper understanding of evolution, but it is rarely considered explicitly. This point is so important, because it is at the root of why evolution represents a nontrivial extension of the sorts of dynamical processes we encounter in condensed matter physics. In condensed matter physics, there is a clear separation between the rules that govern the time evolution of the system and the state of the system itself. For example, in studying fluid dynamics, a firm basis for theory is provided by the Navier-Stokes equations, and regardless of whether the flow is at low Reynolds number and dominated by viscous effects, or at high Reynolds number and dominated by inertial effects, the underlying equations are capable of capturing all the phenomena. The mathematical reason for this is that the governing equation does not depend on the solution of the equation. The evolution operator is independent of the state of the system. In biology, however, the situation is different. The rules that govern the time evolution of the system are encoded in abstractions, the most obvious of which is the genome itself. As the system evolves in time, the genome itself can be altered; thus, the governing rules are themselves changed. From a computer science perspective, one might say that the physical world can be thought of as being modeled by two distinct components: the program and the data. But in the biological world, the program is the data, and vice versa. For example, the genome encodes the information which governs the response of an organism to its physical and biological environment. At the same time, this environment actually shapes genomes, through gene transfer processes and phenotype selection. Thus, we encounter a situation where the dynamics must be self-referential: The update rules change during the time evolution of the system, and the way in which they change is a function of the state and thus the history of the system. To a physicist, this sounds strange and mysterious: What is the origin of this feature that sets biological systems apart from physical ones? Aren't biological systems ultimately physical ones anyway; thus, why is self-reference an exclusive feature of biological systems (whatever they are!)?

The simple answer seems to be that self-reference arises because the biological components of interest are emergent, and we are seeking a description of biological phenomena in terms of these biological components only. Ultimately, if we used a level of description that was purely atomistic, for example, this self-referential aspect of biology would not arise. This argument does not distinguish biology from condensed matter physics, where many of the degrees of freedom are emergent also.

Thus, it is interesting to ask if there are analogs of this phenomenon in condensed matter physics, generically arising from coarse-grained description of systems with order parameter dynamics. To answer this question, recall, for example, the two types of descriptions that we have of superconductivity. On one hand, there is the Bardeen-Cooper-Schrieffer theory of superconductivity, which works at the level of description of fermions coupled through a pairing interaction (whose microscopic origin need not be specified, but is due to phonons in classic superconductors and perhaps spin or other interactions in high-temperature superconductors). On the other hand, there is the coarse-grained order parameter description due to Ginzburg and Landau. Frequently, physicists use the latter as a convenient model that is easy to calculate with, in systems of arbitrary geometry or with spatial variation. Moreover, this level of description is frequently used to study the time-dependent phenomena in superconductors, given by the time-dependent Ginzburg-Landau equations. Near the superconducting critical point, this description is a generic consequence of critical dynamics. However, away from the

critical region this equation cannot be systematically derived. Similarly, in superfluids and Bose-Einstein condensates, the zero-temperature dynamics can be well-described by the Gross-Pitaevskii equations, and near the critical point, a more complicated dynamic universality class is believed to be appropriate. Away from these two regimes, however, there is no universally-agreed upon description that is systematically accurate. The reason that there is confusion surrounding the dynamics at intermediate temperatures has in fact been well-understood, but not widely appreciated, for many years: The assumption that there exists a description local in both space and time is false. This can be seen from the derivation of the Ginzburg-Landau description from the more microscopic Bardeen-Cooper-Schrieffer theory, which in general involves a memory function that becomes local in space and time only in special limits. The breakdown of locality that accompanies effective descriptions of dynamical phenomena is well-known beyond superconductivity, of course, and is a feature of several approaches to nonequilibrium statistical mechanics, including mode-coupling theory and renormalization group approaches to effective actions in field theory.

Why self-reference is a specific feature of biological systems and not physical systems should now be evident: Self-referential dynamics is an inherent and probably defining feature of evolutionary dynamics and thus biological systems. Therefore, the question really is how self-referential dynamics arises as a universality class from the basic laws of microscopic physics, as an expression of nonequilibrium physics. Although there is recognition of this sort of question in some of the literature on philosophy, artificial life, and the evolution of language, nothing approaching a serious calculation has been done to our knowledge.

That evolution is a process that transcends its realization means that evolution is able to act on its own basic mechanisms. This nonlinearity of the evolutionary process is sometimes referred to as evolvability. It has important generic ramifications that have been explored in a model calculation of protein evolution (115), in particular that evolvability is preferentially selected during periods of increased rate of environmental change. Whether evolvability can be selected for, in the conventional parlance, is a controversial topic, partly because of the unfashionable nonlinearity of the process, and partly because evolvability seems to undermine the robustness of biological organization. Presumably, a detailed quantitative understanding of evolution would flesh out the balance between evolvability and robustness (136).

4.1. Evolution and Complexity

Complex systems are characterized by the presence of strong fluctuations, unpredictable and nonlinear dynamics, multiple scales of space and time, and frequently some form of emergent structure. The individual components of complex systems are so tightly coupled that they cannot usefully be analyzed in isolation, rendering irrelevant traditional reductionist approaches to science, obscuring causal relationships, and distinguishing complexity from mere complication. Biological complexity, is an extreme example of complexity, and arises from the inclusion of active components, nested feedback loops, component multifunctionality, and multiple layers of system dynamics, and is relevant to numerous aspects of the biological, medical, and earth sciences, including the dynamics of ecosystems, societal interactions, and the functioning of organisms. Perhaps the most striking features of biology are the open-ended growth of complexity that we see in the biosphere, the large population fluctuations, and the widespread occurrence of the "law of unintended consequences" when trying to manipulate ecosystems (137). Thus, although complexity is hard to define precisely and usefully, we regard the defining characteristic of complexity as the breakdown of causality (138). Simply put,

complex systems are ones for which observed effects do not have uniquely definable causes, due to the huge nature of the phase space and the multiplicity of paths.

Ecosystems are never static but are continually changing and adapting, and their response involves all levels down to the genome and even smaller (because viruses are an integral part of an ecosystem). In an attempt to capture such complex dynamics, researchers have made extensive use of digital life simulations.

Digital life simulations (28, 114, 139–144) use interacting synthetic organisms, with predefined rules for replication, evolution, and interaction with each other and their digital environment. Experiments on digital organisms are an accurate and informative methodology for understanding the process of evolution because the entire phylogenetic history of a population can be tracked, something that is much more difficult—but not impossible (145)—to do with natural organisms (146). Experiments on digital organisms can be performed over timescales relevant for evolution, and can capture universal aspects of evolutionary processes, including those relevant to long-term adaptation (147, 148), ecological specialization (149, 150), and the evolution of complex traits (151). Despite this progress, the way in which evolution leads to ever increasing complexity of organisms remains poorly understood and difficult to capture in simulations and models to date. Is this because these calculations are not sufficiently realistic, extensive, or detailed, or has something fundamental been left out?

