



## What is life?

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### Abstract

Life is programmed, logic-gate-controlled, and cybernetically processed. Life is *algorithmic* with sequentially completed (“halting”) operations. Homeostatic metabolism is mediated by highly integrated circuits of configurable switch-settings, both genetic and epigenetic. Prescriptive Information (PI) controls, not just constrains, life’s exquisitely functional processes. Life’s instructions are *conceptual*, not just complex. Life is *Computation*. Naturalistic science has been pursuing abiogenesis and life’s definition on a purely physicydynamic basis for many decades with great frustration. Increasingly, investigators have been more willing to acknowledge prominent elements of life’s formal *orchestration*. Physicalism fails to explain the reality of “systems biology,” bona fide formal organization (as opposed to the merely redundant self-ordering of fractal, chaos and complexity theories), ingenious semiosis using *representational* physical symbol vehicles in material symbol systems, various *abstract codes*, *superimposed multidimensional coding* in the same string of symbols, *linguistic-like rules* rather than laws, and *controls* (rather than mere constraints). None of these formal aspects of sub-cellular metabolism are reducible to mere Shannon Uncertainty measures or irreversible nonequilibrium thermodynamic “possibilities.” “Assembly Theory” fails miserably to explain, let alone measure, the difficulty of orchestrating homeostatic metabolism. Life’s processes often seem to be indistinguishable from artificial computation by digital devices. Could it be that computation is the essence of life’s elusive definition? Life is not a thermodynamic state. Life demonstrates persistently programmed computational “*processes*.” Life is *programmed* and conducted by pragmatic cybernetic “*operations*.” Life consists of *Sustained Functional Systems* (SFS) that transduce useless wasted energy into usable energy, carrying life uniquely far from equilibrium. No function known to modern engineering measures up to the sophistication of sub-cellular nanocomputer and molecular machine biofunction. Is life’s computation merely physicydynamic, or is it every bit as abstract, conceptual, nonphysical and formal as the *mathematical* laws that define and govern physicality?

**Keywords:** Life Definition; protocells; Abiogenesis; Life Origin; Molecular Evolution; Chemical Evolution; Pre-Darwinian Evolution; Computational Biology; Self-organization; Emergence

### Introduction

First, we must investigate the hypothesis of whether life is fundamentally formal computation rather than mere physicydynamic interactions. We live in a mass/energy physical world. We also live in an abstract, nonphysical, conceptual, formal world. Hamming [1] and Wigner [2] both pondered “the unreasonable effectiveness of mathematics in the physical sciences.” We

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wish to keep naturalistic science uncompromised. But we also use formal choice-based engineering, mathematics, logic theory, linguistics and computation to accomplish most every naturalistic scientific endeavor. We cannot practice the scientific method without assimilating formalisms into our concept of reality. The highly desired “Theory of Everything” would be mathematical, not physical. Thus, is the effectiveness of mathematics in the physical sciences really “unreasonable?” Perhaps what is unreasonable is demanding that metaphysical physicalism (naturalism) be the starting and limiting axiom of scientific investigation.

### Life has always escaped definition.

Around the turn of the millennium, I spoke at a world-wide conference in Italy of life-origin scientists who sought to define life [3]. A written definition of life was required of every scientist participating in that conference. No two definitions were the same! No satisfactory definition of life has been published since, either. Reasonable *descriptions* of life have been published [4-8]. Science’s reductionism to a single-celled organism helps. We theorize protocell toy models [9-25]. NASA’s emphasis is usually placed on the ability of a cell to grow, reproduce, pursue functional activity, and evolve. Not so clear is how any protocell acquired any of those traits. The elucidation of abiogenesis and the study of protocellular metabolomics offers the best hope of understanding most fundamentally what life is, and exactly how life is distinguished from inanimate physicydynamics.

Perhaps the reason abiogenesis presents such an elucidation problem for science is that philosophic naturalism tends to be unwilling to experiment with anything other than physicydynamic interactions alone. At the same time, biology is constantly confronted with the reality of conceptual and goal-oriented “biochemical pathways” [26-30], highly integrated biological circuits [31-36], exquisitely orchestrated “homeostatic metabolism far from equilibrium [37-39],” “programming” [40-45], Szostak’s “functional information” [46-51], Abel’s more refined “Prescriptive Information” (PI) [52-54], “computational biology” [55-60], “systems biology” [61-66], abstract representational “symbolization with codes” [67-74], superimposed, multidimensional codes [75], chaperone control of protein folding into the needed tertiary structures [76-79], “biosemiosis” [46,73,80-87], “transcription” [88-92] and “translation” [93-96]. A virus doesn’t process anything. A virus performs no operations. A virus is not a system. It pursues no goals. A virus is just an inanimate database. A virus is not alive. Its host is alive. The host incorporates a virus’s Prescriptive Information (PI) [43,52-54,97] into its own genome.

