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A Theory of Circular Organization and Negative Feedback: Defining Life in a Cybernetic Context

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Abstract

All life today incorporates a variety of systems controlled by negative feedback loops and sometimes amplified by positive feedback loops. The first forms of life necessarily also required primitive versions of feedback, yet surprisingly little emphasis has been given to the question of how feedback emerged out of primarily chemical systems. One chemical system has been established that spontaneously develops autocatalytic feedback, the Belousov-Zhabotinsky (BZ) reaction. In this essay, I discuss the BZ reaction as a possible model for similar reactions that could have occurred under prebiotic Earth conditions. The main point is that the metabolism of contemporary life evolved from primitive homeostatic networks regulated by negative feedback. Because life could not exist in their absence, feedback loops should be included in definitions of life. Key Words: Feedback loops—Circular organization—Definition of life. Astrobiology 10, 1031–1042.

1. Introduction

THE CONCEPT OF FEEDBACK is central to control processes in electronics and engineering but is less commonly used to describe the basic organizational principles of life and life-related phenomena. I will argue that a primary characteristic of living systems is derived from, and dependent on, the function of negative feedback cycles. To this end, the first section of this essay is devoted to describing general properties of processes regulated by feedback. I will then go on to apply these principles to a definition of life.

Initially, the principle of feedback and other cybernetic concepts concerned non-living objects. For instance, in attempting to solve tasks of military engineering such as gun-fire control, Wiener (1948) and other mathematicians drew several inferences that had universal importance. The first definition of feedback was formulated as follows:

> In a broad sense it [feedback] may denote that some of the output energy of an apparatus or machine is returned as input.... The term feed-back is also employed in a more restricted sense to signify that the behavior of an object is controlled by the margin of error at which the object stands at a given time with reference to a relatively specific goal. The feed-back is then negative.... (Rosenblueth *et al.*, 1943, p 19)

Wiener and his colleagues introduced the basic principle of cyclic circular organization (Wiener, 1961, p 33) as a property of a certain class of systems in which an output signal of a system, after a chain of transformations in the surroundings, returns to the same system as an input signal. The system reacts to this input signal in a specific way, transforming it back into output and creating a potentially endless closed sequence of regulated processes.

It is notable that Wiener also applied this technical understanding of circular processes to the function of the nervous system:

> The central nervous system no longer appears as a self-contained organ, receiving inputs from the senses and discharging into the muscles. On the contrary, some of its most characteristic activities are explicable only as circular processes, emerging from the nervous system into the muscles, and re-entering the nervous system through the sense organs, whether they be proprioceptors or organs of the special senses. This seemed to us to mark a new step in the study of that part of neurophysiology which concerns not solely the elementary processes of nerves and synapses but the performance of the nervous system as an integrated whole. (Wiener, 1961, p 5)

To fabricate a system with the property of organizational closure, it is necessary to incorporate the output and input signals of a device into a cycle such that the output signal of a previous operation becomes an input signal for the next operation. Von Foerster (1961) designates such a function as recursive and depicts it with a recurrent arrow making a loop. Figure 1 compares linear organization of a cause and effect with negative and positive feedback loops. Linear organization (Fig. 1a) means that an output parameter x has no back effect (feedback) on either input x or on the function of

Editor's note: Sergey Tsokolov was a Ukrainian scientist who died in Germany in 2009. He published an earlier paper in *Astrobiology* (Tsokolov, 2009) which outlined some of the ideas presented here, and this essay was adapted from a book manuscript he was writing at the time of his death.

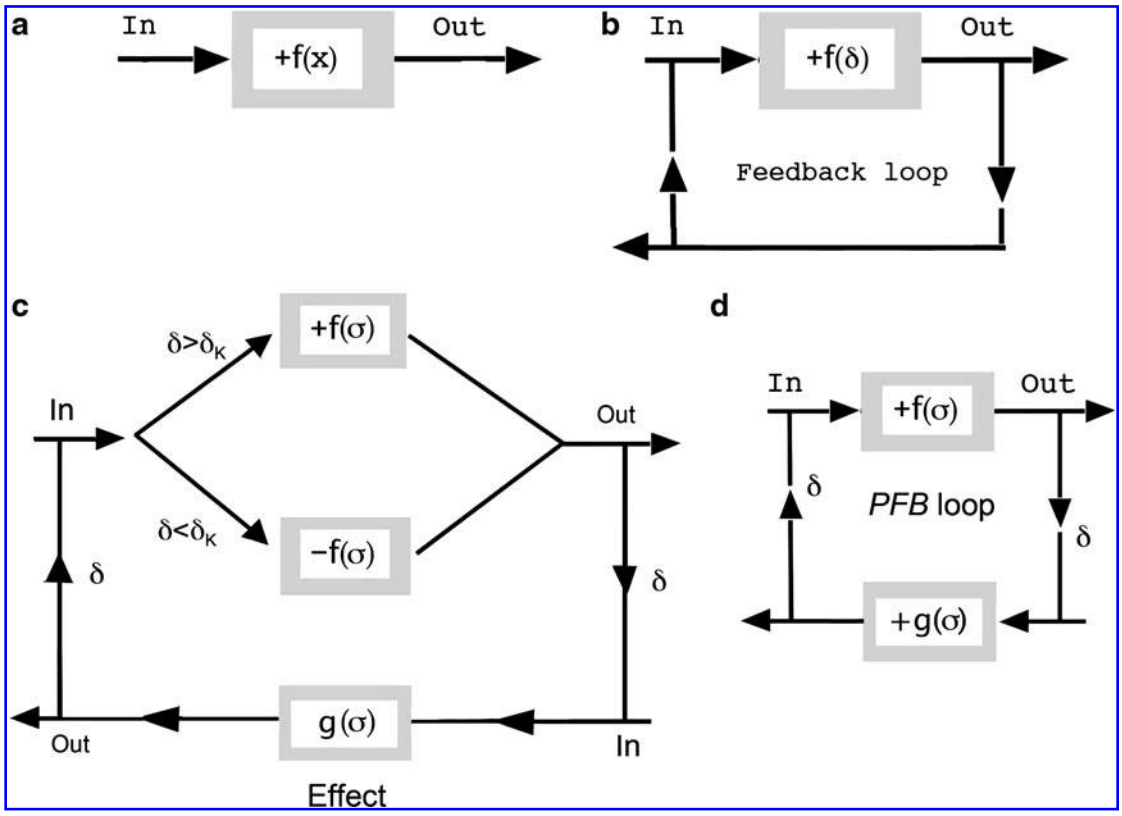

FIG. 1. Schematic comparisons of feedback loops. See text for details.

the system [*i.e.*, operator $f(x)$]. This lack of feedback is evident whether the function designates energy, a signal, or any mathematical variable. It is the lack of feedback that defines the systems as linear regardless of how complex, intricate, and "nonlinear" in a mathematical sense the function or operator $f(x)$ might be.

