

8. The Birth of Protocells*

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Abstract: Could a composome, chemoton, or RNA vesicular protocell come to life in the absence of formal instructions, controls and regulation? Redundant, low-informational self-ordering is not organization. Organization must be programmed. Intertwined circular constraints (e.g. complex hypercycles), even with negative and positive feedback, do not steer physicochemical reactions toward formal function or metabolic success. Complex hypercycles quickly and selfishly exhaust sequence and other phase spaces of potential metabolic resources. Unwanted cross-reactions are invariably ignored in these celebrated models. Formal rules pertain to uncoerced (physiodynamically indeterminate) voluntary behavior. Laws describe and predict invariant physicydynamic interactions. Constraints and laws cannot program or steer physicality towards conceptual organization, computational success, pragmatic benefit, the goal of integrated holistic metabolism, or life. The formal controls and regulation observed in molecular biology are unique. Only constraints, not controls, are found in the inanimate physical world. Cybernetics should be the corner stone of any definition of life. All known life utilizes a mutable linear digital material symbol system (MSS) to represent and record programming decisions made in advance of any selectable phenotypic fitness. This fact is not undone by additional epigenetic formal controls and multi-layered Prescriptive Information (PI) instantiated into diverse molecular devices and machines.

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*Sections from previously published peer-reviewed science journal papers [1-9] have been incorporated with permission into this chapter:

Introduction: Would control and regulation be necessary for protometabolism?

It would be hard to imagine any molecular biologist alive today who would question life's need for extensive control and regulation. The long-overlooked regulatory role of micro RNA's [10-13], peptides and very small proteins [14], for example, has dominated research in the last few years. The phrase "junk DNA" disappeared from the literature overnight.

Even in a theoretical protocell, any hint of a protometabolism would require the steering of biochemical pathways toward contribution to a productive holistic scheme [15]. The simplest pathways are usually quite conceptually complex. Each pathway leads to indispensable players in other pathways. These vital products must be delivered to the right place at the right time in the right form. All of the biochemical pathways need integration into interconnected cycles that contribute to the fulfillment of larger metabolic goals.

Says Tsokolov, "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." [15] Tsokolov points to the Belousov-Zhabotinsky (BZ) reaction as a possible model for chemical "systems" that might spontaneously develop autocatalytic feedback. He argues 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." [15]

But could mere chemical circular constraint feedback achieve formal "regulation" in the sense of fine-tuning homeostatic metabolism? We shall examine this question in great detail in section 9 of this chapter when we examine Tibor Ganti's model. For now we will just take issue with Tsokolov's use of the word "system" to describe mere circular feedback constraint. As discussed in previous chapters, mere circular constraints do not constitute formal control systems. Tsokolov's intuitive sense is quite correct that there must be negative and positive feedback *controls* that make regulation of metabolism possible. But circular constraints are not controls. Circular constraints alone cannot establish formal regulation to the end of optimizing function. Controls are needed. But controls are formal, not physicochemical. Controls must be purposefully chosen in pursuit of formal function.

The simplest protometabolic schemes are highly abstract, formally functional, and goal-oriented. The cooperation of participants is extensive, yet

highly measured. The required organization for even the simplest conceivable protolife is mind-boggling.

To make our models of spontaneous life-origin work, we continue to define down life to something that empirically never seems to come close to adding up to life. Whatever life is, one thing is for certain: it depends upon controls, not just mere physicydynamic constraints. Life never violates the laws of physics and chemistry. But the laws of physics and chemistry cannot generate the Prescriptive Information (PI)[6], controls and finely-tuned feedback *regulation* needed to organize and coordinate even the simplest conceivable protometabolism. Any Metabolism First model must first address the problem that chance and necessity cannot steer events toward pragmatic success. Chance and necessity cannot generate formal controls. Chance and necessity cannot pursue "usefulness." [1, 3-9, 16-20]

1. Emergence of spontaneous controls

The difference between mere self-ordering vs. bona fide organization has been made abundantly clear in the literature [1-4, 6-9, 19]. That difference has even been made clear specifically with reference to life-origin models [9]. The logic of the very notion of "self-organization" has even been challenged [9, 21]. No physical entity can "self-organize" itself into existence. An effect cannot cause itself. Organization is the effect of choice-contingent determinism, not physicydynamic determinism or chance.

Our physical central nervous systems did not organize themselves. Non-physical human consciousness does not even organize itself. Chomsky argued quite successfully that we are born with inherent rules of language [22], for example. Infant minds just find themselves with a certain degree of inherent, pre-existing organizational thought structure that pre-exists empirical learning [22, 23]. Logic theory, mathematical axioms and the rules of mathematical manipulations seem to predate *Homo sapiens'* consciousness altogether in the workings of cosmic physical force interactions. Mathematical laws and their governance of physical interactions predate our discovery and description of them. Underlying formalisms seems to organize every aspect of inanimate physicality even prior to any discussion of life.

Organization always requires steering a course through multiple logic gates. Chance and necessity cannot cohort to make purposeful choices [4, 7, 9, 18]. Dissipative structures can spontaneously self-order into momentary high-energy states. But dissipative structures cannot program, organize or compute sophisticated formal utility. The most highly self-ordered dissipative structure to spontaneously occur in nature is probably the tornado. Tornadoes do not organize anything. Tornadoes only destroy organization at every turn.

Tornados are themselves only self-ordered, not organized [9]. Referring to tornado formation as “self-organization” is a classic case of sloppy definition/terminology that should be altogether unacceptable in any science.

2. What specific natural *mechanisms* of emergence have been elucidated?

Before addressing specifically the self-organization of protometabolism, we need first to take a critical look at the pre-assumption of emergence of any functional “natural process mechanism.” What is a “mechanism”? “Mechanism” is a directed process, programmed procedure, technique, system, or component of a machine that achieves some pragmatic goal. “Mechanism” is a formal term, not a physicydynamic term. “Mechanism,” like the term “useful work,” has no place in pure naturalistic physics and chemistry. The concept of mechanism was simply high-jacked by philosophic naturalism. It was then bastardized to conform to materialistic metaphysical presuppositions.

Metaphysical naturalism presupposes that mass/energy alone is sufficient to explain everything. The etiology of “mechanism” from both Latin and Greek derives from the word “machine.” Metaphysical naturalism has never demonstrated the ability of physicydynamics and so-called “natural process” to produce nontrivial machines or sophisticated utilitarian mechanisms. Naturalism merely pre-assumes what it purports to have scientifically proven. In reality, no purely physicydynamic interactions have ever been able to generate a formal mechanism that yields nontrivial formal function. And no theoretical model of spontaneous emergence of machines or formal mechanism through natural process has ever been demonstrated to actually occur in nature without investigator involvement in experimental design (e.g., so-called “directed evolution” and “evolutionary algorithms,” both of which are self-contradictory non-sense terms. See below.).

Every case of supposed spontaneous self-organization ever published has in fact been a case of mere self-ordered cause-and-effect determinism, not self-organization. Wherever bona fide organization has been experimentally achieved, investigator involvement in the experimental design can always be identified hidden in the background information. More often than not, the steering and artificial selection are frankly acknowledged by the authors themselves right within Materials and Methods of the paper. No natural process tendency exists in inanimate nature to self-organize any utilitarian mechanism. Only experimenter desires and formal controls produce organization.

3. What *observations of spontaneous emergence exist in the literature?*

Many people would point to the experimental evidence of “directed evolution” and “evolutionary algorithms” in answer to this question. To understand why both of these fail to provide any evidence at all of spontaneous self-organization, we must return to a point made in Chapter 2, section 6.1. The choice of particular physical constraints is a formal enterprise, not a spontaneous physycodynamic interaction. The moment that initial conditions (constraints) are *chosen* in designing an experiment, those constraints immediately become formal controls. In such instances, nonphysical formalism has been introduced as a steering and controlling factor. What was supposed to model natural selection in fact models nothing more than artificial selection. Choosing constraints can constitute a very subtle form of “experimenter interference” (“investigator involvement”) in experimental design. The result creates the illusion of empirical support for self-organization and undirected achievement of utility.

The pursuit of potential function guides these choices at true decision nodes. And this pursuit takes place prior to the realization of any naturally selectable fitness. No living organism exists yet to differentially survive.

The most relevant cases of so-called “directed evolution” related to life-origin science are ribozyme engineering papers [24-33] [34, 35]. In these papers investigator involvement is apparent in the purposeful selection of which effluent to use in successive iterations. This creates the illusion of a spontaneous evolutionary pathway. But evolution has no goals or chosen pathways to goals. So-called “directed evolution” is a classic example of formal control. Directed evolution boils down to the purposeful selection of initial conditions *for each iteration* of a highly integrated experimental plan and goal. Such experiments begin with a highly touted initial random phase space of stochastic ensembles of oligoribonucleotides. But the succession of repeated runs uses only carefully selected candidates from each previous iteration [36-39]. The procedure is anything but random. And it is not just constrained by physico-dynamics. It is controlled by the formal choice contingency of the experimenter who pursues his or her own formally desired catalyst or self-replicant. The situation is reminiscent of Dawkins’ embarrassing “target phrase” in *The Blind Watchmaker* [40] evolutionary software. Such a process has absolutely nothing to do with evolution.

So-called “directed evolution” and “evolutionary algorithms” are both self-contradictory terms. If the process is directed, it is not evolution. Evolution has no goal. If the experiment really does model evolution, it is never directed. Similarly, algorithms are always formal processes or procedures un-

dertaken to achieve some function. This means they cannot possibly be evolutionary because evolution is blind to function and its pursuit. Natural selection simply favors the fittest already-programmed, already-living organisms.

The very experiments that were supposed to demonstrate inanimate self-organization invariably prove the opposite—the need for purposeful steering of physicydynamic events in order to achieve the desired formal function.

The result of oligoribonucleotide “evolution” experiments is typically attributed to trial and error. We fail to realize that “trial and error” is itself a telological process of investigating and testing for what might work (inefficient though it may be). The Markov or drunken-walk “process” is erroneously and illegitimately offered as proof of self-organization. This “evidence” is then used in support of the notion of spontaneous generation of life.

The fatal flaw in the notions of “drunken walks,” “directed evolution” and “evolutionary algorithms” is that each selection made by the experimenter is artificial, not natural. Each selection is made at the programming level *in pursuit of a potential function* that does not yet exist. The GS Principle (Genetic Selection Principle) is only affirmed, not falsified, by such engineering experiments [5, 41]. Natural selection favors only the fittest already-existing function. The inanimate environment possesses no ability to select for *potential* function. The inanimate environment cannot even select for *existing* isolated functions. Natural selection is nothing more than differential survival and reproduction of the fittest *already-living organisms*. [5, 41]. No differential survival of living organisms is involved in ribozyme engineering experiments. Directed evolution is nothing more than a string of purposeful logic gate or configurable-switch settings. Directed evolution is controlled, not constrained. The terms “directed” and “process” are quite legitimate in such laboratory procedures. The term “evolution” is not. Remove the hidden experimenter involvement (investigator interference) from Materials and Methods, and nothing of interest has ever been observed to spontaneously evolve. The reason is the loss of formal steering and control. When the experimenter is denied purposeful choices of which iteration to select and utilize at each step, no sustained uphill progress toward nontrivial functionality occurs.

The choice *for potential* function at the decision-node programming level, prior to the realization of any phenotypic fitness, is always artificial rather than natural. No natural mechanism exists for selection of not-yet-existent function or not-yet-existent phenotypes. Natural selection does not even select for isolated existing function. It selects only for the fittest already-programmed, already-living phenotypic *organisms*.

It is incumbent upon “true believers” in spontaneous self-organization out of inanimate physical interactions to demonstrate the same. It remains to

be seen whether any such observation has ever once been made in the history of ordinary human observation, let alone reported in scientific literature. Non-trivial organization is never observed to arise independent of purposeful steering, programming choices, and deliberate pursuits of potential function. Yes, the self-contradictory term "self-organization" is used extensively in scientific literature. But no observations of bona fide "self-organization" exist without behind the scenes purposeful steering of agents.

Theoretically, long RNA chains in an RNA sequence space (Ω) do have the potential to include a stochastic ensemble identical to a prescriptive informational RNA strand. No reason, exists, however, that an instructive polymer would be able to isolate itself out of Ω at the right place and time to instruct multiple formal functions or to cooperate with other random stands to organize metabolism.

A severe competition would have existed in any prebiotic environment for nucleoside resources. Ribonucleosides in a prebiotic environment are very difficult to activate. Even non-cyclic homopolymers of ribonucleosides in an aqueous solution are almost impossible to form. Only 3'5' bonds are acceptable. Only right-handed sugars can be used. Inanimate nature has no goal or straightforward means to distinguish between functional vs. non-functional bonds or the correct optical isomer of each ribose. The statistical prohibitive-ness becomes staggering even with the simplest protometabolic scenario.

Eigen and Schuster, along with others, have pointed out that sequence space and hypercyclic advance would have been greatly limited by competition for resources [42-50]. This would have applied particularly to a theoretical RNA world where the number and length of RNA strands is greatly limited. In non-heated aqueous solution, a maximum of eight to ten RNA mers can polymerize [51, 52]. Up to 55 mers can polymerize on montmorillonite [51], but these chains are homopolymers. These chains are produced only at the expense of information content. Homopolymers like polyadenosines contain essentially no Shannon uncertainty. Such high order could not have contributed to any random algorithmic programming of genes. Even if all the right primary structures (digital messages) mysteriously emerged spontaneously at the same time from Ω , "a cell is not a bag of enzymes." And, as we have pointed out several times, there would be no operating system to read these messages [53].

David Deamer's group showed that *RNA-like* polymers can be synthesized non-enzymatically from mononucleotides in lipid environments [54]. Chemical activation of the mononucleotides was not required. "Synthesis of phosphodiester bonds is driven by the chemical potential of fluctuating anhy-

drous and hydrated conditions, with heat providing activation energy during dehydration. In the final hydration step, the RNA-like polymer is encapsulated within lipid vesicles.”

Ernesto di Mauro’s group recently has been able to produce linear chains of 120 mers of either cAMP or cGMP, without templates or enzymes, through slow heating of activated cyclic monomers in aqueous solution [55]. So far, they have not had much success with pyrimidines. As with clay adsorption, however, these 100-mer strands are sorely lacking in Shannon uncertainty. The RNA stands are so highly ordered that no information-rich instructional PI could be instantiated into them. Genetics could not have been born out of homopolymers. Without functional base sequencing, no biopolymer would be able to instruct the organization of a cooperative metabolic network. Even if a random string *resembled* an informational strand, without a processing system and nanocomputers to read meaning into such strings according to preformed rules of interpretation, they could not contribute to an organized holistic metabolism. No PI exists in random–sequence nucleic acid *or* highly ordered homopolymers.

