THE FALL AND RISE OF SYSTEMS BIOLOGY

BY STUART A. NEWMAN

Recovering from a half-century gene binge

While this year is the 50th since the discovery of the double helical structure of DNA, the molecule of which all animal, plant, and bacterial genes are composed, it is also only a bit more than a century since the very notion of the gene first entered mainstream biology. Throughout the twentieth century, increased knowledge of genes and their structure was supposed to provide an understanding of the material basis of complex traits of organisms, such as the fact that we humans typically have four limbs with five digits on each, and hair all over our bodies, while fruit flies have six legs and two wings, with bodies covered in bristles. Instead, though our knowledge of the chemistry of cells and tissues has grown enormously in the past hundred years, we are still at the point (except for the simplest cases, such as eye color) of only being able to correlate the presence of alternative versions of a gene in an organism with alternative versions of a trait. This is all that Gregor Mendel, the originator of the gene concept, was able to do when he studied traits of the garden pea, such as stem length and flower position, in the 1860s, four decades before the scientific mainstream took note of his work.

Apart from their failure to deliver on scientific promises, notions of genetic reductionism and determinism, in the century just past, provided a pseudoscientific gloss to divisive conceptions of human capability and worth. In the last decade or so, similar ideas, linked to increased capacity for genetic manipulation and computer-aided monitoring of gene activity, have led to calls to refashion people, food crops, and animals to suit narrowly-defined needs. However, recent scientific developments have also afforded the possibility of a more integrated understanding of living systems, and have led to an appreciation of the poor theoretical basis for attempts to explain and manipulate complex traits at the level of the genes.

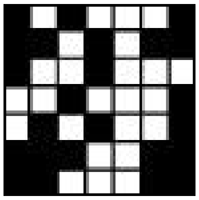
WHAT IS SYSTEMS BIOLOGY?

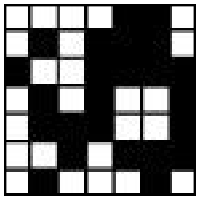
The reason why knowledge of genes – no matter how detailed our sequencing of the human genome may be – cannot provide an understanding of an organism's significant traits, its shape and form, its behaviors, and so forth, is that such traits are generated during the organism's embryonic development or later life by systems of interactions across many scales. Genes, and particularly the RNA and protein products specified by DNA sequences, are only a subset of the components of such systems. Moreover, these systems have physical, as well as chemical, properties.

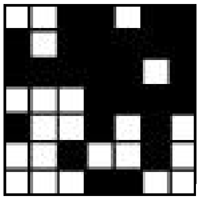
In the last few years, as it has become clear that the emerging human genome sequence would not provide – as had been promised by Human Genome Project (HGP) administrators and scientists – a "blueprint" or "Book of Life" describing what it means to be human, there has been increasing discussion of "systems biology" in the scientific literature. The new standard view, in a turnabout by principal spokespersons of the HGP, is that an organism's genome is only a "parts list." The real work, and real understanding, will come only as we begin to learn how all the parts interact to generate organismal traits.

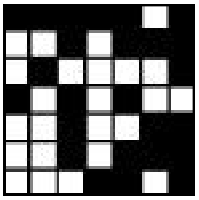
In some ways this is a positive development, but the term "systems biology" can be understood in different ways, not all of which represent a great deal of conceptual or practical progress. For those with a continued stake in a reductionist account of living organisms, the systems in question are just collections of interacting components of a well-defined single type. Thus, one now often hears that organisms are "systems of interacting genes" or, in recognition of new knowledge that one gene may specify many different proteins[1], "systems of interacting proteins." Advocates of single-level explanations include theorists disappointed that deciphering full genomes did not yield the expected revelations, and, importantly, corporate stakeholders who would like to believe that a patentable entity – a gene, a protein, a drug that affects a metabolic step – has a unique causal relationship to a biological function or trait, such as blood pressure, obesity, or depression.

