19

ON FUNDAMENTAL IMPLICATIONS OF SYSTEMS AND SYNTHETIC BIOLOGY

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19.1 SETTING SYSTEMS AND SYNTHETIC BIOLOGY IN CONTEXT

19.1.1 Systems and Synthetic Biology in Context

Systems and synthetic biology promise to revolutionize our understanding of biology, blur the boundaries between the living and the engineered in a vital new bioengineering, and transform our daily relationship to the living world. Their emergence thus deserves to be understood in a wider intellectual perspective. Close attention to their relationship to the larger scientific intellectual frameworks within which they function reveals that systems and synthetic biology raise fundamental challenges to scientific orthodoxy, but stand in the vanguard of an emerging new complex dynamical systems paradigm now sweeping across science.

They emerge from a preceding developmental stage of science where, sketching crudely, biology was divided between molecular biology on the one side and, on the other, physiology (functional biology) and, on a larger scale, population genetics (evolutionary biology), and there was relatively little commerce among these approaches. Molecular biology and evolutionary population biology effectively agreed on assuming simple rules for gene expression that had the effect of reducing organism complexity to genetic complexity and so of treating the organism (reduced

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to a phenotype) as if it consisted simply of a bundle of genes. Whence, with genes directly related to produced phenotypes through the simple gene–trait rules, population gene frequencies could be constructed, and the diversity of complex organic processes could be explained in terms of evolutionary natural selection expressed in population frequency shifts. This left molecular biology to focus on the genes, aka DNA, and evolutionary theory to focus on gene population statistics. Caught between them, physiology focused on its own functional descriptions, cast in terms of organism features like energy fluxes and tissue densities, as, in different ways, did its sister domains of embryology and developmental biology.

Though somewhat a caricature, this division of conception and labor leaves the treatment of biosynthetic pathways out of the picture; however, they are essential for biological understanding. For they are the linkages connecting gene activity through intracellular and then intercellular formation and functioning to organism formation and functioning, and on, finally, to an enriched multilayered conception of evolutionary process (see below at footnote 22). It is exactly at this locus that systems and synthetic biology intervene.

These subdisciplines act, severally and together, as an interlevel bridge between molecular biology and physiology, precisely by developing the treatment of biosynthetic pathways, and in this way create a lively, reinvigorating integration to biology. Despite the complexity of biosynthetic pathways, scientists have been able to study them by carrying over into biology certain engineering modeling tools, such as control theory and electrical circuit theory and its generalization to dynamical network theory. With genes, proteins, and metabolites as components and replication, self-assembly, metabolism, repair, growth/death, signaling and regulation as process elements, systems and synthetic biology using these tools to model the complexes of processes that constitute cells, and interacting multicellular bodies like organs, in ways analogous to those in which engineers model and regulate fighter jet aerodynamics and multistage industrial processes.[1]

Of the two, synthetic biology has a wider scope than systems biology since, beyond the actual life forms of systems biology, the domain of synthetic biology also includes novel viable life forms and bioengineering complexes in which specialized organisms and/or biomaterials/processes play important roles. However, the hope underlying work in both studies is that a cell can be adequately modeled as a dynamical pathway network and a multicelled organism can be adequately modeled as a supernetwork of these (and so on up). Adding inanimate engineering network components then suffices to encompass all the wider domain of synthetic biology.

Methodologically, systems biology and synthetic biology are mutually beneficial (symbiotic); systems biology employs to advantage the perturbational and measurement methods developed by synthetic biology, while systems biology provides knowledge of dynamical models of various useful organisms from which synthetic biology may work. The key to the rise of these two interrelated subdisciplines has been the (accelerating) emergence over the past 50 years of high-throughput experimental

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[1] See, among many recent texts, the nicely diagrammed overview in Ref. [1], Chapter 1.

technologies capable of amplifying trace chemical presences to reliably measurable quantities in practicable times and of doing so simultaneously with increasingly many cellular components. Starting with recombinant DNA techniques for single genes in the 1970s, today the techniques are crossing the threshold of being able to simultaneously monitor all the "omics" for entire, or nearly entire, cellular genomes.[2]

As Palsson says (op cit. footnote 1) the arrival of this data both forces and enables the study of the cell as a system. While the earlier experimental stages were appreciated for their capacity to identify the lists of components involved, once this had been achieved the vast quantities of simultaneous data now available can only be usefully simplified and comprehended in terms the interrelationships they reveal, that is, in terms of a network model.

Method is as yet at a relatively early stage of development compared to engineering theory, confined in many cases to topological considerations backed by stoichiometric considerations like flux measurements.[3] Beyond this "kinetic modeling is still severely hampered by inadequate knowledge of the enzyme–kinetic rate laws and their associated parameter values"[4] and is only recently beginning to enhance stoichiometry with direct dynamical modeling. This is partly because data of the kind and quality required is only recently becoming available,[5] and partly because the dynamical operations of very complex networks are still being only indirectly studied, requiring the development of new data analysis techniques.[6] The methodological challenges in this respect focus around improving the reliable identification of circuit structure, including (1) the discrimination of partial redundancies, (2) the development of recently initiated methods for the treatment of integrated pathways where two or more kinds of links (e.g., metabolic and signaling) are simultaneously partially served by the same chemical elements, (3) better understanding of cross-pathway interaction and whether it should be treated as mere interference or evidence of inappropriate pathway modeling, (4) the resolution of hierarchical functional architectures, and (5) sufficiently increasing the extent and precision of dynamical information required to accomplish all this.

As interlevel bridging theories, the emergence of systems and synthetic biology represents a revolution in scientific biological knowledge. But, as the opening remarks signaled, these developments also have intellectual impacts of a wider and deeper nature that can best be appreciated when set in a wider context. First there is the larger question of the nature of the living domain: against the earlier division between

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[2] See Mitsuro Itaya, Chapter 5 herein and, for example, Ref. [2].

[3] Cf. Joyce and Palsson, Chapter 6 herein for deliberate development of this approach as a constraints-based delineation of possibilities.

[4] Ralph Steuer (Humboldt University, Berlin) "From topology to dynamics of metabolitic networks," lecture to the Bio-Modelling Network, Manchester University, UK, August 29, 2007.

[5] For instance, Ref. [3], noting the capacity to directly observe functional units, remarks "By linking genes and proteins to higher level biological functions, the molecular fluxes through metabolic networks (the fluxome) determine the cellular phenotype. Quantitative monitoring of such whole network operations by methods of metabolic flux analysis, thus bridges the gap by providing a global perspective of the integrated regulation at the transcriptional, translational, and metabolic level."

[6] See, for example, Ref. [4] and the discussion of modeling in Section 20.2.6.

a crude mechanism and a mysterious vitalism, systems and synthetic biology hold out the prospect of a reenergized naturalism for biology in which vital characteristics of organisms are captured as natural features of certain kinds of organized chemical systems. But to do so biological theory will have to meet some larger challenges that stem from the nature of complex adaptive systems more generally. For example, we still have no complete and coherent account of organization in complex systems, much less an account that illuminates the nature of life as a particular species of dynamical organization. Second, as this example indicates, there are still larger issues surrounding the introduction of complex dynamical system concepts, principles, tools/methods, and models into science—where they are now expanding rapidly across most of the sciences.[7] It is to these two larger questions that the remainder of this essay briefly turns—lest, not doing so, they return to confuse us. Only then shall we be able to properly consider the challenges ahead in biology, the topic of the closing chapter.