4. What predictions of emergence have been fulfilled?

Another major component of the scientific method is prediction fulfillment. Have any prediction fulfillments of the self-organization been observed to date? Normally we would emphasize “so far” when asking this question, especially when predictions of a new model have only recently been published. But what about when a theory has been well-published and exercised in scientific literature for 160 years? Macroevolution presupposes and requires the notion of self-organization. Macroevolution is purported to be the only organizing theory that makes any sense of biology. Theodosius Dobzhansky, for example, argued, “Nothing in biology makes sense except in the light of evolution.” But, tens of millions of species are presumed to have self-organized and self-programmed themselves into existence in the last 3.5 billion years. If every single species of living organism arose by duplication plus variation of DNA, wouldn’t one expect to have at least one prediction fulfillment of a bona fide new self-programmed organism in the last 160 years? Most species have already become extinct. But we should have seen at least dozens of new species originate in the last 10 years. Since there is often some question as to exactly what qualifies as a species, it is perhaps best to think in terms of new genera. How many new genera have been observed to evolve in the last 160 years? In truth, not one new genus can be cited as having self-programmed itself via “duplication plus variation.” Thus, not a single prediction fulfillment has been realized since the theory was proposed.

Worse yet, we are not just talking about the self-organization of a new kind of organism. We have not even seen a single prediction fulfillment of the self-organization of something as simple as a paper clip. A paper clip is nothing more than a long uniform cylinder of certain malleability bent back onto itself in such a way as to produce an efficient paper grasper. How many functional paper clips have spontaneously self-organized from the ground's iron ore in the history of human observation? Science is about *repeated* observation and prediction fulfillment. It is also about common sense. The notion of self-organization is not only rationally absurd, it is without both observation and prediction fulfillment.

In the absence of human thought and involvement, we simply have not seen any instances of spontaneous PI generation or formal organization of any kind. And we also have not seen any instances of chaos, probabilistic combinatorial complexity or catastrophe generating PI or formal organization either. Faith in the spontaneous emergence of true formal organization is blind belief.

No random number generator ever produced a nontrivial computational program. No reason or empirical justification exists to suppose that randomness could ever generate nontrivial organization. Random polyamino- acid strings do not fold into specifically needed functional proteins. Only one in 10^{77} stochastic ensembles fold into a functional protein fold of *any* kind [56, 57]. Even protometabolism requires folds of a certain kind at the right place and time. Nucleotide and codon sequencing must first be right in order to prescribe each needed protein fold. In the absence of sophisticated ribosomes (highly conceptually complex RNA and Protein complex machines), any protocell would have no access to proteins. Peptides, like ribozymes, are grossly inadequate to catalyze most of the needed integration functions necessary for even the most rudimentary metabolism and life.

It is not plausible to expect hundreds to thousands of random sequence polymers to all spontaneously and cooperatively self-organize into an amazingly efficient holistic metabolic network. Stochastic ensembles of ribonucleotides do not even generate ribozymes without extensive investigator involvement in experimental design [58]. Extensive artificial selection is required particularly in the choice of which iteration to pursue when starting from a random phase space.

Whereas plausibility used to be a purely qualitative and subjective impression, now, a quantitative cut-off of plausibility exists in science with which to evaluate extremely low probability notions. Plausibility can be measured weighing hypotheses of extremely low probability against highly relevant probabilistic resources [59]. But it is important to understand that The Universal Plausibility Metric (UPM) [60] is not a probability measure. It is a

measure of the *plausibility* of scientific hypotheses. A numerical inequality is provided by the Universal Plausibility Principle (UPP) whereby any chance hypothesis can be definitively falsified when its UPM metric of ξ is < 1 [60]. Both UPM and UPP pre-exist and are independent of any experimental design and data set. Every spontaneous generation model thus far published in peer-reviewed literature is definitively falsified by the Universal Plausibility Metric calculation and Principle (See Chapter 11).

5. Is the hypothesis of self-organized emergence falsifiable?

The notion of *emergence* can be traced back to Aristotle [61], but George H. Lewes was probably the first to define it in 1875: “The emergent is unlike its components insofar as these are incommensurable, and it cannot be reduced to their sum or their difference.” [62. pg. 412]. The idea of emergence blossomed in the 1920’s with contributions from C. Lloyd Morgan [63], Samuel Alexander [64], Roy Sellars [65], Henre Bergson [66], and Arthur O. Lovejoy [67]. Weak and strong versions of emergence exist [68], but life-origin models require convincing models of strong emergence. The whole is greater than the sum of its parts [69]. Novel functional qualities are believed to arise spontaneously from inanimate physical components [70-73]. First, second, third and now fourth order (Types I-IV) emergence are said to exist [74]. Heritable linear digital genetic prescription can produce three-dimensional protein molecular machines that bind, transport and catalyze metabolic integration. Strong and Type IV emergent theory together attempt to explain the source of these phenomena. Admits Mark Bedau, “Although strong emergence is logically possible, it is uncomfortably like magic.” [75].

If Virchow’s and Pasteur’s First Law of Biology (“All life must come from previously existing life”) is to be empirically falsified, direct observation of spontaneous generation is needed. In the absence of such empirical falsification, a plausible model of mechanism at the very least for both Strong and Type IV emergence (formal self-organization) is needed. Manfred Eigen [42-45, 76-83] and Tibor Ganti [84-88] have been leaders in the search for mechanisms of biologic emergence from abiotic environments. Shuster joined with Eigen to hypothesize hypercycles [48, 49, 89-94]. The Edge of Chaos [72, 73, 95-102] has been proposed as a possible source, though the description of all of the above models often seems more poetic or cartoon-like than real. Kauffman’s and Dawkin’s publications, for example, are often devoid of any consideration of the biochemical catastrophic realities that plague life-origin bench scientists [40, 71-73, 103-107].

Attempts to define complexity are on-going [95, 108-114]. Sequence complexity has been extensively studied, though far from exhaustively [8, 115-121].

Much debate has occurred over the relation of linear complexity to semantic information [122-134]. Some have attempted to reduce the information of linear digital prescription in genes to mere thermodynamics, combinatorial probabilism, and physicomplexity [71, 135-149]. Other investigators tend to view genetic information as literal and real [2, 8, 16, 150-155]. The special case of semiotic linear digital complexity has fostered the whole new field of Biosemiotics [2, 156-176].

Wild complexity claims are frequently espoused in the literature [5, 177-184]. How complexity relates to life has attracted innumerable papers [16, 185-191]. Systems Biology emphasizes the growing genomic and epigenetic complexity [192-194]. Attempts to deal with Behe's "irreducible complexity" [195] are appearing more often in scientific literature [196-200]. von Neumann [201] and Pattee [202-204] attempted to deal with the issue of Complementarity between the formal and physical aspects of complexity. Hoffmeyer and Emmeche have addressed the same basic problem with Code Duality [205, 206]. Stein described the different sciences of complexity [207]. Norris has researched hypercomplexity [208]; Garzon dealt with bounded complexity [209]; and Levins the limits of complexity [210]. Bennett originated Logical Depth and its relation to physical complexity [211]. More recently, better quality attempts have been made to explain the cybernetic nature of life naturalistically, from a teleonomic rather than teleological approach [70, 149, 212-239].

The naturalistic scientific community, and complexity theorists in particular, should collectively pursue falsification of the following null hypothesis: "Spontaneous nontrivial algorithmic optimization is never observed in nature apart from either 1) already existing biological prescriptive information, or 2) investigator involvement in experimental design." Falsification of this null hypothesis could be achieved with a single exception. But great care must be taken to expose hidden artificial controls. Such artificial controls are frequently programmed into supposed "evolutionary software" (e.g., the thoroughly embarrassing "target phrase" naively incorporated into Richard Dawkin's "evolutionary" program [40]).

An algorithm is a step-by-step process or procedure for solving a computational problem. Algorithms are formal enterprises requiring optimization. To optimize requires goals and intentionality. By definition, evolution cannot pursue goal-oriented procedures. Evolution is not a programmer of linear digital instructions and code[5]. Natural selection provides no mechanism for the practice of formal representationalism at the genetic level using tokens

in a material symbol system (MSS)[240]. Selection pressure cannot employ a Hamming “block code” of triplet codons to symbolically represent or signify each amino acid. Evolution is after-the-fact differential survival and reproduction of already-living phenotypic organisms. The fittest organisms survive and reproduce best. Less fit living organisms and populations tend to die out faster. Nothing in NeoDarwinism, punctuated equilibrium, or any recent modifications of evolutionary theory explains the initial programming of linear digital prescriptive information.

The latest and best discussion of emergence as it relates to life-origin is found in the October 2010 (No. 4-5) issue of *Origins of Life and Evolution of the Biosphere (OLEB)*, Vol. 40, on contingency vs. determinism and emergence [241-251]. After studying all of these papers, one is still left with no clear sense of how the notion of spontaneous emergence of self-organization might be falsified. If the notion is not falsifiable, it is not scientific.

As pointed out in “The capabilities of chaos and complexity,” [1, 18], stand-alone chaos, complexity and catastrophe should never be confused in our theories with what we intelligent humans do using abstract conceptual nonlinear dynamic models. ProtoBioCybernetics is not interested in:

- a. Modern-day human applications of non-linear dynamical systems theory
- b. Investigator involvement (artificial selection) in chaos, catastrophe, and complexity experimental designs.
- c. Information defined in terms of the reduced uncertainty of subjective “observers” and “knowers” who did not exist 3.5 billion years ago.

Life origin science wants to know the capabilities of stand-alone chaos and complexity before any animal consciousness existed. If all known life depends upon genetic instructions, how was the first linear digital prescriptive genetic information generated by natural process? How were all of the additional layers of biological PI generated and organized? Can chance and/or necessity produce genomic control and regulation schemes?

Can we falsify this null hypothesis?

NH1: Prescriptive Information (PI) [2, 6, 8] cannot emerge spontaneously from physicodynamics alone.

Only one example would suffice to accomplish falsification. Not one example has ever been provided.

As explained in previous chapters, PI refers not just to intuitive or semantic information, but specifically to linear digital *instructions* using a symbol system. 0's and 1's could be used. Letter selections from an alphabet could be used, as could A, G, T, or C from a phase space of four nucleotides. But any symbol system requires the use of agreed-upon formal arbitrary rules by the sender and receiver. PI can also consist of purposefully programmed logic gates that provide cybernetic controls, and configurable switch-settings that integrate formal circuits.

Can we falsify this null hypothesis?

NH2: Formal Organization [9] cannot emerge spontaneously from physiodynamics alone.

By "formal" we mean abstract, nonphysical, mental, choice-contingent, arbitrary, cognitive behavior that is typically goal- and function-oriented. Formal behavior is typically linguistic and/or mathematical. It entails representationalism, generalizations, and groupings into larger classes or categories (forms) rather than specific physical characteristics. Formal behavior is often computationally successful, integrated-circuit producing, or algorithmically optimizing behavior arising from bona fide decision node choices (not just "bifurcation points" (forks in the road) [4, 7].

Providing falsification of the H2 null hypothesis should be easy if physicalism is an accurate total description of objective reality. Yet to date in scientific literature, neither of these two null hypotheses, H1 or H2, has been falsified despite various restatements and appeals having been published in many peer-reviewed papers, academic book chapters, and conference lectures for over a decade now.

Both PI and formal organization are abstract, conceptual, choice-contingent, nonphysical entities [2-6, 8, 9, 16-18, 20, 53, 252]. Scientific endeavors to better understand cybernetic reality in nature are confronted with the uneasy suggestion of its transcendence over the physicality it controls. The chance and necessity of physiodynamics cannot program. At the heart of all naturalistic life-origin models lies the metaphysical pre-assumption of self-organization of inanimate physicality into sophisticated formal utility.

Cellular automata can only be created using algorithms. Algorithms are formal stepwise procedures based on discrete choices. Physiodynamics can-

not generate algorithms. Belief in the self-organization of formalisms from inanimate physicyodynamics is a non-falsifiable notion with zero empirical, prediction-fulfillment, and rational support.

6. What is Life?

Defining life has remained quite elusive despite many papers [253-261] and books [262, 263]. The negentropy concept of life was started by Schrödinger in his *What Is Life?* [264]. Brillouin promoted a physical concept of information and organization [265-267]. Rizotti considered defining life to be the central problem of biology [262].

In 2000 an international conference was called in an attempt specifically to refine a scientific definition of life [263]. All participants at this conference were required to submit in writing their definition of life. This author participated in and lectured at that conference. No two definitions of “life” were the same.

Our best attempts to reduce life to mere combinatorial complexity have often resulted in a rather laughable naiveté [16, 268]. One of the questions raised at that conference by this author was, “To what degree can we reduce life without loss of life?” [252]. If anything is holistic, it is life. Vivisection tends to kill the very life being studied. The pursuit of protocell theory, while necessary, can rapidly lead to a fatal cellular dissection. The reduction of life to something amenable to naturalistic modeling most often seems to result in non-life that is only proclaimed to be living.

In one of the most recent attempts to define life, Bedeau [269] promotes The Program-Metabolism-Container (PMC) model. This model emphasizes that life is a *functionally integrated* triad of chemical systems. The PMC model illustrates the Aristotelian approach to life rather than a Cartesian one. But, as usual, no naturalistic explanation is provided for the phenomenon of “program.” The problem is that “functional integration” is formally generated, not physicochemically generated.

Biophysicist Hubert P. Yockey makes the unique observation that “there is nothing in the physico-chemical world [apart from life] that remotely resembles reactions being determined by a sequence and codes between sequences. The existence of a genome and the genetic code divides living organisms from non-living matter.” (*Computers and Chemistry*, 24 (2000) 105-123). This may well constitute the most concise and parsimonious dichotomization of animacy from inanimacy available in the literature. Yet every definition of life published thus far seems laughably naïve and incomplete [253, 261]. The only significant move towards clarity seems to have come from acknowledging that all known life is cybernetic [255, 256]. But confusion still reigns as to the na-

ture of cybernetics and how nature could have produced steering controls. Howard Pattee sums up the problem quite nicely referring to the problem of symbolization needed to record any form of prescription: "The amazing property of symbols is their ability to control the lawful behavior of matter, while the laws, on the other hand, do not exert control over the symbols or their coded references."

We must remember, however, that the full complement of nucleic acid code, ribosomes, protein enzymes, regulatory peptides, polypeptides and microRNAs are still present immediately after cell death. Life, therefore, would appear not to be reducible to coded prescriptive information (instruction), nanocomputers and their operating systems alone. Formal algorithmic processes must be ongoing for life to be alive.

Decades ago we used to tell students, "Life is more than a bag of enzymes." "Life" is characterized by ongoing holistic, homeostatic, metabolic *processes*, optimized algorithmic function, and successful computation. Intra-cellular life is goal-oriented. This includes development, growth, and reproduction. Many of the key elements of life are related to *formal organization and control* rather than mere physical structure or chemical constraints and interactions. As we learned in earlier chapters, physiodynamics cannot possibly generate nonphysical formalisms. The role of formalism—purposeful decision-node choices needed to effect cybernetic controls—may well turn out to be the best single differentiating criteria of life from nonlife. Yockey's observation of the uniqueness of sequence and codes in life is just a subset of this formalism. *The ability to pursue and select for potential function is formal and unique to life. The use of representational symbol systems is also formal and unique to life.* This is true not only in terms of living organisms' actions. It is also true of the sub-cellular molecular biological programming and algorithmic processing that make life possible.

Neither the DNA molecule nor its instantiated instructions are themselves alive. We cannot underestimate the role that proteins, peptides, polypeptides and microRNAs play in their action *on* DNA, and all of the other processes (e.g., epigenetic) that make life alive. Life is a holistic, highly PI-controlled and regulated cybernetic metasystem of integrated processes and formal procedures. Life is an integrated cooperative concert.