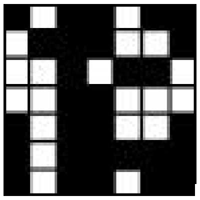
Systems biology can also be understood in a much more integrative sense as multiscale, multilevel explanations of organismal properties. Organisms contain many different

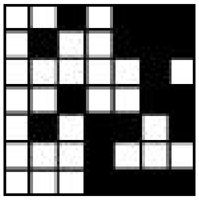












kinds of complex systems. One of these is metabolism: the network of chemical transformations that provide cells with building blocks for large molecules like DNA, proteins, and polysaccharides, and permit them to extract usable energy from cellular fuel sources. Another is the genetic network that operates during embryonic development, in which the products of genes active at particular developmental stages induce or repress the activity of other genes, in a sequential fashion, so as to allow the embryo to advance to successive stages. Signaling networks are systems by which small molecules modulate the rates of cellular processes and permit the coordination of other systems, such as the metabolic and genetic networks just described. The brain's neural network is still another system, one in which the electrical activities of tens of millions of nerve cells are coordinated by the mutual exchange of chemical signals. Each of these biological systems, and all others, has an evolutionary history, in which not only its particular internal character, but its relationship to other systems, has undergone change. This adds a further complexity: relationships between the same systems in different organisms will not always be the same.

Multileveled, multiscale approaches have long characterized the nonbiological sciences. When a chemist wants to understand a chemical reaction rate – how fast carbon dioxide and water are formed when propane is burned, for example – she is not only concerned with what molecules are involved, but with the particular values of external physical parameters such as temperature and pressure. An astronomer's assessment of the nature of an event in a distant galaxy draws simultaneously on his knowledge of physical systems on the scale of light years as well as systems at the submillimeter scale. No significant phenomenon in nature can be accounted for in terms of a single process measured on one scale of space or time. The twentieth century notion that genes represent a privileged level of explanation of the development and evolution of organismal traits is therefore a fantasy, and a distraction from the development of biology as a science.

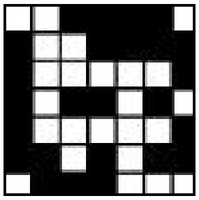
Biological systems are currently the subject of profuse scientific efforts involving mathematical modeling, computer simulation, and experimental analysis. Many techniques are used to study a given system, and many systems enter into the comprehension of any biological phenomenon–cell division, or an animal's feeding behavior, for example. This work is only at its beginning stages. But understood in this sense, the new systems biology represents a return of biology to the world of the other sciences after a century-long focus on genetic mechanisms which, in its latter half, became a veritable DNA binge.

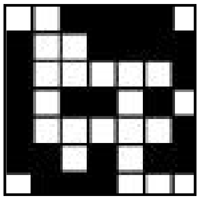
SYSTEMS BIOLOGY BEFORE THE GENE

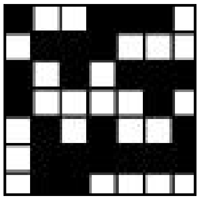
Observers of the current DNA celebrations might find it surprising that throughout the eighteenth and nineteenth centuries, biologists, despite their ignorance of genes, saw themselves as active participants in a vibrant scientific culture that had produced laws of mechanical stasis and motion, the atomic theory of chemical transformations, principles of conservation and dissipation of energy, and an understanding of electricity and magnetism. Advances had been made in describing the microscopic structure of cells and the macroscopic organization of tissues, such as bones and muscles. The growing recognition that life on earth has an evolutionary history, a notion first introduced in the modern era (the ancient Greeks had their own version) by Lamarck in 1800, and later provided with the plausible mechanism of natural selection – not dependent on any particular concept of genes – by Darwin in 1857, led to scenarios of organismal transformation and diversification that remain sound to this day. And the visible evidence that complex organisms take their form in each generation by a sequence of steps beginning with a single fertilized egg, gave rise to a descriptive and experimental developmental mechanics of cells and tissues, for which modern genetics has provided molecular correlates, but has not replaced.