Figure 1b depicts a system with circular organization in which a parameter or a set of parameters repeatedly changes its value or values in a closed manner. In other words, circular organization is a process in which a conventional signal σ circulates uninterruptedly along one or more feedback loops. The signal σ is embodied in a specific physical parameter that is altered within the system's function: examples include temperature in a thermostat, concentration of chemicals in autocatalysis, electrical current in relays and communicators, as well as multiple biological components such as enzymes, hormones, pheromones, neuronal impulses, and gene expression. The abstract signal σ and its qualitative and quantitative transformations can serve as universal characteristics for any kind of feedback system. To avoid conceptual confusion, I will propose a classification of systems with circular organization and feedback functions. This classification also incorporates aspects of biological complexity, as defined by Hazen *et al.* (2007), which serves as a context for understanding and defining life phenomena.

2. Systems with Negative Feedback Organization (NFB Systems): Equifinality

The general schematic function of negative feedback systems (NFB systems) is illustrated in Fig. 1c, in which the function $f(\sigma)$ splits into two opposite directed processes: conventionally increasing function $+f(\sigma)$ and decreasing $-f(\sigma)$. The input signal, or homeostatic parameter σ, determines which of the two processes is "on." To be more exact, its deviation from the critical value σ_k is the point of measurement. The parameter σ does not necessarily remain stationary between its output and feedback input of the function f. The part of the feedback loop designated as function g can be altered, modulated, or perturbed, sometimes in unpredictable ways. The function g can represent either another NFB system or just environmental effects on parameter σ. Thus, the NFB system can operate in two basic ways: (a) in a dynamic, stable fashion during which the function $g(\sigma)$ remains unchanged over a period of time, and (b) in a homeostatic way in which parameter σ is affected by environmental perturbations and the function $g(\sigma)$ is unpredictable.

Within certain limits, NFB-system functions are stable in the absence of external influences or perturbations. For example, a thermostat that consists of both heating and cooling devices operates in a stable oscillatory way. It controls temperature by switching from alternative heating and cooling states. If the temperature of air inside the thermostat chamber does not undergo any external thermal effects, it will oscillate around the critical value of temperature to which the device is set. The same basic oscillatory behavior is inherent in every NFB system.

The principle of uninterrupted oscillating behavior creates another important feature of NFB systems known as equifinality. The term is used to describe the stable end point of a variety of dynamical systems, but its biological application was introduced by von Bertalanffy as a generalization of his

experimental observations in the field of morphogenesis: "Characteristic for organic processes however, is, that in a great measure, the same final state, the same 'goal' can be achieved beginning with different initial conditions and following different ways." (von Bertalanffy, 1940, p 528). Von Bertalanffy relates the equifinal behavior to living systems as a defining feature: "A profound difference between most inanimate and living systems can be expressed by the concept of equifinality.... Here [in vital phenomena], to a wide extent, the final state may be reached from different initial conditions and in different ways. Such behavior we call equifinal" (von Bertalanffy, 1950, p 25). Babloyantz (1986, p 147) also recognized the role played by periodic motions in living systems: "The existence of such periodic motions are of crucial importance for the regulatory processes of biological organisms, which can only be a function of various parameters of the system and are completely independent of any initial conditions."

The feature of equifinality underlies the other basic quality of NFB systems known as self-maintenance. Some investigators designate self-maintenance as a key property of life: "Life is a self-sustained chemical system capable of undergoing Darwinian evolution" (Joyce, 1994) or "Living systems are open systems, maintaining themselves in exchange of materials with environment, and in continuous building up and breaking down of their components" (von Bertalanffy, 1950, p 23). In its relation to equifinality, self-maintenance implies that any NFB system, including living organisms, can maintain its identity by opposing potentially destructive effects of the environment. A living system can exist only to the extent that it can compensate for environmental perturbations and reinstate homeostasis.

3. Positive Feedback (PFB) and Autocatalysis

Positive feedback systems (PFB systems) are those circular organized systems that function from cycle to cycle in a self-amplifying regime. In other words, the output value of the parameter σ is always greater than the input value of the same parameter σ. The most significant characteristics of the PFB system are the absence of a critical homeostatic referential value σ_k and a self-regulating mechanism (Fig. 1d). This differentiates them from NFB systems in that the function $f(\sigma)$ has only one unchangeable regime, $+f(\sigma)$. Typical PFB systems include chemical reactions in which one of the products catalyzes its own production in the course of the reaction. These reactions are called autocatalytic and the process designated as autocatalysis.

Positive feedback systems occur at all organizational levels. Important examples in biology include the cascades that function in amplifying the initial interaction of a photon with rhodopsin in the retina, the immune response to minute amounts of certain antigens, and triggering by an action potential arriving at a synaptic junction to cause depolarization of a postsynaptic cell. In contrast to the stabilizing and self-maintaining effect of the NFB processes, the very principle of self-amplification and self-acceleration of PFB systems leads to an inevitable change of the system's state. Here, we delineate four basic final scenarios of the PFB process.

State of exhaustion and equilibrium. In autocatalytic chemical reactions, such as hydrolysis of amyl acetate or the reaction of permanganate with oxalic acid, the system finally comes to thermodynamic equilibrium after the initial materials are exhausted. In principle, this process does not differ much from any other (non-autocatalytic) chemical reaction but reaches its final state of equilibrium faster than in the absence of cyclic self-acceleration.

Collapse of the system. Often PFB systems undergo full destruction after the uncontrolled release of their energy content, such as the explosive reaction of hydrogen and oxygen.

State of passive stability. In some cases, the PFB process becomes stabilized after losing its self-amplifying effect. Stabilization in the PFB system can occur by achieving a definite "threshold of potentials." An amusing example is the self-amplification of sound level at a party, which is incidentally catalyzed by the disinhibiting effect of ethanol on the human nervous system. It is not possible to elevate voices indefinitely in a noisy place because vocal cords have physical limits. At some point the noise will reach a plateau when the self-amplifying process (PFB system) becomes a simple feedback cycle.

State of active stability. Sometimes a process that starts as a PFB cycle transforms or incorporates into an NFB system. In complex systems like living organisms, saltation between two homeostatic NFB states usually proceeds via an unstable PFB state. For example, the initial human immune response to a virus is avalanche-like. Antibody proliferation follows the PFB pattern, but after the virus blood level stabilizes, the concentration of antibodies is maintained at a homeostatic level when a new critical value σ_k is established.

4. Chemical Systems with NFB Organization

The principle by which negative feedback can control an oscillating reaction is illustrated by chemical systems such as the Belousov-Zhabotinsky (BZ) reaction. I will describe the BZ reaction in some detail because it is an example of how a chemical system with homeostatic feedback control can emerge spontaneously under certain conditions. Belousov's first results were reported in an abstract published by a Russian scientific journal (Belousov, 1959). The mechanism was further elucidated by Anatoly Zhabotinskii (1964).