Whatever life is, its programming, processing with logical operations, and subcellular systems seem to be life’s essence. That is worth repeating:

Life is most fundamentally *controlled* (not merely constrained!) by cybernetic *processes*. Life involves what artificial cybernetics calls “*operations*” purposely directed toward *computational success (halting)*. Life is characterized by *integrated circuits* and formally orchestrated highly cooperative formal *biosystems*. Life pursues the undeniable *goal* of being alive and staying alive. Something is very wrong with limiting biology’s attempts to elucidate life’s mechanisms to nothing more than inanimate physicydynamics. Inanimacy is simply not capable of accomplishing the wish-fulfillments of “self-organization” or “emergence” [98,99]. The latter two concepts are nothing more than pre-biotic pipe dreams. There is absolutely nothing scientific about either. Prigogine’s mere self-ordering was distinguished from formal organization years ago in life-origin science [99,100].

If we are ever able to define life, that definition will be derived from *programming, cybernetic processing, logic gate operations, well-orchestrated systems, and continual fully-realized homeostatic metabolic integration and goals far from equilibrium in Sustained Functional Systems (SFS) [101]*. Such systems invariably require Maxwell’s demon’s Choice Causation of when to open and close the trap door between thermodynamic compartments. If we disallow active selection of when the demon opens and closes his trap door, not even the simplest conceivable heat engine can be generated by thermodynamics [101], complexity [102-106], chaos [103,107-109] or “Assembly Theory [110-115].”

But now we have a problem. The demon’s trap door must be controlled, not merely constrained. All of the necessary causes of orchestration and bona fide organization are formal, not physical. The choice of when to open or close the demon’s trap door between thermodynamic compartments must be an active selection, not a passive selection [116]. The openings and closings of the trap door are not caused by any later-realized superior functional fitness as with environmental selection. Maxwell’s demon’s choices cause the potential function. They are as abstract and conceptual as mathematics itself. Such active selections cannot be reduced to mere physical complexity [117]. The self-ordering of chaos theory cannot explain a single one of these phenomena. Irreversible nonequilibrium thermodynamics cannot orchestrate formal organization. Assembly Theory cannot actively select for “useful” moieties over non-useful moieties. An inanimate environment shows no preference for function over non-function. Physicydynamics has no goals. The required active selection simply transcends irreversible nonequilibrium thermodynamics, chaos theory, molecular evolution and Assembly Theory’s capabilities.

But all the molecules and energy of life are physical, aren’t they? It could be argued that this manuscript is physical. But in reality, the concepts herein presented are purely abstract,

conceptual, linguistic, mathematical, hopefully logical, nonphysical and formal. This paper's formalisms are just instantiated into physicality using digital recordation and retention methods, along with use of other physical media like molecules of ink and paper. Yet this manuscript simply cannot be reduced to physicality. Neither can the scientific method or reality in general.

### What exactly is computation?

We tend to think of computation as an act of mathematical calculation. But as Babbage's co-worker—mathematician Ada Lovelace in 1843 first pointed out, computation does not have to be arithmetic. It does not actually have to be a “calculation,” either. Computation's broader meaning is simply “information processing” [118]. Here we would first have to differentiate between Shannon Uncertainty (misnamed “information”) and real information. Real information is Szostak's “functional information” [46-51] and Abel's more refined “Prescriptive Information” [43,52-54,119]. The human mind can compute, but physically instantiated cybernetic technology can compute ever so much faster, more reliably and more efficiently. Initial “technology” may have been the abacus. But the abacus required direct human involvement in each step of computation.

In one of the most profound engineering feats of all time, Jacques de Vaucanson in 1745 invented a mechanical device in the form of a semi-automated loom. The machine read punched paper tapes down to the next row. The loom was still manually controlled, however. Joseph-Marie Jacquard's card-punched looming machine in 1804 was probably the first mechanical automated “machine” capable of executing commands and producing functional algorithmic success.

“Punch cards” were creatively used to instantiate “active selections”—purposeful choices—into a physical medium of choice retention and readable commands used to prescribe automated desired utility. The cause was choice contingency. The effects were “useful results” as judged by agents. The punched holes *prescribed* which thread should be used in what position in the fabric. de Vaucanson and Jacquard had found a way to *instantiate abstract concepts of the mind into physicality*. Of greatest interest were ideas that issued *instructions and commands* that could direct physical operational functions. The location of the holes was used as a modified sign or symbol to *represent* the idea's *meaning, purpose and commands*.