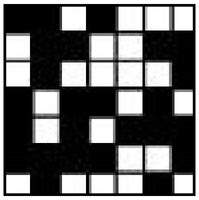
A characteristic of most European science before the twentieth century was that, while the preeminence of matter and its laws of motion was acknowledged, how matter wound up assuming particular configurations and arrangements was still a mystery. The matter described by Isaac Newton, the great codifier of the science of mechanics, is inert. Although the motions of billiard balls and planets are governed by mathematically precise laws, the outcome of such motion is entirely dependent on the initial preparation of the system – the arbitrarily given starting position and velocity of each particle. In order for the matter in a many-body system to become organized in a complex fashion it would have to be 'set up' in an appropriate way. This is why Descartes, Newton, and the other founders of the mechanistic worldview could simultaneously be physical determinists and religious believers: God, they opined, was in the initial conditions.

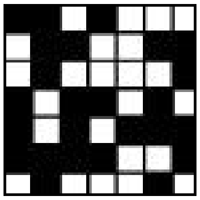
Biology in the nineteenth century developed fully within this same tradition. Along with their recognition that living organisms were composed of the same atomic constituents found in nonliving nature (the chemist F. Wöhler synthesized the biological molecule urea from inorganic materials in 1828, for instance), biologists rightly noted that the arrangement and organization of molecules in living systems was not

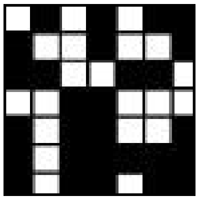












By the end of the twentieth century, the capacity to had become enormous. Still, no satisfying picture had organized forms, structures, and behaviors had emerged

automatically dictated by their identity. In this regard, they were following the eighteenth century philosopher Immanuel Kant, who dismissed the hope that the principles upon which organisms were constructed could be derived solely from causal analysis based on physical science[2].

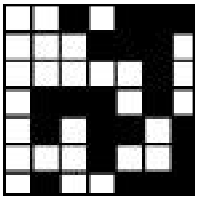
On the larger scale of organismal construction – the arrangement of bones, muscles and other parts – the conceptual separation between the lawful behavior of the material constituents and the origin of those constituents also held sway. Early in the nineteenth century, Georges Cuvier, the founder of paleontology and comparative anatomy, held that all the parts and functions of an organism are interrelated with one another by strict laws of nearly mathematical regularity. Any deviation from these preordained relationships would yield an impossible organism–one whose structure and function did not "compute." His main intellectual rival, Etienne Geoffroy St. Hilaire, claimed, instead, that the material nature of tissues led to their being governed by "laws of form" analogous to, but more complex than, those discerned by Newton for billiard balls and planets. These involved the molding, folding and segmentation of tissue masses. In distinction to Cuvier, who asserted that special creation devised anatomical arrangements to suit an animal's "conditions of existence," Geoffroy held that an animal's anatomy determined its "mode of life." Despite the evident differences in the "form follows function" and "function follows form" viewpoints, Cuvier and Geoffroy, like Newton and Kant before them, both understood that the origination of the biological organizing principles they were proposing could never be derived solely from the details of their operation.

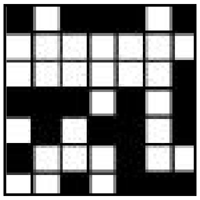
In one sense, though, Geoffroy, more than Cuvier, was a progenitor of modern systems biology. The "systems" approach swept through the sciences during the twentieth century, with the exception of biology, where it was derailed by the "rediscovery" of Mendel's work by several scientists in 1901, and the subsequent focus on genes. A systems analysis is not all-embracing: no scientific theory has ever explained, nor claimed to explain, all aspects of its field of discourse. Even modern fundamental particle theory, the most sophisticated analysis of matter and its origins yet devised, cannot explain why there is something rather than nothing, and why the various physical constants have their particular values. But beginning in the nineteenth century, and throughout the twentieth, physical science has incessantly pushed back the point at which there is an opening for non-naturalistic explanations, i.e., ones that take recourse in inexplicable, or specially arranged, conditions. In contrast to Cuvier's notion of the "correlation of parts," arranged at creation in conformity with the organism's essential nature, Geoffroy's concept that tissues themselves generate different types of organisms by means of "laws of form" implies that proximate biological development has a naturalistic explanation. Indeed, twentieth century advances in the sciences of complex systems and condensed materials have permitted new insights into the laws of form that pertain to living tissues. Before this new program took hold, however, the era of the gene intervened.

