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SO WHAT IS LIFE?

> "Now one could say, at the risk of some superficiality, that there exist principally two types of scientists. The ones, and they are rare, wish to *understand* the world, to know nature; the others, far more frequent, wish to *explain* it. The first are searching for truth, often with the knowledge that they will not attain it; the second strive for plausibility, for the achievement of an intellectually consistent, and hence successful, view of the world."
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> Erwin Chargaff (1)

AN INGENIOUS MACHINE?
COMPLEX SYSTEMS
LIVING BY THE SECOND LAW
A UNICORN ON THE WALL

Fifty years after Schrödinger wrote his little book, his challenge still hangs in the air. What *is* life? Having learned so much about molecules and mechanisms, structures and functions, physiology and ecology and ontogeny and phylogeny, why are we still at a loss for a satisfying answer? Schrödinger himself posed the riddle with a flourish, but wisely refrained from offering a solution; today we are quick to deflect the mystery with a wry smile, a parable, or a joke (2). The reason has much to do with the difference between explanation and understanding. We are quickly learning to explain the workings of the biological machinery and even how organisms came to be as we find them, but we have no persuasive answer to the question why life exists in the first place. Loren Eiseley, thirty years ago, was baffled by "the hunger of the elements to become life," and we are not much wiser today. There is nothing in the textbooks of physics and chemistry to forbid a world that teems with bacteria and butterflies, but there is also nothing that would lead one to expect the world to be of this nature. The crux of the matter is that living organisms cannot be rationally and systematically deduced from the principles that generally do account for the properties of inanimate matter.

We biologists claim for our science a high degree of autonomy from chemistry and physics, and rightly so. Organisms are historical creatures, the products of evolution; we should not expect to deduce all their properties from universal laws. The antics of a troop of monkeys in the forest canopy are doubtless consistent with all of physics and chemistry, but this knowledge supplies no insights that will be useful to a student of animal behavior. All the same, the autonomy of biology must ultimately trouble those who, with the late Jacob Bronowski, "seek to find nature one, a coherent unity" (3). The reason that many thoughtful persons continue to find life perplexing, even mysterious, is that sharp division between the organic and inorganic spheres (Chapter 2). The distinction turns on those characteristics that are universally associated with entities we designate as living, but essentially absent from nonliving ones: intricate organization and purposeful behavior that unfold over time, both on the individual level and that of the total assemblage. Here yawns a great chasm that all biological scientists recognize, but many are deeply reluctant to acknowledge.

There is clearly something special about living things that has not declared itself from beneath our vast heap of knowledge, and that seems to stand outside the circle of light that contemporary research strives to enlarge. What we lack is an understanding of the principles that ultimately make living organisms living, and in their absence we cannot hope to integrate the phenomenon of life into the familiar framework of physical law. I am not here to advocate a veiled vitalism, nor to sneak in a creator by the back door. But I do insist that until we have forged rational links between the several domains of science, our understanding of life will remain incomplete and even superficial. Until that impasse is overcome, we cannot refute philosophers, skeptics, religious believers and mystics who suspect that science is sweeping out of sight the very mystery that it purports to elucidate.

I do not have the answer to Schrödinger's riddle; no one does. It is even conceivable that we stand here at one of the limits of science, but it would be quite premature to concede defeat. We are gravely hampered by having but a single kind of life to ponder, and it may turn out that we cannot fully grasp the general phenomenon until we have either found additional versions of life or produced one in the laboratory.

Neither prospect seems bright at present. In the meantime, however, we can wander a little down earthly paths that may, perhaps, offer glimpses of that elusive consilience between the physical world and the biological one.

AN INGENIOUS MACHINE?

We shape our buildings, Winston Churchill once said, and then they shape us. In just this fashion, the questions we ask about life and what we take for answers have been molded by two figures of speech: first the metaphor of the machine, and latterly that of the computer.