Computation is not caused by indifferent constraints or invariant physical law. The holes in certain places of the physical card medium represented active selections from among real physical options. They provided not constraints on physicality, but bona fide formal actively selected *controls of physicality*. The reason these inventions were so significant

is that The Cybernetic Cut [120,121] had been traversed by technology across an infinitely deep ravine from its far *formal* side to its near *physicodynamic* side. Abstract, nonphysical actively selected *concepts* had caused effects into the physical world using a machine. Choice Causation had been successfully automated into mass/energy effects. The holes in the physical cards instantiated the desires and purposeful choices of the weaver agent. The formalism of conceptual, abstract Choice Causation (as opposed to chance and necessity) was transcribed and translated into a physical medium [43,122,123]. The cards were physical; the machine was physical. But the *controls* that produced the sophisticated physical product *were purely formal*.

How could this infinitely deep Cybernetic Cut ravine possibly have been traversed? It was traversed via the very narrow one-way bridge called the ‘Configurable Switch Bridge’ [120,121,124]. This bridge is constructed through the design and engineering of physical configurable switch-settings capable of recording, storing and executing voluntary conceptual formal commands. The commands consist of decision-node choices in pursuit of functionality. That functionality is *desired* by agent programmers and algorithmic optimizers. Certain configurable switch-settings were made using active selections from among real physical options. Circuits can only be integrated by formal Choice Causation, not by irreversible nonequilibrium thermodynamic “possibility space.” The light switches on our walls provide a simple example. The configurable switches themselves are physical. But their causal operation and control is altogether abstract, conceptual, nonphysical and formal. The force of gravity doesn't turn the light off. Only active selection of which configurable switch setting is desired turns the light switch off. The light is operated by Choice Causation, not by *physicodynamic causation*. Configurable switches are designed and engineered so that none of the four known forces of physics can select the switch-setting. Only one cause turns the light off—active selection—purposeful choice, not the force of gravity.

Improving card-punching methodologies further advanced computational technology. Babbage's later Analytical Machine just expounded on the same basic *ideas* into “autonomous operations.” Eventually, mechanical machines were replaced with electronic devices that came to be called “computers.” Cards with holes punctured in certain locations were replaced with electromagnetic tapes. These tapes in turn were replaced with stamped integrated circuits and many other later technologies. All of these approaches involved the instantiation into physicality of *purely formal purposeful choices made ultimately by agents doing the programming of physical machines and their operations/processes*. Eventually, it was realized in the 20<sup>th</sup> century that programming did not have to be sequential. “Conditional

branching” would eventually allow control transfer to a different instruction stream depending on the value of specified data.

### What are Operations?

Another term of interest in Babbage’s history was “Operations.” What do we mean by “operations”? Operations perform some task, procedure or process that is useful according to some agent’s definition of “useful.” The agent *desires* the completion of some task or procedure for some reason of perceived value: some desired final function. Remove the inventor agent from the equation, and no analytical machine would have ever “self-organized” or “emerged” in any amount of eons of time in any multiverse. All that would have occurred would have been sequences of undirected physical interactions. This is an absolute logic-theory prohibition, not a relative best-thus-far inductive prohibition. The Church/Turing thesis declares that computable “*functions*” are accomplished only by “*effective procedures*”—purposeful operations that achieve some goal—that can be conducted by a Turing “*machine*.”

To explore this thesis, we must first ask, “What is a “function?” A function is normally the product of a formally directed process, not a physiodynamic or thermodynamic state. Second, what is a “procedure, and what is meant by “effective?” A procedure that is “effective” (efficacious) is typically a processed step-wise algorithm. To be most effective (produce the “fittest” product), *algorithms must be optimized*. All of these concepts are formal, not physical.

Finally, what is a “machine?” A machine, including subcellular nanocomputers and molecular machines, are devices capable of processing those efficaciously programmed procedures—certainly nothing merely physiodynamic. Such machines have to be designed and engineered into existence. Like cell phones, they don’t just happen. Electronic configurable switches instantiate logic gate choices that permit cybernetic “operations.” Physical methyl groups mediate epigenetic configurable switches. Sequential specific nucleoside active selections program sequential codon and translational pausing instructions. Although physical, their effects all depend upon formal Choice Causation of which nucleoside to polymerize next in the string, not thermodynamic possibility, chaos or mere complexity.