19.1.2 The Wider Problem of the Life Sciences

During the century bounded by the rise of organized modern public science 1850–1875 and its expansion to the massive institutions of 1950–1975, the intellectual conception of science was dominated by its fundamental and most excitingly progressive discipline: physics. The philosophy of science followed suit, entranced by the prospect of simple universal laws induced from rigorous evidence and with multifarious practical applications as the truest revelation of the creator's rationality, or anyway of the nature of prediction and explanation, theory and justification. This conception encompassed chemistry, if with some difficulty, and also engineering, medicine, and "biophysics," at least while these studies were confined to physics-like objectives such as building houses, simple surgery, and osmotic pressure and all their apparent other complexities were set aside as "merely practical."

However, the hope of a universal "physics vision" would later collapse as more lifelike systems were studied. Indeed, the chief problem with this vision became the lack of any obvious way to incorporate the sciences of living organisms, cellular biology, evolution, and ecology, extending to sociology, economics, and the humanities generally. By the end of the nineteenth century, the prospect of a separate vitalist foundation for these studies, where one looks to principles for living organisms that are fundamentally independent of those for inanimate systems, was successfully exorcised from mainstream science. The vitalist view, the critique of which dates back at least to Robert Boyle, offended against both unity under physics and the practical naturalism—often expressed in terms of materialism, mechanism or both—that has

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[7] Something of the reach and richness of the complex systems revolution sweeping the sciences will be able to be gleaned from a volume for the first time devoted to this task with 30 plus contributions by researchers across the sciences. For author abstracts see http://www.johnwoods.ca/HPS/#Complexity. Part of a multivolume *Handbook of the Philosophy of Science* now in publication and preparation, the volume's current working details are Cliff Hooker (Ed.) *Philosophy and Foundations of Complex Systems*, Vol. 10 of D Gabbay, Paul Thagard, and John Woods (Eds) *Handbook of the Philosophy of Science*, Amsterdam: Elsevier, 2006–2009.

successfully guided scientific advance for 400 years. So the life sciences were held in abeyance, some day to be somehow subsumed under the great general mechanical laws. Of course, those within the excluded domains felt obliged to declare their difference, perpetuating an often tragic conflict.[8]

Thus providing a more adequate understanding of the nature of the life sciences is an urgent intellectual problem. Indeed, we still see the old opposition in action in the latest volume by Ernst Mayr [5], a book by a prominent research biologist who has been reflecting on the nature of biology for 40 years and through many books. Mayr argues that biology is unique, distinct from physics, chemistry, engineering, and all their applied forms from rockets to robotics. Although biological entities are subject to physical and chemical laws, he says, what makes them unique is essentially that they exhibit a suite of properties not possessed by the inanimate objects of these disciplines, namely metabolism, regeneration, regulation, growth, replication, evolution, and developmental and behavioral teleology.

There is no doubt that Mayr is right that these are significant features of the living world. Thus, it becomes a pressing issue to understand how systems and—especially—synthetic biology are possible, and how they are to be understood. To do that we need to briefly review the historical tradition that culminates in Mayr's contention—for it will also reveal the seeds of the contemporary promise of its resolution through systems and synthetic biology, even while calling attention to outstanding issues.

19.2 FORMATION OF INTELLECTUAL ORTHODOXY FOR THE FIRST SCIENTIFIC–INDUSTRIAL REVOLUTION

19.2.1 Establishment of a Physics-Based Framework for Biology

For roughly 250 years from the publication of Newton's *Principia* to the close of the Second World War in 1945, the defining characteristic of fundamental advance in physics was the understanding of dynamical symmetry and conservation. A symmetry is an invariance under some operation, for example, of spherical shape under rotation. In physics, the relevant symmetries are the invariances, that is, the conservation, of dynamical quantities under various continuous space–time shifts, for example, conservation of linear motion (momentum) under shift in spatial position or of energy under time shift. Noether gave systematic form to this in 1918 and showed that it was the invariance of the form of the dynamical laws themselves that was expressed. Collections of the same space–time shifts form mathematical groups, and the corresponding invariances then form dynamical symmetry groups.

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[8] This conflict within the research community formed the roots of Snow's two cultures, the gulf between the tools, styles, and goals of the sciences and the humanities. It will take at least another century to tackle this issue properly, but within this and the closing essay the reader will find an array of systems tools, beginning with (but by no means ending with) systems and synthetic biology, that bid fair to resolve the basic root of the problem, if not all of its branches.

For instance, Newton's equations obey the Galilean symmetry group. Symmetry forms the deepest principle for understanding and investigating fundamental dynamical laws.[9]

In addition to their general dynamical symmetries, many states have additional symmetries, for example, the lattice symmetries of a crystal. Within this framework thermodynamics emerged, with thermodynamic equilibrium the only dynamical state condition that could be identified for dealing with complex systems. The advantage of thermodynamic equilibrium states is their greater internal symmetry because all residual motion is random (a gas is stochastically spatially symmetric). When each equilibrium state is invariant with respect to transitory pathways leading to it (the outcome is independent of those initial conditions), so its history can be ignored in studying its dynamics. The dynamics itself can then be developed in a simplified form, namely in terms of local, small and reversible—hence linearizable—departures from stable equilibria, yielding classical thermodynamics.

The study of simple physical systems of a few components and of many component systems at equilibrium supported the idea that the paradigm of scientific understanding was linear causal analysis and reduction to linear causal mechanisms, with the real as what was stable, especially invariant. Paradigm cases were Newton's Laws and two-body solar system dynamics, engineering lever and circuit equations, simple two-component chemical rate equations, crystal lattices, and equilibrium thermodynamics of gases.

The philosophy of science was shaped to suit, focusing on determinism, universal atemporal (hence acontextual) causal laws, analysis into fundamental constituents then yielding bottom-up mechanical synthesis. To this was added a simple deductive model of explanation and prediction—deduction from theory plus initial conditions gives explanation after the event and prediction before it—with reduction to fundamental laws and separate contingent initial conditions becoming the basic explanatory requirement. This supports an ideal of scientific method as logical inference: induction from the data, where the most probable correct theory is logically inferred from the data (cf. statistical inference in bioinformatics), deduction from theory for prediction and explanation, and falsification: deduction from data that conflict with prediction to a failure of the predicting theory (or other assumptions).[10] However, it turns out (interestingly!) that neither the logical nor the

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[9] For instance, the shift from Newtonian to relativistic dynamics is a shift from Euclidean to Minkowski space–time and a corresponding shift from the Galilean to the Lorentz symmetry group, while the shift to nonrelativistic quantum theory, which exhibits stronger symmetries (expressing indistinguishable states), is a shift to the unitary symmetry group. Currently the as-yet-incomplete development of relativistic quantum theory is explored in terms of the further symmetry groups involved. Further see any of the many textbooks on this subject. If all this seems somewhat impenetrable to a life scientist, it suffices to grasp the idea that symmetry is the central structural feature of dynamics in physics. On the stability–equilibrium framework see, for example, Refs [6–8] and on symmetry disruption by newer systems dynamics ideas see these and, for example, Refs [9,10] and Brading's *Stanford Encyclopedia of Philosophy* entry at http://plato.stanford.edu/entries/symmetry-breaking/.