A theoretical spontaneously self-replicating ribozyme, if one existed without extensive human engineering, would not be alive either. It might undergo self- or mutual-replication. It would likely accrue errors ("mutations") that we would label "evolution." But random self-replicative errors ("typographical errors") have never been shown to improve the PI of any instruction set or computational program. A self-replicative crude ribozyme with low

fidelity would most likely quickly lose its happenstantially acquired self-replicative trait. There is no good reason other than wish-fulfillment to expect the noise pollution that degrades its self-replicative function to prescribe other needed and even more sophisticated protometabolic functions. No empirical evidence, prediction fulfillments, or sound reason provides plausibility to the contention that a crudely self-replicative ribozyme would spontaneously improve, acquire additional metabolic capabilities, or become alive. In addition, no explanation has ever been provided by theorists as to how the initial self-replicative ribozyme would have acquired its initial PI syntax.

Gerald Joyce is generally credited with being the source of the so-called “NASA definition of life” [254]. This definition attempts to reduce life to little more than self-replication and mutability. But many questions have been raised pointing to the inadequacy of this definition. The imaginary primordial life upon which most investigators wish to base a definition of life currently has no empirical accountability. We tend to “define down” life to make our models of life-origin “work for us.” But at what point does our stripped-down definition of life cease to adequately describe life, let alone define life? The indivisible unit of life is the cell. No entity less than a cell has ever been found to be alive. We have not even observed non-living “chemotons”[88] spontaneously generate, let alone living ones.

A common misconception in life-origin literature is that being “far from equilibrium” is somehow synonymous with being alive. It is not. Both candle flames and tornadoes are “far from equilibrium” (FFE). But obviously neither is alive. A hurricane is a dissipative structure that is extremely far from equilibrium. A hurricane is not only not alive, it is not even organized! It is only self-ordered. *Organization requires purposeful choices in pursuit of formal utility.* Pure physiodynamics knows nothing of the kind. *Physiodynamics knows only cause-and-effect determinism that is oblivious to any goal or means of achieving pragmatism.* Thus, spontaneous inanimate self-ordering structure, just like order and pattern, has little to do with prescription of formal function.

Just because we *say* a minimal system is alive doesn’t make it alive. Often our imaginings of what life is are in reality quite sterile. Nothing clarifies our understanding and appreciation of life better than death. We are able to smell death much better than we are able to define life. Absolutely no confusion exists about the difference between life and death when we smell death. We have no problem differentiating life from nonlife when we view a loved one in a casket.

What is far more important than the definition of life is the question of what *prescribes* life? How could inanimacy have become animate? This tran-

sition had to occur prior to natural selection [5, 41]. Natural selection depends upon life already existing. Natural selection cannot explain life origin. Say Koch and Silver, "The moment of origin of The First Cell is in a fundamental sense also the moment of the start of Darwinian organismic evolution." [270, pg. 5]. Notice that evolution cannot even begin until after life exists. Few evolutionary biologists, unfortunately, appreciate, let alone verbalize this insight. Even micro-evolution cannot begin until after living reproducing organisms already exist. Environmental selection is nothing more than differential survival and reproduction of already-programmed, already-living, fittest organism. Selection pressure does not explain how inanimate nature assembled all the needed components, instruction set, algorithmic processes, coherent integration, and successful computations leading to life-creating and life-sustaining metabolism. Say Kock and Silver,

"The First Cell arose in the previously pre-biotic world with the coming together of several entities that gave a single vesicle the unique chance to carry out three essential and quite different life processes. These were: (a) to copy informational macromolecules, (b) to carry out specific catalytic functions, and (c) to couple energy from the environment into usable chemical forms. . . . but only when these three processes occurred together was life jump-started and Darwinian evolution of organisms began." [270, pg. 227]

Notice in this quote that "informational macromolecules" are just presupposed, not explained. The initial interest is merely in *copying* this information. Nobody seems to have a clue how this initial information that needs copying got written in the first place. For most of the last century life-origin science has centered on biochemistry and astrobiology. The problem of the source of initial formal Prescriptive Information has rarely been reluctantly acknowledged by metaphysical naturalism. The problem is in fact regularly swept under the rug. Evolution theory concerns itself only with the duplication and variation of already existing information.

The RNA World model provided hope of a catalytic biochemical system that could double as an information carrier. But to date no explanation has been provided as to how the sequencing of initial single positive strands of RNA could have acquired their functional sequence specificity needed for the strand to double back onto itself to form each secondary and tertiary catalytic structure.

The Gene Emergence Project and Origin of Life Prize have both sought to stimulate naturalistic models of how an initial linear digital symbol system

and bijection (mapping) code could have been generated by physiodynamics alone, without any formal components. First we need to explain how arbitrary rules were set up to achieve such formally organized systems. We then can begin to try to explain how the specific instructions for each function were written into each biopolymeric informational strand. The point of focus of research needs to be how symbols were selected at the molecular/genetic level and how configurable switches were set and linked together with rigid covalent bonds prior to any folding, and prior to any phenotypic function. These are the questions that best define life and its uniqueness. But they are formal questions that mere physiodynamic interactions cannot answer.

Thus far, all attempts to define life have proved unsuccessful. The following is an editable attempt to provide an irreducible *description* of existing life. It is taken with permission from the discussion section of the Origin of Life Prize website (www.lifeorigin.org). Listed are essential characteristics and criteria exhibited by *all known free-living organisms*. Minimal empirical life could be described as any system which from its own inherent set of biological instructions, however crude, can perform all ten of the following functions:

- 1) Delineate itself from its environment through the production and maintenance of membrane equivalent, most probably a rudimentary or quasi-active-transport membrane necessary for selective absorption of nutrients, excretion of wastes, and overcoming osmotic and toxic gradients,
- 2) Write, store, and pass along into progeny Prescriptive Information (PI; linear digital cybernetic programming) needed for organization; provide steering, control, regulation, and management for usable energy derivation and for needed metabolite production and function; symbolically encode and communicate functional messages through a transmission channel to a receiver/decoder/destination/effector; establish and operate a semiotic material symbol system (MSS [240, 271, 272]) using "messenger molecules;" integrate past, present and future time into its biological prescriptive information content,
- 3) Bring to pass through algorithmic processing the above recipe instructions into the production or acquisition of actual catalysts, coenzymes, cofactors, small RNAs, etc.; physically orchestrate the biochemical processes/pathways of metabolic reality; manufacture and maintain physical cellular architecture. The algorithmic processing of PI must also be inherited.
- 4) Capture, transduce, store, call up when needed, and carefully utilize energy for formal, useful work,

- 5) Actively self-replicate and eventually reproduce, not just passively polymerize or crystallize; pass along the apparatus and "know-how" for homeostatic metabolism and reproduction into progeny,
- 6) Self-monitor and repair its constantly deteriorating physical matrix of bioinstruction retention/transmission, and its architecture,
- 7) Develop and grow from immaturity to reproductive maturity,
- 8) Productively react to environmental stimuli. Respond in an efficacious manner that is supportive of survival, development, growth, and reproduction,
- 9) Possess relative phenotypic stability, yet sufficient genetic variability to allow for adaptation and potential evolution.
- 10) Be capable of dying

Differences of opinion still seem to prevail as to whether *Mycoplasma genitalium* is a free-living organism. Certainly the even simpler organism *Carsonella ruddii*, the endosymbiont of psyllids, is not free-living. But even *Mycoplasma genitalium* manifests nearly all (if not all) ten of the above characteristics. All classes of archaea, bacteria, and every other known free-living organism, meet *all* ten of the above criteria. Eliminate any one of the above ten requirements, and it remains to be demonstrated whether that system is or could be considered truly "alive." Simpler descriptions and definitions of life arising from abiogenic imaginings suffer from fictional departures from known responsible parameters of life. Purely metaphysical imperatives then elevate such imaginings to the level of scientific necessity: "The spontaneous generation of life HAD to have happened because here we are." What an absurd, embarrassing contention for any academic to seriously state! We just presuppositionally pre-assume what we purport to have proven. We have not proven the spontaneous generation of life. The original First Law of Biology, "all life must come from previously existing life," is still alive and well.

Ribozyme, polypeptide, protein, prion, riboprotein, aptamer and ligand conglomerations do not meet many of these minimal criteria of free-living life. Neither do viroids and viruses. Even in historical science, there must be some degree of empirical accountability to our theories. *Proposing a plausible mechanism that explains the origin of life must not consist of "defining down" the meaning and essence of the observable phenomenon of "life" to include "nonlife" in order to make our theories "work for us."* Any scientific life-origin theory must connect with "life" as we observe it (the "continuity principle"). Science will never be able to abandon its empirical roots in favor of purely theoretical conjecture. Science must also constantly guard itself against Kuhnian paradigm ruts. The fact that most scientists currently believe a cer-

tain model does not establish its veracity. But we must also be open-minded to the possibility that life has not always existed in the form that we currently observe. And we must take into consideration the limitations of any historical science where the observation of past realities is impossible.

7. Can a computer analogy be applied to life?

Recently the exaggerated claim has been made of the creation of synthetic life [272]. Anyone doubting the role of and necessity for PI in life should listen to Craig Venter's discussion of his own claims of having synthesized life:

<http://www.guardian.co.uk/science/video/2010/may/20/craig-venter-new-life-form>

The discussion only affirms the contention that "All known life is cybernetic." Venter's methodologies always start with what he calls "software." Says Donald E. Johnson (who holds Ph.Ds in both chemistry and Information/Computer Science), "Since all of the components used to manufacture Craig Venter's synthetic organism were produced by living organisms, Craig Venter's accomplishment was definitely not life from non-life." But Johnson agrees with Venter's cybernetic paradigm of life:

The DNA is equivalent to physical memory (RAM, ROM, disk) – the memory hardware. The genome is the memory content: the implemented prescriptive algorithm with its functional data. DNA is hardware. Genome is formal software instantiated into the material symbol system of DNA. Both hardware and software must be designed to have a working system. Any functional hardware is an implementation of a prescriptive algorithm. The control unit of a CPU, for example, can have the control algorithm implemented in hardware (electronics), firmware (microcode ROM), or software (writable control store). There are many aspects of the computing systems of life that are not yet known, such as how much of the operating system is "firmware" (designed into the hardware as an integral part of the instruction set) and how much is software (interpreted by the hardware)." [personal communication].

Johnson's insights are spelled out in great detail in his chapter in this anthology, in an excellent book entitled *Programming of Life* [273] and also in a book entitled *Probability's Nature and Nature's Probability (A call to scientific integrity)* [274].

Perhaps the DNA hardware is the concert of collective interaction of the DNA, body of proteins, peptides, polypeptides, ribosomes, and regulatory microRNAs of the cell. These players constitute the primary algorithmic processors in millions of nanocomputers in each cell. The linear digital prescription instantiated into nucleotide sequencing is a little like a Turing Tape, except that the multi-dimensional nature of genomics renders the Turing tape analogy far too simplistic. The rapidly unfolding added dimensions of biological PI include:

- Transcriptional editing
- reading DNA in both directions
- the non-protein-coding prescription of sRNAs by the anti-sense strand
- gene overlapping
- the assembling of gene fragments from multiple chromosomes
- the spatial grouping of related genes in the mass of chromosomes
- proof reading and error repair mechanisms
- the editing of post translational polyamino acid strings

The rapid growth of recognized multiple layers of PI only compound the sophistication of life's control mechanisms. To try to attribute all of these ingenious cybernetic innovations to mere "duplication plus variation (noise)" is nothing less than laughable.

The heuristic/operational value of using linguistic and computational analogies to describe genetic programming is widely accepted by naturalistic science. Some try to dismiss parallels with cybernetics as being merely metaphorical. The limits of the metaphor have been explored [141, 275-281].

Some investigators have questioned whether semantic information about phenotypic traits exists at all [143, 144, 154, 282-286]. Lwoff felt that we often take the genetic information and linguistic metaphors too far [287]. Others assert that the metaphor is misleading [71, 142-145, 288, 289]. Rocha [290, 291] seeks to explain formal self-organization and sign systems physcodynamically despite acknowledging the reality of Pattee's epistemic cut [292] and the need for semantic closure [204]. Others view genetic information as quite real [2, 4-6, 8, 20, 150-155], though not the sole key to understanding life.

The contention that biological programming is merely metaphorical and nothing more than a heuristic tool of molecular biology professors is simply not tenable. Linear digital prescription and the codon table both predate humans, their consciousness, and the very existence of metaphors. In addition, the entire field of computer science was inspired by molecular biology, not the

other way around. Turing [293], von Neumann [294], and Wiener [295, 296] all got most of their ideas, inspiration and understanding of cybernetic principles from observing the growing knowledge of Mendelian genetics, Watson and Crick's discovery, and various cellular control mechanisms. If what is known today about molecular biology had been known 40 years ago, computer science would have advanced far faster.

8. Astrobiological and multiverse considerations of life-origin

Few seem to think through the value, or lack thereof, of appealing to panspermia to overcome the scientific implausibility of spontaneous abiogenesis on earth. The age of the cosmos is estimated to be only three times that of the age of the earth. Of what value is a mere time factor of 3 in solving the statistical prohibitiveness of spontaneous generation on earth?

It is for good reason that many theorists have found it necessary to appeal to the purely metaphysical notion of "multiverse" to salvage any naturalistic hope of spontaneous life-origin. Multiverse models imagine that our universe is only one of perhaps countless parallel universes [297-299]. It could be argued that multiverse notions arose only in response to the severe time and space constraints arising out of Hawking, Ellis and Penrose's singularity theorems [300-302]. Solutions in general relativity involve singularities wherein matter is compressed to a point in space and light rays originate from a curvature. These theorems place severe limits on time and space since the Big Bang. Many of the prior assumptions of limitless time and sample space in naturalistic models were eliminated by the demonstration that time and space in the cosmos are quite finite, not infinite. For instance, we only have 10^{17} - 10^{18} seconds at most to work with in any responsible cosmological universe model since the Big Bang.

The notion of multiverse is literally "beyond physics and astronomy," the very meaning of the word "metaphysical." Appeals to the Multiverse worldview are becoming more popular in life-origin research as the statistical prohibitiveness of spontaneous generation becomes more incontrovertible in a finite Universe [303-305]. The problem is that belief in multiverse is no more scientifically responsible than appealing to superstition. If the only way we can prop up a supposedly scientific model is to appeal to the equivalent of superstition, the plausibility and worth of such a notion as a scientific theory are virtually non-existent. It has no place in science. Such notions belong only in science fiction novels.

The notion of multiverse has no observational support, let alone repeated observations. Empirical justification is completely lacking. It has no testability: no falsification potential exists. Multiverse imagination provides no pre-

diction fulfillments. The non-parsimonious construct of multiverse grossly violates the principle of Ockham's (Occam's) Razor [306]. No logical inference seems apparent to support the strained belief other than a perceived need to rationalize what we know is statistically prohibitive in the only universe that we *do* experience. Multiverse fantasies tend to constitute a back-door fire escape for when our models hit insurmountable roadblocks in the observable cosmos. When none of the facts fit our favorite model, we conveniently create imaginary extra universes that are more accommodating. This is not science. Science is interested in falsification within the only universe that science can address. Science cannot operate within mysticism, blind belief, or superstition. A multiverse may be fine for theoretical metaphysical models. But no justification exists for inclusion of this "dream world" in the observational science of astrophysics.