### What is Cybernetics?

Cybernetics refers most fundamentally to the communication of “steering” and “control.” Automated control systems in both machines *and in living things* are addressed by Cybernetics. Cybernetic control includes circular processes such as feedback mechanisms where outputs can serve as inputs. But mere recursiveness does not necessarily

establish any useful control. Presupposed in any means of bona fide control is the motive to achieve utility of some sort. Vast technological improvements have not altered the basic *modus operandi* of automated cybernetics. A cybernetic logic gate is the equivalent of a physical configurable switch. The machines needed to process programming have to be designed and engineered into existence. The few “simple machines” that might be mentioned as exceptions are only machines when agents use them as machines. For example, an inclined plane is not a machine when the wind blows a tumble weed up a hill. An inclined plane is only a simple machine if an agent uses the inclined plane to accomplish some useful goal (pushing a heavy crate up some steps). Following publication of Kurt Gödel’s famous incompleteness theorems in 1931, many of the refiners of modern cybernetics got their ideas from the progressive discovery of the cybernetics of subcellular digital controls that were just beginning to be elucidated more fully in the 1950’s” [125-133]. The parallels they perceived between real subcellular cybernetics and potential artificial cybernetics were profound. Thus, it might behoove naturalistic abiogenists to address the question, “How did computer-like computation get started at the sub-cellular level in a purely physiodynamic prebiotic world?”

### The capabilities of physiodynamics

Countless interactions and reactions occur spontaneously in nature. These interactions can self-order into dissipative structures a la chaos theory [134-139]. But they have never been observed to formally self-organize into formally controlled processes or systems in pursuit of sophisticated functions. Undirected physiodynamics is blind to utility. Programming or engineering is required to generate an “effective functional procedure,” otherwise known as an algorithm. Thus, physiodynamics can self-order, but physiodynamics cannot orchestrate or organize anything into existence, let alone itself. Self-organization is a nonsense naturalistic term. Neither Chance nor necessity can organize anything.

For constraints to become controls requires an agent to actively select those constraints, usually by orchestrating initial conditions. It’s called “investigator involvement” in experimental design. This flaw results in the illusion of physiodynamic events having formal capabilities. Typically, the ultimate source of steering and control is what philosophers of science call “agency.” Agency refers to the ability to choose from among real options within and despite the context of physical law constraints. Purposeful operations are undertaken only by agents. Instrumentality is engineered to optimize efficiency of tasks. Non-trivial algorithmic optimization has never been observed to arise out of anything other than Choice Causation attributable to agents. We dichotomize “natural process” from engineering for good



reason. Virtually every sophisticated entity known to science arose from engineering, not “natural process.” We see self-ordering in nature all the time in the form of dissipative structures. But we have never observed a simple piece of wire with constant diameter and the needed malleability and tensile strength spontaneously emerge from unaided, uncontrolled physicyodynamics (See Figure 1).



**Figure 1:** An old, oxidized piece of wire. What empirical evidence can we cite of this simple long piece of metal alloy with constant diameter ever having spontaneously “self-organized” or “emerged” from iron ore in the ground? How did this simple piece of wire come into existence with just the right tensile strength and malleability to make even a crude paper clip?

Figure 1 offers the scientific reductionism needed to appreciate the silliness of believing in the spontaneous generation of life. If a simple piece of wire has never “self-organized” or “emerged” from the forest floor by physicyodynamic interactions alone, what would be the rational or empirical basis for any competent scientist seriously believing in the spontaneous generation of life?

### Algorithms are crafted to solve problems.

An algorithm is an operation consisting of a finite sequence of instructions or commands undertaken to solve a class of problems. Note first that even the statement of a “problem” that needs solving is formal, not physical. Algorithms are instructions of well-defined step-wise processes made in pursuit of functional goals. The goal of solving any problem is formal, not physical.

The formal terms “operation,” “process,” “organization,” and “system” are often bastardized into illegitimate use as physicyodynamic terms. Examples include naturalists’ use of the term “natural process” and meteorologists use of the formal term “system” to refer to a mere weather front. “Natural process” is actually nothing more than an un-steered sequence of cause-and-effect physicyodynamic interactions. Physical law causations of effects such as Prigogine’s self-ordered states (dissipative structures like tornadoes) are not formal “processes.” They involve no controls, only fixed laws and constraints [140]. No steering or purposefully controlled algorithmic procedures are involved. Weather fronts, tornadoes and hurricanes have nothing to do with

“systems” or “processes” in pursuit of utility. They are merely a rapid sequence of inanimate cause-and-effect self-ordered physicyodynamic states. Dissipative structures of chaos theory only destroy algorithmically processed organization, systems and computational feats. They never create orchestration or formal organization of any kind.

Today, algorithmic operations are usually *programmed* to run autonomously on computers. Such well-defined step-wise processes are governed by rules, not laws. Formalisms are choice-based with intent to achieve a “desired” result. They cannot be generated by “chance and necessity.” Rules address contingency not eliminated by the laws of motion. Rules are formally generated to strongly recommend voluntary behavior. Rules outline what choices would be wise and efficacious in the accomplishment of some goal. Rules are purely formal because they guide effectual active selections at true decisions nodes toward utility. Rules, unlike physical laws, can be broken. Rules can be misunderstood and knowingly or unknowingly disobeyed. The typical result of failing to obey rules is loss of final function for which the rules were written. The breaking of rules does not break any laws.