[10] See classics of the time like Ref. [11] on induction and reduction, and on falsification see Ref. [12]. For a contemporary version in systems and synthetic biology see Breiman in Section 20.2.6.

methodological situation is so simple; both scientific practice and rational method are, and must be, much more complex than this.[11]

The philosophy of science and the scientific paradigm together constituted the intellectual framework of scientific orthodoxy for a century of scientific understanding and the evident fit between philosophy and paradigm supported the conviction that both were right, the logical clarity and elegance of the philosophy reinforcing that conviction. From within this framework, the greatest challenge is that of quantum theory to determinism and simple causality. But while this is a profound problem, the immediate theoretical challenge is also limited since the fundamental dynamical idea of a universal deterministic flow on a manifold characterized by its symmetries remains at the core.[12]

The great formation period of modern biology, characterized by the rise of genetics and its incorporation into evolutionary theory, and the subsequent emergence of elementary molecular genetics in its support, was understood within this orthodox framework. The simple fundamental laws of evolutionary population genetics and of molecular genetics that underlay them were held to provide the universal, unchanging causal reality underlying the apparently bewildering diversity of biological phenomena. The observed diversity was to be seen simply as reflecting a diversity of initial conditions independent of these laws, whether generated as exogenous geoecological events or as endogenous random mutations.

Reduction to molecular genetics thus became a defining issue. Initially this took the form, noted earlier, of treating the phenotype as effectively just a bundle of gene–trait pairs that determined fitness. This simplification sufficed, given their developmental stages, for population genetics and molecular biology, at the time. For the longer term the reductionist paradigm, based on analysis and bottom-up synthesis, assumed that the information gained by unraveling the separate simple mechanisms of all the different molecular components could be used to provide adequate linear assembly models of cellular and multicellular organisms. Functional analysis was based on the similar idea of dissecting a complex system into its functional components, all the way down to its simplest basic functions, then reducing the basic functions to simple mechanisms, and resynthesizing. This research paradigm dominated twentieth century mainstream biology, a time in which enormous progress also took place in accumulating molecular information.

19.2.2 Framework-Induced Dichotomy in the Life Sciences

The consequence of this approach to biology is that either life is radically reduced to simple chemical mechanisms and then to physics, or it has to be taken outside the paradigm altogether and asserted as metaphysically *sui generis*, a realm in itself from which flowed all of the distinctive features Mayr lists (see Section 19.1.2, especially regeneration, replication, and teleology). Both implausible positions had

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[11] For overview and discussion of the situation, see, for example, Ref. [13], Chapter 2.

[12] However, as the dispute between Bohr and Einstein suggests, there may be implicit in this challenge more profound issues that do at least call into question the nature of intelligible reality, cf. Ref. [14].

devoted proponents. In particular, expressed as various forms of vitalism, the latter position has had a long history in Western thought; especially as science emerged from a Christian religious framework, it freed up investigation of the physical body while leaving the mind and soul to religious teaching. Descartes, for example, drew a sharp distinction between human body and spirit (other organisms were simply clever automatons), regarding the human organism as a hybrid, hierarchical control system: the spirit carried all the initiative, expressed perhaps through the pineal gland, while the material body was reduced to an automaton responding to control orders, a deterministic machine explained by simple physics. Kant similarly ascribed biological processes to teleology that, while embodied, escaped material scrutiny in themselves.

This situation formed the general approach to the scientific treatment of living entities, whether in psychology, sociology, economics or history, and other cultural studies. In psychology, for example, the corresponding primary choice is that between reductionist materialism and dualism (Cartesianism). Behaviorism was a particularly severe form of reductionist materialism that dominated in the first half of the twentieth century. It was followed by the currently dominant artificial intelligence version, a functionally generalized behaviorism where the mind is modeled as internal deterministic assembly and control programs, ultimately representable as digital software. This respectively parallels the transparent phenotype and molecular mechanism assembly stages of biological theory as successively reductionist input/output black box and then gray box input/output transform models. In economics we similarly begin with Homo economicus, where agents are reduced to sets of preferences, behaviorally revealed (in principle), plus a simple welfare optimization program; only recently are agents beginning to be fleshed out with preference dynamics, decision psychology, and collective interactions (e.g., through multiagent models and evolutionary game theory). The philosophy of these disciplines was shaped to suit in ways analogous to those for biology.

These are undoubtedly the early theory building stages through which any science has to go as it laboriously assembles better understanding. Possibly this was itself intuitively understood by many scientists. Even so, there was enough dogmatic conviction in science, and certainly in philosophy of science, that the results were not pleasant for dissenters who were denied a hearing and research funding and often ostracized. One might recall, as examples of this, the fates of Baldwin and Lamarck and others in biology, and of Piaget in biology and philosophy, all now being at least partially rehabilitated as the old simple dogmas breakdown, not to mention those in entire subdisciplines such as embryology and ecology who were sidelined for many years before they have again returned to the forefront of scientific progress.[13] Yet the problem of reconciling biology and physics was always a dilemma: either the organic

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[13] Ultimately, embryology must become a vital application of systems and synthetic biology, since all living systems exhibit complex developmental histories. Similarly, ecological systems theory must ultimately become its sister science focused at the organism and population levels instead of the cellular and cell assembly levels—exhibited, for example, through the network models of Levins [15,16] and the dynamical resilience models of Gunderson, Holling, and others [17,18]. However, these interrelationships are as yet in their early development.

dwelled in a realm *sui generis*, or the reductive paradigm of physics was too restrictive to give a realistic account of any but the simplest of natural systems.

19.3 QUIET PREPARATIONS FOR A REVOLUTION

19.3.1 How the Emergence of the New Orthodoxy-Breaking Concepts is Tied to the Emergence of the Basic System Tools Used by Systems and Synthetic Biology

Yet all the while scientific work itself was quietly and often unintentionally laying the groundwork for superseding these approaches, both scientifically and philosophically. To understand why this might be so one has only to contemplate what the previous paradigm excludes, namely all irreversible, far-from-equilibrium thermodynamic phenomena. This comprises the vast majority of subject matter of interest to science, everything from supergalactic formation in the early cooling of the universe down to planet formation, all or most of our planet's geoclimatic behavior, all phase change behavior, natural to the planet or not, and of course all life forms, since these are irreversible far-from-equilibrium systems. What all of these phenomena exploit is spontaneous instability, specifically nonlocal, irreversible dynamical departure from their present state, whether it be the instability of a gas cloud condensing to a star, or that of a collection of chemicals forming a continuously self-regenerating life form. Moreover, all of these transitions represent the formation of nonequilibrium structures and the formation of increased complexity through symmetry breaking. This is starkly clear for cosmic condensation: the universe begins as a superhot supersymmetric expanding point sphere, but as it expands it cools and differentiates, breaking its natal supersymmetry; the four fundamental forces differentiate out, their nonlinearities amplifying the smallest fluctuational differences into ever-increasing structural features. In sum, all of these vast sweeps of phenomena are characterized by the opposite of the symmetry/equilibrium paradigm.[14]