The most fascinating property of a BZ reaction is its oscillating behavior, which can appear in several forms. Most simply, liquid in a flask changes color periodically for up to half an hour. Depending on the metal ions participating in the reaction, these colors may be red/blue (Fe^{2+}/Fe^{3+}) or colorless/yellow (Ce^{3+}/Ce^{4+}). Other oscillating patterns can be observed under different physical and chemical conditions, including regular stripes in a test tube, circular waves in a Petri dish, or a variety of rotating spirals. Most of the chemicals participating in the reaction undergo oscillations of concentration.

A typical reaction mixture contains an oxidizer (bromate BrO_3^-), a reducing agent [malonic acid $CH_2(COOH)_2$], cerium Ce^{3+} and bromide Br^- ions. The overall reaction can be understood in terms of oxidation of the malonic acid by bromate with an end product of carbon dioxide. The reaction proceeds in several steps, giving rise to intermediate compounds with different redox states. Usually the whole process is presented as a sequence of the following chemical reactions:

$$BrO_3^- + Br^- + 2H^+ \rightarrow HBrO_2 + HBrO \quad (1)$$

$$HBrO_2 + Br^- + H^+ \rightarrow 2HBrO \quad (2)$$

$$HBrO + CH_2(COOH)_2 \rightarrow BrCH(COOH)_2 + H_2O \quad (3)$$

$$BrO_3^- + HBrO_2 + H^+ \rightarrow 2BrO_2 + H_2O \quad (4)$$

$$2BrO_2 + 2Ce^{3+} + 2H^+ \rightarrow 2HBrO_2 + 2Ce^{4+} \quad (5)$$

$$2HBrO_2 \rightarrow BrO_3^- + HBrO + H^+ \quad (6)$$

$$BrCH(COOH)_2 + 4Ce^{4+} + HBrO + H_2O \rightarrow 2Br^- + 4Ce^{3+} + 3CO_2 + 6H^+ \quad (7)$$

To better understand the mechanism of appearance of chemical waves, the process of malonic acid oxidation is divided into two stages. The first stage—oxidation of malonic acid to bromomalonic acid—includes steps 1 to 3. The second stage—further oxidation of bromomalonic acid to carbon dioxide—occurs during reactions 4 to 7. The characteristic feature of the second stage is that it is inhibited by bromide ions, which are among its products. The inhibiting effect is a result of the active bonding of bromide (Br^-) with bromous acid ($HBrO_2$) (reaction 2), which prevents the bromous acid ($HBrO_2$) from interacting with bromate BrO_3^- (reaction 4). It means that the second stage cannot be initiated because of the deficiency of the bromous acid ($HBrO_2$) being consumed by reaction 2).

As the bromide ions interact with bromous acid, the first stage begins. To summarize this stage, bromide ions are exhausted from the reaction medium. The second stage remains inhibited unless the concentration of bromide ions falls to a critical value. Then, reaction between bromate and bromous acid (reaction 4) proceeds, and stage two starts again and closes the circle. The critical value of the concentration of bromide ions can be calculated from $[Br^-]_k = k_4/k_2[BrO_3^-] = 5 \cdot 10^{-6}[BrO_3^-]$, where k_2 and k_4 are rate constants of the reactions that compete for the bromous acid ($HBrO_2$), reactions 2 and 4, respectively.

The concentration of bromide ions is the key homeostatic parameter in the system, although all chemicals play roles in transformation of the general signal σ (Fig. 2). Nevertheless, it is a critical value of the bromide ions (σ_k) to switch between two opposite directed processes: bromide increasing ($+f(\sigma)$) and bromide decreasing ($-f(\sigma)$).

Colored periodic effects seen in the liquid are due to participation of metal ions (cerium or iron) serving as catalysts. The process of catalysis implies alteration of a chemical state of the catalyst involved and its reinstatement after the reaction is complete. That is why the ionic catalyst periodically alters its state, specifically its redox state, and consequently the color, during the alternating process of each two-stage chemical cycle.

Like any NFB system, BZ reactions are thermodynamically open dissipative systems that require an uninterrupted flux of energy. The chemical potential is provided by the reduced state of malonic acid, one of the key incoming chemicals of the system. In the course of reaction, atoms of bromine and carbon change their redox state in a gradual manner. The end state of the lower potential of energy is carbon dioxide, which dissipates from the system in the gaseous phase. Under closed conditions, the oscillating process fades away as the reducer (malonic acid) is exhausted. However, if the energy flow is supplied in an uninterrupted way (in special reactors), the oscillating process continues indefinitely.

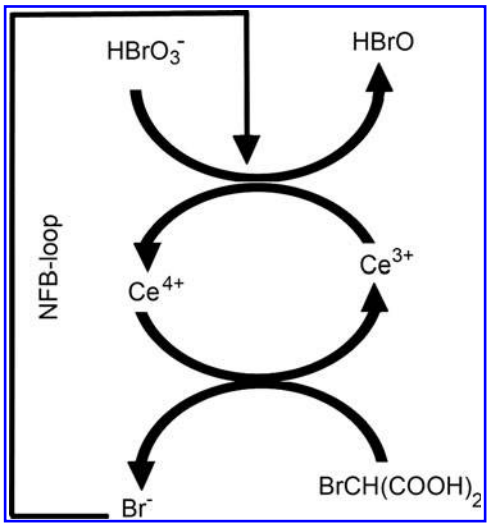

FIG. 2. The negative feedback (NFB) loop in the Belousov-Zhabotinsky reaction.

Belousov-Zhabotinsky reactions possess the key characteristic of equifinality. If during the normal oscillatory reaction one of the reactants is added, the periodic process will be disturbed, but a few cycles later the normal oscillatory pattern will be reinstated. This quality of the chemical self-oscillating NFB system is so universal that it is observed in all kinds of biochemical metabolic processes.

The chemical autocatalytic self-oscillating reactions have characteristic NFB cycles and homeostatic values such that they organize, maintain, and sustain themselves spontaneously. *It seems plausible that prebiotic evolution incorporated some version of an autocatalytic self-regulating reaction. Emergence of the first negative feedback loop in a natural chemical system represents the point of transition from a linear chemical evolution of matter to a prebiotic system incorporating negative feedback required for the origin of life.*

Significantly, a variety of metallic catalysts other than cerium can be used, including common elements such as iron, manganese, copper, nickel, and cobalt. It is also interesting that the original reducing agent employed by Belousov was citrate, the central reactant of the citric acid cycle. A fruitful research direction will be to explore alternative chemical oscillators that incorporate plausible components that would be available in the prebiotic environment.