### Shannon Uncertainty and Possibility measures

Shannon theory can quantify the number of physical options. It cannot quantify effectual choices. Prior to specific selection of a real option, a binary decision node appears as a mere fork in the road. Forks-in-the-road can be altogether physical. The *question* of which fork should be taken to optimize one’s journey is altogether formal. The choice is an active selection, not a passive or secondary selection as we might see with natural selection. To program computational function, active selections must be made at bona fide decision nodes according to rules set prior to the realization of beneficial results. The choices are prescribed prior to the completed execution of the computational operation. There’s no way of knowing for sure whether the computation will even finish. This is what is known as the Church/Turing Halting problem [141] [142]. Halting refers to the program successfully computing the task for which the programming choices were made, and the computer halting its operation. Computation is altogether choice-based at bona fide “decision nodes,” not mere “bifurcation points.” “Bifurcation points” (forks-in-the-road) are not synonymous with “decision nodes.” Forks in the road correspond to physical configurable switches that have not yet been set by choice contingency. Once a setting is chosen, only then does the fork-in-the-road become a functional “decision node” and configurable switch *setting*. Decision node choices comprise 90% of what makes reality really interesting. Algorithms can only be optimized by improving the quality of choices which constitute the instructions. Can chance and necessity make or refine programming choices? Can mutations selectively generate

or optimize algorithms? Can Prescriptive Information be programmed and improved by physiodynamics? Philosophic naturalism knows full well the answers to these questions, but continues to disingenuously obfuscate.

### What is Formalism?

Dictionary definitions of “formalism” relate to adherence to “prescribed forms” of voluntary behavior. In natural science and philosophy, these prescribed forms are usually defined mathematically, logically and linguistically. The bottom line of formalisms is Concept in pursuit of *Functionality, Steering and Control*.

Note that “mathematical,” “logical,” “linguistic,” “prescribed,” “controlled,” “operations,” “procedures,” “processes,” “abstractions,” “calculations,”

“computations,” “function,” “utility,” “usefulness,” “behavior,” “orchestration,” “organization,” “classes” and “forms” are all nonphysical, abstract concepts of mentation. Formalisms, including the manipulation of mathematical equations, invariably involve choice-contingent causation, not physiodynamic causation. Formalisms all arise from the far side of the Cybernetic Cut [120,121,124], not the near physiodynamic side.

Active selections are made prior to the realization of any final function that might later be judged to be “fittest” or “favored.” “Survival of the fittest” is always after-the-fact of optimized algorithmic function. Evolution tells us absolutely nothing about how those algorithms were written or optimized at the genetic and epigenetic levels [143,144].

Co-evolution models exist. But upon careful analysis of all these models, formal elements are at play that deny the contention that the models were purely physiodynamic. Usually, experimental confirmation is lacking. Models are more wish-fulfillments consisting of “could have’s . . .” than empirical science. Neither chance nor necessity can explain algorithms, algorithmic optimization, the valuing and pursuit of utility, computation, or successful computational halting success. Chance and necessity cannot explain the programming of Prescriptive Information (PI) instantiated into genetics and epigenetics [52-54]. Biological controls and systems are a cybernetic and engineering problem, not a natural science problem. One can spend a lifetime studying physics and chemistry without ever being able to explain efficacious programming choices. They are active selections, not physiodynamic effects. They are formal, not physical. They are not passive secondary selections based on already achieved final phenotypic fitness. Non-trivial fitness can only be genetically and epigenetically caused by formal active selection. This is known as The Genetic Selection Principle:

The GS (Genetic Selection) Principle states that biological selection must occur at the nucleotide-sequencing molecular-

genetic level of 3'5' phosphodiester bond formation and selective methylation of epigenetic configurable switches. After-the-fact differential survival and reproduction of already-programmed, already-living phenotypic organisms (natural selection) does not explain polynucleotide sequence prescription, efficacious epigenetic configurable switch-settings, and other forms of biological coding prescription [105,145-147]. Synthetic organic chemistry requires tightly controlled conditions and a highly specific order of reactions. Choices have to be made long before any usable yields of moieties are produced, especially with the extremely high purity that is required [148-150].