Even if multiple physical cosmoses existed, it is still a logically sound deduction that linear digital genetic instructions using a representational material symbol system (MSS) [291] cannot be programmed by the chance and/or fixed laws of physiodynamics [1-6, 8, 9, 17, 20, 41]. This fact is not only true of the physical universe, but would be just as true in any imagined physical multiverse. Physicality cannot generate nonphysical PI [6]. Physiodynamics cannot practice formalisms (The Cybernetic Cut) [4, 307]. Constraints cannot exercise formal control unless those constraints are themselves chosen to achieve formal function [1]. Environmental selection cannot select at the genetic level of arbitrary [308] symbol sequencing (e.g., the polymerization of nucleotides and codons) (The GS Principle [Genetic Selection Principle] [5]). Polymeric syntax (sequencing; primary structure) prescribes future (potential; not-yet-existent) folding and formal function of small RNAs and DNA. Symbol systems and configurable switch-settings can only be programmed with choice contingency, not chance contingency or fixed law, if nontrivial coordination and formal organization are expected [6, 9]. The all-important determinative sequencing of monomers is completed with rigid covalent bonds before any transcription, translation, or three-dimensional folding begins. Any editing of the initial sequence is highly refined and purposeful, not haphazard. It is only made possible by extremely sophisticated molecular machines and highly tailored helper molecules. Very specific microRNAs regulate real time transcription of newly edited PI in order to meet metabolic goals and needs. Thus, imagining multiple physical universes or infinite time does not solve the problem of the origin of *formal* (nonphysical) biocybernetics and biosemiosis using a linear digital representational symbol system. The source of PI [6, 309] in a metaphysically presupposed material-only world is closely related to the problem of gene emergence from physiodynamics alone. The latter hurdles remain

the number-one enigmas of life-origin research [310] when begun from purely physicalistic metaphysical presuppositions.

The main subconscious motivation behind multiverse conjecture seems to be, “Multiverse models can do anything we want them to do to make our models work for us.” We can argue Multiverse models ad infinitum because their potential is limitless. The notion of Multiverse has great appeal because it can explain everything (and therefore nothing). Multiverse models are beyond scientific critique, falsification, and prediction fulfillment verification. They are purely metaphysical.

Even if panspermia or the notion of multiverse were accurate descriptions of a presumed objective reality, the origin of the extraordinary array of nanohardware, firmware, wetware, operating systems, languages, software applications, and specific prescriptive genetic information (source code and ap) would remain unexplained. No fixed laws or formulae can program metabolic programming and computation. Instruction is abstract and conceptual. Yet instruction and control are exactly what genomes and epigenetics do. In addition to instructing, they actually perform and regulate through algorithmic processing the entire metabolic symphony. They achieve such integrated and holistic function through the same formal hardware and firmware implementation as our engineered computers. The only difference is that our finest computers seem archaic compared to the cybernetics found within any prokaryote, let alone eukaryotic and metazoan cell systems.

9. Mere replication is not the primary issue of life origin

Base-pairing is easy to explain. It is purely physicydynamic. It has nothing to do with the generation of the initial informational sequence. Base pairing cannot possibly program the algorithmic instructions instantiated into the positive informational DNA strand. Yet the particular sequencing of nucleotides and codons in the positive strand is not the only controller of life. As we shall see, the negative strand is filled with PI too. Multiple layers of PI exist that prescribe the integration and computation of cellular metabolism. How did the inanimate environment program linear digital instructions (PI) using a material symbol system (MSS) [271]? How did nature know how to write noise-correcting Hamming block codes (a fixed number of nucleotides *representing* each amino acid letter of the protein word) in order to reduce noise pollution in the Shannon channel? How did a purely physical nature encrypt and decrypt arbitrary (choice-contingent) coding? Coding and translation are formal functions, not physicydynamic interactions or phase changes. There is no direct physicochemical reaction between mRNA and amino acids. The mRNA is dynamically inert in its instructive role. The codon table is arbitrary

[5] and formal [4], not physical. It is also conceptually ideal [311-313]. The prescription is all in the physicomodynamically indeterminate sequencing of nucleotides and codons, not in chemical reactions [308]. Says Stegmann, "Aboutness, misrepresentation and storage are semantic properties, but such properties are not posited by ordinary biochemistry." [154]

Inanimate mass/energy interactions cannot generate computational solutions. Physicality cannot program integrated circuits. Only already-existing algorithms from a pool of "potential solutions" can be optimized. The inanimate physical environment cannot generate or optimize algorithms. Prior to an algorithm having computational function, no basis exists in nature for selection. So the question becomes, "How did *any* computational program arise in nature? Computation is formal, not physical. Natural selection cannot generate formalisms. It can only prefer *the results* of formal computations, and only then after those computations have generated living organisms [5]. What would be the basis of natural selection favoring a half-written program that does not yet compute? Even if a formal computational program were to somehow spontaneously arise, why would an inanimate environment value and preserve it? What would process it? No basis for recognition of computational success exists in a prebiotic environment.

The only basis for natural selection from Darwin to this day has been survival of the fittest already-living organisms. But *no* organism exists without hundreds of cooperating formal algorithms all organized into one holistic scheme. The more computational steps that are required to achieve integrative success and computational halting, the harder it becomes for an inanimate environment to explain optimization of any purposeful multi-step procedure. Nature doesn't pursue formal function. And the more algorithms that must be simultaneously optimized and integrated to achieve overall organization, the harder it is to explain homeostatic metabolism.

Natural selection resembles public consumption of the best available software. The programming details and methodology of production are of no interest to retail purchasers of software. Pre-programmed, bug-free, superior utility is the only criterion of public selection. The consumer plays no role whatever in the writing or refinement of the program's computational efficiency. The finished product with the best reputation, availability, and lowest cost becomes "the fittest species." Just as consumers are oblivious to how the best software was produced, natural selection is oblivious to how the fittest species was produced. Natural selection offers no explanation whatever for programming at the genetic level. Similarly, natural selection does not explain the derivation of the many cooperative computational processes leading up to the origin of metabolism or life.

10. The generation of initial Prescriptive Information is the real issue of life origin.

When it comes to life-origin studies, we have to address how symbol selection in the genetic material symbol system came about objectively in nature [2]. Life origin science must address the derivation of objective organization and control in the first protocells. How did prescriptive information and control arise spontaneously out of the chaos of a Big Bang explosion, primordial slime, vent interfaces in the ocean floor, or mere tide pools?

Self-ordering phenomena arise spontaneously out of phase space, but we have no evidence whatsoever of formal organization arising spontaneously out of physical chaos or self-ordering phenomena [9]. Chance and necessity has not been shown to generate the choice contingency required to program computational success, algorithmic optimization, or sophisticated function [53].

If chance and necessity, order and complexity cannot produce formal function, what does? *Selection for potential* utility is what optimizes algorithms, not randomness (maximum complexity), and not fixed law (highly patterned, unimaginative, redundant order with no information retaining potential). Utility lies in a third dimension imperceptible to chance and necessity (See Chapter 4, Figure 3). What provides this third dimension is when each token in a linear digital programming string is arbitrarily (non-physicodynamically, but formally) selected for potential function. The string becomes a cybernetic program capable of computation only when signs/symbols/tokens are purposefully *chosen* from an alphabet to *represent* utilitarian logic-gate and configurable-switch settings. The choice represented by that symbol can then be instantiated into physicality using a dynamically inert (physicodynamically decoupled or incoherent) [290, 291, 314] configurable switch setting. At the moment the switch knob seen in Chapter 2, Figure 1a is pushed, nonphysical formalism is instantiated into physicality. Then and only then does algorithmic programming become a physical reality. Once instantiated, we easily forget the requirement of instantiation of *formal instructions and controls* into the physical system to achieve engineering function. It was the formal voluntary pushing of the configurable switch knob in a certain direction that alone *organized* physicality [3, 4, 8, 9, 17, 20, 315].

Degrees of integration are achieved through *a combination* of configurable switch-settings which we can reduce to binary representation. The selection of any combination of multiple switch settings to achieve degrees of organization is called programming. But purposefully flipping the very first binary configurable switch is the foundation and first step of any form of programming. Programming requires purposeful choice contingency. The measure of

algorithmic compressibility requires a second dimension to visualize from the bidirectional vector graph of order vs. complexity. Only this 2nd dimension shows us where to place a sequence on the uni-dimensional vector graph showing varying degrees of order and complexity (see Figs 1 and 2 in Chapter 4, section 1).

Just as it takes an additional dimension to measure the algorithmic compressibility of a sequence, it takes a third dimension to measure the formal utility of any sequence. Formalisms are abstract, conceptual, representational, algorithmic, choice-contingent, nonphysical activities of mind. Formalisms typically involve steering toward utility. Formalisms employ controls rather than mere physiodynamic constraints. Formalisms require obedience to arbitrarily prescribed rules rather than forced laws. Physiodynamics cannot visualize, let alone quantify formal utility. No known natural process spontaneously writes an informational message string. As Howard Pattee has repeatedly pointed out, any type of measurement is a formal function that cannot be reduced to physiodynamics [204, 292, 316, 317]. We do not plug initial conditions into the formal equations known as "the laws of physics." We plug *symbolic representations* of those initial conditions into the laws of physics. Then we do formal mathematical manipulations of these equations to reliably predict physiodynamic interactions and outcomes. In this sense formalism governs physicality. The role that mathematics plays in physics is alone sufficient to argue for formalism's transcendence over physicality.

11. Mutations do not produce new Prescriptive Information

Stunningly, information has been shown *not* to increase in the coding regions of DNA with evolution. Mutations do not produce increased information. Mira et al [318] showed that the amount of coding in DNA actually decreases with evolution of bacterial genomes, not increases. This paper parallels Petrov's papers starting with [319] showing a net DNA loss with *Drosophila* evolution [319, 320]. Konopka [128] found strong evidence against the contention of Subba Rao et al [321, 322] that information increases with mutations. The information content of the coding regions in DNA does not tend to increase with evolution as hypothesized. Konopka also found Shannon complexity not to be a suitable indicator of evolutionary progress over a wide range of evolving genes. Konopka's work applies Shannon theory to known functional text.

Kok et al. [323] also found that information does not increase in DNA with evolution. As with Konopka, this finding is in the context of the change in mere Shannon uncertainty. The latter is a far more forgiving definition of information than that required for *Prescriptive Information* (PI) [6, 8, 9, 121].

It is all the more significant that mutations do not program increased PI. PI either instructs or directly produces formal function in an appropriately designed operating system and hardware. No increase in Shannon or PI occurs in duplication. What the previous chapters in this anthology show is that not even *variation* of the duplication produces new information, not even Shannon “information,” and certainly not PI. Variation can reduce sequence order, moving the sequence toward randomness and thereby increasing its bit content of Shannon uncertainty. But it cannot generate a nontrivial increase in Functional Information (FI), of which PI is a subset along with merely Descriptive Information (DI).

All of the above work correlates well with Weiss et al [324] finding only 1% deviation from randomness in coding regions. One cannot increase “information” (really “uncertainty”) very much when starting from only 1% deviation from randomness in the coding regions. Only 1% deviation from randomness is already nearly maxed out in uncertainty. How did a text that deviates only slightly from seeming randomness get *so* instructional and biofunctional? Clearly, mere combinatorial uncertainty is not going to explain the phenomenon of cybernetic genetic prescription.

No empirical evidence exists of mere variation ever having generated sophisticated PI, computational halting, or cybernetic integration of large numbers of pathways and cycles, or the achievement of metabolic goals.

12. Evolution requires a mutable genetic MSS separate from its phenotype

In all known current life, a Material Symbol System (MSS) using nucleotide and codon tokens is used to “represent” genetic instruction not only of the genes themselves, but of microRNAs that regulate those genes. Regulatory peptides and polypeptides much shorter than proteins are also prescribed by the DNA MSS. Many of the microRNAs are transcribed in reverse direction from the antisense strand unwound from the sense strand that prescribes the gene that instructs polyamino acid sequencing. Says Rocha, “Representations are used to, literally, materialize dynamical systems.” [291, pg. 15] “Syntax is required for communication in reproduction and for variation, both essential for natural selection and [open-ended evolution] OEE.” [291, pg. 14]

Physicist Howard Pattee explains that the matter symbol-problem is referred to as Philosophy’s “problem of reference.” Since all known life depends upon a MSS, one of the most fundamental questions of life-origin science is “How do symbols come to stand for material structures [325-327].” [204, pg. 11] Pattee also points out that,

Self-reference that has open-ended evolutionary potential is an autonomous closure between the dynamics (physical laws) of the material aspects and the constraints (syntactic rules) of the symbolic aspects of a physical organization. I have called this self-referent relation semantic closure [328] because only by virtue of the freely selected symbolic aspects of matter do the law-determined physical aspects of matter become functional (i.e., have survival value, goals, significance, meaning, self-awareness, etc). Semantic closure requires complementary models of the material and symbolic aspects of the organism. [204, pg. 9-10]

Pattee and Rocha have demonstrated in many publications [329-336] that open-ended evolution (OEE) is impossible without a linear digital genetic symbol system *that can mutate independent of the real-time living of the phenotypic organisms that harbor them*. Outwardly, the same relatively stable phenotypes exist and mate while tremendous modifications can be occurring in their genomes.

Ruiz-Mirazo, et al. agree with the necessity of "phenotype-genotype decoupling" for open-ended evolution to be possible [222, 260]. Open-ended evolution (OEE) requires a mutable genetic Material Symbol System (MSS) separate from its phenotype. The linear digital genome must be able to undergo substantive changes in its instructive PI sequencing without disrupting phenotypic viability. Says Howard Pattee, "Separate description and construction components are necessary for complex systems that can adapt and evolve." [337, pg 261]

In addition, Pattee points out that, "A necessary condition for hereditary transmission is a classification process or a many-to-one mapping." [338, pg. 410]. Three nucleotide selections are mapped to one amino acid prescription. This many-to-one bijection, along with codon redundancy with multiple codons all prescribing the same amino acid, affords degrees of freedom for the genome to vary during maintenance of phenotypic form and function. The many non-critical regions of nucleotide sequence also permits random drift without affecting genetic prescription of proteins. Nucleotide sequencing in DNA is now known to prescribe significantly more critical function than gene coding [339, 340]. This will greatly reduce the number and size of sections considered to be inconsequential.

Most mutations are silent. Genetic drift would be impossible without a genetic material symbol system (MSS) that can experience abundant variation within the same basic "phenotype" [240, 272, 291]. The phase space of potential new instructional sequences would be severely limited if genetic drift via

successive point mutations, duplications, inversions, and transpositions could not progress at the genetic level independent of initial phenotype realization.

How were metabolic unity and coherence established in any living organism? The lone answer that withstands careful scrutiny is, "Only algorithmically; only cybernetically; only computationally." All of these enterprises are nonphysical, choice-based, and formal. They depend upon sign/symbol/token use. The programming choices are represented by each physical nucleoside token selection. But the *selection* of each token itself is nonphysical. It is decoupled from physicydynamic determinism. It is a programming feature that requires freedom of selection at bona fide decision nodes. Only secondarily does each selection become instantiated into the physical medium of nucleotide syntax.