5. Living Organisms Are Dissipative Systems Regulated by Negative Feedback

That living organisms are open systems, existing far from thermodynamic equilibrium, has become a widely accepted

view. Transformations of the energetic fluxes in a living system can be viewed according to the following parameters: Initial external sources of energy in a living system can be presented by a substrate or a factor of the environment that is "charged" with some energetic potential, or free energy. The living organism extracts from this source some quantity of energy and returns heat and "waste products" with a lower potential back to the environment.

Several external sources of energy are utilized by living organisms, leading to their classification as heterotrophs and autotrophs. While helpful in characterizing certain metabolic aspects (for example, sources of carbon-based compounds), this distinction is misleading with respect to the general organization of living beings as dissipative systems. The term autotroph, when translated literally from the Greek *autos* for "self" and *trophe* for "nutrition," has the sense of being self-nourishing. A typical autotroph uses light energy to reduce carbon dioxide to carbon compounds such as glucose, and the energy is stored as chemical bonds in the reduced compounds. In heterotrophs, molecules of glucose or other reduced compounds such as fatty acids first undergo chemical breakdown called catabolism in order to extract the energy of their chemical bonds and to obtain initial building blocks. Only afterwards does the organism synthesize its own components by the process called anabolism. Therefore, molecules of glucose in metabolic pathways of a heterotrophic organism can arise from both nutrient intake and metabolic processes.

The primary energy flux through a living system can be provided by various components of the environment, each having its energetic input and output (primary dissipation). The difference between input and output is determined by the portion of energy that "maintains biological order." For this reason, it is useful to classify organisms according to sources of energy as shown in Table 1.

For the purposes of this review, it is useful to distinguish between organisms that utilize inorganic and organic substances as sources of reducing power. If the primary flux of energy is created as a flow of electrons from reduced organic compounds to relatively oxidized organic and inorganic compounds, I will refer to those organisms as organotrophs.

Table 1. Examples of Trophic Energy Sources Used by Living Organisms

	Products	*Organism*
Energy source, organotrophs		
$Glucose + O_2$	CO_2, H_2O	Aerobes
Glucose	Lactic acid	Anaerobes
Glucose	$Ethanol + CO_2$	Yeasts
Alanine, glycine	Acetic acid, NH_3, CO_2	Clostridium
Energy source, chemotrophs		
Fe^{2+} (reduced iron)	Fe^{3+} (oxidized iron)	Iron bacteria
$4H_2 + CO_2$	$CH_4 + 2H_2O$	Methanogens
$4H_2 + SO_4{}^{2-} + H^+$	$HS^- + 4H_2O$	Desulfobacterales
$NH_4{}^+ + NO_2{}^-$	$N_2 + 2H_2O$	Planctomyces
Energy source, phototrophs		
Visible light	Reduced carbon, O_2	Cyanobacteria, green plants

The primary energy flux in chemotrophic organisms is similar to that of organotrophs except that the source of electrons is in the form of reduced atoms or ions incorporated in different inorganic compounds or free in solution. In phototrophs, the primary energy source is light. Photons are absorbed by a pigment molecule to produce an excited state electronic structure, which is followed by a series of complex electron transfer reactions that deliver the electrons to a highly reduced compound such as NADPH. Because photons are absorbed completely, phototrophs have virtually no primary dissipation products because the light energy is spread through synthetic and catabolic processes. Molecular oxygen is expelled from the system as an end product.

The word phototrophy (light "eating") should not be confused with photosynthesis (building with the help of light). These are different processes, even though tightly coupled. In green plants, photons are absorbed and converted into chemical energy during the light reactions before any synthetic processes have been initiated, such as the dark reactions of the Calvin cycle. The pigment bacteriorhodopsin of certain halophilic bacteria is an even simpler example. Bacteriorhodopsin absorbs light energy and uses it directly to pump protons and develop a chemiosmotic potential across the membrane. Nothing is synthesized when light is absorbed by bacteriorhodopsin, but the energy of the proton gradient is then used to drive adenosine triphosphate (ATP) synthesis.

As a dissipative system far from equilibrium, a living system does not differ from other dissipative systems that consume energy sources other than those used by life processes. For instance, the BZ reaction can be viewed as analogous to typical organotrophic metabolism. In a reaction controlled by feedback, it consumes reduced atoms of carbon in the form of an organic compound (malonic acid) and dissipates oxidized atoms of carbon as carbon dioxide. The flux of electrons, together with NFB mechanisms for control of bromide ion concentration, lead to a life-like self-maintained order in the system.

The main result of the primary energy flux in metabolism is synthesis of the universal energetic currency ATP, which is a source of energy for most other metabolic processes. The other result of metabolism is production of many intermediates that are used as building blocks in subsequent biosynthetic processes. Two additional notes concerning energy fluxes need to be made. The first is that all transformations in the living body during metabolism are followed by irreversible losses of energy (in accordance with the second law of thermodynamics). The total of these losses can be defined as a secondary dissipative process. The other note is that, once synthesized, the molecular compounds and supramolecular structures are not permanent but instead undergo turnover and replacement at variable rates. This continuing self-renovation is a fundamental way in which a living organism differs from non-living matter. A quartz crystal is also highly orderly and grows out of a disordered medium; but, once formed, its atoms remain in place indefinitely. In contrast, a living organism can be thought of as a complex pattern, a molecular scaffold through which matter and energy endlessly flow as long as the organism is alive.

The process of metabolism is not a mere cascade of gradually lowered energetic potentials. Simultaneously in the living cell there occurs synthesis of chemical compounds whose level of complexity and energetic potential

considerably exceeds the level of complexity of initial primary nutrients. For example, biopolymers such as proteins, nucleic acids, and polysaccharides are charged with higher energetic potential than the monomers that compose them. The reason is that, for synthesis of a polymeric molecule such as glycogen, multiple molecules of glucose are required. Some are used as building blocks, while others are used as a source of energy for creating chemical bonds of higher complexity. Such processes are unique to life. The polymerization reactions are not forbidden by physical or chemical laws, but they cannot occur spontaneously with the precision of life. Only in living organisms are polymers with exact ordering of monomers ubiquitous and inherent. The polymers of life constitute the very essence of the self-organizational processes of order creation and maintenance, and these are the thermodynamic and cybernetic criteria of life.

6. Enzymes as Intermediates in NFB Cycles

The key function of enzymes in metabolic processes includes both catalytic and regulatory roles. Enzymes ensure a stepwise course of the chemical reactions by keeping release and consumption of energy within physiologically acceptable ranges. Enzymes also regulate and direct biochemical processes, such that metabolism is organized as a network of coupled reactions. The direction of a reaction in the living system is determined not by its general chemistry or equilibrium constants that characterize progress of reaction under standard thermodynamically equilibrium conditions. The course of reaction strictly depends on the whole thermodynamic context in which other reactions and processes are participating. No transformation within living systems occurs as an independent event without being tightly interwoven into the general network of homeostasis. Each stage is catalyzed by a specific enzyme, which is coupled to other reactions and controlled by NFB loops.