Thus it is not surprising that from early on, even while the elegantly simple mathematics of the stability–symmetry paradigm were being developed and its striking successes explored, scientists sensed the difficulties of remaining within its constraints, albeit in scattered and hesitant forms. Maxwell, who formulated modern electromagnetic theory in the later nineteenth century and sought to unify physics, drew explicit attention to the challenge posed by instability and failure of

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[14] An early mathematical classic on nonlinear instabilities referred to the old paradigm as the "stability dogma,"see Ref. [19], pp. 256ff. See also the deep discussion of the paradigm by the Nobel prize winning pioneer of irreversibile thermodynamics, Prigogine, in Refs [20–22]. I add the phase-shift cosmogony of Daodejing, Chapter 42, translated by my colleague Dr Yin Gao, because the West has been slow to appreciate the deep dynamical systems orientation of this tradition in Chinese metaphysics, for instance, in medicine [23]:

> The dao (the great void) gives rise to one (singularity)
> Singularity gives rise to two (yin and yang)
> Yin and yang give rise to three (yin, yang, and the harmonizing force)
> Yin, yang, and the harmonizing force give birth to the 10,000 things/creatures.

universality for formulating scientific laws, while his young contemporary Poincaré spearheaded an investigation of both nonlinear differential equations and instability, especially geometric methods for their characterization.[15] By the 1920s static, dynamic, and structural equilibria and instabilities had been distinguished.[16] A static equilibrium requires no irreversible process to maintain it while a dynamic equilibrium does. Living organisms illustrate dynamical equilibria since they only persist if maintained by flows of energy and matter through them. Either equilibrium is unstable if its conditions are sufficiently perturbed. The system is then on a transient trajectory until a new equilibrium is reached. Phase changes illustrate structural instabilities, where the dynamical form itself changes during the transient trajectory. It was discovered in the 1950s and 1960s that simple chemical reaction systems, like that studied by Belousov and Zhabotinskii, show phase changes among dynamical equilibria.

In engineering, nonlinearity and emergent dynamics appeared in an analytically tractable manner with the discovery of feedback and the development of dynamical (as distinct from later programming) control theory. Maxwell in 1868 provided the first rigorous mathematical analysis of a feedback control system (Watt's 1788 steam governor). By the early twentieth century General Systems Theory was developed by von Bertalanffy and others, with notions like feedback/feedforward, homing-in, and homeostasis at their basis, while later Cybernetics (the term coined by Weiner in 1948) emerged from control engineering as its applied counterpart.[17] Classical control theory, which became a disciplinary paradigm by the 1960s, forms the basis of the use of dynamical system models in contemporary systems and synthetic biology.

In 1887 Poincaré had also become the first person to discover a chaotic deterministic system (Newton's three-body system), later introducing ideas that ultimately led to modern chaos theory. Meanwhile Hadamard 1898 studied a system of idealized "billiards" and was able to show that all trajectories diverge exponentially from one another (sensitivity to initial conditions), with a positive Lyapunov exponent. However, it was only with the advent of modern computers in the 1960s that investigation of chaotic dynamics developed, beginning with Lorenz whose model of atmospheric dynamics as a simple convective cell revealed sensitivity to initial

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[15] This sensitivity was already evident in the 20 years Newton delayed publication of his magisterial *Principia Mathematica*, while he searched for a principled way to encompass the treatment of lunar dynamics within its framework, a classical nonlinear three-body gravitational problem for which his doubts have subsequently been shown amply justified.

[16] Thanks to Birkhoff and Andropov, following Poincaré. Lyapunov's study of the stability of nonlinear differential equations was in 1892, but its significance was not generally realised until the 1960s.

[17] In 1840, Airy developed a feedback device for pointing a telescope, but it was subject to oscillations; he subsequently became the first to discuss the instability of closed-loop systems, and the first to use differential equations in their analysis. Following Maxwell and others, in 1922, Minorsky became the first to use a proportional–integral–derivative (PID) controller (in his case for steering ships), and considered nonlinear effects in the closed-loop system. By 1932, Nyquist derived a mathematical stability criterion for amplifiers related to Maxwell's analysis and in 1934 Házen published the *Theory of Servomechanisms*, establishing the use of mathematical control theory in such problems as orienting devices (e.g., naval guns). Later development of the use of transfer functions, block diagrams, and frequency-domain methods saw the full development of classical control theory.

conditions, which offered a possible explanation of why, even with enormously increased data collection, long-term weather prediction remained elusive. By the mid-1970s chaos had been found in many diverse places, including physics (both empirical and theoretical work on turbulence), chemistry (the Belousov–Zhabotinskii system), and biology (logistic map population dynamics and Lotka–Volterra equations for four or more species), and the mathematical theory behind it was solidly established (Feigenbaum, Mandelbrot, Ruelle, Smale, and others).

This historical account is unavoidably selective and sketchy, but it sufficiently indicates the slow build up of an empirically grounded conceptual break with the simple symmetry/equilibrium orthodoxy. However the new approach still often remained superficial to the cores of the sciences themselves. In physics this is for deep reasons to do with the lack of a way to fully integrate instability processes, especially for structural instabilities, into the fundamental dynamical flow framework (at present they remain interruptions of flows), the lack of integration of irreversibility into fundamental dynamics,[18] and the related difficulty of dealing with global organizational constraints in flow characterization (specifically the difficulty of dealing with the autonomy constraint that characterizes coherent metabolisms for living creatures[19]). For biology all that had really developed was a partial set of mathematical tools applied to a disparate collection of isolated examples that were largely superficial to the then core principles and dynamics of the field.

We now say complexity was discovered, and indeed science came to distinguish a range of new systems from those that could be more thoroughly treated because they were few bodied with simple dynamics or many bodied but either unordered (random) or highly ordered (crystal-like). But there was then no principled framework for understanding systems that were many bodied, nonlinear, sufficiently ordered to be organized, and dynamically labile; indeed, the problem of fully characterizing complexity in a principled manner remains open.[20]

Nonetheless, by the late 1970s it is clear in retrospect that science had begun to pull together many of the major ideas and principles that would undermine the hegemony of the simple symmetry/equilibrium orthodoxy. Instabilities were seen to play crucial roles in many real-life systems—they even conferred sometimes valuable properties on those systems, such as sensitivity to initial conditions and structural lability in response. These instabilities broke symmetries and in doing so produced the only way to achieve more complex dynamical conditions. The phenomenon of deterministic chaos was not only surprising to many, but to some extent it pulled apart determinism from analytic solutions, and so also from prediction, and hence also pulled explanation

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[18] Prigogine [21] had even proposed to modify the Schrodinger equation to circumvent its entrenched linearity and accommodate irreversible dissipation. However irreversible thermodynamics has subsequently made some internal progress through the work of Morowitz and others. As for quantum theory (about which Einstein had earlier similarly complained) subsequent experience with relativistic quantum theory suggests that the problem has to be tackled at a much deeper level, if it can be tackled at all from within our present flow conception of dynamics.

