TOWARDS A DEFINITION OF LIFE

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ABSTRACT This article offers a new definition of life as a "self-contained, self-regulating, self-organizing, self-reproducing, interconnected, open thermodynamic network of component parts which performs work, existing in a complex regime which combines stability and adaptability in the phase transition between order and chaos, as a plant, animal, fungus, or microbe." Open thermodynamic networks, which create and maintain order and are used by all organisms to perform work, import energy from and export entropy into the environment. Intra- and extracellular interconnected networks also confer order. Although life obeys the laws of physics and chemistry, the design of living organisms is not determined by these laws, but by Darwinian selection of the fittest designs. Over a short range of normalized energy consumption, open thermodynamic systems change from deeply ordered to chaotic, and life is found in this phase transition, where a dynamic balance between stability and adaptability allows for homeokinesis. Organisms and cells move within the phase transition with changes in metabolic rate. Seeds, spores and cryo-preserved tissue are well within the ordered regime, while health probably cannot be maintained with displacements into the chaotic regime. Understanding life in these terms may provide new insights into what constitutes health and lead to new theories of disease.

BECAUSE BIOLOGISTS are concerned with life in all its forms, and physicians deal with life and death on a daily basis, it is crucial that they explicitly understand what life is. Nevertheless, a clear idea of what life means remains elusive, and there is no universally accepted definition. Therefore, we offer our own:

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> Life is a self-contained, self-regulating, self-organizing, self-reproducing, interconnected, open thermodynamic network of component parts which performs work, existing in a complex regime which combines stability and adaptability in the phase transition between order and chaos, as a plant, animal, fungus, or microbe.

This definition describes life as we know it here on earth and makes no attempt to include other forms of life that await discovery in the universe. In offering this definition, we hope to stimulate reflection and discussion that will lead to a more complete understanding of the meaning of life.

The rest of this article will attempt to explain the components of our definition, beginning with thermodynamic systems.

THERMODYNAMICS

Life is a very special thermodynamic system, best understood by considering the second law of thermodynamics. This law states that systems tend to evolve from statistically improbable configurations to statistically more probable ones. If one blows a smoke ring, the particles of smoke first appear in a statistically improbable highly organized doughnut shape. Gradually, the smoke particles disperse and become randomly distributed within the room. Ordered systems become more disordered with time, and entropy, a measure of disorder, inexorably increases. The second law has three features that make it unique in physics: (1) it is the only physical law dealing with order; (2) it states that time has an arrow that tracks irreversible processes; and (3) it predicts the future as statistical probabilities, not certainties. All three make it highly pertinent to the understanding of life.

Nevertheless, at first glance, the second law doesn't seem to apply to life. Life is about the creation of order not its degradation over time. Ever-more improbable forms of life have arisen through Darwinian evolution over the millennia. Fetal growth and development require a rapid *decrease* in entropy, with the development of the stunning order that characterizes living organisms. Thus, both over eons of evolution and over much shorter gestational times, life goes in the opposite direction from that predicted by the second law, from statistically probable configurations to statistically more improbable ones. This fact prompted the Nobel prize–winning physicist, Erwin Schrödinger to wonder how this was possible. In his classic monograph *What Is Life?* (1944), he made the point that the essential thing in metabolism is that the organism succeeds in freeing itself from all the entropy it cannot help producing while alive. Here, then, is a key concept: entropy defined as a measure of disorder must always increase in any irreversible process, like life, that changes over time. Schrödinger realized that life, in creating order, produces even larger quantities of disorder that it *must* get rid of. Without the exportation of entropy, we cannot exist.

How does life do this? In a closed thermodynamic system with no exchange of energy or entropy with the environment, exporting entropy is impossible. But life, as Schrödinger's student Ilya Prigogine pointed out, is an *open* thermodynamic system, in which energy is constantly imported from and entropy released into the environment (Prigogine and Stengers 1984). The importation, utilization, and dissipation of energy is called *metabolism*. The efficiency of metabolic processes—defined as the ratio of useful work performed to the amount of energy consumed—is, as for all machines, considerably less than one. Entropy results from the dissipation of energy that fails to produce useful work, and fortunately, we successfully rid ourselves of this entropy. This is a neat trick. By exporting our entropy we avoid the inexorable decay into disorder predicted by the second law. (However, the second law still holds, because when we rid ourselves of our entropy, the entropy of the universe increases.)