For the purposes of this review it is important to understand the role of enzymes in regulatory processes. There are many mechanisms of regulated enzyme activity: competitive inhibition (succinic dehydrogenase), allosteric effects (L-threonine dehydratase), covalent modulation (glycogen phosphorylase), activation of a precursor (pepsin, trypsin), genetic induction (β-galactosidase), and repression (tryptophan synthetase). An important feature common to such regulatory mechanisms is product inhibition, which means that enzymes are not simply embedded in catalytic networks but instead are organized and controlled by NFB cycles.

For example, consider the regulation of threonine dehydratase activity, which involves a sequence of reactions by which L-threonine is converted into L-isoleucine. The total reaction is divided into five catalyzed steps. The main regulatory role involves the first step in which a water and amine group are removed from L-threonine to produce 2-oxobutyric acid. The dehydratase activity in this step depends on the concentration of the end product of the reaction, L-isoleucine, which binds allosterically to the enzyme and inhibits its catalytic activity (Fig. 3). Whether enzyme activity is "on" or "off" depends on the concentration of the final product of the catalyzed process, but this is true only for experiments *in vitro.* In living systems, there is constant outflow of L-isoleucine, which is a significant part of the regulatory process.

The conversion of L-threonine into L-isoleucine incorporates a single NFB loop and resembles other NFB systems described previously. The homeostatic parameter (conventional signal σ) of the Thr/Ile-system is the concentration of L-isoleucine [Ile]. The σ-increasing process is the chemical reaction of L-isoleucine synthesis from L-threonine, catalyzed by the active form of threonine dehydratase. The σ-decreasing process occurs when the enzyme is inhibited by L-isoleucine, on the one hand, and L-isoleucine is consumed for the metabolic needs of the cell. Consequently, there must exist a critical value $\sigma_k = [\mathrm{Ile}]_k$ which is responsible for on/off switching between the two processes. This value should somehow reflect a steady state between consumption and synthesis of L-isoleucine.

This Thr/Ile-system is incorporated in the metabolic pathway of the organism and functions as a source of L-isoleucine in bacterial cells. From this point, it is clear that the low molecular compound L-isoleucine plays the key role in regulating the entire five-step reaction, not the enzyme. Instead of being directors and controllers, the enzymes are intermediates in the metabolic and homeostatic network of the organism. No special commands regarding what to produce, and how much, come from enzymes or their genes.

7. Genes as Intermediates in NFB Cycles

Within the homeostatic network of a living organism, enzymes are the most effective regulatory biochemical agents. However, control of enzymatic activity in the system

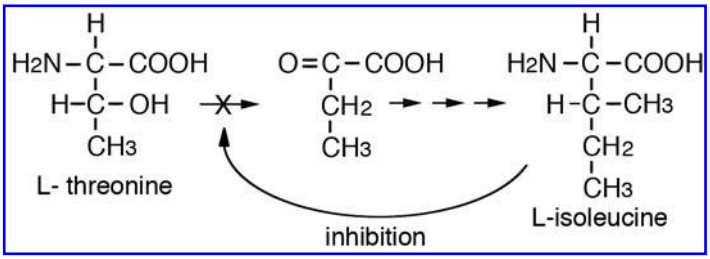

FIG. 3. An NFB loop controls threonine dehydratase activity by product inhibition.

is sometimes implemented not by direct binding of an agent to the enzyme complex but by regulating the quantity of the enzyme present in the system. All enzymes are polypeptides synthesized by ribosomes, so regulation of transcription and translation controls the rates at which an enzyme is synthesized. Thus, important regulatory steps have been shifted from the level of enzymatic activity to the level of gene expression.

A classic example of an NFB loop involving genes as regulatory intermediates is catabolic transformation of lactose regulated by the lactose operon. This was first described in detail by F. Jacob and J. Monod in 1961. Later, other regulatory systems operated via gene expression were discovered, including operons for galactose, arabinose, tryptophan, guanine, arginine, and others as well. Because of the importance of the mechanisms of genes involved in the metabolic NFB cycles, the model of the lactose operon (lac-operon) will be considered here in more detail.

Lactose is an energy alternative to glucose for bacterial cells. In the presence of glucose, the genes coding lactose-utilizing enzymes are inactive. But if lactose replaces glucose in the medium, genes necessary for lactose utilization are activated (β-galactosidase and β-galactoside permease). The key aspect of the system is the fact that the process of enzyme synthesis is regulated by the presence or absence of the substrate (galactose) in the medium. The lactose is first converted into the inducer (allolactose), which binds to a polypeptide repressor that unblocks gene activity by removing a repressor from the operator part of the operon. An RNA polymerase then binds to the promoter, followed by transcription, splicing, and finally synthesis of the required enzymes.

As a functional unit, the lac-operon regulatory complex can be viewed as an NFB system incorporated into the organism's general homeostasis. The homeostatic parameter σ is the critical concentration of lactose that switches between two functional regimes. If lactose is present, the system switches to enzyme production, but in the absence of lactose the lac-operon turns off. Because the system does not possess any way to actively increase the lactose in the medium, the only σ-increasing factor is the supply of lactose from an independent environmental source.

It is worthwhile drawing an analogy between regulatory cycles of lactose utilization by induction of the lac-operon and L-isoleucine synthesis by allosteric inhibition of threonine dehydratase. Both cycles are described by the same general scheme, and any differences are determined by the effect of the main homeostatic factor σ on the increasing and decreasing regimes of function. In the Thr/Ile system, the regulatory mechanism is inhibition (inactivation) of the enzyme by its product L-isoleucine, while in the case of lac-operon systems, the regulation is implemented by induction (activation) of the gene-enzyme chain by its substrate lactose. Respectively, the complementary factor of regulation is metabolic consumption of L-isoleucine in the first case and supply of lactose from an independent resource in the second case.

Analyzing the function of lac-operon and other regulatory systems leads to the conclusion that genes should be incorporated in the general NFB cycle as intermediate elements. There is no special regulatory program encoded in the genes that directs their function. Instead, structural and regulatory genes are switched on and off as needed, in response to signals that are typically external in origin, such as lactose, or components of intermediary metabolism.

8. Cybernetic Criteria for Life

The basic principle to be emphasized here is that NFB organization is intrinsic to all of biology and must be included in a definition of life. A controlled function of two opposing processes maintains a living system in a state of homeostasis. This dynamic also incorporates equifinality, which does not occur in any linear organized dynamic system. The switching between two alternative functions serves as a buffer to damp perturbations and thereby maintain a steady state of dynamic equilibrium. Every NFB system has its own characteristic state or states regulating its behavior.