Wander the corridors of a biology building to eavesdrop on the residents, and you'll find them preoccupied with nuts and bolts. We argue about the mechanism of photosynthesis, of embryonic development or even of evolution. We speak earnestly of the "machinery of life," of biological "building blocks," of traits "hard-wired" in the "blueprint"; and we prepare students for careers in the new manipulative science, particularly in "genetic engineering." Even medicine, that most humane of arts, seems to be turning into a science of spare parts, plastic or molecular. Isak Dinesen caught the mood early (4): "What is man, when you come to think upon him, but a minutely set, ingenious machine for turning with infinite artfulness the red wine of Shiraz into urine."

A machine, Webster informs us, is "an assembly of parts that transmit force, motion and energy to one another in some predetermined manner and to some desired end." It is a stretch, but seemingly not an excessive one, to apply this definition to living things: chemical machines, whose object is to make two where there was one before. The metaphor carries immense heuristic power. It conjures up a system of interacting parts with well-defined functions, joined together in service to a greater whole; of energy supporting useful work, and of powers emerging in the machine as a whole that were not present in the isolated parts. Every time we announce the unraveling of another mechanistic puzzle, we pay tribute to the metaphor of the machine: mechanisms are a real feature of living beings. Besides, the metaphor resonates with our deepest conceptions about the way things are. For three hundred years now, scientists have perceived the world through the eyes of Descartes and especially of Newton: a universe of particles moving in fields of force, whose behavior is fully determined by the overarching laws of physics. For those who subscribe to this viewpoint, biology is little more than a collection of special cases that must be accommodated within the general framework; no deep mysteries there.

Well then, what is wrong with the assertion that a cell—*E. coli*, say, or a ciliate—is just a particularly intricate and ingenious machine? The fault is that the claim begs the central issue. If a cell is just another machine, what is the basis for the distinction that has been drawn from ancient times between objects that are alive and those that are not? After all, what we seek to understand is not what these two categories have in common, but what sets them apart! The answer came in the eighteenth century from the German philosopher Immanuel Kant (5), and turns on the existence of a special category of objects called organisms. In a machine, Kant said, the parts exist for each other but not by each other; they work together to accomplish the machine's purpose, but their operation has nothing to do with building the machine. It is quite otherwise with organisms, whose parts not only work together but also produce the organism and all its parts. Each part is at once cause and effect, a means and an end. In consequence, while a machine implies a machine maker, an organism is a self-organizing entity. Unlike machines, which reflect their maker's intentions, organisms are "natural purposes." Kant's vision was eminently sensible and remains true, but even he was stymied by the next stage: How can we ever discover the cause of that purposeful organization that is the hallmark of organisms?

Time and the advance of science have supplied a partial solution to that enigma, and produced a more nuanced view of the relationship between organisms and machines. To Kant's distinction between machines that are made and organisms that make themselves, we would add that machines can be built singly as the need arises; some are unique. Organisms, by contrast, invariably occur as members of an ecosystem, a historical community whose transformation over time molds the forms and functions of its members. Most contemporary scientists, if they give any thought at all to such abstruse matters, will subscribe to a conception that incorporates elements of both organism and machine, and which is grounded in our new understanding of heredity, biochemistry and evolution. The metaphor of the day, not surprisingly, describes organisms as information-processing devices, computers of sorts. The image leaps to the eye: behold the DNA tape whose nucleotide sequence stores information that can be replicated, read out and expressed in the language of proteins, those minuscule devices that do all the work. Thanks to rare but unavoidable errors the tape is altered over time, generating new versions for natural selection to sift. If organisms are still machines they are exceedingly artful ones, that do not fit easily into the traditional understanding of mechanical appliances.

For all its contemporary tone, the metaphor of the computer has substantial historical depth. Webster and Goodwin (5) trace it back to

August Weismann who, at the end of the nineteenth century, drew a sharp line between the germ line and the soma. In place of Kant's self-organizing whole, Weismann preached a fundamental duality, which pervades our thinking to this day. The genome, continuous from the very dawn of time and in principle immortal, serves as the central directing agency for the production of the visible animal or plant. These bodies, made by executing the instructions contained in the genome, are effectively artifacts; they mediate between the genome and the environment (to borrow a phrase from Jeffrey Wicken), but have no intrinsic significance. Details aside, there is no denying that this way of looking at life has a tremendous hold on all our imaginations. One cannot help wondering, as Webster and Goodwin do, how much that grip owes to the far more ancient dualities of body and soul, matter and spirit.