[19] On this use of autonomy, see, for example, Refs [24–26]. Its incorporation into systems and synthetic biology remains an outstanding theoretical task (see the concluding essay herein).

[20] See further Section 19.7 and the concluding essay herein and Ref. [27].

apart from prediction. It also emphasized a principled, as opposed to a merely pragmatic, role for human finitude in understanding the world.[21] The models of phase change especially, and also those of far-from-equilibrium dynamical stability, created models of emergence with causal power (“top-down” causality), and hence difficulty for any straightforward idea of reduction to components.[22] And, although not appreciated until recently, they created an alternative paradigm for situation-dependent rather than universal, laws.[23] Thus, responses like that of Duhem in *The Aim and Structure of Physical Theory* to retain the simple symmetry/equilibrium orthodoxy despite being aware of the results of Poincaré and Hadamard became less and less reasonable, and a new appreciation for the sciences of complex dynamical systems began to emerge. These are the very ideas that, allied to the development of generalized network analysis emerging from circuit theory, chemical process engineering, and elsewhere would later underlie contemporary systems and synthetic biological modeling.

19.3.2 Preparations for Change in Biology

This period also quietly set the stage for the undoing of geneticism, the simple gene–trait model noted at the outset, and that later paved the way for the more intimate introduction of complex systems methods into the heart of biology. Genetics had of course emphasized the importance of what lay inside the cell but, as noted in Section 19.1.1, geneticism made the phenotype irrelevant to biological theory and explanation. However, in physics Prigogine (following Schrodinger and Turing) worked on irreversible thermodynamics as the foundation for life (Footnotes 14, 18), modeling organisms as far-from-equilibrium systems sustained only by a continuous throughput of matter and energy, thereby importing suitably ordered energy (negative entropy) from their environment in order to create and maintain internal organization and discharging the inevitable less ordered waste products that result. (Biologically, this amounts to food and water intake and excreta output.) This generates a (high level) metabolic picture in which the full internally regulated body is essential to life. In this conception, it is organism activity, metabolic and behavioral, that supports development, regeneration, reproduction, and senescence for individuals and ultimately also for communities and ecosystems. This encompasses all Mayr’s distinctive properties (see Sections 19.2 and 19.4.1).[24]

During the immediate postwar period in which Prigogine and others were developing these ideas, cellular biology was revived and underwent a rapid development, partly driven by new, biochemical-based problems (understanding kinds and rates of chemical reactions like electron transport, and so on) and partly by new instrumentation (electron microscope, ultracentrifuge) that allowed much more

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[21] The point being that any finite creature can only make finitely accurate measurements, independently of any further constraints arising from specific biology or culture; there is always a residual uncertainty, and chaotic dynamics will amplify that uncertainty over time.

[22] For a systems biology illustration and discussion see Refs [28,29].

[23] See further Section 19.7 below and the concluding essay herein; for the basic idea, see Ref. [30].

[24] See also, for example Ref. [31].

detailed examination of intracellular structure and behavior. In consequence, there was an increasing molecular understanding of genetic organization, especially development of RNA roles in relation to DNA, of regulator genes and higher order operon formation and of the roles of intracellular biochemical gradients, intercellular signaling, and the like in cellular specialization and multicellular development. All this prepared the ground for envisioning the cell as a site of many interacting biochemical processes, in which DNA played complex interactive roles as some chemicals among others, rather than the dynamics being viewed as a consequence of a simple deterministic genetic program. Genetics was replaced by "omics" (genomics, proteomics, metabolomics, and so on).[25]

During roughly the same period, 1930–1960, Rashevsky and others pioneered the application of mathematics to biology. With the slogan *mathematical biophysics: biology:mathematical physics:physics*, Rashevsky proposed the creation of a quantitative theoretical biology and was an important figure in the introduction of quantitative dynamical models and methods into biology, ranging from models of fluid flow in plants to various medical applications. That general tradition was continued by his students, among them Rosen, whose edited volumes on mathematical biology of the 1960s and 1970s did much to establish the approach. Indeed, as Rosen remarks, "It is no accident that the initiative for System Theory itself came mostly from Biology; of its founders, only Kenneth Boulding came from another realm, and he told me he was widely accused of 'selling out' to biologists."[26]

In this tradition various physiologists began developing the use of dynamic systems to model various aspects of organism functioning. In 1966, for example, Guyton developed an early computer model that gave the kidney preeminence as the long-term regulator of blood pressure, with other systems only able to regulate pressure in the short term, and went on to develop increasingly sophisticated dynamical network models of this kind. The next generation expanded these models to include intracellular dynamics. Tyson, for example, researched mathematical models of chemical systems like Belousov–Zhabotinskii in the 1970s, passing to cellular aggregation systems like *Dictyostelium* in the 1980s and to intracellular network dynamic models in the 1990s, and this was a common progression.[27] See also the increasingly sophisticated models of timing.[28] In this manner physiology has supported a smooth introduction of increasingly refined dynamical models into biology, providing a direct resource for contemporary systems and synthetic biology.

There has also been a correlative revival of a developmental perspective in biology, in embryology generally and early cellular differentiation in particular. This became

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[25] See, for example Refs [32,33]

[26] On Rashevsky see, for example Ref. [34], http://www.kli.ac.at/theorylab/AuthPage/R/RashevskyN.html. For many years (1939–1972) he was editor and publisher of the journal *The Bulletin of Mathematical Biophysics*. For Rosen, see http://www.panmere.com/rosen/booklist.htm#bkrosen and the concluding essay. The quote comes from his *Autobiographical Reminiscence* at http://www.rosen-enterprises.com/RobertRosen/rrosenautobio.html.

[27] Among other resources see respectively http://www.umc.edu/guyton/, http://mpf.biol.vt.edu/people/tyson/tyson.html. Compare the work of Hogeweg, for example: http://www.binf.bio.uu.nl/master/.

[28] Refs [35–38].

linked to evolutionary "bottlenecks" and evolutionary dynamics generally to form evo-devo as a research focus. Added to this was work on epigenetics and nonnuclear inheritance, especially maternal inheritance, and early work on enlarging evolutionary dynamics to include roles for communal (selection bias, group selection) and ecological factors, culminating in the holistic "developmental systems" movement.[29]

Ecology too has been studied as a dynamic network (Lotka/Volterra, May, Levins, and others), as an irreversible far-from-equilibrium dissipative flux network (Ulanowicz) or food-web energetics system (Odum), as a spatiotemporally differentiated energy and matter flow pathway network (Pahl–Wostl) self-organizing through interorganism interaction (Holling, Solé/Bascompte) and as an organized complex dynamic system employing threshold (bifurcation) dynamics, spatial organization and exhibiting adaptive resilience (Holling, Walker, and others), responding in complex, often counterintuitive, ways to policy-motivated inputs.[30] All these features are found within cells, albeit more tightly constrained by cellular regenerative coherence, and fruitful cross-fetilization should eventually be expected, perhaps particularly with respect to the recent emphasis in both on understanding the coordination of spatial with functional organization.