From this, we can formulate a cybernetic criterion for life: *all living systems are defined as organized molecular systems controlled by negative feedback with properties of equifinality, homeostasis, and self-maintenance.*

The idea of the constancy of the internal environment of the body was first proposed by the French physiologist Claude Bernard, who later formulated a well-known postulate (Bernard, 1877): "The constancy of the internal environment is the condition for free and independent life: the mechanism that makes it possible is that which assured the maintenance, within the internal environment, of all the conditions necessary for the life of the elements." This statement unambiguously related the idea of the constancy of the internal environment of the organism (*i.e.,* homeostasis) as an essential characteristic of life.

The definition of homeostasis was first introduced by Cannon (1929) and later elaborated by Norbert Wiener (1975), who combined this idea with the principal of feedback. He designated the combination as a "central phenomenon of life" and wrote:

> All of these devices in which an apparatus assumes a specific structure or functions on the basis of past experience lead to a very interesting new attitude both in engineering and in biology. Biologically, we have at least an analogue to what is perhaps the central phenomenon of life. Some sort of feedback is not only exemplified in physiological phenomena but is absolutely essential for the continuation of life as found in what is known as homeostasis. (Wiener, 1961, pp 112 and 114)

9. The Cell as an Integrated Homeostatic Net

The next step toward defining a living system is construction of a basic organizational scheme of metabolism/homeostasis that would characterize any form of life with respect to component molecules, energy flux, metabolism, and regulatory processes. This can be done within the context of functional cycles, defined as energy-requiring processes controlled by NFB loops. Cyclic organization of biological functions have previously been described by Manfred Eigen and Peter Schuster (1979) and Stuart Kauffman (1993), so I will not include a detailed presentation of the general concepts. Instead, I will present two examples that are relevant to defining life and understanding its origin.

Membrane compartmentalization. All known terrestrial forms of life possess membranous complexes that protect the living cell from its environment and maintain an internal spatial order. Both the living cell and its environment are assumed to exist in a thermodynamic steady state away from equilibrium, which means that they have a tendency to mix. Without a specialized protective mechanism, the highly concentrated and organized cell contents would disperse into the

surrounding fluid. It follows that the membrane boundary complex has a primary biological function of compartmentalization and self-assembled boundary structures defined the first forms of cellular life (Deamer *et al.,* 2002).

Membrane-based functional cycles include permeability and transport properties with respect to the external environment, and synthesis, assembly, and renovation of the membrane components from the cytoplasmic side. Those processes are mutually regulated. The membrane has a regulatory impact on the whole process of metabolism, providing proper conditions for maintenance of a cell. On the other hand, in the course of metabolism, all essential membrane components (lipids, glycolipids, specific proteins, ion channels, etc.) are produced internally, resulting in a closed functional cycle: the membrane also makes possible the synthesis and ordering of compounds that are components of the membrane.

Maintenance of cellular genetic stock. Maintenance of genetic stock is another functional cycle. The main primary products of structural genes are polypeptides of very different properties. Having been synthesized, they go immediately into metabolic networks or other functional cycles, where they work as enzymes, structural or regulatory elements. The feedback influence of metabolism on the genome is determined by synthesis of the nucleotides and amino acids that participate in gene expression, and functional circularity in the genome can be understood as the synthesis of proteins coded by the genome, which in turn regulate and replicate the genetic information of the genome.

The structural genes can be viewed as a kind of library, and as for any library the stock must be kept in a highly ordered state to provide quick access and precise copying of the information. This task is fulfilled by special machinery that includes enzymatic complexes for monitoring and repairing DNA (exonucleases, polymerases, ligases), packing and unpacking chromosomes and DNA fragments, transmission of genetic "text" from DNA to polypeptides (transcription, RNA processing, translation), and, finally, regulatory genes that control biosynthesis and metabolism. Moreover, in the case of cellular division, the genetic library should double and be equally distributed among offspring.

In summary, the basic organizational pattern of living systems implies the following consequences:

(1) In contrast to fluxes of matter and energy in ordinary chemical reactions in which the channels of input and output are distinguishable, the regulatory NFB loops that constitute homeostatic networks are circular and closed. In the closed network of metabolism it is not possible to define which chemicals are initial, which are intermediate, and which are end products. Similarly, it is not possible to determine which chemical reaction is governed and which governs. Components of the external environment involved in the homeostatic system undergo various transformations, become transient parts of the system, and then return to the environment. However, the overall pattern of life processes remains unchanged, so there is no "flux of information" through the system in the same sense as the flux of matter and energy.
(2) With the possible exception of lipid insertion into membranes and permeation of small molecules like water, oxygen, and carbon dioxide, there are no unregulated spontaneous processes in the living organism. Every biochemical reaction is integrated within complex networks of other reactions. As a consequence, it is possible in principle to define an NFB loop between any two arbitrarily chosen life functions that are coupled and mutually regulated.
(3) In a more general view, metabolism is not restricted to processes of catabolism and anabolism. The network of transformations and coupled reactions includes processes characterized as functions. Synthesis and assembly of membranous boundaries, maintenance of genomic stock, and signal transduction are parts of an integrated metabolism. As single functions, they tend to be seen in isolation by an observer, but this simply reflects the cause and effect characteristic of human thought processes. Therefore, defining life in terms of "metabolism" seems not to be useful, because everything that happens in a living system is metabolism incorporated within feedback loops.

From the basic organizational model of metabolism, it is clear that every NFB loop can consist of several other regulatory circuits. Yet an NFB loop can also be a component of a more complex NFB system. Extrapolation of NFB hierarchy to the level of living organism as a whole leads to the conclusion that the living organism can be viewed as integrated complex NFB systems. In a living system, the conventional parameter σ takes a great variety of forms. It can consist of chemical, mechanical, osmotic, thermal, and electrical signals and many others. Sometimes the modulatory effect $g(\sigma)$ belongs to other organisms. In turn, in respect to that organism the function $f(\sigma)$ of the first organism is the factor of modulation, or perturbation as well. If the mutual impact between two organisms becomes relatively stable and of vital importance for both organisms, a symbiotic unit has been created. Interaction of two or more living systems in a circular way presents a general mechanism of origin of integrated biological units of higher order. At the cellular level, examples include the mitochondria and chloroplasts descended from an earlier bacterial symbiosis, and an example at the organismal level is the Portuguese man-of-war, which consists of a colony of four different polyps and medusoids bound in a symbiotic relationship.

10. Minimal Life as Minimal Metabolism?

The metabolic scheme of living systems brings us back to the basic postulate that all observed phenomena of life incorporate the principle of negative feedback. The differences between living organisms are defined in the most general way by differences of complexity of their NFB loops. It follows that, to reconstruct a minimal living system, we should start from the basic organizational scheme of extant life and proceed in the direction of simplification. That means that with every step in this thought experiment a single feedback loop is removed from the general homeostatic and metabolic network until we end up with only one autocatalytic NFB cycle.