The philosopher Alfred North Whitehead put this in perspective: There are no whole truths, he said, all truths are half-truths; the trouble comes from treating them as whole truths. The informational metaphor is assuredly a substantial half-truth but still only that, and readers who have trudged through the preceding six chapters will see why. Organisms process matter and energy as well as information; each represents a dynamic node in a whirlpool of several currents, and self-reproduction is a property of the collective, not of genes. Form, structure and function are not straightforward expression of the gene's dictates; there is more to heredity than what is encoded, and you can only go from genotype to phenotype by way of epigenetics. DNA is a peculiar sort of software, that can only be correctly interpreted by its own unique hardware. Only in fiction will fossil dinosaur DNA, nurtured by a crocodile egg, bring forth a live dinosaur (or so we fervently hope); and sending aliens the genome of a cat is no substitute for sending the cat itself—complete with mice. An organism is, in fact, a self-organizing entity and more than the sum of its molecular parts. The informational metaphor all but ignores the multiple webs of relationships that make up physiology, development, evolution and ecology. Still, the tape and its reader set in order a portion of what we know, and the power of the analogy is reinforced every time a gene is altered, knocked out or replaced in the quest for knowledge or profit; within limits, the metaphor works and instructs.

All the metaphors in common use have merit, but none is altogether satisfying; and as Kant already noted, none of them makes comprehensible the existence of even a single blade of grass. It must be significant that we still have no language that makes organisms look at home in the physical universe; they are evidently much queerer than we suppose. It may be the case that our understanding of physics and chemistry lacks an essential girder that, when found, will span the gap. But it is also conceivable that there is a deeper flaw in the contemporary research program—Schrödinger's program, if you will—of bringing the science of life wholly under the umbrella of the physical sciences.

COMPLEX SYSTEMS

Complexity studies is a fresh label for a well-worn pigeonhole: general systems theory, that was pioneered by Ludwig von Bertalanffy in the thirties, and searches for laws common to systems of all sorts, whether living or not. What is new is, of course, the advent of the computer, which rejuvenated this plodding subject and made it, to some degree, an experimental one (6).

Most of us understand intuitively what is meant by a "system": an entity consisting of interacting parts that are arranged in some definite relationship to each other. A bicycle, the planets in orbit around the sun, and Colorado State University are all systems; a lump of granite or a sandpile is not. Complexity is much harder to grasp, and one of the perennial topics in the literature is just what makes a system complex, as distinct from merely complicated. Formalities aside, complexity is not hard to recognize and is commonly more a matter of degree than of kind. Diagnostic features include the emergence in the system as a whole of properties that cannot be assigned to any one of its components, invariance of the whole even though its components fluctuate, and a complementary interplay between local causes and global ones, such that each level constrains the other. Complex systems are commonly (though not necessarily) dynamic rather than static, and open to the input of energy and matter from the environment. Above all, they always display "some kind of non-reducibility: the behavior we are interested in evaporates when we try to reduce the system to a simpler, better-understood one" (7). Living systems, of course, represent the epitome of complexity by these (or any other) criteria, but they are not alone: a flame, a whirlpool, many electrical circuits and the circulation of currents in the oceans and the atmosphere come to mind. Even a sandpile can display complex behavior.

Robert Rosen (8), in what is perhaps the most rigorous and radical critique of the mechanistic approach to biology, has spelled out what the irreducibility of complex systems consists of. First, a complex system cannot be fractionated: there is no one-to-one relationship of parts to functions because one or more of the parts play several roles at once.

Second, while aspects of a complex system may have simple mechanistic descriptions, there exists no such description that embraces the system as a whole. Third, even those apparently simple partial functions change over time and diverge from what would have been their behavior in isolation. For all those reasons, complex systems are in principle not wholly reducible to simpler ones, and the Newtonian paradigm cannot be applied to them. By way of a pertinent example, biochemists may find it instructive to reflect on the folding of a linear chain of amino acids into the three-dimensional shape of the corresponding protein. Most proteins know how to fold up correctly, quickly, and spontaneously, but determined efforts to predict the final form by summing up the interactions of individual amino acids have been largely unproductive. Could it be, as Rosen believes, that the fault is not in the calculations but in the way the problem has been perceived? It is intriguing to read of novel and more holistic approaches (9), based on the premise that the amino acid chain is a complex system engaged in the molecular equivalent of morphogenesis.