As early as 1971, Woese speculated on the emergence of genetic organization (152). He was concerned with the evolution of complexity, but from a molecular viewpoint, namely that of the origin of quaternary structure in proteins. Woese portrayed evolution as a cyclic process, in which gene products evolved first to a dimerized state, followed by gene duplication, and separate evolution of the gene products so that the dimer finally consists of related but not identical subunits. If the two genes that code for the two distinct halves of the dimer subsequently fuse, a new composite molecule arises, which he called a "co-dimer." In this co-dimer, the two previously-related components can evolve separately but in a complementary fashion, as long as the biochemical properties of the co-dimer as a whole are not adversely affected. In this way, one half of the co-dimer could, for example, evolve into a control site for the enzyme that is the other member of the co-dimer. This argument provides a molecular realization of how evolution can cross wide fitness valleys (66). Woese argued that the dynamics of co-dimerization, repeated ad infinitum, led to the growth of complexity of all macromolecular components of the cell, including proteins and the translational machinery itself. If codimerization were an important part of the evolutionary process, it would perforce entail there being a high abundance of homodimeric proteins in the cell, and moreover that the number of subunits would be an even number. At the time Woese's paper appeared, the paucity of available data did not permit a test of these predictions. Early protein structures were limited to small molecules because of the difficulty of crystallizing larger molecules, so that when the Protein Data Bank was surveyed in 1995, 66% were found to be monomeric (153). By 2000, the situation had dramatically changed, with 19% of the proteins surveyed being monomeric. Of the remainder, 59% were either dimers or tetramers, with a clear preference for even numbers of subunits (154, 155). More recent analyses confirm these findings and are even able to probe the evolutionary dynamics that has led to the observed structure of protein complexes (156). Moreover, not only has the detailed structural evidence consistent with the co-dimerization model been fully elaborated, but also it appears that the assembly of proteins follows the evolutionary development of their subunit structure (157).

Co-dimerization and gene duplication are examples of how biological systems exploit redundancy as one of the prime mechanisms for evolution. This insight re-emerges in recent simple models of evolutionary dynamics, which show that open-ended complexity is only

possible as an outcome of complexity-scale-invariant genomic operators, such as gene duplication (90). That is, if there are genetic operators that bias organisms to have a specific complexity, then the complexity of the system will not increase without bound. This invariance is similar in spirit to that which lies at the heart of the Richardson cascade in turbulence (158, 159). Guttenberg & Goldenfeld (90) showed in an explicit model of digital life how different genetic operations behaved with regard to this invariance criterion, and thus were able to devise ecosystem models that evolved open-ended complexity. Despite its popularity, a static "fitness landscape" (56–58) picture of evolution does not satisfy the proposed invariance criterion and is indeed conceptually insufficient to account for the open-ended growth of complexity. Thus, digital life simulations do not generally evolve qualitatively new responses or modes of behavior; they cannot "think outside the box."

The emphasis on redundancy as a motif suggests that a component of evolution is multifunctionalism. To see why, consider how a system is modeled, perhaps as a set of differential equations or lattice update rules. These rules themselves need to evolve, but how? We need an additional set of rules describing the evolution of the original rules. But this upper level of rules itself needs to evolve. Thus, we end up with an infinite hierarchy, an inevitable reflection of the fact that the dynamic we are seeking is inherently self-referential. The way that the conundrum can be resolved is to begin with an infinite-dimensional dynamical system that spontaneously undergoes a sequence of symmetry-breaking or bifurcation events into lower-dimensional systems. Such transitions can be thought of as abstraction events: Successive lower dimensional systems contain a representation in them of upper levels of the original system. A precise mathematical prototype of such a construction can be constructed from consideration of the dynamics of functions on a closed one-dimensional interval (160), admittedly with very little direct biological interpretation, but with the positive outcome of generating a hierarchically entangled dynamical network. Such networks are not simple tree structures, which means that the nodes and links of the network drive each other in a way that a biologist would interpret as coevolutionary. Another way to interpret such dynamical systems is that the elements are multifunctional: Their input-output map depends on the state of the system, rather than being a constant in time. Such systems can have no static fixed point to their dynamics: In the language of an earlier work (90), they must exhibit a complexity cascade, just as Woese had earlier argued in the context of co-dimerization.

4.2. Coevolution and Game Theory

An alternative to treating organisms as evolving in a fixed environment or fitness landscape is coevolution (161). In coevolution, organisms interact and their interactions drive each to evolve, leading to a continuing process of phenotype evolution, although not necessarily an increase in complexity, as occurs in the complexity cascade (90). Examples include mutualism and antagonistic coevolution. In mutualism, the interaction is basically symbiotic and frequently occurs between plants and animals (162), microbes and plants (163) and, gaining increasing attention in the past few years, humans and their microbiomes (164). Antagonistic coevolution describes how opposing organisms, such as predators and prey, develop an arms race (165, 166) as a result of their competition, an effect generally referred to as the Red Queen effect (165).

There is a growing empirical literature (167–173) on the way in which antagonistic coevolution can accelerate evolution and dominate a system's response to changing environmental conditions. However, this topic has received much less theoretical attention to date. To investigate the interaction of genomic evolution and population dynamics, we require that the matrix describing the interactions between predator and prey evolve with genomic fitness (174, 175).

In these approaches, the interaction matrix is a linear function of either the fitness of the predators or the relative fitness of a pair, which is appropriate to describe the stabilization of complex foodwebs with a large number of species, but probably not adequate to describe systems with a Red Queen dynamics, where the genomic fitness is a distribution for a species instead of a single number. In this case, the evolution of the interaction matrix is nonlinear, and the dynamics needs to be treated as a stochastic individual-level model.

Coevolutionary dynamics is also an important arena for game theory dynamics to play out in evolution and ecology, because the level of cooperation between organisms can be analyzed on an encounter-by-encounter basis as the repetition of a cooperative game, such as the Prisoner's Dilemma (176–180). In the Prisoner's Dilemma, the two players have two states: They can either "cooperate" or "defect." If they cooperate, they receive a reward R; if they both defect, they receive a punishment P; and if one defects while the other cooperates, the former receives a temptation T whereas the latter receives the sucker's reward S. If $T > R > P > S$, then the following dilemma arises: A rational player would defect, because it yields the highest reward independent of the state of the other player. So in a contest with two rational players, each will end up with the punishment P, which is a shame, because if they had both cooperated, they would have received the reward R. This game illustrates the paradoxical nature of two-body interactions in cooperative dynamical systems, but can sometimes provide an accurate idealization of actual biological interactions, if the biology can be meaningfully mapped into simple game theory interactions terms.