Prigogine won the Nobel prize in chemistry for showing how importation of energy into an open thermodynamic system could give rise to order. He described three fundamental thermodynamic states: equilibrium thermodynamics in closed systems, with no exchange of energy or entropy with the environment; near-to-equilibrium open thermodynamic systems, with linear dynamics and frozen order (for example, crystals); and far-from-equilibrium open thermodynamic systems, with nonlinear dynamics, deterministic chaos, instability and evanescence (for example, weather).

The second law only applies to the first of these states. At thermodynamic equilibrium no energy gradients exist, there is no response to external stimuli, all chemical reactions go equally in both directions, the forces within an organism cancel out, no motion is possible, and no work can be performed. This is not life. We only reach thermodynamic equilibrium when we die. While alive, we continually import energy from the environment in the form of food, oxygen, or light, and we export entropy in the form of waste products. However, life is characterized by nonlinear dynamics. Thus, we do not behave like crystals, and our thermodynamics is not close to equilibrium. On the other hand, the instability and evanescence of weather doesn't describe us either. We appear to be a unique thermodynamic system existing somewhere between deeply ordered, near-to-equilibrium crystals and far-from-equilibrium chaotic weather.

SELF-ORGANIZATION

Self-organization means that we sculpt ourselves and maintain the order that develops from fertilized seed to maturity. No external agency does it for us. How is this accomplished? Prigogine discovered that energy dissipated in open chemical thermodynamic systems could create order spontaneously (Prigogine and Stengers 1984). The energy is utilized to reverse the progression from order to disorder predicted by the second law.

Insight into the role of imported energy in creating order can be gained from considering the vortex funnel of air that appears in a bathtub when the plug is pulled (see Figure 1). It is an example of spontaneous development of order. We

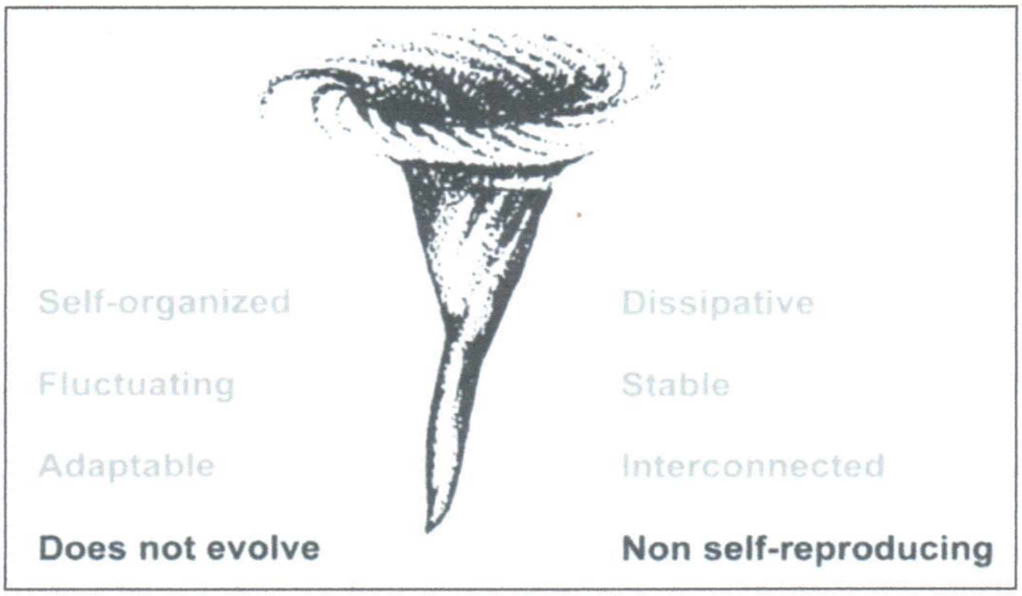

FIGURE 1

Vortex funnel of air in a bathtub.