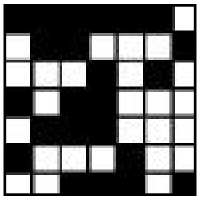
THE RETREAT FROM SYSTEMS BIOLOGY

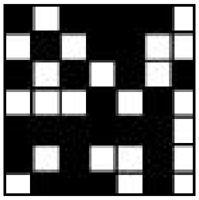
It is not that the "rational morphology" approaches associated with Cuvier, Geoffroy, and other nineteenth century biologists, have proven incorrect. It is well known that modern-day fossil reconstruction draws on the general validity of the assumption that the organization of (even previously unknown) organisms is discernible from a set of principles that make no reference to regularities at the molecular level. Nonetheless, the major trend of twentieth century biology was to reject the idea that a system of global organizing principles sets the terms for more small-scale processes. What replaced it was the opposite notion: that a privileged set of small-scale processes – interactions of genes and their products – is where one's attention must be focused when biological organizing principles are sought.

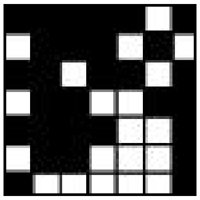
A key figure in the turning away from a systems approach to understanding biological organization was William Bateson. Paradoxically, Bateson began as a strong advocate of the notion of laws of form. In his book *Materials for the Study of Variation*, published in 1894, he concerned himself with the repetitive organization of certain animal parts, such as the

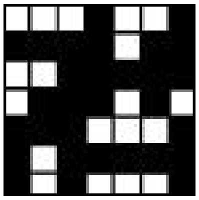












identify genes, their products and their interactions, appeared of how processes capable of generating over the course of evolution.

segments of earthworms, the backbones of vertebrates, and the digits of the hand. He proposed a physical metaphor for the generation of such repetitions in terms of "Chladni figures," the wave-like patterns that form when a fine powder is placed on a vibrating surface, such as a sounding violin. Changing the frequency of the vibration could also change the features of the pattern in a dramatic fashion, so the Chladni figures were not only a metaphor for the production of repetitive patterns during individual development, but also a metaphor for the discontinuous change of biological form during evolution.

Powder on the surface of a sounding violin is not a living embryo, however, and knowledge at the time did not permit making a mechanistic connection between them. In the 1950s, the mathematician Alan Turing would show that the reacting and diffusing molecules in living tissues could spontaneously arrange into Chladni-like concentration distributions, thus providing the conceptual link that Bateson lacked. Though Turing's work, along with other physics-based phenomena of "self-organization" [3], would prove seminal for a new wave of systems biology that began to emerge later in the century, it did not come early enough for Bateson. Once Mendel's work on the inheritance of discrete "factors" – genes – gained wide attention in 1900 (due, in large degree, to Bateson's enthusiastic promotion), Bateson's program for a systems approach to understanding biological form was written out of the scientific mainstream, as even he proved unable to cast it in fashionable Mendelian terms.

The scientific conversion of the prominent embryologist Thomas Hunt Morgan, who rejected his earlier systems approach to biological development in favor of a strict Mendelian focus, was also a key turning point in early twentieth century biology. From this point on, there was a heightened emphasis on the rules of transmission of factors that influenced form and function (transmission genetics), the rules by which such factors are distributed in populations under varying conditions (population genetics), and the chemical nature of such factors (molecular genetics). Such work met with great success, and established itself as the mainstream of biological science. None of these branches of genetics, however, attempted to account, in causal terms, for biological forms and complex functions.