### Cybernetic Abstractions are formal.

Programming functions (typically, series of commands) can be condensed by abstractions. Abstractions are summary statements and names (formal representations or symbolizations) of calls to function. They encapsulate the details of how a problem-solving effort will be implemented [151,152]. The abstractions describe the modules and sometimes the abstract class of desired goal details in a project. The abstraction represents what that module does to contribute to solving a problem. The abstraction does not go into detail of how it codes for the solution to that problem.

Abstractions wisely focus on the most important aspects of solving a complex problem first, to the exclusion of less important aspects of that problem. Abstractions can be quite complex, consisting of many layers or dimensions of smaller commands or modules that are organized into “libraries.” They not only offer the simplicity of brief description of complex function, but of composability in abstracting many modules into larger programming modules. But, of course, all this has to be planned. Programmers call this “analysis and design.” The abstractions have to be very creative and manifest optimized algorithmic efficiency. Why are we talking about artificial cybernetic programming abstractions in a life-definition paper? The answer is that Life at the subcellular level uses extensive abstractions in its programming to solve many multifaceted metabolic problems.

The most conceptually complex (not just complex) problems known to science are those of orchestrating homeostatic metabolism at the subcellular level. Even a theoretical protometabolism requires ingenious organization and controls. These facts constitute the reality to which so many naturalistic abiogenists are blind, or choose to be blind: the abstractions of programming code are nonphysical and formal. They cannot be reduced to physiodynamics. They cannot be addressed by the “natural sciences.” The abstractions of program modules are engineering realities. If chance and necessity cannot generate a simple piece of wire, how did chance and necessity abstract the programming concepts needed to generate ribosomes? Ribosome anatomy

alone is mind-boggling even before analyzing these highly sophisticated digital device “operations.” The extraordinary function of chaperones only compounds the problem of even beginning to provide a physiodynamic explanation for such exquisite orchestration of the protein tertiary structure roles of each highly functional player.

### Subcellular computer-like computation.

Inanimate nature knows nothing of “goals,” “directed processes,” “intent,” “desire” “instructions,” “commands,” “algorithms,” “usefulness” or “function.” Why are such human-generated artificial cybernetics concepts so prominent in subcellular metabolism?

It is not a matter of how human experimenters conceive molecular assemblies, as Assembly Theorists argue. Abiogenesis by definition must arise out of inanimacy [153]. Inanimacy produced stand-alone physiodynamic causation. Present-day human conceptualizations of moieties are irrelevant to abiogenesis research.

Life uses Material Symbol Systems [154,155]. Physical symbol vehicles (tokens) *represent* cybernetic commands (e.g., triplet codons) [156]. Such representationalism is formal, not physical [14]. But how could a physical symbol vehicle be generated with “meaning” that could execute the desired command and function? Nucleoside selection for polymerization at a certain locus in the string of commands is not physiochemically mandated. All chemical bonds are the same 3’5’ phosphodiester bonds. No physical determinism of coding in polymerization exists. If it did, instead of Prescriptive Information we would have nothing but meaningless homopolymers. The problem of prescription of biofunction is by far the most plaguing problem of abiogenesis research [53,54,119].

Life’s symbol systems needed formal rules of interpretation and execution, not fixed laws. Where did these formal rules come from? With the representation of commands came the possibility for the first time of a machine being designed and engineered to “read” and execute each command *formally represented by* a physical symbol vehicle. This didn’t happen first with de Vaucanson, Jacquard or Babbage. *It happened first at the subcellular level with abiogenesis!* [157]. Sometimes, multiple signs or symbols were needed to express a simple command. Other times, multiple commands were needed to complete even a simple task. The sequence of symbolized commands was the equivalent of language syntax (e.g., a “phrase” or “clause” of instruction). This resulting linguistic syntax gave rise to the first “program.” It’s instantiation into the physical world gave rise ultimately to a prebiotic “Turing tape.” The Turing tape was like a bunch of punch cards scotch-taped together in a long string. But the latter was worthless without a very sophisticated “reading head” and Turing-like machine. A large percentage of life’s description, if not definition, falls into the engineering category, not the

natural science category. Life is fundamentally formal rather than physical, although the formalisms are instantiated into physicality with physical configurable switch and logic gate settings. But those switches and logic gates can only be set for function by formal active selections. The after-the-fact “natural selection” of fittest already-halted computations will never explain the programming, processing and computation that is the essence of life.

### Life is Unique

The programming of life is undeniably digitally prescribed and cybernetically processed [4,52-54]. Subcellular nanocomputers convert the linear digital sequencing of material symbol systems (mRNA “Turing tapes”) into digitally prescribed primary poly-amino-acid strings that only secondarily fold into needed three-dimensional tertiary structures [158]. Various semiotic codes are not always read from the 5’ to 3’ direction. Various codes are superimposed and are sometimes read in both directions.