SOURCE: AFTER FIGURE 7–4 IN CAPRA 1996.

are so familiar with this phenomenon that it doesn't induce the wonder it should. How does that funnel of air penetrate below the surface of the water, apparently defying the laws of gravity? The funnel never appears when the plug is not pulled, so what's so special about pulling the plug? How do millions of previously highly disordered water molecules become so rapidly ordered, swirling in unison around and around the funnel of air? What's happened to all that entropy the water once had? The answer is that pulling the plug converts the potential energy of the water to kinetic energy, and the entropy goes down the drain. An essentially closed thermodynamic system is converted into an open one, and the energy imported is used to create the vortex funnel of air.

The vortex funnel illustrates a fundamental property of life. When the plug is pulled it creates an energy gradient. "Nature abhors a gradient" say Eric Schneider and Dorion Sagan (2005), and it will take the most efficient means possible to abolish it. A ball rolling down a hill will automatically find the fall line that is the fastest, most efficient pathway to get to the bottom. (Skiers, who have a choice, try to do the same thing, but the ball is better at it.) Stated as a generality, wherever there is an energy gradient nature attempts to abolish it by always choosing the path of least resistance. Evidently the vortex funnel in the tub is the most efficient way of dissipating the energy gradient that is established by pulling the plug; other examples include hurricanes, tornados, and whirlpools. As the water drains out of the tub, the funnel becomes smaller and smaller as a function of the decrease in kinetic energy as the water level falls. The funnel disappears when the energy gradient is completely dissipated.

To maintain the vortex funnel, the tap must be turned on so the water flows in at the same rate that it flows out, thus maintaining the energy gradient. This mimics life—indeed, life exists *because* we have energy gradients. Chemical gradients determine the direction of chemical reactions; temperature gradients determine the flow of heat; and force or pressure gradients produce motion. While nature will seek to dissipate all gradients, the energy we import, like turning on the tap, thwarts nature and our order remains. With these energy gradients all living organisms perform work and the work we perform is cyclical (Kauffman 2000). All engines carry out thermodynamic work cycles, and life's engine is no exception: the work we do, whether chemical, mechanical, or in transportation, is done primarily in cycles. In fact, cycles characterize much of life. Neurological oscillators determine respiratory and cardiac rhythms; circadian sleep/wake cycles determine the values of many physiologic and biochemical parameters; we have metabolic cycles, positive and negative feedback loops, menstrual cycles, and many cyclical diseases (Glass and Mackey 1988).

The vortex funnel also mimics life in another way: it is self-contained. Like all living organisms, it has well-defined boundaries that do not diffuse away into the environment. Prigogine discovered that in autocatalytic chemical systems, in which a catalyst is produced by a chemical reaction that it catalyzes, order could spontaneously develop. In fact, he declared that autocatalytic loops are the only chemical reactions in which self-organization occurs. (Prigogine and Stengers 1984). An autocatalytic system is a positive feedback loop with inherent nonlinearities. Prigogine deduced that nonlinear dynamics were essential for self-organization in far-from-equilibrium systems, and he pointed out that "being far from equilibrium is a necessary requirement [for self-organization in chemical systems], but not a sufficient one" (pp. 144–45). A threshold or critical distance from equilibrium was also required, an example being Reynold's number, which describes the threshold at which laminar flow becomes turbulent.

Stuart Kauffman has taken another approach to explain the origins of order (Kauffman 1993, 1995). He posited an interconnected network of lightbulbs, where each bulb's state, either on or off, is governed by the state of the bulbs connected to it. The total number of possible states, or state space of the system, is 2^N, where N is the number of bulbs in the system. But when each bulb's state is determined by its interconnections with its neighbors, the state space is reduced to $\sqrt{N}$. As Kauffman says, this is "order for free" (Kauffman 1995, p. 71).