All of these scientific developments, still in process, work toward replacing black box geneticism with a larger model of a mutually interacting set of evolutionary/developmental/communal/ecological dynamic processes.[31] Although still a collection of diverse models and methods, dynamical network methods are emerging across these disciplines as a shared methodological toolkit.[32] In combination, these developments present a picture of life as a complex system of dynamic processes running on different groups of timescales at different spatial scales, with longer term, more extended processes setting more local conditions for shorter term, less extended processes, while shorter term, local products accumulate to alter longer term, more extended processes.

This conception now extends into medicine (especially through Chinese medicine), psychology (through mathematical psychology, especially neuropsychological and social interaction dynamical modeling), and economics (through econophysics, evolutionary economics).[33] From there the conception extends still more widely (but more diffusely) through the social sciences and management (dynamical/evolutionary game theory, human–natural interaction dynamical networks), military theory, technology theory, and even the nature of science itself (research resource webs, economic and interactionist dynamics of knowledge).

The earlier physics paradigm of simple universality, symmetry, and (static) equilibrium no longer dominates. The new dynamical ideas are still based in the same fundamental dynamics, but derive from an aspect of them that has hitherto remained hidden, the complex spatiotemporal coordination of nonlinear dynamical

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[29] See, respectively, for instance, Refs [39–43], the title itself indicating something of the macro intellectual landscape in which the idea emerged, and Ref. [44].

[30] See, among many others, the following works and their references: Refs [16–18,45–53].

[31] Cf., for example, Ref. [54] and references in footnote 29.

[32] For a recent review see Ref. [55].

[33] See, respectively, and among many others, Refs [23,56–59].

interactions to form organized, far-from-equilibrium systems that arise through symmetry-breaking amplification and propagation of asymmetrical variations (however generated). It is this aspect of dynamics that is now coming to dominate research across the sciences. Although biology will come to have an unprecedented centrality for it, this century will not be known as the century of biology (as is sometimes said), but, more fundamentally, as the *century of complex systems dynamics*. And it offers for the first time the genuine prospect of natural, productive integration among a range of scientific disciplines based on interrelating the dynamical models being employed in each.

19.4 TOWARD A NEW COMPLEX SYSTEMS PARADIGM AND PHILOSOPHY

19.4.1 Complexity of Complex Systems and the Uniqueness of Biology

The complex systems that constitute our life world are characterized by deterministic dynamics that manifest the following properties:

(1) Nonlinear interactions; nonadditivity
(2) Irreversibility; nonequilibrium constraints; dynamical stabilities
(3) Amplification; sensitivity to initial conditions, especially to “rare” events
(4) Finite deterministic unpredictability; edge-of-chaos criticality
(5) Symmetry breaking; self-organization; bifurcations; emergence
(6) Enabling and coordinated constraints
(7) Coordinated spatial and temporal differentiation with functional organization
(8) Intrinsically global coherence and organization; modularity; hierarchy
(9) Path dependence and historicity
(10) Constraint duality; supersystem formation
(11) Autonomy; anticipativeness; adaptiveness
(12) Multiscale and multiorder functional organization; learning
(13) Model specificity/model plurality; model centeredness

Roughly, properties lower on the list are increasingly richly possessed by living systems and present increasing contemporary challenges to our dynamical understanding. The diversity and the domain-specificity of these properties explain the diversity of notions of complexity, and the challenges to understanding that they continue to pose undermines hope for any unified account of complexity in the near future.

Many of these terms are well known and have already been explained or illustrated; they will be assumed understood. Some are in common usage and often considered well known but in fact present ongoing challenges to understanding (self-organization, emergence, and organization); these will be assumed here as sufficiently intuited and briefly reconsidered in the closing essay. Finally, some others are likely less well known though straightforward: constraints (enabling, coordinated and dual),[34] path dependence,[35] and model specificity/plurality and centeredness,[36] while autonomy (cf. footnote 20), anticipativeness, and adaptiveness are briefly discussed in the concluding essay.

It should be noted that the shift to complex systems represents enrichment—albeit a massive enrichment—of the classical symmetry–stability–invariance dynamical framework, not its wholesale abrogation. It is just that it took some centuries to understand this. For instance, a dynamical attractor basin specifies a set of dynamical states within which the dynamical laws take on a stable, self-contained form. For a dynamics with several attractor basins and energetically determined transient paths connecting them, this provides an immediate model of sets of local, energetically dependent laws. Parameter-dependent deformations of this basin topology, where some basins may disappear and others arise, then provide cases of the emergence of higher order context (parameter) dependent law domains. More disruptive discontinuous bifurcations, for example, from fluid conduction to convection or blastula formation and internal phase difference, represent a more serious rift in the classical

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[34] The term ‘‘constraint’’ implies limitation, most generally in the present context it refers to limited access to dynamical states (equivalently limiting dynamical trajectories to subsets of state space); this is the common disabling sense of the term. But it is crucial to appreciate that constraints can at the same time also be enabling, they can provide access to new states. Thus, a skeleton is a disabling constraint, for example limiting the size of hole through which a body can fit; but by providing a jointed frame for muscular attachments it also acts to enable a huge range of articulated motions, transforming an organism’s accessible niche, initiating armor and predator/prey races, and so on. This is the general aspect of the duality of constraints, but it has a specific application in the system/supersystem context where system constraints may contribute to enabling supersystem capacities, for example the role of mitochondria in eukaryote energy production, and supersystem constraints may free up system constraints, for example wherever multicellular capacities permit member cells to specialize. In all of these cases there has to be a coordination of component constraints to achieve the final effect: the many component bones of a skeleton have to be quite specifically coordinated so as to achieve an articulation that facilitates fitness-providing behaviors, mitochondrial functioning has to be integrated with the larger cellular processesfor its products to innervate the cell.

[35] Path dependence occurs when initially nearby dynamical trajectories subsequently diverge as a function of small differences in their initial conditions. It is brought about by amplification, for example in selection-reinforced amplification of small genetic differences generating diverging developmental or speciation trajectories, where the source of amplification may be bifurcations, feedback, or simply suitable nonlinearities.

[36] Complex systems of the kind described typically require many parameters to adequately characterize, for example specifying the rate and storage characteristics of the many processes they sustain. Model specificity refers to the capacity to select parameter values so as to specialize the model to the characterization of some unique individual and/or situation, while model plurality refers to the converse capacity to capture the characterization of a plurality of individuals/situations within its parameter ranges. These features are the basis for formulating valid generalizations across populations and, conversely, for deducing feature ranges in individuals from more broadly characterized populations. Model centeredness refers to the fact that systems of these kinds typically manifest nonanalytic dynamics (their dynamical equations lack analytical solutions) whence it is necessary to explore their dynamics computationally. This places computational modeling at the center of their scientific investigation in a strong manner and highlights the unique contribution of computers to cognition (all its other uses being pragmatic, if often valuable).

fabric since the idea of an analytic but condition-dependent superdynamics for state space fails, or has so far eluded construction; but even here both the conditions under which they occur and the nature of their outcomes arise from the underlying general dynamics.