Prebiotic metabolic unity and coherence could only have been established through genetic algorithms, formal optimizations for utility, and cybernetic programming. Holistic protometabolism would have needed successful formal computation. The self-ordering processes of chaos theory can generate none of these formal interventions [2, 16, 53]. Despite abundant confusion in the literature, self-ordering is not self-organization. Physicydynamic constraint cannot steer toward formal function. Life cannot arise from order and monotonous patterning. It arises from cybernetic management mediated through linear digital programming. Life requires controls and constant regulation, not mere constraints. Four-way configurable switch settings (in the form of each nucleotide selection from among four options) must be set a certain way to prescribe integrated circuits and pragmatic computational success.

Howard Pattee argues that living matter is distinguished from nonliving matter by its ability to select particular initial conditions. But what aspect of physicality would enable it to "choose" its own initial conditions? The ability *to select constraints* prior to the unfolding of cause-and effect necessity amounts to *formal control*. The exercise of formal control over physicality traverses The Cybernetic Cut [4, 307] (Section 3.4) via the one-way Configurable Switch (CS) Bridge. The CS Bridge permits formalisms to be instantiated into physicality either through the selection of physical tokens or through the setting of physicydynamically indeterminate configurable switches and logic gates [4, 307]. No return traffic across the one-way CS Bridge occurs. Physicydynamics is never observed arbitrarily controlling formalisms. Formalisms require freedom from physical constraints.

The formal aspects of programming and Prescriptive Information (PI) using a Material Symbol System (MSS) must experience semantic closure with the physicydynamics into which the instructions and control mechanisms are instantiated. Says Pattee:

“I have called this self-referent relation semantic closure [328] because only by virtue of the freely selected symbolic aspects of matter do the law-determined physical aspects of matter become functional (i.e., have survival value, goals, significance, meaning, self-awareness, etc). Semantic closure requires complementary models of the material and symbolic aspects of the organism.” [204, pg. 9-10]

13. Evolution cannot *pursue* organization and *potential* protometabolic schemes

No natural basis exists for optimization of a ribozyme’s primary structure leading to folds that will only later enable self-replication, specific catalyses, or participation in *potential* protometabolic schemes.

As explained in Chapter 7 (The GS Principle), evolution cannot work at the molecular/genetic level of nucleic acid sequence prescription. And clearly chance and necessity cannot program functional nucleic acid sequence.

The genetic-like function of ribozymes is quite different from DNA’s prescription of function. Much of DNA’s prescription is indirect via codon sequencing, transcription, transcription-editing, micro RNA regulation, and translation into a completely different language. Ribozymal prescription, however, is direct. The sequencing of ribonucleotides directly determines secondary and tertiary folding and catalytic function. In addition, this form of linear digital prescription of folds and catalysis is only half of ribozymal capabilities. The other half consists of their direct genetic potential through self-replication.

The first problem, however, with evolution of both ribozymal functions is that neither function is selectable until after it exists. Catalytic function exists only after the ribozyme sequence polymerizes and folds. Any genetic-like function of ribozymes can only be realized through self-replication of the particular sequence optimized for self-replication. This is not the same sequence as one that would contribute best to some protometabolic function. Selection must take place at each decision node or logic gate of ribonucleotide selection. At that point in time (polymerization of the primary structure), no naturalistic (purely physicydynamic) basis for selection for function exists. Programming is finished before selection begins. Selection, therefore, is all or none.

Function must be optimized prior to natural selection by the prebiotic environment. But this leaves no basis for selection at each decision node—each nucleotide polymerization—where the sequence is established that determines folding and function. No evolutionary mechanism exists. It is just

imagined. What was supposed to be the scientific explanation of progress is found to be a fairy tale.

14. Conclusions

By what supposedly “natural” process did inanimate nature generate phenomena like

- 1) A genetic representational sign/symbol/token system?
- 2) Bona fide decision nodes and logic gates (as opposed to just random “bifurcation points”)?
- 3) Physicodynamically-indeterminate (dynamically inert, incoherent) [291] configurable switch-settings that instantiate functional “choices” into physicality?
- 4) formal operating system and the hardware on which to run such software?
- 5) an abstract encoding/decoding system jointly intelligible to both source and destination?
- 6) many-to-one Hamming “block codes” (triplet-nucleotide codons prescribing each single amino acid) used to reduce the noise pollution in the Shannon channel of genetic messages?
- 7) the ability to achieve functional computational success in the form of homeostatic metabolism?

All of these attributes of life are nonphysical and formal, not physical and natural. They cannot have a materialistic, naturalistic explanation.

References

1. Abel, D.L. 2009, The capabilities of chaos and complexity, *Int. J. Mol. Sci.*, 10, (Special Issue on Life Origin) 247-291 Open access at <http://mdpi.com/1422-0067/10/1/247>
2. Abel, D.L.; Trevors, J.T. 2006, More than metaphor: Genomes are objective sign systems, *Journal of BioSemiotics*, 1, (2) 253-267.
3. Abel, D.L. 2007, Complexity, self-organization, and emergence at the edge of chaos in life-origin models, *Journal of the Washington Academy of Sciences*, 93, (4) 1-20.
4. Abel, D.L. 2008, 'The Cybernetic Cut': Progressing from description to prescription in systems theory, *The Open Cybernetics and Systemics Journal*, 2, 234-244 Open access at www.bentham.org/open/tocsj/articles/V002/252TOCSJ.pdf
5. Abel, D.L. 2009, The GS (Genetic Selection) Principle, *Frontiers in Bioscience*, 14, (January 1) 2959-2969 Open access at <http://www.bioscience.org/2009/v14/af/3426/fulltext.htm>.
6. Abel, D.L. 2009, The biosemiosis of prescriptive information, *Semiotica*, 2009, (174) 1-19.
7. Abel, D.L. 2010, Constraints vs. Controls, *Open Cybernetics and Systemics Journal*, 4, 14-27 Open Access at <http://www.bentham.org/open/tocsj/articles/V004/14TOCSJ.pdf>.
8. Abel, D.L.; Trevors, J.T. 2005, Three subsets of sequence complexity and their relevance to biopolymeric information., *Theoretical Biology and Medical Modeling*, 2, 29 Open access at <http://www.tbiomed.com/content/2/1/29>.
9. Abel, D.L.; Trevors, J.T. 2006, Self-Organization vs. Self-Ordering events in life-origin models, *Physics of Life Reviews*, 3, 211-228.
10. Lagos-Quintana, M.; al., e. 2001, Identification of novel genes coding for small expressed RNA's, *Science*, 294, 853-858.
11. Lau, N.C.; Lim le, E.P.; Weinstein, E.G.; Bartel da, V.P. 2001, An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*, *Science*, 294, (5543) 858-62.
12. Misteli, T. 2002, A new continent in the RNA world., *Trends Cell Biol*, Feb 12, (2) 61-2.
13. Riddihough, G. 2002, The other RNA world., *Science*, May 17;296, (5571) 1259.
14. Dinger, M.E.; Pang, K.C.; Mercer, T.R.; Mattick, J.S. 2008, Differentiating Protein-Coding and Noncoding RNA: Challenges and Ambiguities, *PLoS Computational Biology*, 4, (11) e1000176.
15. Tsokolov, S. 2010, A Theory of Circular Organization and Negative Feedback: Defining Life in a Cybernetic Context, *Astrobiology*, 10, (10) 1031-1042.
16. Abel, D.L. 2002, Is Life Reducible to Complexity? In *Fundamentals of Life*, Palyi, G.; Zucchi, C.Caglioti, L., Eds. Elsevier: Paris, pp 57-72.
17. Abel, D.L. 2006 Life origin: The role of complexity at the edge of chaos, Washington Science 2006, Headquarters of the National Science Foundation, Arlington, VA
18. Abel, D.L. 2008 The capabilities of chaos and complexity, Society for Chaos Theory: Society for Complexity in Psychology and the Life Sciences, International Conference at Virginia Commonwealth University, Richmond, VA., Aug 8-10.
19. Abel, D.L. 2011, Moving 'far from equilibrium' in a prebiotic environment: The role of Maxwell's Demon in life origin. In *Genesis - In the Beginning: Precursors of Life, Chemical Models and Early Biological Evolution* Seckbach, J.Gordon, R., Eds. Springer: Dordrecht.
20. Abel, D.L.; Trevors, J.T. 2007, More than Metaphor: Genomes are Objective Sign Systems. In *BioSemiotic Research Trends*, Barbieri, M., Ed. Nova Science Publishers: New York, pp 1-15
21. Overman, D.L. 1997, *A Case Against Accident and Self-Organization*. Rowman and Littlefield Publishers, Inc.: New York.
22. Chomsky, N. 1957, *Syntactic Structures*. Mouton: The Hague/Paris.
23. Sullivan, A. 2000, The problem of naturalizing semantics", *Language & Communication* 20, (2 April) 179-196.
24. Cheng, L.K.L.; Unrau, P.J. 2010, Closing the Circle: Replicating RNA with RNA, *Cold Spring Harb Perspect Biol*.
25. Ma, W.; Yu, C.; Zhang, W.; Zhou, P.; Hu, J. 2009, The emergence of ribozymes synthesizing membrane components in RNA-based protocells, *Biosystems*.
26. Fedor, M.J. 2009, Comparative Enzymology and Structural Biology of RNA Self-Cleavage, *Annual Review of Biophysics*, 38, (1) 271-299.
27. Bagby, S.C.; Bergman, N.H.; Shechner, D.M.; Yen, C.; Bartel, D.P. 2009, A class I ligase ribozyme with reduced Mg²⁺ dependence: Selection, sequence analysis, and identification of functional tertiary interactions, *Rna*, 15, (12) 2129-46.
28. Szathmary, E. 2007, Coevolution of metabolic networks and membranes: the scenario of progressive sequestration, *Philos Trans R Soc Lond B Biol Sci*, 362, (1486) 1781-7.

29. Vorobjeva, M.; Zenkova, M.; Venyaminova, A.; Vlassov, V. 2006, Binary Hammerhead Ribozymes with Improved Catalytic Activity, *Oligonucleotides*, 16, (3) 239-252.
30. Szathmary, E. 2006, The origin of replicators and reproducers, *Philos Trans R Soc Lond B Biol Sci*, 361, (1474) 1761-76.
31. Shechner, D. 2009, Revealing the RNA World?, *Science*, 326, (5957) 1159-a-.
32. Link, K.H.; Breaker, R.R. 2009, Engineering ligand-responsive gene-control elements: lessons learned from natural riboswitches, *Gene Ther*, 16, (10) 1189-201.
33. Jonikas, M.A.; Radmer, R.J.; Laederach, A.; Das, R.; Pearlman, S.; Herschlag, D.; Altman, R.B. 2009, Coarse-grained modeling of large RNA molecules with knowledge-based potentials and structural filters, *RNA*, 15, (2) 189-99.
34. Paul, N.; Joyce, G.F. 2002, Inaugural Article: A self-replicating ligase ribozyme, *PNAS*, 99, (20) 12733-12740.
35. Hutton, T.J. 2002, Evolvable self-replicating molecules in an artificial chemistry, *Artif Life*, 8, (4) 341-56.
36. Ellington, A.D.; Szostak, J.W. 1990, In vitro selection of RNA molecules that bind specific ligands, *Nature*, 346, (6287) 818-822.
37. Tuerk, C.; Gold, L. 1990, Systematic evolution of ligands by exponential enrichment -- RNA ligands to bacteriophage - T4 DNA-polymerase, *Science*, 249, 505-510.
38. Robertson, D.L.; Joyce, G.F. 1990, Selection in vitro of an RNA enzyme that specifically cleaves single-stranded DNA, *Nature*, 344, 467-468.
39. Tuerk, C.; Gold, L. 1990, Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase, *Science*, 249, (4968) 505-10.
40. Dawkins, R. 1986, *The Blind Watchmaker*. W. W. Norton and Co.: New York.
41. Abel, D.L. The GS (Genetic Selection) Principle [Scirus Topic Page].
http://www.scitopics.com/The_GS_Principle_The_Genetic_Selection_Principle.html (Last accessed September, 2011).
42. Eigen, M. 1971, Self-organization of matter and the evolution of biological macromolecules, *Naturwissenschaften*, 58, (In German) 465-523.
43. Eigen, M. 1971, Molecular self-organization and the early stages of evolution, *Experientia*, 27, (11) 149-212.
44. Eigen, M. 1983, Life from the test tube?, *MMW Munch Med Wochenschr*, Suppl 1, S125-135.
45. Eigen, M. 1987, New concepts for dealing with the evolution of nucleic acids, *Cold Spring Harb Symp Quant Biol*, 52, 307-320.
46. Eigen, M. 1992, (with Winkler-Oswatitsch, R.), *Steps Toward Life: A Perspective on Evolution*. Oxford University Press: Oxford, UK.
47. Smith, J.M. 1979, Hypercycles and the origin of life, *Nature*, 280, (5722) 445-446.
48. Eigen, M.; Gardiner, W.C., Jr.; Schuster, P. 1980, Hypercycles and compartments. Compartments assists--but do not replace--hypercyclic organization of early genetic information, *J Theor Biol*, 85, (3) 407-411.
49. Eigen, M.; Schuster, P.; Sigmund, K.; Wolff, R. 1980, Elementary step dynamics of catalytic hypercycles, *Biosystems*, 13, (1-2) 1-22.
50. Schuster, P. 1984, Polynucleotide evolution, hypercycles and the origin of the genetic code, *Adv Space Res*, 4, (12) 143-151.
51. Ferris, J.P.; Hill, A.R., Jr.; Liu, R.; Orgel, L.E. 1996, Synthesis of long prebiotic oligomers on mineral surfaces, *Nature*, 381, (6577) 59-61.
52. Joyce, G.F.; Orgel, L.E. 1999, Prospects for understanding the origin of the RNA World. In *The RNA World*, Second ed.; Gesteland, R. F.; Cech, T. R. Atkins, J. F., Eds. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, pp 49-78.
53. Trevors, J.T.; Abel, D.L. 2004, Chance and necessity do not explain the origin of life, *Cell Biology International*, 28, 729-739.
54. Rajamani, S.; Vlassov, A.; Benner, S.; Coombs, A.; Olasagasti, F.; Deamer, D. 2008, Lipid-assisted synthesis of RNA-like polymers from mononucleotides, *Orig Life Evol Biosph*, 38, (1) 57-74.
55. Costanzo, G.; Pino, S.; Ciciriello, F.; Di Mauro, E. 2009, RNA: Processing and Catalysis: Generation of Long RNA Chains in Water, *J. Biol. Chem.*, 284, 33206-33216.
56. Axe, D.D. 2000, Extreme functional sensitivity to conservative amino acid changes on enzyme exteriors, *J Mol Biol*, 301, (3) 585-95.
57. Axe, D.D. 2004, Estimating the prevalence of protein sequences adopting functional enzyme folds, *J Mol Biol*, 341, (5) 1295-315.
58. Lohse, P.A.; Szostak, J.W. 1996, Ribozyme-catalysed amino-acid transfer reactions, *Nature*, 381, (6581) 442-4.
59. Dembski, W. 1998, *The Design Inference: Eliminating Chance Through Small Probabilities*. Cambridge University Press: Cambridge.
60. Abel, D.L. 2009, The Universal Plausibility Metric (UPM) & Principle (UPP), *Theor Biol Med Model*, 6, (1) 27
Open access at <http://www.tbiomed.com/content/6/1/27>.
61. Aristotle *Metaphysics*, Book 8.6.1045a:8-10 In.