It will be difficult, if not impossible, to reconstruct this evolutionary process in any detail. However, we can start at

the other end of this spectrum of complexity by investigating autocatalytic self-oscillatory NFB processes such as the BZ reaction, which is reproducible under comparatively simple laboratory conditions. Both living systems and BZ systems fall under the same criterion of NFB systems, and it is helpful to make a direct comparison. The main conceptual resemblance of the two systems is determined by their function. The mechanism to maintain thermodynamic order in the BZ reaction is the same as maintaining any single metabolic value in a living system. The BZ system switches between two oppositely directed chemical processes that are self-regulated by the concentration of bromide ions [Br^-]. In the living system, thermodynamic (biological) order is maintained by the self-oscillatory functioning of a great number of coupled parameters: concentrations of metabolites, catalytic activity of enzymes, control of gene expression, different kinds of mediators (hormones), physical factors (membrane envelopment), and functional cycles (motility).

The fluxes of energy in both dissipative systems are similar. A reduced compound of carbon serves as an energy source, for instance, malonic acid for BZ reactions and lactose or glucose for bacterial cells. During metabolism they are oxidized to carbon dioxide or some other intermediate products; the oxidants are bromate in the BZ reaction, oxygen or other inorganic compounds in living systems. It is characteristic that the general redox process occurs stepwise, with a gradual decrease of reduction potential of the energy source (food). In the living cell, the process of energy consumption includes three main stages: glycolysis, the citric acid cycle, and the electron transport chain. In BZ systems, malonic acid is first oxidized to bromomalonic acid and then to its final product, CO_2. However, the process of reduction of the brome-containing oxidizer undergoes several steps, each with a different redox state of the bromine.

Even though the class of BZ reactions presents the simplest known self-oscillating, self-ordered NFB systems, they cannot be considered as candidates for initiating prebiotic evolution. We know that no highly ordered process can proceed in an unlimited space with free access to solvent and other chemicals. Therefore, as with any other NFB system, the BZ reaction requires an enclosed space with selective permeability for key components. The other reason is that BZ reactions are organized (self-organized), they proceed under very strict physical and chemical conditions, and they are very sensitive to perturbations. Both limitations have been successfully overcome in the laboratory, but this was hardly the case in the prebiotic environment.

Given the example of BZ reaction systems, we can consider how primitive NFB systems might emerge in the prebiotic environment. The first question concerns compartmentalization, which could be solved several ways. For instance, porous minerals such as those composing the matrix of hydrothermal vents have been proposed as a possible site where chemical processes would gain some degree of isolation (Martin and Russell, 2007). The mineral pores have the additional advantage that their surface is usually charged electrically and can provide selectivity for incoming and outgoing chemicals.

Another solution for compartmentalization is surface films at interfaces that are maintained by adsorption of solutes (Wächtershäuser, 1988). Finally, vesicles can self-assemble in media containing organic amphiphiles (Deamer *et al.*, 2002). Formation of the lipid vesicles could not only serve to isolate chemical processes but also provide different physical conditions between external and internal environments.

Given an enclosure of some sort, how could self-regulating NFB loops be initiated within the compartment? It seems reasonable to think that the variability and concentrations of potentially reactive chemicals on early Earth were such that emergence of an NFB system would not be a unique event. Rather, the appearance and disappearance of multiple self-regulating loops in the primordial milieu would occur spontaneously. Stuart Kaufman characterized this concentration as a critical complexity threshold: "The origin of life, rather than having been vastly improbable, is instead an expected collective property of complex systems of catalytic polymers and the molecules on which they act" (Kauffman, 1993, p 285).

11. Chemical and Prebiotic Evolution

Usually, all the processes leading to the origin of life are referred to as chemical or prebiotic evolution without distinguishing one from the other. The main emphasis has been put on two aspects, which in turn have led to two investigational programs. The first attempts to discover how complex chemical elements of existing living systems could have been synthesized abiotically. As a result, we know a great deal about the synthesis of amino acids, purines, pyrimidines, nucleotides, carbohydrates, fatty acids, and so on. The second research approach attempts to establish how the first living cell could self-assemble within the complex chemical and physical environment of early Earth. "At some point, either on Earth or elsewhere in the Cosmos, a collection of inanimate organic molecules found themselves assembled in a way that supported Darwinian evolution.... Only by creating life in the laboratory will we demonstrate that we truly understand life" (Ricardo and Benner, 2007, p 154).

The definition of life developed in this review suggests another approach to investigating the origin of life. First, we should clearly distinguish between the chemical evolution of matter and prebiotic evolution of processes. Chemical evolution involves primary synthesis, diversification, complication, and accumulation of chemical compounds under abiogenic conditions. There is no reason to assume that so-called "biomolecules" deserve special attention. The only constraints are due to local physical and thermodynamic conditions. Nothing like "Darwinian evolution," "template-and-sequence reactions," "informational molecules," or "homochirality" that characterize modern living forms would have any priority in the primordial soup.

From this, I propose that closed autocatalytic chains must be taken into account in attempts to define life and furthermore to design experiments aimed at elucidating the origin of such chains. As we see from the example of BZ reactions, no particular set of biologically relevant molecules is needed to start the "first" self-oscillatory NFB system. The BZ reaction also shows that experimental models of spontaneous reactions incorporating NFB loops are possible.

12. Autopoesis and Definitions of Life

The principle of self-production, especially in relation to living systems, constitutes the nucleus of the theory of autopoiesis developed by H. Maturana and F. Varela (1980). Autopoesis was postulated to begin when a critical

complexity of chemical composition, diversity, and concentration had been reached and emergence of autocatalytic self-maintaining cycles became an ordinary event. However, single autocatalytic chains could not lead to the origin of life, because the probability of their decay is very high. Emergence of the prebiotic systems (pre-life) is a property of the whole environment, not just those particular systems. Perhaps the first stable protobionts occurred as the result of fusion of several less stable autocatalytic reactions. The main problem in this scenario concerns the requirement for sufficient chemical abundance. Both chemical and prebiotic evolution would require a highly reactive mixture composed of organic compounds delivered during late accretion or synthesized by atmospheric or geochemical reactions. This logic leads to the conclusion that chemotrophic (autotrophic), and not organotrophic (heterotrophic), organisms are later products of evolution. The first cellular forms of life emerged as encapsulation of protobionts (when those protobionts had learned to synthesize and to assemble membrane components). It is obvious that they could not initially develop complex enzymatic nets and only afterward protect themselves from the environment. The nutrients of the first cells (protocells) should have been the same as those of the protobionts from which they originated, represented by relatively complex organic compounds with accessible energetic potentials. This is understandable according to the logic of evolutionary processes. Only after the energy content of the primordial soup became exhausted would protocells have needed to evolve other sources of energy and invent specialized enzymatic machinery to utilize them.