Comparing this list of complex system properties with Mayr's earlier list characterizing biological systems (Section 19.2) we can see that, at least in principle, complex systems provide resources for modeling, and hence explaining, each of them: metabolism, regeneration, growth, replication, evolution, regulation, and teleology (both developmental and behavioral). Metabolism, for example, refers to the organized network of biochemical interactions that convert input matter and negentropy (food and water) into usable forms and direct their flows to various parts of the body as required, for example, for cellular respiration. The individual biochemical reactions are largely known. However it remains a challenge to characterize multilevel processes like respiration, comprising processes from intracellular Krebs Cycles to somatic cardiovascular provision of oxygen and removal of carbon dioxide, processes that must be made coherent across the entire body. In this conception, global coherence is a result of internal regulation at various functional levels (intracellular and intercellular, organ and body), and we now have massive information about the individual multifarious feedback and switching processes that contribute to somatic and, neurally, to behavioral regulation. These same capacities, placed in the context of globally organized multiscale functional organization and adaptive retention, in principle also model all the basic properties of agency, including human agency, in particular the teleology distinctive of intentional intelligence.[37] The challenge global coherence poses is to understand how these processes are interrelated so as to produce the regulated dynamical labilities and equilibria that the explanation of organism capacities demands. Here systems and synthetic biology, together with neurobiology, have a central contribution to make.

Pursuit of every scientific framework, that is, of a philosophy and paradigm, is underwritten by a practical act of faith that its cognitive apparatus, including concepts, classes of models and underlying mathematics, and experimental instruments, techniques, and interpretations, is adequate to understand the domain concerned. Here that faith revolves around the adequacy of complex systems concepts, models, and techniques as deployed in roughly the scheme just presented.

19.4.2 Need for a New Scientific Framework

The world has turned. The old orthodox framework for science that sufficed for the study of simpler systems, physical systems of a few components and of many-component equilibrium systems, no longer suffices; science has discovered the power of complex systems. The Bénard cell, Belousov–Zhabotinsky reaction, and *Dictyostelium* aggregation have replaced the slingshot, gas, and crystal as model systems. With them has emerged the general model of a complex organization of dynamic processes running on different groups of timescales at different spatial

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[37] For an outline, see Refs [25,26] and the concluding essay.

scales, with longer term, more extended processes setting more local conditions for shorter term, less extended processes and shorter term, local products accumulating to alter longer term, more extended processes. Minimally this development calls for the articulation of a new framework adequate for the de facto deployment of complex systems models throughout the sciences, and especially in biology.

The old framework that supported a paradigm of linear causal analysis, reduction, symmetry, static stability (equilibrium), and invariance is being replaced by a new complex systems paradigm focused on multiscale nonlinear networked dynamical interrelationships, symmetry-breaking self-organization of complexity, partial unpredictability, context-dependent laws, complex global organization with partial hierarchical modularity, path dependence and historicity, and the unavailability of closed-formed analytic solutions and consequent model centeredness.

Correlatively, instead of a philosophy of science focusing on determinism, identification of universal atemporal (hence acontextual) causal laws and reduction achieved through analysis followed by linear, bottom-up analysis reduced to closed formed analytic solutions, we now need a philosophy of science focusing on dealing with multiple simultaneous, multiscale interdependencies, validity of top-down as well as bottom-up analysis, the entwinement of emergence and reduction, domain-bound (context-dependent) dynamical laws (causality makes limited sense in these contexts) that accept historically unique individuals as the norm, and limited knowability and controllability. In consequence, the simple induction-based resolution of theory development must be replaced (it never worked anyway), but now with an account rich enough to encompass these complications, and while the bare logical forms of deductive explanation and falsification survive, they too will need correlative enrichment to illuminate realistic scientific method. In short, a substantially revised philosophy of science is required.

These are still new ideas in science, despite their being manifest everywhere, and the new philosophy of science will need to be underpinned by clarified conceptual/theoretical accounts of these new features, especially complexity, self-organization, emergence, order/organization, information, system causality, reduction, and analysis/synthesis. Some progress has been made and will be commented on in the closing essay. Often this will have counterintuitive (really counterclassical) consequences, for example, reduction as naturalization (kind reduction through function-to-dynamics mapping) is entwined with emergence as antireductive top-down constraint formation, each relying on the other and both dictated by nonlinear dynamics. These in turn are needed to rethink explanation, prediction, control, and scientific method, for example, the statistical treatment of data and error identification. A coherent form of all of this is the necessary foundation for continuing to embrace the practical act of faith in the adequacy of the dynamical systems approach (Section 19.7), and its empirical confirmation the necessary ground for affirming that commitment as rational rather than merely faith.

These new ideas and practices also create new, and sometimes unexpected, scientific associations. In particular we note that, whereas biology and engineering were divided literally by the study of the living and the dead under the old paradigm, under the new complex systems paradigm they acquire a mutual affinity. As engineers have increasingly studied systems with similar complexity characteristics to those listed above, whether as sophisticated aeroplane control systems, multisensor, ‘‘intelligent’’ distributed signaling systems, or traffic flow systems, they have been forced to face the same issues over multiscale functional organization as do biologists. They have pursued robotics, their version of organisms, and used such exploratory methods as genetic algorithms, their version of evolution. Bioengineering increasingly integrates organisms into engineering designs, such as using bacteria to process waste water in artificial wetland design or, genetically engineered, to generate energy in industrial photosynthesis, and conversely in the synthesis of artificial life forms using engineering genome models. Thus, contemporary engineers would recognize the complex systems characterizations of Mayr’s biologically distinctive features as belonging in principle to their field as well.

Further afield, multiagent adaptive modeling in economics, social organization, intelligent firms, military conflict, and much more now find affinity with the general methods of the complex systems approach. So the developments considered in this book are themselves taking place in the wider context of a systems-led transformation of scientific concepts, principles, and methods that are having an increasingly deep impact.

REFERENCES

1. Palsson B. *Systems Biology: Properties of Reconstructed Networks*. New York: Cambridge University Press, 2006.
2. Borodina I, Nielsen J. From genomes to *in silico* cells via metabolic networks. *Curr Opin Biotechnol* 2005;16(3):350–355.
3. Sauer U. High-throughput phenomics: experimental methods for mapping fluxomes. *Curr Opin Biotechnol* 2004;15(1):58–63.
4. Joyce A, Palsson B. The model organism as a system: integrating ‘omics’ data sets. *Nat Rev Mol Cell Biol* 2006;7:198–210.
5. Mayr E. *What Makes Biology Unique?* Cambridge, UK: Cambridge University Press, 2004.
6. Brading K, Castellani E, editors. *Symmetries in Physics: Philosophical Reflections*. Cambridge, UK: Cambridge University Press, 2003.
7. Stewart I, Golubitsky M. *Fearful Symmetry. Is God a Geometer?* Oxford: Blackwell, 1992.
8. van Fraassen B. *Laws and Symmetry.* Oxford: Oxford University Press, 1989.
9. Mainzer K. *Symmetry and Complexity: The Spirit and Beauty of Non-Linear Science*. Singapore: World Scientific, 2005.
10. Schmidt J. *Instability in Nature and Science: A Philosophy of Late-Modern Physics*. Berlin: De Gruyter, 2007.
11. Nagel E. *The Structure of Science*. London: Routledge & Kegan Paul, 1961.
12. Popper K. *Conjectures and Refutations.* London: Routledge & Kegan Paul, 1972.
13. Hooker C. *Reason, Regulation and Realism.* Albany, NY: SUNY Press, 1995.
14. Hooker C. Physical intelligibility, projection, objectivity and completeness: the divergent ideals of Bohr and Einstein. *Br J Philos Sci* 1991;42:491–511.
15. Levins R, Lewontin R. *The Dialectical Biologist.* Harvard University Press, 1985.