In a remarkable experiment, Turner & Chao (181) studied the evolution of fitness (measured in terms of population growth) of phages that can multiply infect the same bacterial cell. Viruses can cooperate by sharing intracellular enzymes needed for reproduction and can defect by sequestering the enzymes. Turner and Chao engineered two strains to behave as cooperators and defectors, and found that the strain with a high rate of coinfection initially increased in fitness over time, but eventually evolved lower fitness, a counter-example to the usual cavalier assumption that "fitness always increases." In this case, Turner and Chao were able to show that this decline in fitness arose from collective effects: The fitness of the virus strains conformed to the Prisoner's Dilemma, whose payoff matrix they were able to measure. Game theory is not the only way to interpret this finding (182), but the key point is that collective effects provide important and sometimes counter-intuitive influences in ecological and evolutionary interactions. The huge literature on this area is beyond the scope of this review, but other ecological interactions are measurable and interpretable in game theory terms (183, 184).

We have emphasized in this review that the essence of evolution is self-reference, but it is apparent that this is not captured by the game theory models described above. The problem is that the payoff matrix is given a priori and is not able to evolve with the system itself. Thus, the effect of each agent's actions on the behavior of other players and the dynamics of the environment are neglected. A bona fide game theory approach to evolution would allow the game rules themselves to change as a function of the state of the players and their intrinsic dynamics. This is important for the following reason: In the usual formulation of game theory (177), there is an equilibrium state known as an evolutionary stable strategy that can arise. Loosely speaking, this can arise when a population of individuals plays in a cooperative game in which the payoff represents the fitness, and selection is assumed to be operating. An evolutionary stable strategy is a strategy that if used by a large enough number of individuals in a population is resistant to invasion by alternative strategies, and as such represents some sort of equilibrium [in fact a Nash equilibrium (185)]. This equilibrium state is in some sense analogous to thermal equilibrium and reflects the static nature of the game itself. If the game was allowed instead to be

dynamic, with the rules of the game able to change due to the states of the players, then in addition to static equilibria there could also be dynamic equilibria, analogous to a nonequilibrium steady state. Such a game could describe a steadily evolving system, one with a stationary complexity cascade (which itself is analogous to a turbulent nonequilibrium state).

Akiyama & Kaneko (186, 187) seem to be the only researchers who have explicitly argued along these lines, making a first step toward a theory for truly-evolving games using dynamical systems theory to analyze a cooperative game with an evolving payoff matrix. Other game theoretic models that include some sort of dynamical or learning behavior, such as players using their scores to adjust the frequency of a finite set of a priori given responses, have been developed, describing the system trajectories, showing that chaotic dynamics can arise, and shedding doubt about the applicability of Nash equilibria in the real world of dynamical games (188)—and by extension to evolution.

A related development is the dynamics of spatially extended game theoretic models that study the evolution of cooperation, in which there is coevolution of the network of connections between players (189, 190) and the players' strategies as the game progresses. Typically, players update their strategy on the basis of their interactions with their network neighbors during the game, representing perhaps the simplest game theory models where there is feedback between the environment and the agents (191). Finally, there has been progress in the most difficult aspect of the relationship between game theory and evolutionary biology: understanding how effective game theoretic description can arise from the macroscopic dynamics of agents interacting with their environment (192). We conclude this section by recalling that evolutionary dynamics is more general than biology itself; thus, it should come as no surprise that there are applications of evolutionary game theory to evolutionary finance (193, 194) and indeed meaningful analogies between ecosystem dynamics and finance (195).

5. IS EVOLUTION RANDOM?

We would be remiss in ending this review without briefly mentioning the fascinating question, Is evolution random? More precisely, does variation precede but not cause adaptation—the central tenet of the Modern Synthesis—or do environmental changes alter the stochastic nature of the evolutionary process? Any indication that organisms can choose which mutations arise after an environmental stress has been applied would be anathema to the central tenet of the Modern Synthesis and would require a re-evaluation of how evolution is widely understood.

In a classic experiment involving the exposure of a strain of *E. coli* to bacteriophages, Luria & Delbrück (196) showed that the probability distribution for the number of mutants exhibited the characteristics expected only if random mutations had been present before exposure to the phage, apparently ruling out the hypothesis that mutations occurred as a result of the phage. This might seem to put the matter to rest, but because there is a priori no theoretical reason why a cell could not sense environmental stress and respond in a nonrandom way, researchers have persisted in exploring this issue experimentally. Although early experiments are generally recognized as not being properly analyzed (197), a plethora of mechanisms have now been reported to give rise to an adaptive response to stress, including regulation of mutation rates (nonrandom in time) and localized variation along the genome (nonrandom in genome space) (88, 91, 198).

There is also compelling evidence that not only may mutations be nonrandom, but horizontal gene transfer, too, need not be random. *Enterococcus faecalis*, a gut-dwelling bacterium, can be resistant to certain antibiotics if it contains the plasmid (an extrachromosmal loop of DNA)

pCF10. Through the process of conjugation, this plasmid can be horizontally transferred from a donor to a recipient initially lacking it. The remarkable feature of this organism, however, is that the transfer is controlled and initiated by signals sent from the recipient (199). The vancomycin-resistant strain V583 of this organism is now one of the leading causes of hospital-acquired infection, spreading rapidly through horizontal gene transfer (200).

6. CONCLUSION

In the natural development of the sciences, issues of complexity are sensibly postponed until they can no longer be avoided. Physics was able to delay serious consideration of collective effects for nearly 300 years, and only in the past 30 years or so has it confronted complex collective phenomena involving multiple scales of space and time, unpredictable dynamics, and large fluctuations. Its track record of success is mixed.

Biology was not so lucky: At its outset, complex phenomena were encountered, but tools were lacking to cope with the difficulty. Rather than abiding by ignorance, a language culture was developed to explain away the conceptual difficulties using guesswork solutions such as "natural selection." As Schrödinger wrote,

> Instead of filling a gap by guesswork, genuine science prefers to put up with it; and this, not so much from conscientious scruples about telling lies, as from the consideration that, however irksome the gap may be, its obliteration by a fake removes the urge to seek after a tenable answer.—E. Schrödinger (201, pp. 7–8).

Today, with the "urge" removed, the development of sophisticated technology has allowed biology to take refuge in single-molecule biophysics, genomics, and molecular biology. But the stultifying language culture still remains. This sanctuary is an illusionary respite: The core problems of biology remain irksome to some and are inextricably interwoven with evolution. Indeed, the very existence of biological phenomena is an expression of physical laws that represent a new asymptotic realm in nonequilibrium statistical physics. Ulam famously quipped (202, p. S419), "Ask not what physics can do for biology; ask what biology can do for physics." Our answer is clear.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank the following for their helpful comments on earlier versions of this manuscript: Elbert Branscombe, Lynn Caporale, Jim Davis, Michael Deem, Barbara Drossel, Freeman Dyson, George Dyson, Larry Gold, Leo Kadanoff, Alan McKane, Tim Newman, Jim Shapiro, and especially James Langer and Kalin Vetsigian. This work was partially supported by the US National Science Foundation under grants NSF-EF-0526747 and NSF-PFC-082265, through the Center for the Physics of Living Cells.