It should be stressed that neither chemical nor prebiotic evolution, at least in its early stages, requires any "informational molecules," matrix synthesis, or molecular replication. No matter how important those properties become for further life, they are still later inventions. Matrix synthesis is so deeply rooted in all extant forms of life, underlying the mechanism of (Darwinian) evolution, that it makes some investigators state a question: "Which was first to appear on Earth—replicating molecules or metabolic processes?" (Shapiro, 2007, p 142). Under metabolic processes, they usually understand the autocatalytic properties of polypeptides, with emphasis on the role in replication: "A protein enzyme was needed for the copying process to take place" (Shapiro, 2007, p 144). It is true that complex replicating processes require a whole network of enzymatic activity. However, enzymatic activity does not require a replicating process. The origin of matrix synthesis is a separate problem, and there is no direct connection to circular NFB processes or their role in the origin of life. Otherwise we face the familiar epistemological problem of deciding the precise boundary between life and pre-life.

13. Conclusions

Pier Luigi Luisi wrote:

> A definition of life should permit one to discriminate between the living and non-living in an operationally simple way and it should not be too restrictive (*i.e.*, the discrimination criterion should be applicable over a large area and should be capable of including life as it is as well as hypothetical previous forms). All forms of life we know about should be covered by such a definition. (Luisi, 1998, p 617)

Luisi's advice is well taken. The act of definition is to discover a suitably succinct phrase that by consensus discriminates a given set of observations from all other sets. A definition of life should be constructed in a purely physical-chemical context yet must avoid being misleading by setting exact borderlines between life and non-life. This is why I emphasized that one of the primary characteristics of the living state—regulatory feedback loops—can also arise spontaneously in purely chemical systems. In this regard, Noam Lahav wrote:

> The closure of the first feedback loop is suggested to be considered as the origin of life, since the general organizational pattern of the primordial feedback loops is basically identical to that of extant living organisms. This then implies that the organizational principle embedded in the feedback loops under consideration has been a common denominator for all forms of life since their first emergence, during the transition from inanimate to animate matter and beyond, covering the entire history of life on earth. (Lahav *et al.*, 2001)

By "closure of the first feedback loop" the authors are referring to NFB loops and the origin of metabolism. There are definitions of life in which metabolism is assumed to be a fundamental property, but the notion of metabolism itself remains undefined. The main point of this essay is that metabolism in living systems is identical to biochemical homeostatic networks organized on the principle of negative feedback. The first or minimal metabolism corresponds to a minimal NFB system, and future research on the origin of life should be directed toward determining how such systems can spontaneously emerge in the prebiotic environment.

Author Disclosure Statement

The author and the editor of this essay have no commercial associations that might create a conflict of interest in connection with the concepts presented here.

Abbreviations

ATP, adenosine triphosphate; BZ, Belousov-Zhabotinsky; lac-operon, lactose operon; NFB, negative feedback; PFB, positive feedback.

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Comments from Referee 1

I note that definitions of life that are focused on self-maintenance, such as this article, exclude viruses and prions, whereas definitions that focus on information include them. Many would like to include the first and exclude the second, but definitions create cases of the excluded middle. The growth of a virus in a cell is a logarithmic growth (positive feedback) which is terminated when the cell dies and viruses escape. The virus itself shows neither positive nor negative feedback, and all the work is done for it! Indeed, as I understand, all it does is make a hole and squirt. And the prion is information stored in protein folding that breaks the Central Dogma of DNA, and it does nothing, though external systems maintain it, too.

The positive feedback saturation is an automatic product of a Malthusian process of logarithmic growth. The process of reaching a limit with life is not different from that of an avalanche in a Geiger counter. All kinds of processes may limit a system before it utilizes all the available energy of the environment. Some of them are external and some internal. I do not see these as specifically associated with life. The question is whether positive and negative feedback are characteristic of all dissipative systems, living or not. I did not find that distinction discussed.

I am in agreement with the author that a precise definition of life is problematic. I find it particularly a problem because higher levels of survival selection can mimic the processes of the lower levels by other means. Genes can store information; but, in addition, we have memory and also books and computers. Because higher levels gain capability, we can define the new characteristics associated with transition from a lower level to a higher one, but those characteristics do not limit the upper state achieved. When defining the pre-life to life transition, that which is past the threshold could be biological or postbiological.

The author makes a distinction between non-dissipative non-living systems and life. However the distinction between dissipative non-living systems and life appeared to be only one of quantity of feedback loops. The issue of whether there is a further discriminative factor (such as information) does not appear, and even there the distinction is also quantitative—amount of information.

I have a problem with the author's statement that all living systems are defined as organized molecular systems controlled by negative feedback with properties of equifinality, homeostasis, and self-maintenance. All dissipative systems are of necessity limited in their positive feedback by environmental limitations, which can be seen as negative feedback. The combination of the two feedbacks produces the three properties discussed above. Thus from my perspective the definition is not sufficiently exclusive as to omit hurricanes, forest fires, continent building, star formation, etc.

The author states that "In the closed network of metabolism it is not possible to define which chemicals are initial, which intermediate, and which are end products." This seems true of any self-maintained system, living or not. Are rock-building processes any more initial than the erosion which creates the materials? That also demonstrates the flow of materials through a system, yet the author uses such flow as a distinction for living organisms.

The author states that, "However, the overall pattern of life processes remains unchanged, so there is no 'flux of information' through the system in the same sense as the flux of matter and energy. In this respect there are neither directing 'programs' nor 'aims' to be achieved by the living organism." This statement treats the individual organism as in the role of system. But the system that has all the feedback processes applied to it is the species, or equivalent similarity group. There are acute problems in applying the concept of "life" to an individual, as the author notes. The effect of all the processes is to select for group survival. The program self-develops to produce survival, and in so far as there is any system "aim," survival is it.

Equally the effect of evolution, while maintaining a population of simple organisms, is to develop more complex structures with multiple components that can explore the survival value of higher complexity. There is a flow of information into these systems that is now also flowing into nonbiological forms. The Great Chain of Being does not represent current understanding, but there is a related structure defined by the levels of survival development. This seems to be part of the nature of existence, of great importance in the search for and understanding of the possible forms of extraterrestrial intelligence.

The author also states that "However, enzymatic activity does not require a replicating process." It is certainly true that the first enzyme could not have been replicated. However, an enzyme is a Brownian motion catalyst that operates by molecular fit that holds another molecule or molecules in place so that linkage or separation can develop. The minimal number of atoms that can form a structure like this is in the hundreds. The cube root of this number must at least be one of the larger digits. Random development of such molecules is highly improbable (Monod's problem). Therefore, although precision replication is excluded because it has not yet developed, imprecise replication must have been essential in limiting the chemical options.

—Nick Woolf, Reviewer
August 13, 2010