Long before Babbage, prebiotic nature had already made sure that each individual operation would finish (halt) before the next operation was commanded. Are life’s programmed processing “commands” physiodynamic causes, or cybernetic engineering causes? What does physico-chemistry “command.” Laws don’t need to command; they simply constrain and force outcomes. The context of “Commands” is to strongly suggest actively selecting *certain* options from within Shannon possibility space in order to achieve utility. But at the programming and operational Turing machine level, those suggestions have been converted into *prescriptions* (choice-contingent efficacious orders). The “interpretive competence” of subcellular biosemiotics and biocybernetics cannot be reduced to physiodynamic laws and constraints. Neither is the formal orchestration of life’s bioengineering reducible to metaphysically-motivated physicalistic philosophy.

### Discussion

Is “computation” an accurate descriptor of life? Absolutely. Subcellular computation is what life does. Information processing is the very essence of life. Life also depends upon sophisticated equipment—subcellular nanocomputers and exquisitely tailored and engineered molecular machines. For even the simplest heat engine to form, Maxwell’s demon must make intelligent choices of when to open and close his trap door [101]. If Maxwell’s demon’s trap door is operated either by chance or necessity, no simple heat engine will arise.

How did all of these devices come into existence in a prebiotic environment at the same time and place? This equipment must “speak the same language” at the messages’ destination that was spoken at the messages’ source.



Any model of hypothetical spontaneous production of these machines by irreversible nonequilibrium thermodynamics, “assembly theory,” chaos theory, or complexity theory models is statistically prohibitive. In addition, such models measure out with a Universal Plausibility Metric of  $\xi < 1.0$ , requiring their rejection by peer review as plausible scientific models of origin [159-161]. Such wish-fulfillment models are unworthy of grant funding or publication.

When no Choice Causation is allowed into scientific study, not even the source of a simple heat engine can be elucidated. Maxwell’s demon cannot be excluded from any mechanism of non-trivial machine formation. No Choice Causation—no subcellular nanocomputer or molecular machines! No Choice Causation—no Life! It’s that simple. The superimposition of a completely different coding scheme for translational pausing on top of the codon scheme in the same mRNA further compounds the incredible degree of formalism.

The codon table and other biosemiotic code systems are highly conceptual. Homeostatic metabolism manifests innumerable purely formal concepts and controls, not just physicochemical interactions. Life’s processes are beyond ingenious. The sub-cellular cybernetics of life is more sophisticated than the finest mainframe computer systems.

NeoDarwinism doesn’t select nucleosides or program their sequencing. Evolution is nothing more than the differential survival and reproduction of the fittest already-programmed, already-cybernetically processed, already-living organisms. The model is worthless in trying to explain abiogenesis. Co-evolution models of code-origin can only go so far before their brevity, simplism and naivete become painfully obvious. Transcription and translation are vastly more extensive, cybernetically creative and refined than cartoon co-evolution models will ever be able to explain. What directed biochemical pathways toward undeniable goals of metabolic holism? NeoDarwinism only selects for the fittest already-living *organisms*, not the fittest stand-alone functions. All of the biochemical pathways must be first integrated into unified protometabolic schemes. Not even natural selection can advance without prior active selection. Only formal algorithmic optimization could have produced the fittest organisms for evolution to secondarily prefer [145-147]. Evolution has no goal, and no pursuit of function or efficiency. NeoDarwinian evolution can play no role whatsoever in abiogenesis. There has to be at least viable reproducing protocells that can differentially die or survive better for natural selection to begin. There’s good reason why we dichotomize “Science and Engineering.” Engineering requires controls, not mere constraints. Naturalistic neuroscience has failed miserably to reduce *formal controls* to nothing more than fixed laws and physical constraints [140].

When science restricts its study to Chance and Necessity, it hits a brick wall explaining what makes most of reality “effective.” To exclude repeatedly observable active selection and its considerable effects from the study of objective reality leaves the science of biology severely crippled. Science cannot practice its trade while in denial of the F > P Principle: “The F > P Principle (Formalism > Physicality) states that “Formalism not only describes, but preceded, prescribed, orchestrated, organized, and continues to govern and predict Physicality.” The F > P Principle is an axiom that defines the ontological primacy of formalism in a presumed objective reality that transcends both human epistemology, our sensation of physicality, and physicality itself. The F > P Principle works hand in hand with the Law of Physicodynamic Incompleteness, which states that physicochemical interactions are inadequate to explain the mathematical and formal nature of physical law relationships [162,163]. Physicodynamics cannot generate formal processes and procedures leading to nontrivial function. Chance, necessity and mere constraints cannot steer, program or optimize algorithmic/computational success to provide desired nontrivial utility.” [143,144]. Naturalistic biological science cannot continue to bury its head in the sand by studying only physicodynamic causation. Any theory of everything would itself be a formalism. It would have to address the reality and origin of formalisms that transcend and control all aspects of physicality, not just life [43,116,119,143,144,163-166]. Naturalistic science is absolutely crippled by its failure to admit the clear dichotomy between mere physicodynamic constraints vs. formal choice-contingent controls. Unfortunately, this is quite deliberate. It is metaphysically motivated in violation of Einstein’s wise advice to minimize metaphysics. The inability to define life and explain its abiogenesis by the naturalistic scientific community stems directly from its refusal to acknowledge that life is fundamentally formal rather than physical [167].