LITERATURE CITED

1. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. 2001. Initial sequencing and analysis of the human genome. *Nature* 409(6822):860–921

2. Clamp M, Fry B, Kamal M, Xie X, Cuff J, et al. 2007. Distinguishing protein-coding and noncoding genes in the human genome. *Proc. Natl. Acad. Sci. USA* 104(49):19428–33
3. Gould SJ. 2001. Humbled by the genome's mysteries. *New York Times*, Feb. 19:A15
4. Ochman H, Lawrence J, Groisman E. 2000. Lateral gene transfer and the nature of bacterial innovation. *Nature* 405(6784):299–304
5. Waters CM, Bassler BL. 2005. Quorum sensing: cell-to-cell communication in bacteria. *Annu. Rev. Cell Dev. Biol.* 21:319–46
6. Harshey RM. 2003. Bacterial motility on a surface: many ways to a common goal. *Annu. Rev. Microbiol.* 57(1):249–73
7. Copeland M, Weibel D. 2009. Bacterial swarming: a model system for studying dynamic self-assembly. *Soft Matter* 5(6):1174–87
8. Shapiro JA. 1998. Thinking about bacterial populations as multicellular organisms. *Annu. Rev. Microbiol.* 52(1):81–104
9. Woese CR, Goldenfeld N. 2009. How the microbial world saved evolution from the Scylla of molecular biology and the Charybdis of the modern synthesis. *Microbiol. Mol. Biol. Rev.* 73(1):14–21
10. Herz AVM. 1994. Collective phenomena in spatially extended evolutionary games. *J. Theor. Biol.* 169(1):65–87
11. Nowak MA. 2006. *Evolutionary Dynamics: Exploring the Equations of Life*. Cambridge, MA: Belknap. 384 pp.
12. Goldenfeld N, Woese C. 2007. Biology's next revolution. *Nature* 445:369
13. Shapiro JA. 2010. Mobile DNA and evolution in the 21st century. *Mobile DNA* 1(4):1–14
14. Levin SA. 1992. The problem of pattern and scale in ecology: the Robert H. MacArthur Award lecture. *Ecology* 73(6):1943–67
15. Toner J, Tu Y, Ramaswamy S. 2005. Hydrodynamics and phases of flocks. *Ann. Phys.* 318(1): 170–244
16. Sumpter DJT. 2006. The principles of collective animal behaviour. *Philos. Trans. R. Soc. B* 361 (1465):5–22
17. Schweitzer F, Farmer JD. 2007. *Brownian Agents and Active Particles: Collective Dynamics in the Natural and Social Sciences*. New York: Springer-Verlag. 434 pp.
18. Haloin JD, Strauss SY. 2008. Interplay between ecological communities and evolution: review of feedbacks from microevolutionary to macroevolutionary scales. *Ann. NY Acad. Sci.* 1133:87–125
19. Cohen IR, Harel D. 2007. Explaining a complex living system: dynamics, multi-scaling and emergence. *J R Soc. Interface* 4(13):175–82
20. Cohen IR. 2007. Real and artificial immune systems: computing the state of the body. *Nat. Rev. Immunol.* 7(7):569–74
21. Ben-Jacob E, Cohen I, Levine H. 2000. Cooperative self-organization of microorganisms. *Adv. Phys.* 49(4):395–554
22. Wingreen N, Levin S. 2006. Cooperation among microorganisms. *PLoS Biol.* 4(9):1486–88
23. Velicer GJ, Vos M. 2009. Sociology of the myxobacteria. *Annu. Rev. Microbiol.* 63:599–623
24. Lenton TM, Held H, Kriegler E, Hall JW, Lucht W, et al. 2008. Tipping elements in the Earth's climate system. *Proc. Natl. Acad. Sci. USA* 105(6):1786–93
25. Bardgett RD, Freeman C, Ostle NJ. 2008. Microbial contributions to climate change through carbon cycle feedbacks. *ISME J.* 2(8):805–14
26. Cuddington K, Wilson WG, Hastings A. 2009. Ecosystem engineers: feedback and population dynamics. *Am. Nat.* 173(4):488–98
27. Maynard Smith J. 1993. *The Theory of Evolution.* Cambridge: Cambridge Univ. Press. 380 pp.
28. Drossel B. 2001. Biological evolution and statistical physics. *Adv. Phys.* 50(2):209–95
29. Sapp J. 2009. *The New Foundations of Evolution: On the Tree of Life*. New York: Oxford Univ. Press. 448 pp.
30. Salyers AA, Amabile-Cuevas CF. 1997. Why are antibiotic resistance genes so resistant to elimination? *Antimicrob. Agents Chemother.* 41:2321–25
31. Gatenby RA. 2009. A change of strategy in the war on cancer. *Nature* 459(7246):508–9