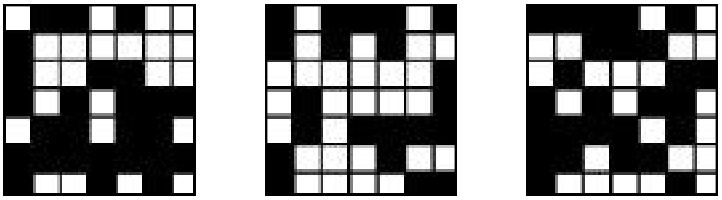
Less successful was early work that did attempt to formulate such accounts in genetic terms (physiological genetics), such as that of Richard Goldschmidt and C. H. Waddington in the 1930s to 1950s. Both these scientists understood that a systems approach was needed to address these questions, but, like their contemporaries, they were tied intellectually to the gene as the privileged level of biological explanation. Real progress required moving beyond this level.

By the end of the twentieth century, the capacity to identify genes, their products and their interactions, had become enormous, and some claimed the genetic approach to development had finally succeeded. Entire genomes had been sequenced; gene interactions involved in establishing boundaries and structures during insect development had been the subject of the shared 1995 Nobel Prize. Still, no satisfying picture had appeared of how processes capable of generating organized forms, structures, and behaviors had emerged over the course of evolution. Evelyn Fox Keller's recent *Making Sense of Life*, focusing on the elaborate nature of genetic mechanisms of modern-day development (but not on the origination of such mechanisms early in evolution), concludes that organisms are, in fact, too "irreducibly complex" to yield such a picture.

TOWARD A NEW SYSTEMS BIOLOGY

The obstacles that have stood in the way of creating a successful systems biology are partly technical and conceptual, but to a great extent they have also been ideological.

To take these up in order, detailed knowledge of gene sequences, processing of gene products (RNAs and proteins), and gene-gene product interactions will undoubtedly be essential to a comprehensive systems biology, and neither these, nor the computers necessary to keep track of numerous interacting components changing through time, were available in the early part of the twentieth century. Conceptually, understanding the laws of form for complex materials, such as living tissues, requires, in addition to genetic information, an understanding of chemical dynamics, including oscillations, pattern forming processes, and chaotic behavior[3]. Also required is an under-



The preceding illustrations are screen captures of a computer simulation running mathematician John Conway's Game of Life. Invented in 1970 to illustrate how complex patterns emerge from simple behaviors, the Game is 'played' on a grid of cells which 'live', 'die' or 'give birth' according to the state of adjacent cells. Though the outcome of a given set of initial conditions is theoretically predetermined, it is impossible to predict what will happen.

standing of the physics of condensed, viscoelastic materials, including fractal phenomena. These were not developed until the last quarter of the past century.

However, the ideological barriers were perhaps most important. Gene products can participate in self-organizing physical processes, but the ideas of pioneers in this way of thinking, such as Turing and D'Arcy W. Thompson[4], were kept on the sidelines, muscled out by the notion that genes could do everything by themselves. As Erwin Schrödinger, a physicist who should have known better, wrote in his influential 1945 book, *What is Life?*, "The chromosome structures are instrumental in bringing about the development they foreshadow. They are the law-code and executive power – or to use another simile, they are the architect's plan and builder's craft in one."

As noted above, no scientific theory can avoid leaving the door open to some assumptions beyond its explanatory capabilities. But by marginalizing the role of naturalistic physical organizing principles, the gene-centered view of biological causation has left itself susceptible to the notion of "intelligent design," an unfortunate throwback to Cuvierian creationism. Moreover, genetic determinism has suffused the worst political movements and social policies of the twentieth century [5], and has pointed towards experimental manipulations of the germ line that could be the bane of the present one [6].