Although this cannot be applied directly to biological networks, all cells have interconnected intracellular networks; the genome with its epigenetic gene regulatory network is an obvious example. If the gene regulatory network that determines the expression of structural genes behaves in a way somewhat similar to Kauffman's lightbulb network, and we have 25,000 genes, either on or off, the possible gene state space is 225,000. Although the inputs from the regulatory genes to the structural ones are probably not binary—in other words, not only either on or off, but also dimly lit (Siegal, Promislow, and Bergman 2007)—Kauffman's discovery that regulation of networks confers order still applies. Presumably the regulatory network that determines which genes are expressed, and by how much, is different for each cell type and is responsible for cellular differentiation. The fact that there are ~210 different cell types in the human, a minuscule fraction of the state space of an unregulated network of 25,000 genes, is a clear demonstration of the power of regulation in producing self-organization.

This source of order also applies to multicellular organisms, all of which have interconnected extracellular networks (for example, hormones, nerves, chemotaxis, cytokines, ligand-receptor interactions, and so forth) that control the activities of cells, organs, and systems. A network of cells regulated by a critical number of inputs can spontaneously become ordered and self-organized, and this provides a source of order different from that in open thermodynamic systems that can both evolve and adapt while remaining reasonably stable.

Like Prigogine, Kauffman also deals with autocatalytic sets, but he does not use them to produce order from nonlinear chemical reactions. Kauffman investigated the spontaneous emergence of autocatalytic sets and concluded that they are almost inevitable. In a chemical soup of peptides, Kauffman demonstrated that as the number of peptides increases, the probability that one of the peptides would catalyze the reaction between two others increases as well:

> as the diversity of molecules in our system increases, the ratio of reactions to chemicals . . . becomes ever higher [and] the number of reactions that are catalyzed by the molecules in the system increases. When the number of catalyzed reactions [becomes sufficiently high] a giant catalyzed reaction web forms, and a collectively autocatalytic system snaps into existence. A living metabolism crystallizes. Life emerges as a phase transition. (Kauffman 1995, p. 62)

Ghadiri et al. (1993) have created such autocatalytic sets in the laboratory.

So far we have described how life's order arises through the laws of chemistry and physics. But life is not reducible to physicochemical laws (Kaufman 2008; Polanyi 1968). As Polanyi puts it, the laws of physics and chemistry determine the properties of the paint on a canvas, but the meaning of the picture is determined by the artist. Does this mean that the design of living things (a crucial aspect of our order) is under the control of some intelligent designer? We doubt it. Our designer is Darwinian evolution (Macklem 2008). Bad designs become extinct, good designs survive.

SELF-REGULATION

As discussed above, regulation of intra- and intercellular networks is a potent means of self-organization. Neither order nor regulation are imposed on us from without. We are self-regulating by a process we call *homeostasis*, defined in the *Dictionary of Science and Technology* as "the ability of an organism to maintain a constant internal environment by regulating its physiological processes and by making adjustments to the external environment" (Morris 1991). The problem with homeostasis is the word *constant*. There is abundant evidence that "homeostatically" controlled parameters fluctuate continuously (Suki 2002). This is true for heart rate, blood pressure, minute ventilation, tidal volume, breathing frequency, airway resistance, and renal blood flow, to name a few (Bruce 1996; Kobayashi and Musha 1982; Que et al. 2001; Wagner 1994, 1995). *Homeokinesis* is a better term: it has been tentatively defined as "The ability of an organism to utilize external energy sources to maintain a highly organized internal environment fluctuating within acceptable limits in a far from equilibrium state" (Que et al. 2001, p. 1137).