32. Langer JS. 1980. Instabilities and pattern formation in crystal growth. *Rev. Mod. Phys.* 52(1):1–28
33. Van Helmont JB. 1648. *Ortus Medicinae*, pp. 108–109. Amsterdam: Ludovicum Elzevirium. Transl. ML Gabriel, S Fogel, eds., 1961, in *Great Experiments in Biology*, p. 155. Englewood Cliffs N.J.: Prentice Hall (From Dutch)
34. Einstein A. 1922. *Theoretische Bemerkungen zur Supraleitung der Metalle*. Transl. B. Schmekel, 2005, in Theoretical remark on the superconductivity of metals. Leiden: Eduardo Ijdo (available online at **http://arxiv.org/abs/physics/0510251**) (From German)
35. Sauer T. 2007. Einstein and the early theory of superconductivity, 1919-1922. *Arch. Hist. Exact Sci.* 61(2):159–211
36. Feynman RP. 1953. Atomic theory of the λ transition in helium. *Phys. Rev.* 91(6):1291–301
37. Alford MG, Schmitt A, Rajagopal K, Schäfer T. 2008. Color superconductivity in dense quark matter. *Rev. Mod. Phys.* 80(4):1455–515
38. Gladyshev EA, Meselson M, Arkhipova IR. 2008. Massive horizontal gene transfer in bdelloid rotifers. *Science* 320(5880):1210–13
39. Keeling PJ, Palmer JD. 2008. Horizontal gene transfer in eukaryotic evolution. *Nat. Rev. Genet.* 9(8):605–18
40. Palenik B, Ren Q, Tai V, Paulsen I. 2009. Coastal *Synechococcus* metagenome reveals major roles for horizontal gene transfer and plasmids in population diversity. *Environ. Microbiol.* 11(2):349–59
41. Monier A, Pagarete A, de Vargas C, Allen MJ, Read B, et al. 2009. Horizontal gene transfer of an entire metabolic pathway between a eukaryotic alga and its DNA virus. *Genome Res.* 19(8):1441–49
42. Pace JK, Gilbert C, Clark MS, Feschotte C. 2008. Repeated horizontal transfer of a DNA transposon in mammals and other tetrapods. *Proc. Natl. Acad. Sci. USA* 105(44):17023–28
43. Danovaro R, Dell'Anno A, Pusceddu A, Gambi C, Heiner I, Møbjerg Kristensen R. 2010. The first metazoa living in permanently anoxic conditions. *BMC Biol.* 8(1):30
44. Kimmel M. 2010. Evolution and cancer: a mathematical biology approach. *Biol. Direct* 5(1):29
45. Attolini C, Michor F. 2009. Evolutionary theory of cancer. *Annal. N.Y. Acad. Sci.* 1168:23–51
46. Duffy S, Shackelton LA, Holmes EC. 2008. Rates of evolutionary change in viruses: patterns and determinants. *Nat. Rev. Genet.* 9(4):267–76
47. Neher RA, Leitner T. Recombination rate and selection strength in HIV intra-patient evolution. *PLoS Comput. Biol.* 6(1):e10006600
48. Falkowski PG, Godfrey LV. 2008. Electrons, life and the evolution of Earth's oxygen cycle. *Philos. Trans. R. Soc. B* 363(1504):2705–16
49. Delbruck M. 1949. A physicist looks at biology. *Trans. Conn. Acad. Arts Sci.* 38:173–90
50. Wang JC. 1998. Moving one DNA double helix through another by a type II DNA topoisomerase: the story of a simple molecular machine. *Q. Rev. Biophys.* 31(02):107–44
51. Wang JC. 2009. A journey in the world of DNA rings and beyond. *Annu. Rev. Biochem.* 78:31–54
52. Wallace AR. 1858. On the tendency of varieties to depart indefinitely from the original type. *J Linn. Soc. Lond. Zool.* 3:53–62
53. Darwin C. 1859. *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London, UK: J. Murray. 501 pp.
54. Huxley J. 1942. *Evolution: The Modern Synthesis*. Cambridge, MA: MIT Press. 645 pp.
55. Kimura M. 1985. *The Neutral Theory of Molecular Evolution*. New York: Cambridge Univ. Press. 384 pp.
56. Wright S. 1932. The roles of mutation, inbreeding, crossbreeding and selection in evolution. *Proc. Six. Intl. Congr. Genet.* 1(6):356–66
57. Gavrilets S. 2004. *Fitness Landscapes and the Origin of Species*. Princeton: Princeton Univ. Press. 432 pp.
58. Orr HA. 2005. The genetic theory of adaptation: a brief history. *Nat. Rev. Genet.* 6(2):119–27
59. Park S-C, Simon D, Krug J. 2010. The speed of evolution in large asexual populations. *J. Stat. Phys.* 138(1–3):381–410
60. Neher RA, Shraiman BI. 2009. Competition between recombination and epistasis can cause a transition from allele to genotype selection. *Proc. Natl. Acad. Sci. USA* 106(16):6866–71
61. Gingerich PD. 2009. Rates of evolution. *Annu. Rev. Ecol. Evol. Syst.* 40:657–75

62. Fisher DS. 2007. Course 11: evolutionary dynamics. *Les Houches* 85:395–446
63. Desai MM, Fisher DS, Murray AW. 2007. The speed of evolution and maintenance of variation in asexual populations. *Curr. Biol.* 17(5):385–94
64. Brunet É, Rouzine IM, Wilke CO. 2008. The stochastic edge in adaptive evolution. *Genetics* 179(1):603–20
65. Fogle CA, Nagle JL, Desai MM. 2008. Clonal interference, multiple mutations, and adaptation in large asexual populations. *Genetics* 180(4):2163–73
66. Weissman DB, Desai MM, Fisher DS, Feldman MW. 2009. The rate at which asexual populations cross fitness valleys. *Theor. Popul. Biol.* 75(4):286–300
67. Moore JH. 2005. A global view of epistasis. *Nat. Genet.* 37(1):13–14
68. Segré D, Deluna A, Church GM, Kishony R. 2005. Modular epistasis in yeast metabolism. *Nat. Genet.* 37(1):77–83
69. Vetsigian K, Goldenfeld N. 2005. Global divergence of microbial genome sequences mediated by propagating fronts. *Proc. Natl. Acad. Sci. USA* 102(20):7332–37
70. Chen J-Q, Wu Y, Yang H, Bergelson J, Kreitman M, Tian D. 2009. Variation in the ratio of nucleotide substitution and the indel rates across genomes in mammals and bacteria. *Mol. Biol. Evol.* 26(7):1523–31
71. McClintock B. 1984. The significance of responses of the genome to challenge. *Science* 226:792–801
72. Shapiro JA. 2009. Revisiting the central dogma in the 21st century. *Ann. N. Y. Acad. Sci.* 1178:6–28
73. Syvanen M. 1994. Horizontal gene transfer: evidence and possible consequences. *Annu. Rev. Genet.* 28(1):237–61
74. Filee J, Forterre P, Laurent J. 2003. The role played by viruses in the evolution of their hosts: a view based on informational protein phylogenies. *Res. Microbiol.* 154:237–43
75. Weinbauer MG, Rassoulzadegan F. 2004. Are viruses driving microbial diversification and diversity? *Environ. Microbiol.* 6(1):1–11
76. Frost LS, Leplae R, Summers AO, Toussaint A. 2005. Mobile genetic elements: the agents of open source evolution. *Nat. Rev. Microbiol.* 3(9):722–32
77. Babic A, Lindner AB, Vulić M, Stewart E, Radman M. 2008. Direct visualization of horizontal gene transfer. *Science* 319(5869):1533–36
78. Pal C, Macia MD, Oliver A, Schachar I, Buckling A. 2007. Coevolution with viruses drives the evolution of bacterial mutation rates. *Nature* 450:1079–81
79. McDaniel LD, Young E, Delaney J, Ruhnau F, Ritchie KB, Paul JH. 2010. High frequency of horizontal gene transfer in the oceans. *Science* 330:50
80. Hotopp JCD, Clark ME, Oliveira DCSG, Foster JM, Fischer P, et al. 2007. Widespread lateral gene transfer from intracellular bacteria to multicellular eukaryotes. *Science* 317(5845):1753–56
81. Biémont C, Vieira C. 2006. Genetics: junk DNA as an evolutionary force. *Nature* 443(7111):521–24
82. Schaack S, Gilbert C, Feschotte C. 2010. Promiscuous DNA: horizontal transfer of transposable elements and why it matters for eukaryotic evolution. *Trends Ecol. & Evol.* 25(9):537–46
83. Rankin DJ, Rocha EPC, Brown SP. 2011. What traits are carried on mobile genetic elements, and why? *Heredity* 106:1–10
84. Venner S, Feschotte C, Biémont C. 2009. Dynamics of transposable elements: towards a community ecology of the genome. *Trends Genet.* 25(7):317–23
85. de Lamarck J-B. 1809. *Philosophie Zoologique*, ed. C Martins. Paris: F. Savy. 506 pp.
86. Koonin EV, Wolf Y. 2009. Is evolution Darwinian or/and Lamarckian? *Biol. Direct* 4(42):1–14
87. Jablonka E, Lamb MJ. 1998. Epigenetic inheritance in evolution. *J. Evol. Biol.* 11(2):159–83
88. Rando OJ, Verstrepen KJ. 2007. Timescales of genetic and epigenetic inheritance. *Cell* 128(4):655–68
89. Nowacki M, Landweber LF. 2009. Epigenetic inheritance in ciliates. *Curr. Opin. Microbiol.* 12(6):638–43
90. Guttenberg N, Goldenfeld N. 2008. Cascade of complexity in evolving predator-prey dynamics. *Phys. Rev. Lett.* 100(5):058102
91. Caporale L. 2003. *Darwin in the Genome: Molecular Strategies in Biological Evolution.* Columbus, OH: McGraw-Hill. 256 pp.