LOOKING AHEAD

SYSTEMS BIOLOGY GONE WRONG

The comprehensive, integrative perspective of systems biology is not immune to abuse — a fact represented all too clearly in a recent report jointly sponsored by the NSF and the U.S. Department of Commerce, "Converging Technologies for Improving Human Performance." According to that report's executive summary:

> *Convergence of diverse technologies is based on material unity at the nanoscale [i.e., submicroscopic, molecular scale] and on technology integration from that scale. The building blocks of matter that are fundamental to all sciences originate at the nanoscale. Revolutionary advances at the interfaces between previously separate fields of science and technology are ready to create key transforming tools for NBIC [nano-, bio-, information and cognitive] technologies. Developments in systems approaches, mathematics and computation in conjunction with NBIC allow us for the first time to understand the natural world, human society, and scientific research as closely coupled complex, hierarchical systems. At this moment in the evolution of technical achievement, improvement of human performance through integration of technologies becomes possible.*

The report goes on to outline a future in which the "ability to control the genetics of humans, animals, and agricultural plants will greatly benefit human welfare" and "[f]ast, broadband interfaces directly between the human brain and machines will transform work in factories, control automobiles [and] ensure military superiority…"

The report can be found in its chilling entirety at http://www.wtec.org/ConvergingTechnologies.

Systems biology is on the rise, though so far it is more of an agenda than a body of results. In response to new interest and activities in these fields (and the failed promises of genetic reductionism), the U.S. National Science Foundation (NSF) has begun funding multi-million dollar programs in "integrative biology" and "biocomplexity." A recent solicitation for applications to establish a center for "synthesis in biological evolution" states the unexceptionable objective of fostering "synthetic, collaborative, cross-disciplinary studies [and] further unification of the biological sciences [by drawing] together knowledge from disparate biological fields to increase our general understanding of biological design and function." The National Institutes of Health, a scientifically more conservative agency, is also, for the first time, allocating funds for systems approaches.

In its most intellectually fertile form the new systems biology is bringing mathematical and computational methods to bear on genetics, physiology, development and evolution, so as to deal with multiscale complexities without losing sight of them. In its scientifically sound form, moreover, this improved approach to biology does not seek to replace cognitive or social sciences. If such a research program is permitted to flourish, in a few years the twentieth century's gene bender will be just a memory, and biology will again take its place among the subtle products of the human mind. However, if systems biology spawns a new reductionism of social integration through molecular manipulation [*see sidebar*], we may witness another regression into oversimplification and misunderstanding that could set back our knowledge of ourselves and the natural world by at least another century. Another binge on reductionism could be the fatal one, putting not only our science, but our lives and natures, at risk. ■■■

Stuart A. Newman *is Professor of Cell Biology and Anatomy at New York Medical College, where his research focuses upon cellular and molecular mechanisms of vertebrate limb development; the physical mechanisms of morphogenesis — development of the size, form, or other structural features of an organism — and mechanisms of morphological evolution. His* Origination of Organismal Form, *co-edited with Gerd B. Müller, was released in February by the MIT Press.*

FOOTNOTES **1** *See Barry Commoner, "Unraveling the DNA Myth: The Spurious Foundation of Genetic Engineering."* Harper's Magazine, *February 2002.* **2** *See Timothy Lenoir,* The Strategy of Life, *Univ. of Chicago Press, 1982, for a full discussion of this "teleomechanist" framework.* **3** *See Gerd B. Müller and Stuart A. Newman, Eds.,* Origination of Organismal Form, *MIT Press, 2003.* **4** *D'Arcy W. Thompson authored the classic* On Growth and Form, *Cambridge Univ. Press, 1919, rev. 1942.* **5** *See Daniel J. Kevles, In The Name Of Eugenics: Genetics And The Uses Of Human Heredity, Knopf, 1985.* **6** *See Lee M. Silver,* Remaking Eden: How Genetic Engineering And Cloning Will Transform The American Family, *Avon Books, 1998, and Gregory Stock,* Redesigning Humans: Our Inevitable Genetic Future, *Houghton Mifflin, 2002, for positive views of genetically manipulating humans.*