Homeokinesis requires adaptability to new conditions. And adaptability requires that living organisms respond to stimuli. Adaptation in response to external stimuli in turn requires feed-forward loops that allow the organism to enter a new physiologic state: sweating, for instance, when it is too hot, or shivering when it is too cold. Feed-forward loops run the risk of running away with themselves and fundamentally changing the whole system (this is a characteristic feature of weather, where the famous butterfly beating its wings in Rio can cause a typhoon in Tokyo), but life could not survive such radical transformations. Yet to maintain stability, the feed-forward systems must be controlled somehow, and this is usually accomplished by negative feedback loops. The dynamic balance between the yin and yang of adaptability and stability, feed-forward and negative feedback loops, is, we believe, the cause of the continuous fluctuations in homeokinetically controlled parameters. If life lies somewhere between near-to-equilibrium crystals on the one hand, which are fixed and stable but inadaptable and non-fluctuating, and weather on the other, which is unstable and evanescent with excessive fluctuations, it is not surprising that the amplitude of our fluctuations is maintained within acceptable limits.

Consider again the vortex funnel of air. It is not just a model of spontaneous self-organization, cyclical behavior and self-containment. It is also adaptable yet structurally stable. With the tap running so that the water level in the tub remains constant, there is a continual flow of energy into the system and of entropy down the drain. The funnel fluctuates continuously within acceptable limits, so that the fluctuations never alter its basic shape. If one were to increase the inflow of water, the energy gradient, size of the funnel, and amplitude of fluctuations would all increase, but the shape would remain the same as would the fluctuations relative to funnel size. The vortex funnel, homeokinetic and self-regulating, is, like life, both adaptable and stable. These opposing tendencies are in a dynamic balance.

But the vortex funnel also illustrates the size independence of its lifelike behavior. Small animals behave like large ones, in spite of the fact that their rates of energy consumption are vastly different. Said in another way, the morphology of the vortex funnel is independent of scale. From a tiny funnel in a nearly empty tub to a dangerous whirlpool in the ocean, its shape and the magnitude of fluctuations relative to its size remain essentially constant. It is a three-dimensional fractal. From unicellular organisms to the largest fungi, trees and whales the characteristic features of life do not change.

The ability to respond to external stimuli and perform work is shared by all of life's organisms. Although these activities are the result of persistent energy gradients and are required for homeokinesis, they of course serve a whole variety of other functions, in particular growth, the search for food, finding a favorable environment in which to live, and reproduction.

COMPLEXITY AND PHASE TRANSITIONS

There is a continuum of open thermodynamic systems from near-to-equilibrium, deeply ordered, stable, linear systems to far-from-equilibrium, nonlinear, evanescent, chaotic systems. Where a given system is found on the continuum depends on the amount of energy consumed and dissipated per unit of system size. Systems that are neither linear nor chaotic—like life—are called *complex*, and the science of complexity has been developed to characterize them. Complex systems are stable like crystals, but nonlinear like weather; they adapt to perturbations, but the perturbations do not reverberate through the system and change it completely.

Both Prigogine and Kauffman argue that life emerges in a "phase transition" between ordered and chaotic systems, and there is excellent evidence that this is the case for individual cells (Fabry et al. 2003; Trepat et al. 2007). We define a *phase transition* as a transformation of a substance from one phase to another at a critical threshold; e.g., ice to water at 0° Celsius. As illustrated in the schematic in Figure 2, this implies that over a narrow range of energy consumption (in the case of animal life, metabolic rate per unit body surface area), there is a steep transition from crystalline to weather-like behavior. Life is found in the phase transition between order and chaos (Fabry et al. 2003; Fessler and Macklem 2007; Kauffman 1993, 1995; Macklem 2008; Prigogine and Stengers 1984; Trepat et al. 2007).

We have described how life requires stability of ordered systems and adaptability on both micro (intracellular) and macro (multicellular) levels. The dynamic balance between these two, resulting in continuous fluctuations, are only found in the phase transition. Darwinian evolution has long since disposed of any form of life that lack these characteristics: life exists in the phase transition because it is the only place it can exist.