92. Hairston NG Jr, Ellner SP, Geber MA, Yoshida T, Fox JA. 2005. Rapid evolution and the convergence of ecological and evolutionary time. *Ecol. Lett.* 8(10):1114–27
93. Cowen LE, Lindquist S. 2005. Hsp90 potentiates the rapid evolution of new traits: drug resistance in diverse fungi. *Science* 309(5744):2185–89
94. Thompson JN. Rapid evolution as an ecological process. 1998. *Trends Ecol. & Evol.* 13(8):329–32
95. Carroll SP, Hendry AP, Reznick DN, Fox CW. 2007. Evolution on ecological time-scales. *Ecology* 21:387–93
96. Steinhauer DA, Holland JJ. 1987. Rapid evolution of RNA viruses. *Annu. Rev. Microbiol.* 41(1):409–33
97. Zhang ZD, Weinstock G, Gerstein M. 2008. Rapid evolution of positive Darwinian selection in T-cell antigen CD4 in primates. *J. Mol. Evol.* 66(5):446–56
98. Summers K, Crespi B. 2008. Molecular evolution of the prostrate cancer susceptibility locus *RNASEL*: evidence for positive selection. *Infect. Genet. Evol.* 8(3):297–301
99. Meyer JR, Ellner SP, Hairston NG Jr, Jones LE, Yoshida T. 2006. Prey evolution on the time scale of predator–prey dynamics revealed by allele-specific quantitative PCR. *Proc. Natl. Acad. Sci. USA* 103(28):10690–95
100. Hillesland KL, Velicer GJ, Lenski RE. 2009. Experimental evolution of a microbial predator's ability to find prey. *Proc. Biol. Sci.* 276(1656):459–67
101. Palkovacs EP, Post DM. 2009. Experimental evidence that phenotypic divergence in predators drives community divergence in prey. *Ecology* 90(2):300–5
102. Bailey JK, Hendry AP, Kinnison MT, Post DM, Palkovacs EP, et al. 2009. From genes to ecosystems: an emerging synthesis of eco-evolutionary dynamics. *New Phytol.* 184(4):746–49
103. Pelletier F, Garant D, Hendry AP. 2009. Eco-evolutionary dynamics. *Philos. Trans. R. Soc. B* 364 (1523):1483–89
104. Jones LE, Becks L, Ellner SP, Hairston NG Jr, Yoshida T, Fussmann GF. 2009. Rapid contemporary evolution and clonal food web dynamics. *Philos. Trans. R. Soc. Lond. B* 364(1523):1579–91
105. terHorst CR, Miller TE, Levitan DR. 2010. Evolution in prey in ecological time reduces the effect size of predators in experimental microcosms. *Ecology* 91(3):629–36
106. Yoshida T, Ellner SP, Jones LE, Bohannan BJM, Lenski RE, Hairston NG Jr. 2007. Cryptic population dynamics: rapid evolution masks trophic interactions. *PLoS Biol.* 5(9):e235
107. Bulmer M. 1987. Coevolution of codon usage and transfer RNA abundance. *Nature* 325(6106):728–30
108. Bulmer M. 1991. The selection-mutation-drift theory of synonymous codon usage. *Genetics* 129 (3):897–907
109. Vetsigian K, Goldenfeld N. 2009. Genome rhetoric and the emergence of compositional bias. *Proc. Natl. Acad. Sci. USA* 106(1):215–20
110. Hartwell LH, Hopfield JJ, Leibler S, Murray AW. 1999. From molecular to modular cell biology. *Nature* 402:C47–52
111. Barabási A-L, Oltvai ZN. 2004. Network biology: understanding the cell's functional organization. *Nat. Rev. Genet.* 5(2):101–13
112. Kashtan N, Alon U. 2005. Spontaneous evolution of modularity and network motifs. *Proc. Natl. Acad. Sci. USA* 102(39):13773–78
113. Kashtan N, Noor E, Alon U. 2007. Varying environments can speed up evolution. *Proc. Natl. Acad. Sci. USA* 104:13711–16
114. Holland J. 1992. *Adaptation in Natural and Artificial Systems: An Introductory Analysis with Applications to Biology, Control, and Artificial Intelligence.* Cambridge, MA: MIT Press. 228 pp.
115. Earl DJ, Deem MW. 2004. Evolvability is a selectable trait. *Proc. Natl. Acad. Sci. USA* 101(32): 11531–36
116. He J, Sun J, Deem MW. 2009. Spontaneous emergence of modularity in a model of evolving individuals and in real networks. *Phys. Rev. E* 79(3):31907
117. Pál C, Papp B, Lercher MJ. 2005. Adaptive evolution of bacterial metabolic networks by horizontal gene transfer. *Nat. Genet.* 37(12):1372–75
118. Parter M, Kashtan N, Alon U. 2007. Environmental variability and modularity of bacterial metabolic networks. *BMC Evol. Biol.* 7:169