A candle and a university can both be regarded as complex systems, but neither is alive; what then defines the subclass of complex systems to which organisms belong? Rosen seeks criteria that will be universally applicable to any form of life, even to life beyond the solar system or to fabricated organisms. Such criteria will be independent of any particular material incarnation, and must be drawn from those abstract principles of organization that make living systems living.

For Rosen, the heart of biology is that it revolves around the pattern of connections between components, and that allows him to offer a solution to Schrödinger's riddle: "A material system is an organism if, and only if, it is closed to efficient causation" (8). That is to say, if *f* is any component of a living system and we ask what is the cause of *f*, the question has an answer within the system. This would obviously not be true of the bicycle, and only partially true of the candle or the university. Actual organisms will be realizations of this general and abstract principle of organization. Note that Rosen, pursuing his quarry by formal logic, arrives at an insight remarkably like that attained by Maturana and Varela before him (Chapter 2): living organisms are autopoietic systems, they make themselves. Incidentally, in Rosen's view evolution is secondary: one can imagine life forms that did not evolve (e.g., fabricated ones), but evolution without life is inconceivable.

In an interesting and altogether constructive sense, Rosen can perhaps be described as a latter-day vitalist. His quest for the principles that make organic systems different form inorganic ones does not lead him to invoke mysterious forces that breathe life into the common clay, but he does bid us to rethink the relationship between biology and physics, and that is quite radical enough. Both disciplines deal with systems, and for the past two centuries biologists have sought to interpret their subject by the extension of laws inferred by physicists from the study of simple mechanisms. That, in Rosen's view, puts the cart before the horse: in reality, simple systems such as gases or planetary orbits are special and limited instances, while complex systems represent the general case. If organisms are ever to be understood as material physical entities, physics will first have to be transformed into a science of complex systems. This metamorphosis is already under way, but has proven neither quick nor painless: after half a century, the thermodynamics of irreversible processes (those that predominate in the real world) has chalked up few concrete achievements and remains largely outside the main stream of both physics and biology. I am not at all certain where this line of inquiry can lead; but Rosen's viewpoint will intrigue anyone who suspects, as I do, that the elusive relationship between physics and biology holds the key to Schrödinger's riddle.

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Granted, then, that living organisms make up a subclass of the category of material, complex, dynamic systems; does this assignment entail any specific expectations concerning their properties, behavior, or genesis? We should not look to formal logic to predict particulars of form and function, which are bound to have a large element of the contingent, but we can hope for general, statistical features such as those that make all river valleys alike even though each one is unique. This project has already generated a large and confusing literature, and a growing number of prophesies. Of these, the one I find most convincing is also the most general: complex systems of the proper sort generate order spontaneously. The nature of this order varies. It may be spatial, as in the case of Prigogine's dissipative systems; examples include the convection cells that arise in a heated pan of oil, and the traveling waves displayed by certain chemical reactions (Chapter 7). But order can also refer to the interactions among elements of a network, such as those studied by Stuart Kauffman. The implication is that natural selection is not the sole source of order in the living world, but complements order that arises by the self-organization of complex systems.

Kauffman's books (10), written in a high-colored and at times oracular style, display both the power and the limitations of a computer-driven approach to reality by way of the utmost abstraction. Imagine a huge network of interacting elements, 100,000 of them, these may be pixels on a screen or light bulbs. Each element is linked to others, perhaps just to one or two others or to dozens of them, and its response is governed by the rules of algebraic logic. For example, a particular element may flash when both of its two inputs turn on (a logical function corresponding to AND); another element may respond whenever either one of its two inputs turns on (an OR gate). Both the pattern of linkage and the rules that control any one element are assigned at random. We now start the network in some arbitrary state, and ask whether any regular pattern can be made out in the twinkling of lights. A naïve observer may well expect sheer chaos, lights popping on and off at random like a "berserk Christmas tree," but this is not necessarily what happens. The network's behavior depends strongly on the coupling rules, first of all upon the average number of inputs to each element. When that number is large, the network does indeed fall into apparent chaos. Conversely, when each element receives input from only one other, a simple fixed sequence quickly emerges. But when the number is a little larger, around two, something unexpected happens: the system settles down into a cycle consisting of a small number of states, about three hundred of them, which then repeats indefinitely. The cycle is robust: flip one element into its alternate state, and the network soon returns to its previous pattern. It displays something akin to homeostasis. Kauffman thinks of such cycles as "attractors" in the space of possible configurations that the network can adopt, and notes that they represent a minute fraction of an astronomically large number. Such compression represents "vast, vast order" arising of its own accord, guided neither by selection nor by intelligence.