16. Haila Y, Levins R. *Humanity and Nature: Ecology, Science and Society*. London: Pluto Press, 1992.
17. Gunderson L, Holling C, Pritchard L, Peterson G.Resilience in Ecosystems, Institutions and Societies, Stockholm, Beijer International Institute of Ecological Economics, Beijer Discussion Paper Series, No. 95, 1997.
18. Gunderson L, Holling C, editors. *Panarchy: Understanding Transformations in Human and Natural Systems*. Washington, DC: Island Press, 2002.
19. Guckenheimer J, Holmes P. *Non-Linear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. New York: Springer, 1983.
20. Prigogine I. *Thermodynamics of Irreversible Processes*, 3rd ed. Wiley Interscience, 1967.
21. Prigogine I. *From Being to Becoming*. San Francisco: W. H. Freeman, 1980.
22. Prigogine I, Stengers I. *Order Out of Chaos*. Boulder, CO: Shambhala, 1984.
23. Herfel W, Rodrigues D, Gao Y. Chinese medicine and the dynamic conceptions of health and disease. *J Chinese Philos* 2007;3:58–80.
24. Etxeberria A, Moreno A, Umerez J, editors. *Commun Cogn* 2000;17:3–4 (Special ed., *The Contribution of Artificial Life and the Sciences of Complexity to the Understanding of Autonomous Systems*).
25. Christensen W, Hooker C.Self-directed agents. In: MacIntosh J, editor. Contemporary Naturalist Theories of Evolution and Intentionality, Canadian Journal of Philosophy, Special Supplementary Volume, 2002, pp.19–52.
26. Hooker C.Interaction and bio-cognitive order. Synthese, Special Edition on Interactionism, in press.
27. Collier J, Hooker C. Complex organised dynamical systems. *Open Syst Inform Dyn* 1999;6:241–302.
28. Bruggeman FJ, Westerhoff HV, Boogerd FC. BioComplexity: a pluralist research strategy is necessary for a mechanistic explanation of the 'live' state. *Philos Psychol* 2002;15(4): 411–440.
29. Boogerd FC, Bruggeman FJ, Richardson RC, Stephan A, Westerhoff HV. Emergence and its place in nature; a case study of biochemical networks. *Synthese* 2005;145:131–164.
30. Hooker C. Asymptotics, reduction and emergence. *Br J Philos Sci* 2004;55:435–479.
31. Brooks D, Wiley E. *Evolution as Entropy, Toward a Unified Theory of Biology*. Chicago: University of Chicago Press, 1986.
32. Bechtel W. An evolutionary perspective on the re-emergence of cell biology. In: Hahlweg K, Hooker C, editors. *Issues in Evolutionary Epistemology*. Albany, NY: State University of New York Press, 1989.
33. Westerhoff H, Palsson B. The evolution of molecular biology into systems biology. *Nat Biotechnol* 2004;22:1249–1252.
34. Rashevsky N. *Some Medical Aspects of Mathematical Biology*, Springfield, IL: Thomas, 1964.
35. Glass L, Mackey M. *From Clocks to Chaos*. Princeton: Princeton University Press, 1988.
36. Kaplan D, Glass L. *Understanding Nonlinear Dynamics*. New York: Springer-Verlag, 1995.
37. Winfree A. *The Timing of Biological Clocks*. Scientific American Library, New York: W. H. Freeman, 1987.

38. Winfree A. *When Time Breaks Down*. Princeton: Princeton University Press, 1987.
39. Solé R, Salazar I, Garcia-Fernandez J. Common pattern formation, modularity and phase transitions in a gene network model of morphogenesis. *Physica A* 2002;305:640–647.
40. Raff R, Kaufman T. *Embryos, Genes, and Evolution*. New York: Macmillan, 1983.
41. Goodwin B, Saunders P. *Theoretical Biology: Epigenetic and Evolutionary Order from Complex Systems*. Edinburgh: Edinburgh University Press, 1989.
42. Jablonka E, Lamb M. *Epigenetic Inheritance and Evolution: The Lamarckian Dimension*. Oxford: Oxford University Press, 1995.
43. Gray R. Death of the gene: developmental systems strike back. In: Griffiths P, editor. *Trees of Life: Essays in Philosophy of Biology.* Dordrecht: Kluwer, 1992.
44. Oyama S, Griffiths P, Gray R, editors. *Cycles of Contingency: Developmental Systems and Evolution*. Cambridge, MA: MIT Press, 2001.
45. May R, editor. *Theoretical Ecology: Principles and Applications*. Saunders: Philadelphia, 1976.
46. Ulanowicz R. *Ecology: The Ascendant Perspective*. New York: Columbia University Press, 1997.
47. Odum H. *Environment, Power and Society.* New York: Wiley, 1971.
48. Pahl-Wostl C. *The Dynamic Nature of Ecosystem: Chaos and Order Entwined*. New York: John Wiley & Sons, 1995.
49. Holling C. Cross-scale morphology, geometry and dynamics of ecosystems. *Ecol Monogr* 1992;62(4):447–502.
50. Solé R, Bascompte J. *Self-Organization in Complex Ecosystems*. Princeton: Princeton University Press, 2006.
51. Dieckmann U, Law R, Metz J,editors. *The Geometry of Ecological Interactions: Simplifying Spatial Complexity.* Cambridge, UK: Cambridge University Press, 2000.
52. Cash D, editor. Scale and Cross-Scale Dynamics: Governance and Information in a Multilevel World. http://www.ecologyandsociety.org/.
53. Scheffer M, Westley F, Brock W, Holmgren M. Dynamic interaction of societies and ecosystems—linking theories from ecology, economy and sociology. In: Gunderson L, Holling C, editors. *Panarchy: Understanding Transformations in Human and Natural Systems*. Washington, DC: Island Press, 2002.
54. Jablonka E, Lamb M. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*. Boston: MIT Press, 2005.
55. Strogatz S. Exploring complex networks. *Nature* 2001;410:268–277.
56. Goldberger A. Fractal variability versus pathologic periodicity: complexity loss and stereotypy in disease. *Pers Biol Med* 1997;40(4):543.
57. Anderson R, May R. *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford University Press, 1991.
58. Heath R. *Nonlinear Dynamics: Techniques and Applications in Psychology.* Mahwah, NJ: Lawrence Erlbaum Associates, 2000.
59. Mantegna R, Stanley H. *An Introduction to Econophysics: Correlations and Complexity in Finance*, Cambridge, UK: Cambridge University Press, 1999.