119. Kreimer A, Borenstein E, Gophna U, Ruppin E. 2008. The evolution of modularity in bacterial metabolic networks. *Proc. Natl. Acad. Sci. USA* 105(19):6976–81
120. Sullivan MB, Lindell D, Lee JA, Thompson LR, Bielawski JP, Chisholm SW. 2006. Prevalence and evolution of core photosystem II genes in marine cyanobacterial viruses and their hosts. *PLoS Biol.* 4(8):e234
121. Anderson ES. 1966. Possible importance of transfer factors in bacterial evolution. *Nature* 209:637–38
122. Anderson NG. 1970. Evolutionary significance of virus infection. *Nature* 227:1346–47
123. Sonea S. 1988. A bacterial way of life. *Nature* 331(6153):216
124. Johnson R, Evans J, Robinson G, Berenbaum M. 2009. Changes in transcript abundance relating to colony collapse disorder in honey bees (*Apis mellifera*). *Proc. Natl. Acad. Sci. USA* 106(35):14790–95
125. Horie M, Honda T, Suzuki Y, Kobayashi Y, Daito T, et al. 2010. Endogenous non-retroviral RNA virus elements in mammalian genomes. *Nature* 463(7277):84–87
126. Belyi VA, Levine AJ, Skalka AM. 2010. Unexpected inheritance: multiple integrations of ancient Bornavirus and Ebolavirus/Marburgvirus sequences in vertebrate genomes. *PLoS Pathog.* 6(7): e1001030
127. Wallace A. 1855. On the law which has regulated the introduction of new species. *Ann. Mag. Nat. Hist.* 16(2):184–96
128. Ibrahim KM, Nichols RN, Hewitt GM. 1996. Spatial patterns of genetic variation generated by different forms of dispersal during range expansion. *Heredity* 77(3):282–91
129. Hallatschek O, Nelson DR. 2008. Gene surfing in expanding populations. *Theor. Popul. Biol.* 73(1):158–70
130. Hallatschek O, Korolev KS. 2009. Fisher waves in the strong noise limit. *Phys. Rev. Lett.* 103 (10):108103
131. Korolev KS, Avlund M, Hallatschek O, Nelson DR. 2010. Genetic demixing and evolutionary forces in the one-dimensional stepping stone model. *Rev. Mod. Phys.* 82:1691–1718
132. McKane AJ, Newman TJ. 2004. Stochastic models in population biology and their deterministic analogs. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 70(4):41902
133. Butler T, Goldenfeld N. 2009. Robust ecological pattern formation induced by demographic noise. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 80(3):030902
134. Odling-Smee F, Laland K, Feldman M. 2003. *Niche Construction: The Neglected Process in Evolution.* Princeton, NJ: Princeton Univ. Press. 468 pp.
135. Day RL, Laland KN, Odling-Smee JF. 2003. Rethinking adaptation: the niche-construction perspective. *Perspect. Biol. Med.* 46(1):80–95
136. Lenski RE, Barrick JE, Ofria C. 2006. Balancing robustness and evolvability. *PLoS Biol.* 4(12):2190–92
137. Palumbi SR. 2009. Better evolution through chemistry: rapid evolution driven by human changes to the chemical environment. In *Chemical Evolution II: From the Origin of Life to Modern Society*, ed. L Zaikowski, J Friedrich, SR Seidel, 333–43. Oxford: Oxford Univ. Press. 376 pp.
138. Goldenfeld N. 2009. No man is an island. *Nat. Phys.* 5:1
139. Ray TS. 1991. Evolution and optimization of digital organisms. In *Scientific Excellence in Supercomputing: The IBM 1990 Contest Prize Papers*, *Athens, GA, 30602* ed. KR Billingsley, E Derohanes, H Brown III, pp. 489–531. The University of Georgia: Baldwin Press
140. Adami C, Brown CT. 1994. Evolutionary learning in the 2D artificial life systems: Avida. In *Artificial Life IV: Proceedings of the Fourth International Workshop on the Synthesis and Simulation of Living Systems,* ed. R Brooks, P Maes, pp. 377–381. Cambridge, MA: MIT Press. 772 pp.
141. Caldarelli G, Higgs PG, McKane AJ. 1998. Modelling coevolution in multispecies communities. *J. Theor. Biol.* 193(2):345–58
142. Adami C. 2002. What is complexity? *Bioessays* 24(12):1085–94
143. McKane AJ. 2004. Evolving complex food webs. *Eur. Phys. J B* 38(2):287–95
144. Maron M, Fernando CT. 2006. Food webs and the evolution of organism complexity. In *Artificial Life X: Proceedings of the Tenth International Conference on the Simulation and Synthesis of Living Systems*, ed. LM Rocha, LS Yaeger, MA Bedau, D Floreano, RL Goldstone, A Vespignani. Cambridge, MA: MIT Press. 575 pp.

145. Elena SF, Lenski RE. 2003. Evolution experiments with microorganisms: the dynamics and genetic bases of adaptation. *Nat. Rev. Genet.* 4(6):457–69
146. Adami C. 2006. *Nat. Rev. Genet.* Digital genetics: unraveling the genetic basis of evolution. 7:109–18
147. Wilke C, Adami C. 2002. The biology of digital organisms. *Trends Ecol. & Evol.* 17(11):528–32
148. Lenski RE, Ofria C, Collier TC, Adami C. 1999. Genome complexity, robustness and genetic interactions in digital organisms. *Nature* 400:661–64
149. Adami C, Brown CT, Haggerty MR. 1995. Abundance-distributions in artificial life and stochastic models: age and area revisited. In *Proceedings of the Third European Conference on Advances in Artificial Life*, ed. F Morán, A Moreno, JJ Merelo P Chacón, pp. 503–14. Berlin/New York: Springer-Verlag. 960 pp.
150. Ostrowski EA, Ofria C, Lenski RE. 2007. Ecological specialization and adaptive decay in digital organisms. *Am. Nat.* 169:E1–20
151. Lenski RE, Ofria C, Pennock RT, Adami C. 2003. The evolutionary origin of complex features. *Nature* 423:139–44
152. Woese CR. 1971. Evolution of macromolecular complexity. *J. Theor. Biol.* 33(1):29–34
153. Jones S, Thornton JM. 1995. Protein-protein interactions: a review of protein dimer structures. *Prog. Biophys. Mol. Biol.* 63(1):31–65
154. Goodsell DS, Olson AJ. 2000. Structural symmetry and protein function. *Annu. Rev. Biophys. Biomol. Struct.* 29:105–53
155. Plaxco KW, Gross M. 2009. Protein complexes: the evolution of symmetry. *Curr. Biol.* 19(1):R25–6
156. Pereira-Leal JB, Levy ED, Kamp C, Teichmann SA. 2007. Evolution of protein complexes by duplication of homomeric interactions. *Genome Biol.* 8(4):R51
157. Levy ED, Erba EB, Robinson CV, Teichmann SA. 2008. Assembly reflects evolution of protein complexes. *Nature* 453(7199):1262–65
158. Richardson LF. 1922. *Weather Prediction by Numerical Process.* Cambridge, UK: Cambridge Univ. Press. 262 pp.
159. Kolmogorov AN. 1941. Local structure of turbulence in an incompressible fluid at very high Reynolds numbers. *Dokl. Acad. Nauk USSR* 30:299–303
160. Kataoka N, Kaneko K. 2003. Dynamical networks in function dynamics. *Physica D* 181(3–4):235–51
161. Anderson RM, May RM. 1982. Coevolution of hosts and parasites. *Parasitology* 85(2):411–26
162. Bascompte J, Jordano P. 2007. Plant-animal mutualistic networks: the architecture of biodiversity. *Annu. Rev. Ecol. Evol. Syst.* 38:567–93
163. Kiers ET, Denison RF. 2008. Sanctions, cooperation, and the stability of plant-rhizosphere mutualisms. *Annu. Rev. Ecol. Evol. Syst.* 39:215–36
164. Dethlefsen L, McFall-Ngai M, Relman DA. 2007. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 449(7164):811–18
165. Van Valen L. 1973. A new evolutionary law. *Evol. Theory* 1(1):1–30
166. Weitz JS, Hartman H, Levin SA. 2005. Coevolutionary arms races between bacteria and bacteriphage. *Proc. Natl. Acad. Sci. USA* 102(27):9535–40
167. Brockhurst MA, Morgan AD, Rainey PB, Buckling A. 2003. Population mixing accelerates coevolution. *Ecol. Lett.* 6(11):975–79
168. Brockhurst MA, Rainey PB, Buckling A. 2004. The effect of spatial heterogeneity and parasites on the evolution of host diversity. *Proc. Biol. Sci.* 271(1534):107–11
169. Fussmann GF, Loreau M, Abrams PA. 2007. Eco-evolutionary dynamics of communities and ecosystems. *Functl. Ecology* 21:465–77
170. Gandon S, Buckling A, Decaestecker E, Day T. 2008. Host-parasite coevolution and patterns of adaptation across time and space. *J. Evol. Biol.* 21(6):1861–66
171. Brockhurst M. 2010. Using microbial microcosms to study host–parasite coevolution. *Evol. Educ. Outreach* 3:14–18
172. Paterson S, Vogwill T, Buckling A, Benmayor R, Spiers AJ, et al. 2010. Antagonistic coevolution accelerates molecular evolution. *Nature* 464:275–78