Not only do we live in the phase transition, there is excellent evidence that we move within it. Fredberg and his colleagues measured the rheology of cells and found that all cells studied collapsed to a single relationship when their rheological behavior was plotted against a factor *x*, which they referred to as "effective" temperature (Fabry et al. 2003). As *x* cooled, all cells became more solid-like; as they warmed, they behaved more as a liquid, a bit like slush between ice

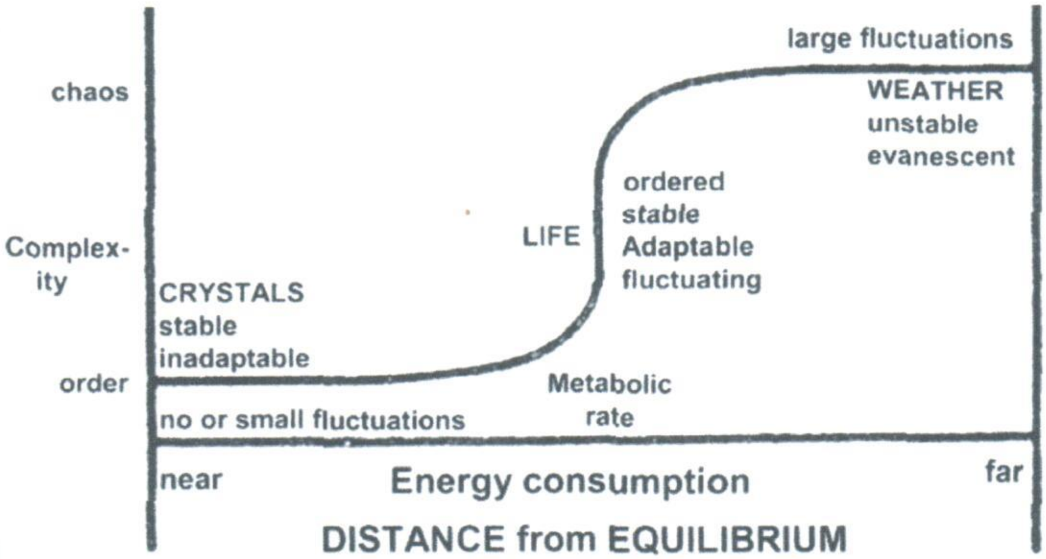

FIGURE 2

The continuum of open thermodynamic systems from near-to-equilibrium crystals to far-from-equilibrium weather. Life is found in the phase transition, in which systems move rapidly between order and chaos over a small range of energy consumption and dissipation.

SOURCE: REPRODUCED, WITH PERMISSION, FROM MACKLEM 2008.

and water. The take-home message is that all cells moved within the phase transition between solid and liquid, depending upon their energetic state. The "effective" temperature was not the thermodynamic temperature, as there was a missing source of energy which they thought might be the folding and unfolding of proteins (Fabry et al. 2003). Later they discovered that for lung cells, the stretch of lung inflation imparted the missing source of energy (Trepat et al. 2007).

For a given organism, one's position in the phase transition depends upon one's metabolic rate. For humans, the limits of healthy displacements within the transition presumably range from deep non-REM sleep to heavy exercise. Although this has not yet been tested in the laboratory, it may be that the magnitude of fluctuations of physiologic parameters depends significantly on metabolic rate.

Probably healthy life cannot exist much closer to chaos than it already is, but goodness knows where on the stability-to-chaos continuum one would situate the sulfur-metabolizing hyperthermophilic microorganisms that live in the hot vents on the ocean floor and hot springs. On the other hand, it seems that many forms of healthy life can exist deep within the ordered regime, as evidenced by hibernation, dormancy in plants, and cryo-preservation of sperm, embryos, cells, and tissues. Spores and seeds can become quasi-crystalline for indefinite periods, until conditions are ripe for germination, growth, and reproduction. Thus, mobility within the phase transition seems to be an essential feature of life.

CONCLUSION

We believe that a proper understanding of life—as an open thermodynamic system with a dynamic balance between adaptability and stability, conferring self-regulation through interconnections of component parts, existing in a phase transition between near-to-equilibrium and chaotic systems—can provide new insights into what constitutes health and may well lead to a new theory of disease (Bates et al. 2007; Costa, Goldberger, and Peng 2005; Que et al. 2001; Trepat et al. 2007). This requires an understanding of the science of complexity, yet the meaning of life and the behavior of complex systems are not emphasized in most medical curricula. This must change.

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