62. Lewes, G.H. 1875, *Problems of Life and Mind (First Series)*. Trübner London, Vol. 2.
63. Morgan, C.L. 1925, *Emergent Evolution*. Henry Holt and Co.
64. Alexander, S. 1920, *Space, Time, and Deity* Kessinger Publishing reprint.
65. Sellars, R.W. 1922, *Evolutionary Naturalism*. Open Court, pdf file: Chicago.
66. Bergson, H. 1911, *Creative Evolution*. Henry Holt and Company.
67. Lovejoy, A.O. 2008, The meanings of 'emergence' and its modes, with an introduction by Alicia Juarrero and Carl A. Rubino, *E:CO*, 10, (1) 62-78.
68. Chalmers, D.J. 2006, Strong and Weak Emergence. In *The Re-Emergence of Emergence*, Clayton, P.Davies, P., Eds. Oxford Univeristy Press: Oxford.
69. Steels, L. 1991, Towards a Theory of Emergent Functionality In *Animals to Animats 1*, Meyer, J.-A.Wilson, S., Eds. MIT Press: Cambridge, Mass.
70. Corning, P.A. 2002, The Re-Emergence of "Emergence": A Venerable Concept in Search of a Theory, *Complexity*, 7, (6) 18-30.
71. Kauffman, S.A. 1993, *The Origins of Order: Self-Organization and Selection in Evolution*. Oxford University Press: Oxford.
72. Kauffman, S. 1995, *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity*. Oxford University Press: New York.
73. Kauffman, S.A. 2000, *Investigations*. Oxford University Press: New York.
74. Fromm, J. 2005, Types and Forms of Emergence, arXiv:nlin, 0506028v1 [nlin.AO].
75. Bedau, M.A. 1997, Weak emergence. In *Philosophical Perspectives: Mind, Causation, and World*, Tomberlin, J., Ed. Blackwell Publishers: pp 375-399.
76. Eigen, M. 1993, The origin of genetic information: viruses as models, *Gene*, 135, (1-2) 37-47.
77. Eigen, M. 1994, Selection and the origin of information, *Int Rev Neurobiol*, 37, 35-46; discussion 47-50.
78. Eigen, M.; Biebricher, C.K.; Gebinoga, M.; Gardiner, W.C. 1991, The hypercycle. Coupling of RNA and protein biosynthesis in the infection cycle of an RNA bacteriophage, *Biochemistry*, 30, (46) 11005-18.
79. Eigen, M.; de Maeyer, L. 1966, Chemical means of information storage and readout in biological systems, *Naturwissenschaften*, 53, (3) 50-7.
80. Eigen, M.; Winkler-Oswatitsch, R. 1981, Transfer-RNA: the early adaptor, *Naturwissenschaften*, 68, (5) 217-28.
81. Eigen, M.; Winkler-Oswatitsch, R. 1981, Transfer-RNA, an early gene?, *Naturwissenschaften*, 68, (6) 282-92.
82. Eigen, M.; Winkler-Oswatitsch, R. 1990, Statistical geometry on sequence space, *Methods Enzymol*, 183, 505-30.
83. Eigen, M.; Winkler-Oswatitsch, R.; Dress, A. 1988, Statistical geometry in sequence space: a method of quantitative comparative sequence analysis, *Proc Natl Acad Sci U S A*, 85, (16) 5913-7.
84. Gánti, T. 1975, Organization of chemical reactions into dividing and metabolizing units: the chemotons, *Biosystems*, 7, (1) 15-21.
85. Gánti, T. 1980, On the organizational basis of the evolution, *Acta Biol*, 31, (4) 449-59.
86. Gánti, T. 1997, Biogenesis itself, *J Theor Biol*, 187, (4) 583-93.
87. Gánti, T. 2002, On the early evolutionary origin of biological periodicity, *Cell Biol Int*, 26, (8) 729-35.
88. Gánti, T. 2003, *The Principles of Life*. Oxford University Press: Oxford, UK.
89. Eigen, M.; Gardiner, W.; Schuster, P.; Winkler-Oswatitsch, R. 1981, The origin of genetic information, *Sci Am*, 244, (4) 88-92, 96, et passim.
90. Eigen, M.; Gardiner, W.; Schuster, P.; Winkler-Oswatitsch, R. 1981, The origin of genetic information, laws governing natural selection of prebiotic molecules have been inferred and tested, making it possible to discover how early RA genes interacted with proteins and how the genetic code developed, *Scientific American*, 244, 88-118.
91. Eigen, M.; Schuster, P. 1977, The hypercycle. A principle of natural self-organization. Part A: Emergence of the hypercycle, *Naturwissenschaften*, 64, (11) 541-65.
92. Eigen, M.; Schuster, P. 1979, *The Hypercycle: A Principle of Natural Self Organization*. Springer Verlag: Berlin.
93. Eigen, M.; Schuster, P. 1981, Comments on "growth of a hypercycle" by King (1981), *Biosystems*, 13, (4) 235.
94. Eigen, M.; Schuster, P. 1982, Stages of emerging life--five principles of early organization, *J Mol Evol*, 19, (1) 47-61.
95. Waldrop, M.M. 1992, *Complexity*. Simon and Schuster: New York.
96. Kauffman, S.A.; Johnsen, S. 1991, Coevolution to the edge of chaos: coupled fitness landscapes, poised states, and coevolutionary avalanches, *J Theor Biol*, 149, (4) 467-505.
97. Bratman, R.L. 2002, Edge of chaos, *J R Soc Med*, 95, (3) 165.
98. Ito, K.; Gunji, Y.P. 1994, Self-organisation of living systems towards criticality at the edge of chaos, *Biosystems*, 33, (1) 17-24.
99. Munday, D. 2002, Edge of chaos, *J R Soc Med*, 95, (3) 165.
100. Forrest, S. 1999, Creativity on the edge of chaos, *Semin Nurse Manag*, 7, (3) 136-40.
101. Innes, A.D.; Campion, P.D.; Griffiths, F.E. 2005, Complex consultations and the 'edge of chaos', *Br J Gen Pract*, 55, (510) 47-52.

102. Mitchell, M.; Hraber, P.T.; Crutchfield, J.T. 1994, Dynamics, computation, and "the edge of chaos:" a re-examination. In *Complexity: Metaphors, Models, and Reality*, Cowan, G. P., D. and Melzner, D. , Ed. Addison-Wesley: Reading, MA pp 1-16.
103. Kauffman, S. 1970, Behavior of randomly constructed genetic nets. In *Towards a Theoretical Biology Vol. 3*, Waddington, C. H., Ed. Aldine Publishing Co.: Chicago, Vol. 3, p 18.
104. Kauffman, S. 2007, Beyond Reductionism: Reinventing the Sacred, *Zygon*, 42, (4) 903-914.
105. Kauffman, S.A. 2001, Prolegomenon to a general biology, *Ann N Y Acad Sci*, 935, 18-36; discussion 37-8.
106. Dawkins, R. 1976, *The Selfish Gene*. 2 ed., Oxford Univerisy Press: Oxford.
107. Dawkins, R. 1996, *Climbing Mount Improbable*. W.W. Norton & Co: New York.
108. Gell-Mann, M. 1995, What is complexity?, *Complexity*, 1, (1) 16-19.
109. Ricard, J. 2003, What do we mean by biological complexity?, *C R Biol.*, Feb;326, (2) 133-40.
110. van de Vijver, G.; van Speybroeck, L.; Vandevyvere, W. 2003, Reflecting on complexity of biological systems: Kant and beyond?, *Acta Biotheoretica*, 51, (2) 101-109.
111. Edelman, G.M.; Gally, J.A. 2001, Degeneracy and complexity in biological systems, *PNAS*, 98, 13763-13768.
112. Simon, H.A. 1962, The architecture of complexity, *Proc.Am. Philos. Soc.*, 106, 467-482.
113. Nicolis, G.; Prigogine, I. 1989, *Exploring Complexity*. Freeman: New York.
114. Badii, R.; Politi, A. 1997, *Complexity : hierarchical structures and scaling in physics*. Cambridge University Press: Cambridge ; New York.
115. Yockey, H.P. 1992, *Information Theory and Molecular Biology*. Cambridge University Press: Cambridge.
116. Yockey, H.P. 2005, *Information Theory, Evolution, and the Origin of Life*. Second ed., Cambridge University Press: Cambridge.
117. Lenski, R.E.; Ofria, C.; Collier, T.C.; Adami, C. 1999, Genome complexity, robustness and genetic interactions in digital organisms, *Nature*, 400, (6745) 661-4.
118. Lempel, A.; Ziv, J. 1976, On the complexity of finite sequences, *IEEE Trans Inform. Theory*, 22, 75.
119. Konopka, A.K.; Owens, J. 1990, Complexity charts can be used to map functional domains in DNA, *Genet Anal Tech Appl*, 7, (2) 35-8.
120. Adami, C.; Cerf, N.J. 2000, Physical complexity of symbolic sequences, *Physica D*, 137, 62-69.
121. Durston, K.K.; Chiu, D.K.; Abel, D.L.; Trevors, J.T. 2007, Measuring the functional sequence complexity of proteins, *Theor Biol Med Model*, 4, 47 Free on-line access at <http://www.tbiomed.com/content/4/1/47>.
122. Ebeling, W.; Jimenez-Montano, M.A. 1980, On grammars, complexity, and information measures of biological macromolecules, *Math. Biosciences*, 52, 53-71.
123. Gell-Mann, M.; Lloyd, S. 1996, Information measures, effective complexity, and total information, *Complexity*, 2, (1) 44-52.
124. Zurek, W.H. 1990, *Complexity, Entropy, and the Physics of Information*. Addison-Wesley: Redwood City, CA.
125. Farre, G.L.; Oksala, T. 1998, Emergence, Complexity, Hierarchy, Organization; Selected and Edited Papers from ECHO III. *Acta Polytechnia Scandinavica*;Espoo: Helsinki.
126. Rosen, R. 1985, On information and complexity. In *Complexity, Language, and Life: Mathematical Approaches*, Casti, J. L.Karlqvist, A., Eds. Springer: Berlin.
127. Zvonkin, A.K.; Levin, L.A. 1970, The complexity of finite objects and the development of the concepts of information and randomness by means of the theory of algorithms, *Russ. Math Serv*, 256, 83-124.
128. Konopka, A.K. 1984, Is the information content of DNA evolutionarily significant?, *J Theor Biol*, 107, (4) 697-704.
129. Konopka, A.K. 1985, Theory of degenerate coding and informational parameters of protein coding genes, *Biochimie*, 67, (5) 455-468.
130. Konopka, A.K. 1994, Sequences and Codes: Fundamentals of Biomolecular Cryptology. In *Biocomputing: Informatics and Genome Projects*, Smith, D., Ed. Academic Press: San Diego, pp 119-174.
131. Konopka, A.K. 2003, Systems biology: aspects related to genomics. In *Nature Encyclopedia of the Human Genome*, Cooper, D. N., Ed. Nature Publishing Group Reference: London, Vol. 5, pp 459-465.
132. Konopka, A.K. 2003, Information theories in molecular biology and genomics. In *Nature Encyclopedia of teh Human Genome*. Cooper, D. N., Ed. Nature Publishing Group Reference: London, Vol. 3, pp 464-469.
133. Konopka, A.K. 2003, Sequence complexity and composition. In *Nature Encyclopedia of the Human Genome. Vol. 5.*, Cooper, D. N., Ed. Nature Publishing Group Reference: London, pp 217-224.
134. Koonin, E.V.; Dolja, V.V. 2006, Evolution of complexity in the viral world: the dawn of a new vision, *Virus research*, 117, (1) 1-4.
135. Toussaint, O.; Schneider, E.D. 1998, The thermodynamics and evolution of complexity in biological systems, *Comp Biochem Physiol A Mol Integr Physiol*, 120, (1) 3-9.
136. Barham, J. 1996, A dynamical model of the meaning of information, *Biosystems*, 38, (2-3) 235-41.
137. Stonier, T. 1996, Information as a basic property of the universe, *Biosystems*, 38, (2-3) 135-40.
138. Boniolo, G. 2003, Biology without information, History and Philosophy of the Life Sciences, 25, 255-73.