173. Hillesland KL, Stahl DA. 2010. Rapid evolution of the stability and productivity at the origin of a microbial mutalism. *Proc. Natl. Acad. Sci. USA* 107(5):2124–29
174. Kondoh M. 2003. Foraging adaptation and the relationship between food-web complexity and stability. *Science* 299(5611):1388–91
175. Ackland GJ, Gallagher ID. 2004. Stabilization of large generalized Lotka-Volterra foodwebs by evolutionary feedback. *Phys. Rev. Lett.* 93(15):158701
176. Axelrod R, Hamilton W. 1981. The evolution of cooperation. *Science* 211(4489):1390–96
177. Smith JM. 1982. *Evolution and the Theory of Games.* Cambridge, UK: Cambridge Univ. Press. 226 pp.
178. Nowak MA, Sigmund K. 2004. Evolutionary dynamics of biological games. *Science* 303(5659):793–99
179. Nowak Martin A. 2006. *Evolutionary Dynamics: Exploring the Equations of Life*. Cambridge, MA: Belknap Press. 384 pp.
180. McGill BJ, Brown J. 2007. Evolutionary game theory and adaptive dynamics of continuous traits. *Annu. Rev. Ecol. Evol. Syst.* 38:403–35
181. Turner PE, Chao L. 1999. Prisoner's dilemma in an RNA virus. *Nature* 398(6726):441–43
182. Brown SP. 2008. Collective action in an RNA virus. *J. Evol. Biol.* 14(5):821–28
183. Kirkup BC, Riley MA. 2004. Antibiotic-mediated antagonism leads to a bacterial game of rock-paper-scissors *in vivo*. *Nature* 428(6981):412–14
184. Gore J, Youk H, van Oudenaarden A. 2009. Snowdrift game dynamics and facultative cheating in yeast. *Nature* 459(7244):253–56
185. Nash JF. 1950. Equilibrium points in n-person games. *Proc. Natl. Acad. Sci. USA* 36(1):48–49
186. Akiyama E, Kaneko K. 2000. Dynamical system game theory and dynamics of games. *Physica D* 147(3–4):221–58
187. Akiyama E, Kaneko K. 2002. Dynamical system game theory II: a new approach to the problem of the social dilemma. *Physica D* 167(1–2):36–71
188. Sato Y, Akiyama E, Doyne Farmer J. 2002. Chaos in learning a simple two-person game. *Proc. Natl. Acad. Sci. USA* 99:4748–51
189. Zimmermann M, Eguíluz V, Miguel M. 2001. Cooperation, adaptation and the emergence of leadership. In *Economics with Heterogeneous Interacting Agents*, ed. AP Kirman, J-B Zimmerman, pp. 73–86. New York: Springer
190. Ebel H, Bornholdt S. 2002. Coevolutionary games on networks. *Phys. Rev. E* 66(5):056118
191. Perc M, Szolnoki A. 2009. Coevolutionary games—a mini review. BioSystems 99(2):109–25
192. Sato Y, Akiyama E, Crutchfield JP. 2005. Stability and diversity in collective adaptation. *Physica D* 210(1–2):21–57
193. Doyne Farmer J, Lo AW. 1999. Frontiers of finance: evolution and efficient markets. *Proc. Natl. Acad. Sci. USA* 96(18):9991–92
194. Hens T, Schenk-Hoppé KR. 2005. Evolutionary finance: introduction to the special issue. *J. Math. Econ.* 41(1–2):1–5
195. May RM, Levin SA, Sugihara G. 2008. Complex systems: ecology for bankers. *Nature* 451(21):893–95
196. Luria SE, Delbrück M. 1943. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* 28(6):491–511
197. Sniegowski PD, Lenski RE. 1995. Mutation and adaptation: the directed mutation controversy in evolutionary perspective. *Annu. Rev. Ecol. Syst.* 26(1):553–78
198. Galhardo R, Hastings PJ, Rosenberg S. 2007. Mutation as a a stress response and the regulation of evolvability. *Crit. Rev. Biochem. Mol. Biol.* 42(5):399–435
199. Dunny GM. 2007. The peptide pheromone-inducible conjugation system of *Enterococcus faecalis* plasmid pCF10: cell-cell signaling, gene transfer, complexity and evolution. *Philos. Trans. R. Soc. B* 362(1483):1185–93
200. Manson J, Hancock L, Gilmore M. 2010. Mechanism of chromosomal transfer of *Enterococcus faecalis* pathogenicity island, capsule, antimicrobial resistance, and other traits. *Proc. Natl. Acad. Sci. USA* 107(27):12269–74
201. Schrödinger E. 1954. *Nature and the Greeks.* Cambridge, UK: Cambridge Univ. Press. 97 pp.
202. Frauenfelder H, Wolynes PG, Austin RH. 1999. Biological physics. *Rev. Mod. Phys.* 71(2):S419–30