Does this sort of abstruse model-mongering have anything to do with the birds and the bees? On the face of it, no—but wait. The genetic circuitry of a cell can be seen as a network of logical elements that switch each other on and off, and Kauffman claims that such networks will spontaneously adopt highly ordered regimes, even in the absence of natural selection. Spontaneous self-organization, "order for free," then becomes a background of regularity upon which natural selection acts, and against which its effects should be measured. Indeed, self-organized order will persist even in the face of pressure from natural selection.

The order that arises from self-organization, and that laboriously built by variation and selection, should not be seen as mutually antagonistic. On the contrary, Kauffman and others argue that natural selection can only succeed with logical networks that lend themselves to adaptive change by small incremental steps. Michael Conrad put it thus: "Why does evolution work? The reason is not to be found solely in the magic optimizing power of natural selection. It is as much due to the organizational structure that undergoes the variation. Evolution works because this organization is amenable to evolution, and because this amenability itself increases in the course of evolution" (11). Evolving networks shift gradually into modes of operation that are neither rigidly frozen nor chaotically fluid, but lie in the zone of transition between these regimes: evolution succeeds at the "edge of chaos." If all this is true (and proponents do emphasize that they are, themselves, walking the edge of uncertainty), real insights into the nature of living systems are emerging from the mist.

There is an evangelical earnestness to much of this literature that cannot fail to lift the skeptic's eyebrows. Earthlier biologists, our heads heavy with observations and experiments, are entitled to ask whether these theoretical generalizations make concrete and testable predictions. Indeed, there are some—albeit not a large crop. The number of states that a network can adopt is a function of the square root of the number of elements; could this be a deep law that underlies the rough correlation between the number of cell types in an organism and the square root of the number of genes (three for yeast with 6,000 genes, 300 for humans with 100,000)? It is also generally the case that the number of regulatory inputs per gene is small—though students of eukaryotic transcription can cite numerous exceptions. And there are some general features of evolution that would be expected from the theory of dynamic networks. Depending on whom one reads (12), these include the emergence of self-replicating and self-maintaining entities; developmental constraints on evolutionary change; punctuated equilibrium; the evolutionary laws of Dollo and Von Baer; even an innate tendency for complexity to increase with the passage of time. But it is only prudent to heed the warning flags before stepping into the deep water. Is it really true that a living system exhibits only a small number of stable states among which selection must choose? If so, laws of order do indeed constrain what natural selection can accomplish, but the astonishing diversity of living forms testifies to an all but untrammelled liberty. And is it really the case that the high degree of biological order could never have been achieved by random variation and selection alone? The life history of, say, the sea urchin displays the kind of capricious adaptations that natural selection would cobble together but highlights no global law of order.

On the outer banks of science, one often suspects that the believer is happy while the doubter is wise; and yet, too critical a spirit is apt to overlook the genuine contribution that complexity studies have already made. The great virtue of systems-thinking is not that it predicts the facts of life, but that it blurs that crisp line which divides the organic world from the inorganic. There is nothing mystical or unnatural about complexity, self-organization, emergence and wholes that are greater than the sum of their parts. These are properties of a large and diverse category of physical systems; even sandpiles do it. Organisms remain special, of course, thanks to their autopoietic character. But when organisms are seen as complex dynamic systems of a peculiar sort, the difference between the organic and the inorganic seems just a little less daunting. One feels encouraged to wonder just how autopoietic entities might have emerged from the much larger category of complex dynamic systems, and here energetics holds the most promising clues.