139. Sarkar, S. 1996, Biological information: a skeptical look at some central dogmas of molecular biology. In *The Philosophy and History of Molecular Biology: New Perspectives*, Sarkar, S., Ed. Kluwer Academic Publishers: Dordrecht, pp 187-231.
140. Sarkar, S. 2000, Information in genetics and developmental biology: Comments on Maynard Smith, *Philosophy of Science*, 67, 208-213.
141. Sarkar, S. 2003, Genes encode information for phenotypic traits. In *Contemporary debates in Philosophy of Science*, Hitchcock, C., Ed. Blackwell: London, pp 259-274.
142. Stent, G.S. 1981, Strength and weakness of the genetic approach to the development of the nervous system, *Annu Rev Neurosci*, 4, 163-94.
143. Griffiths, P.E. 2001, Genetic information: A metaphor in search of a theory, *Philosophy of Science*, 68, 394-412.
144. Godfrey-Smith, P. 2003, Genes do not encode information for phenotypic traits. In *Contemporary Debates in Philosophy of Science* Hitchcock, C., Ed. Blackwell: London, pp 275-289.
145. Noble, D. 2002, Modeling the heart--from genes to cells to the whole organ, *Science*, 295, (5560) 1678-82.
146. Mahner, M.; Bunge, M.A. 1997, *Foundations of Biophilosophy*. Springer Verlag: Berlin.
147. Kitcher, P. 2001, Battling the undead; how (and how not) to resist genetic determinism. In *Thinking About Evolution: Historical Philosophical and Political Perspectives*, Singh, R. S.; Krimbas, C. B.; Paul, D. B. Beattie, J., Eds. Cambridge University Press: Cambridge, pp 396-414.
148. Chargaff, E. 1963, *Essays on Nucleic Acids*. Elsevier: Amsterdam.
149. Kurakin, A. 2010, Order without design, *Theoretical Biology and Medical Modelling*, 7, (1) 12.
150. Jacob, Francois 1974, *The Logic of Living Systems--a History of Heredity*. Allen Lane: London.
151. Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J.D. 2002, *Molecular Biology of the Cell*. Garland Science: New York.
152. Davidson, E.H.; Rast, J.P.; Oliveri, P.; Ransick, A.; Caletani, C.; Yuh, C.H.; Minokawa, T.; Amore, G.; Hinman, V.; Arenas-Mena, C.; Otim, O.; Brown, C.T.; Livi, C.B.; Lee, P.Y.; Revilla, R.; Rust, A.G.; Pan, Z.; Schilstra, M.J.; Clarke, P.J.; Arnone, M.I.; Rowen, L.; Cameron, R.A.; McClay, D.R.; Hood, L.; Bolouri, H. 2002, A genomic regulatory network for development, *Science*, 295, (5560) 1669-78.
153. Wolpert, L.; Smith, J.; Jessell, T.; Lawrence, P. 2002, *Principles of Development*. Oxford University Press: Oxford.
154. Stegmann, U.E. 2005, Genetic Information as Instructional Content, *Phil of Sci*, 72, 425-443.
155. Barbieri, M. 2004, Biology with information and meaning, *History & Philosophy of the Life Sciences*, 25, (2 (June)) 243-254.
156. Deely, J. 1992, Semiotics and biosemiotics: are sign-science and life-science coextensive? In *Biosemiotics: The Semiotic Web 1991*, Sebeok, T. A. Umiker-Sebeok, J., Eds. Mouton de Gruyter: Berlin/N.Y., pp 46-75.
157. Sebeok, T.A.; Umiker-Sebeok, J. 1992, *Biosemiotics: The Semiotic Web 1991*. Mouton de Gruyter: Berlin.
158. Hoffmeyer, J. 1997, Biosemiotics: Towards a new synthesis in biology, *European Journal for Semiotic Studies*, 9, 355-376.
159. Sharov, A. 1992, Biosemiotics. A functional-evolutionary approach to the analysis of the sense of evolution. In *Biosemiotics: The Semiotic Web 1991*, Sebeok, T. A. Umiker-Sebeok, J., Eds. Mouton de Gruyter: Berlin, pp 345-373.
160. Kull, K. 1999, Biosemiotics in the twentieth century: A view from biology., *Semiotica*, 127, 385-414.
161. Kawade, Y. 1996, Molecular biosemiotics: molecules carry out semiosis in living systems, *Semiotica*, 111, 195-215.
162. Barbieri, M. 2005, Life is 'artifact-making', *Journal of Biosemiotics*, 1, 113-142.
163. Pattee, H.H. 2005, The physics and metaphysics of Biosemiotics, *Journal of Biosemiotics*, 1, 303-324.
164. Salthe, S.N. 2005, Meaning in nature: Placing biosemiotics within pansemiotics, *Journal of Biosemiotics*, 1, 287-301.
165. Kull, K. 2005, A brief history of biosemiotics, *Journal of Biosemiotics*, 1, 1-36.
166. Nöth, W. 2005, Semiotics for biologists, *Journal of Biosemiotics*, 1, 195-211.
167. Artmann, S. 2005, Biosemiotics as a structural science, *Journal of Biosemiotics*, 1, 247-285.
168. Barbieri, M. 2006, Is the Cell a Semiotic System? In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed. Springer-Verlag New York, Inc. : Secaucus, NJ, USA
169. Barbieri, M. 2006, *Introduction to Biosemiotics: The New Biological Synthesis*. Springer-Verlag Dordrecht, The Netherlands.
170. Barbieri, M. 2007, Has biosemiotics come of age? In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed. Springer: Dordrecht, The Netherlands, pp 101-114.
171. Jämsä, T. 2006, Semiosis in evolution. In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed. Springer-Verlag New York, Inc. : Dordrecht, The Netherlands; Secaucus, NJ, USA
172. Hoffmeyer, J. 2006, Semiotic scaffolding of living systems. In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed. Springer-Verlag New York, Inc. : Dordrecht, The Netherlands; Secaucus, NJ, USA pp 149-166.

173. Kull, K. 2006, Biosemiotics and biophysics--The fundamental approaches to the study of life. In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed. Springer-Verlag New York, Inc. : Dordrecht, The Netherlands; Secaucus, NJ, USA
174. Barbieri, M. 2007, *The Codes of Life: The Rules of Macroevolution (Biosemiotics)*. Springer: Dordrecht, The Netherlands.
175. Barbieri, M. 2008, Biosemiotics: a new understanding of life, *Naturwissenschaften*, 95, 577-599.
176. Hodge, B.; Caballero, L. 2005, Biology, semiotics, complexity: An experiment in interdisciplinarity *Semiotica*, 2005, Proc. Natl. Acad. Sci. USA.
177. Adami, C.; Ofria, C.; Collier, T.C. 2000, Evolution of biological complexity, *Proc Natl Acad Sci U S A.*, 97, (9) 4463-8.
178. Goodwin, B. 1994, *How the Leopard Changed Its Spots: The Evolution of Complexity*. Simon and Schuster; Charles Scribner & Sons: New York.
179. Mao, C. 2004, The emergence of complexity: lessons from DNA, *PLoS Biol*, 2, (12) e431.
180. Holland, J.H. 1995, *Hidden Order: How Adaptation Builds Complexity*. Addison-Wesley: Redwood City, CA.
181. Mikulecky, D.C. 2001, The emergence of complexity: science coming of age or science growing old?, *Computers Chem.*, 25, 341-348.
182. Salthe, S.N. 1993, *Development and Evolution: Complexity and Change in Biology*. MIT Press: Cambridge, MA.
183. Pattee, H.H. 2000, Causation, Control, and the Evolution of Complexity. In *Downward Causation: Minds, Bodies, and Matter*, Andersen, P. B.; Emmeche, C.; Finnemann, N. O.Christiansen, P. V., Eds. Aarhus University Press: Aarhus, DK, pp 63-77.
184. Szathmary, E.; Smith, J.M. 1995, The major evolutionary transitions, *Nature*, 374, (6519) 227-32.
185. Sole, R.; Goodwin, B. 2000, *Signs of Life: How Complexity Pervades Biology*. Basic Books: New York.
186. Stano, P.; Luisi, P.L. 2007, Basic questions about the origins of life: proceedings of the Erice international school of complexity (fourth course), *Orig Life Evol Biosph*, 37, (4-5) 303-7.
187. Homberger, D.G. 2005, Ernst Mayr and the complexity of life, *J Biosci*, 30, (4) 427-33.
188. Pross, A. 2005, On the emergence of biological complexity: life as a kinetic state of matter, *Origins of life and evolution of the biosphere*, 35, (2) 151-66.
189. Bedau, M.A. 2003, Artificial life: organization, adaptation and complexity from the bottom up, *Trends in cognitive sciences*, 7, (11) 505-12.
190. Umerez, J. 2001, Howard Pattee's theoretical biology--a radical epistemological stance to approach life, evolution and complexity, *Biosystems*, 60, (1-3) 159-77.
191. Branca, C.; Faraone, A.; Magazu, S.; Maisano, G.; Migliardo, P.; Villari, V. 1999, Suspended life in biological systems. Fragility and complexity, *Ann N Y Acad Sci*, 879, 224-7.
192. Oltvai, Z.N.; Barabasi, A.L. 2002, Systems biology. Life's complexity pyramid, *Science*, 298, (5594) 763-4.
193. Rosen, R. 1977, Complexity and system description. In *Systems, Approaches, Theories, Applications*, Harnett, W. E., Ed. D. Reidel: Boston, MA.
194. Rosen, R. 1987, On Complex Systems, *Euro. J. of Operational Rsrch.*, 30, 129-134.
195. Behe, M.J. 1996, *Darwin's Black Box*. Simon & Shuster: The Free Press: New York.
196. Anderson, E. 2004, Irreducible complexity reduced: An integrated Approach to the complexity space, *PCID* 3.1.5 November, 1-29.
197. Thompson, C. 2004, Fortuitous phenomena: on complexity, pragmatic randomised controlled trials, and knowledge for evidence-based practice, *Worldviews Evid Based Nurs*, 1, (1) 9-17; discussion 18-9.
198. Pennock, R.T. 2003, Creationism and intelligent design, *Annu Rev Genomics Hum Genet*, 4, 143-63.
199. Aird, W.C. 2003, Hemostasis and irreducible complexity, *J Thromb Haemost*, 1, (2) 227-30.
200. Keller, E.F. 2002, Developmental robustness, *Ann N Y Acad Sci*, 981, 189-201.
201. von Neumann, J.; Burks, A.W. 1966, *Theory of Self-Reproducing Automata*. University of Illinois Press: Urbana,.
202. Pattee, H.H. 1978, The complementarity principle in biological and social structures, *Journal of Social and Biological Structure*, 1, 191-200.
203. Pattee, H.H. 1979, Complementarity vs. reduction as explanation of biological complexity, *Am J Physiol*, 236, (5) R241-6.
204. Pattee, H.H. 1995, Evolving Self-Reference: Matter, Symbols, and Semantic Closure, *Communication and Cognition-Artificial Intelligence*, 12, 9-28.
205. Hoffmeyer, J. 2000, Code-duality and the epistemic cut, *Ann N Y Acad Sci*, 901, 175-86.
206. Hoffmeyer, J. 2002, Code duality revisited, *SEED*, 2, 1-19.
207. Stein, D.L., Ed 1988, *Lectures in the Sciences of Complexity*. Addison-Wesley: Redwood City, CA.
208. Norris, V.; Cabin, A.; Zemirline, A. 2005, Hypercomplexity, *Acta Biotheor*, 53, (4) 313-30.
209. Garzon, M.H.; Jonoska, N.; Karl, S.A. 1999, The bounded complexity of DNA computing, *Bio Systems*, 52, (1-3) 63-72.

210. Levins, R. 1971, The limits of complexity. In *Biological Hierarchies: Their Origin and Dynamics*, Pattee, H., Ed. Gordon and Breach: New York.
211. Bennett, D.H. 1988, Logical depth and physical complexity. In *The Universal Turing Machine: a Half-Century Survey*, Herken, R., Ed. Oxford University Press: Oxford.
212. Yan, K.-K.; Fang, G.; Bhardwaj, N.; Alexander, R.P.; Gerstein, M. 2010, Comparing genomes to computer operating systems in terms of the topology and evolution of their regulatory control networks, *Proceedings of the National Academy of Sciences*, 107, (20) 9186-9191.
213. Corning, P.A.; Kline, S.J. 2000, Thermodynamics, information and life revisited, Part II: Thermoeconomics and Control information, *Systems Research and Behavioral Science*, 16, 453-482.
214. Corning, P.A.; Kline, S.J. 2000, Thermodynamics, information and life revisited, Part I: To be or entropy, *Systems Research and Behavioral Science*, 15, 273-295.
215. Deacon, T.W. 2010, 8. What's missing from theories of information? In *Information and the Nature of Reality: From Physics to Metaphysics*, Davies, P., Gregersen, N. H., Eds. Cambridge University Press: Cambridge, p In Press.
216. Wills, P.R. 2009, Informed generation: Physical origin and biological evolution of genetic codescript interpreters, *Journal of Theoretical Biology*.
217. Takeuchi, N.; Hogeweg, P. 2009, Multilevel Selection in Models of Prebiotic Evolution II: A Direct Comparison of Compartmentalization and Spatial Self-Organization, *PLoS Comput Biol*, 5, (10) e1000542.
218. Moreno, A.; Ruiz-Mirazo, K. 2009, The problem of the emergence of functional diversity in prebiotic evolution, *Biology and Philosophy*, 24, (5) 585-605.
219. Vesterby, V. 2008, *Origins of Self-organization, Emergence and Cause*. ISCE Publishing: Goodyear, Arizona.
220. Turner, S. 2008, Homeostasis, Complexity, and the Problem of Biological Design, *Emergence: Complexity and Organization*, 10.2.
221. Spinelli, G.; Mayer-Foulkes, D. 2008, New Method to Study DNA Sequences: The Languages of Evolution, *Nonlinear Dynamics, Psychology, and Life Sciences*, 12, (2, April) 133-151.
222. Ruiz-Mirazo, K.; Umeretz, J.; Moreno, A. 2008, Enabling conditions for 'open-ended evolution', *Biol Phil*, 23, (1) 67-85.
223. Raginsky, M.; Anastasio, T. 2008, Cooperation in self-organizing map networks enhances information transmission in the presence of input background activity, *Biological Cybernetics*, 98, (3) 195-211.
224. Juarrero, A.; Rubino, C.A. 2008, *Emergence, Complexity, and Self-Organization: Precursors and Prototypes*. ISCE Publishing: 17947 W. Porter Lane, Goodyear, AZ 85338.
225. Deacon, T.; Sherman, J. 2008, The Pattern Which Connects Pleroma to Creatura: The Autocell Bridge from Physics to Life. In *A Legacy for Living Systems: Gregory Bateson as Precursor to Biosemiotics* Hoffmeyer, J., Ed. Springer Netherlands: Netherlands.
226. Schiffmann, Y. 2007, Self-organization in and on biological spheres, *Prog Biophys Mol Biol*.
227. Lozneau, E.; Sanduloviciu, M. 2007, Self-organization scenario grounded on new experimental results, *Chaos, Solitons and Fractals*.
228. Gershenson, C. 2007, *Design and Control of Self-Organizing Systems*. Vrije Universiteit Brussel, Brussels.
229. Fishkis, M. 2007, Steps towards the formation of a protocell: the possible role of short peptides, *Orig Life Evol Biosph*, 37, (6) 537-53.
230. Ruiz-Mirazo, K.; Moreno, A. 2006, On the origins of information and its relevance for biological complexity, *Biological Theory*, 1, (3) 227-229.
231. Moreno, A.; Ruiz-Mirazo, K. 2006, The maintenance and open-ended growth of complexity in nature: information as a decoupling mechanism in the origins of life. . In *Rethinking Complexity* Capra, F.; Sotolongo, P.; Juarrero, A. van Uden, J., Eds. ISCE Publisher: pp 55-72.
232. Kurakin, A. 2006, Self-organization versus Watchmaker: molecular motors and protein translocation., *Biosystems* 84, (1) 15-23.
233. Jacob, E.B.; Shapira, Y.T., Alfred I. 2006, Seeking the foundations of cognition in bacteria: From Schrödinger's negative entropy to latent information, *Physica A*, 359, 495-524.
234. Humphreys, P. 2006, Self-Assembling Systems *Philosophy of Science*, 73, 595-604.
235. Gabora, L. 2006, Self-Other Organization: Why early life did not evolve through natural selection, *J Theor Biol*, 241, (3) 443-450.
236. Feltz, B.; Crommelinck, M.; Goujon, P. 2006, *Self-organization and emergence in life sciences*. Springer: Dordrecht.
237. Deacon, T.W.; Sherman, J. 2006, How teleology emerged: Bridging the gap from physics to life.
238. Deacon, T.W.; Cashman, T.; Sherman, J. 2006, Disembodiment and Intentionality. Disembodiment: Absence as the root of intentionality. In *Embodiment*.
239. Deacon, T.W. 2006, Reciprocal linkage between self-organizing processes is sufficient for self-reproduction and evolvability, *Biological Theory*, 1, (2) 136-149.

240. Rocha, L.M. 2000, Syntactic autonomy: or why there is no autonomy without symbols and how self-organizing systems might evolve them, *Annals of the New York Academy of Sciences*, 207-223.
241. Luisi, P.L. 2010, Contingency and Determinism in the origin of life, and elsewhere, *OLEB*, 40, (4-5 October) 356-361.
242. Mitchell, S.D. 2010, Determinism vs. Contingency: A false dichotomy, *OLEB*, 40, (4-5 October) 361-362.
243. Pohorille, A. 2010, Was the emergence of life on earth a likely outcome of chemical evolution?, *OLEB*, 40, (4-5) 362-365.
244. Norris, V.; Delaune, A. 2010, Contingency vs. Determinism, *OLEB*, 40, (4-5) 365-370.
245. Bich, L.; Bocchi, G.; Damiano, L. 2010, An epistemology of Contingency: Chance and Determinism at the origin of life, *OLEB*, 40, (4-5) 370-375.
246. Moya, A. 2010, Godel, biology and emergent properties, *OLEB*, 40, (4-5) 375-377.
247. Pizzarello, S. 2010, The chemistry that preceded life's origin: When is an evolutionary story an emergent story?, *OLEB*, 40, (4-5) 378-380.
248. Kauffman, S.A. 2010, On emergence, *OLEB*, 40, (4-5) 381-383.
249. Hanczyc, M.; Ikegami, T. 2010, Emergence of self-movement as a precursor to Darwinian evolution, *OLEB*, 40, (4-5) 383-384.
250. Pohorille, A. 2010, Emerging Properties in the origins of life and Darwinian evolution, *OLEB*, 40, (4-5) 384-386.
251. Norris, V.; Grondin, Y. 2010, Emergence, *OLEB*, 40, (4-5) 386-391.
252. Abel, D.L. 2000 To what degree can we reduce "life" without "loss of life"?, Workshop on Life: a satellite meeting before the Millennial World Meeting of University Professors, Modena, Italy,
253. Cleland, C.E.; Chyba, C.F. 2002, Defining 'life', *Origins of life and evolution of the biosphere*, 32, (4) 387-93.
254. Joyce, G.F. 1994, *Origins of Life: The Central Concepts see Forward*. Jones and Bartlett: Boston, MA.
255. Korzeniewski, B. 2001, Cybernetic Formulation of the Definition of Life, *Journal of Theoretical Biology*, 209, (3) 275-286.
256. Korzeniewski, B. 2005, Confrontation of the cybernetic definition of a living individual with the real world, *Acta Biotheor*, 53, (1) 1-28.
257. Lahav, N. 1985, The synthesis of primitive 'living' forms: definitions, goals, strategies and evolution synthesizers, *Orig Life Evol Biosph*, 16, (2) 129-49.
258. Neelson, K.H.; Tsapin, A.; Storrie-Lombardi, M. 2002, Searching for Life in the Universe: unconventional methods for an unconventional problem, *Int Microbiol*, 5, 223-230.
259. Pereto, J. 2005, Controversies on the origin of life, *Int Microbiol*, 8, (1) 23-31.
260. Ruiz-Mirazo, K.; Pereto, J.; Moreno, A. 2004, A universal definition of life: autonomy and open-ended evolution, *Orig Life Evol Biosph*, 34, (3) 323-46.
261. Tsokolov, S.A. 2009, Why Is the Definition of Life So Elusive? Epistemological Considerations, *Astrobiology*, 9, (4) 401-412.
262. Rizzotti, M. 1996, *Defining Life: The Central Problem in Theoretical Biology*. University of Padova Press: Padova, p 208.
263. Palyi, G.; Zucchi, C.; Caglioti, L. 2002, *Fundamentals of Life*. Elsevier: Paris.
264. Schrödinger, E. 1944, *What is Life: The Physical Aspect of the Living Cell*. Cambridge Univ. Press: Cambridge.
265. Brillouin, L. 1953, The negentropy principle of information, *Journal of Applied Physics*, 24, 1153.
266. Brillouin, L. 1962, *Science and Information Theory*. 2nd ed., Academic Press: New York.
267. Brillouin, L. 1990, Life, thermodynamics, and cybernetics. In *Maxwell's Demon, Entropy, Information, and Computing*, Leff, H. S.Rex, A. F., Eds. Princeton University Press: Princeton.
268. Abel, D.L. 2000 Is Life Reducible to Complexity?, Workshop on Life: a satellite meeting before the Millennial World Meeting of University Professors, Modena, Italy,
269. Bedau, M.A. 2010, An Aristotelian Account of Minimal Chemical Life, *Astrobiology*, 10, (10) 1011-1020.
270. Koch, A.L.; Silver, S. 2005, The first cell, *Adv Microb Physiol*, 50, 227-59.
271. Rocha, L.M. 1997, *Evidence Sets and Contextual Genetic Algorithms: Exploring uncertainty, context, and embodiment in cognitive and biological systems*. State University of New York, Binghamton.
272. Rocha, L.M. 1998, Selected self-organization and the semiotics of evolutionary systems. In *Evolutionary Systems: Biological and Epistemological Perspectives on Selection and Self-Organization*, Salthe, S.; van de Vijver, G.Delpos, M., Eds. Kluwer: The Netherlands, pp 341-358.
273. Johnson, D.E. 2010, *Programming of Life*. Big Mac Publishers: Sylacauga, Alabama.
274. Johnson, D.E. 2010, *Probability's Nature and Nature's Probability (A call to scientific integrity)*. Booksurge Publishing: Charleston, S.C.
275. Konopka, A.K. 2002, Grand metaphors of biology in the genome era, *Computers & Chemistry*, 26, 397-401.
276. Lackoff, G.; Johnson, M. 1980, *Metaphors We Live By*. University of Chicago Press: Chicago, IL.
277. Lackoff, G. 1993, The contemporary theory of metaphor. In *Metaphor and Thought, 2nd Edition*, Ortony, A., Ed. Cambridge University Press: Cambridge, pp 11-52.

278. Fiumara, G.C. 1995, *The Metaphoric Process: Connections Between Language and Life*. Rutledge: London.
279. Torgny, O. 1997, *Metaphor--A Working Concept*. KTH, Royal Institute of Technology. CID: Stockholm, Sweden.
280. Rosen, R. 1993, Bionics revisited. In *The Machine as a Metaphor and Tool*, Haken, H.; Karlqvist, A.Svedin, U., Eds. Springer-Verlag: Berlin, pp 87-100.
281. Emmeche, C.; Hoffmeyer, J. 1991, From language to nature: The semiotic metaphor in biology, *Semiotica*, 84, 1-42.
282. Atlan, H.; Koppel, M. 1990, The cellular computer DNA: program or data, *Bulletin of Mathematical Biology*, 52, (3) 335-348.
283. Maynard Smith, J. 2000, The concept of information in biology, *Philosophy of Science*, 67, (June) 177-194 (entire issue is an excellent discussion).
284. Moss, L. 2003, *What Genes Can't Do*. MIT Press: Cambridge, MA.
285. Sterelny, K.; Smith, K.; Dickison, M. 1996, The extended replicator, *Biology and Philosophy*, 11, 377-403.
286. Wheeler, M. 2003, Do genes code for traits? In *Philosophic Dimensions of Logic and Science: Selected Contributed Papers from the 11th International Congress of Logic, Methodology, and Philosophy of Science*, Rojszczak, A.; Cachro, J.Kurczewski, G., Eds. Kluwer: Dordrecht, pp 151-164.
287. Lwoff, A. 1962, *Biological Order*. MIT Press: Cambridge, MA.
288. Kay, L. 2000, *Who Wrote the Book of Life? A History of the Genetic Code*. Stanford University Press: Stanford, CA.
289. Keller, E.F. 2000, Decoding the genetic program. In *The Concept of the Gene in Development and Evolution*, Beurton, P.; Falk, R.Rheinberger, H.-J., Eds. Cambridge University Press: Cambridge, pp 159-177.
290. Rocha, L.M.; Hordijk, W. 2005, Material representations: from the genetic code to the evolution of cellular automata, *Artif Life*, 11, (1-2) 189-214.
291. Rocha, L.M. 2001, Evolution with material symbol systems, *Biosystems*, 60, 95-121.
292. Pattee, H.H. 1995, Artificial Life Needs a Real Epistemology. In *Advances in Artificial Life* Moran, F., Ed. Springer: Berlin, pp 23-38.
293. Turing, A.M. 1936, On computable numbers, with an application to the *entscheidungs problem*, *Proc. Roy. Soc. London Mathematical Society*, 42, (Ser 2) 230-265 [correction in 43, 544-546].
294. von Neumann, J. 1950, Letter to physicist George Gamow (first scientist to elucidate *triplet* codons) on July 25, 1950. Cited by Steve J. Heims in "John von Neumann and Norbert Wiener: *From Mathematics to the Technologies of Life and Death*," Cambridge, MA, MIT Press, 1980. In.
295. Wiener, N. 1948, *Cybernetics*. J. Wiley: New York.
296. Wiener, N. 1961, *Cybernetics, its Control and Communication in the Animal and the Machine*. 2 ed., MIT Press: Cambridge.
297. Barrau, A. 2007, Physics in the multiverse. In *CERN Courier*, Vol. December.
298. Carr, B. 2007, *Universe or Multiverse?* Cambridge University Press: Cambridge.
299. Garriga, J.; Vilenkin, A. 2008, Prediction and explanation in the multiverse. In *Phys.Rev.D* 77:043526,2008.
300. Hawking, S.; Ellis, G.F.R. 1973, *The Large Scale Structure of Space-Time*. Cambridge University Press. : Cambridge.
301. Hawking, S. 1988, *A Brief History of Time*. Bantam Books: New York.
302. Hawking, S.; Penrose, R. 1996, *The Nature of Space and Time*. Princeton U. Press: Princeton, N.J.
303. Axelsson, S. 2003, Perspectives on handedness, life and physics, *Med Hypotheses*, 61, (2) 267-74.
304. Koonin, E.V. 2007, The Biological Big Bang model for the major transitions in evolution, *Biol Direct*, 2, 21.
305. Koonin, E.V. 2007, The cosmological model of eternal inflation and the transition from chance to biological evolution in the history of life, *Biol Direct*, 2, 15.
306. Vítányi, P.M.B.; Li, M. 2000, Minimum Description Length Induction, Bayesianism and Kolmogorov Complexity, *IEEE Transactions on Information Theory*, 46, (2) 446 - 464.
307. Abel, D.L. The Cybernetic Cut [Scirus Topic Page]. http://www.scitopics.com/The_Cybernetic_Cut.html (Last accessed Sept, 2011).
308. Stegmann, U.E. 2004, The arbitrariness of the genetic code, *Biology and Philosophy*, 19, (2) 205-222.
309. Abel, D.L. Prescriptive Information (PI) [Scirus Topic Page]. http://www.scitopics.com/Prescriptive_Information_PI.html (Last accessed September, 2011).
310. Origin of Life Science Foundation, I. Origin of Life Prize. <http://www.lifeorigin.org>
311. Bradley, D. 2002, Informatics. The genome chose its alphabet with care, *Science*, 297, (5588) 1789-1791.
312. Freeland, S.J.; Hurst, L.D. 1998, The genetic code is one in a million, *Journal of Molecular Evolution*, 47, 238-248.
313. Itzkovitz, S.; Alon, U. 2007, The genetic code is nearly optimal for allowing additional information within protein-coding sequences, *Genome Res*, 17, (4) 405-12.
314. Rocha, L.M. 2001, The physics and evolution of symbols and codes: reflections on the work of Howard Pattee, *Biosystems*, 60, 1-4.

315. Allweis, C. 1988, Proposal for APS-IUPS convention for diagraming physiological mechanisms, *Am J Physiol*, 254, (5 Pt 2) R717-26.
316. Pattee, H.H. 1989, The measurement problem in artificial world models, *Biosystems*, 23, (2-3) 281-9; discussion 290.
317. Pattee, H.H. 2007, Laws, constraints, and the modeling relation--History and interpretations, *Chemistry & Biodiversity*, 4, 2272-2295.
318. Mira, A.; Ochman, H.; Moran, N.A. 2001, Deletional bias and the evolution of bacterial genomes, *Trends Genet*, 17, (10) 589-96.
319. Petrov, D.A.; Chao, Y.C.; Stephenson, E.C.; Hartl, D.L. 1998, Pseudogene evolution in *Drosophila* suggests a high rate of DNA loss, *Mol Biol Evol*, 15, (11) 1562-7.
320. Petrov, D.A.; Hartl, D.L. 1998, High rate of DNA loss in the *Drosophila melanogaster* and *Drosophila virilis* species groups, *Mol Biol Evol*, 15, (3) 293-302.
321. Subba Rao, G.; Hamid, Z.; Subba Rao, J. 1979, The information content of DNA and evolution *J. Theoretical Biology*, 81, 803.
322. Subba Rao, J.; Geevan, C.P.; Subba Rao, G. 1982, Significance of the information content of DNA in mutations and evolution, *J Theor Biol*, 96, (4) 571-7.
323. Kok, R.A.; Taylor, J.A.; Bradley, W.L. 1988, A statistical examination of self-ordering of amino acids in proteins, *Origins of life and evolution of the biosphere*, 18, (1-2) 135-42.
324. Weiss, O.; Jimenez-Montano, M.A.; Herzel, H. 2000, Information content of protein sequences, *J Theor Biol*, 206, (3) 379-86.
325. Whitehead, A.N. 1927, *Symbolism: Its meaning and effect*. Macmillan: New York.
326. Cassirer, E. 1957, *The Philosophy of Symbolic Forms, Vol 3: The Phenomena of Knowledge*. Yale Univ. Press: New Haven, CT.
327. Harnad, S. 1990, The symbol grounding problem, *Physica D*, 42, 335-346.
328. Pattee, H.H. 1982, Cell psychology: an evolutionary approach to the symbol-matter problem, *Cognition and Brain Theory*, 5, 325-341.
329. Pattee, H.H. 1968, The physical basis of coding and reliability in biological evolution. In *Prolegomena to Theoretical Biology*, Waddington, C. H., Ed. University of Edinburgh: Edinburgh.
330. Pattee, H.H. 1986, Universal principles of measurement and language functions in evolving systems. In *Complexity, Language, and Life: Mathematical Approaches*, Casti, J. L.Karlqvist, A., Eds. Springer-Verlag: Berlin, pp 579-581.
331. Pattee, H.H. 1997, The physics of symbols and the evolution of semiotic controls. In *Proc. Workshop on Control Mechanisms for Complex Systems*, Coombs, M. e. a., Ed. Addison-Wesley: p <http://www.ssie.binghamton.edu/pattee/semiotic.html>.
332. Pattee, H.H. 1961, On the origin of macromolecular sequences, *Biophys J*, 1, 683-710.
333. Pattee, H.H. 1969, How does a molecule become a message? In *Communication in Development; Twenty-eighth Symposium of the Society of Developmental Biology.*, Lang, A., Ed. Academic Press: New York, pp 1-16.
334. Pattee, H.H. 1971, The nature of hierarchichal controls in living matter. In *Foundations of Mathematical Biology*, Rosen, R., Ed. Academic Press: New York, Vol. 1, pp 1-22.
335. Pattee, H.H. 1972, Laws and constraints, symbols and languages. In *Towards a Theoretical Biology*, Waddington, C. H., Ed. University of Edinburgh Press: Edinburgh, Vol. 4, pp 248-258.
336. Pattee, H.H. 1973, Physical problems of the origin of natural controls. In *Biogenesis, Evolution, and Homeostasis*, Locker, A., Ed. Springer-Verlag: Heidelberg, pp 41-49.
337. Pattee, H.H. 1977, Dynamic and linguistic modes of complex systems, *Int. J. General Systems*, 3, 259-266.
338. Pattee, H.H. 1967, Quantum mechanics, heredity and the origin of life, *J Theor Biol*, 17, (3) 410-20.
339. Ledford, H. 2010, Mystery RNA spawns gene-activating peptides: Short peptides that regulate fruitfly development are produced from 'junk' RNA. In *NATURE*, Vol. Published online 15 July.
340. Robertson, M. 2010, The evolution of gene regulation, the RNA universe, and the vexed questions of artefact and noise, *BMC Biology*, 8, (1) 97.