The science of Biology must acknowledge the reality of formal programming, the cybernetic processing of that programming, integrated circuits, and the orchestration of highly integrated biosystems if it is to make any real progress in elucidating abiogenesis. Refusal to acknowledge prebiotic flow from the far side of the Cybernetic Cut [120,121,124] precludes understanding the introduction of any abstract concept or formalism into physicality. Disallowing abstract concepts as causation in biological science means disallowing controls and computation. No computation means no information processing, no completed functional operations, and no realized homeostatic metabolism. The F > P Principle cannot be denied or circumvented [143,144]. The time is long overdue to admit the reality of a crippling Kuhnian paradigm rut that dominates naturalistic science [168]. There is a very good reason why computational biology and systems biology



are so effective in studying life and homeostatic metabolism: life itself is fundamentally computation. Computation is as formal as mathematics. That means that life is fundamentally formal even though instantiated into physicality. Formalisms are choice-contingent and are nonphysical. They cannot be reduced to mass/energy and the four known forces of physical nature. Physicalism is dead.

## Conclusions

1. Life is formal computation, not just physicydynamic interactions and reactions.
2. Computation successfully processes efficacious Prescriptive Information (PI), not just Shannon Uncertainty measures of thermodynamic “possibility.”
3. Life is controlled, not constrained.
4. Life manifests not just complexity, but conceptual complexity.
5. Life is orchestrated, not merely self-ordered.
6. Rules govern life, not just laws.
7. All known life is programmed and cybernetically processed.
8. Life performs innumerable conceptual “abstracted operations.”
9. Life’s controls are instantiated into physical logic gate and physical configurable switch-settings that cannot be set for eventual function by physicydynamics.
10. Life executes commands instantiated into physical symbol vehicles (e.g., nucleoside tokens) used in a Material Symbol System (MSS) to represent specific instructions (e.g., the abstract codon table).
11. Life manufactures and employs sophisticated digital equipment (nanocomputers and incredible molecular machines).
12. Representationalism and symbolization are used extensively by life in innumerable biological coding schemes.
13. Programming and computation require active selections at bona fide “decision nodes” made in the clear pursuit of formal utility.
14. Chance and Necessity cannot pursue “usefulness.”
15. Chance and necessity cannot program, cybernetically process that programming, or compute.
16. Most of life’s functions are fundamentally abstract, conceptual, nonphysical and formal rather than physicydynamic.
17. Although instantiated into physicality, life is

fundamentally nonphysical, as are the mathematical laws that govern physics.

18. The only thing that makes #17 above “unreasonable” is the unreasonable pre-assumption (faulty axiom) of physicalism inherent in philosophic naturalism.

**Availability of data and materials:** All results are contained within the manuscript and its references.

**Credit:** Authorship contribution statement David Lynn Abel alone contributed the writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

1. Hamming RW. The unreasonable effectiveness of mathematics. *The American Mathematical Monthly* 87 (1980): 81-90.
2. Wigner EP. The unreasonable effectiveness of mathematics in the natural sciences. *Comm. Pure Appl* 13 (1960)
3. Palyi G, Zucchi C Caglioti. Workshop on Life: a satellite meeting before the Millennial World Meeting of University Professors, Modena Italy (2000).
4. Abel, D.L. Is life unique?. *Life* 2 (2012): 106-134.
5. Kauffman S. Answering Schrödinger’s “What Is Life?”. *Entropy* 22 (2020): 815.
6. Pross A. *What is Life? How Chemistry Becomes Biology*; Oxford University Press: Oxford, UK (2012).
7. Margulis L, Sagan D. *What is Life? Weidenfeld and Nicholson: London* (1995).
8. Schroedinger, E. *What is Life? Cambridge University Press: Cambridge* (1955).
9. Qi C, Ma X, Zeng Q, Huang Z, Zhang S, Deng X, et al. Multicompartmental coacervate-based protocell by spontaneous droplet evaporation. *Nat Commun* 15 (2024): 1107.
10. Mu W, Jia L, Zhou M, Wu J, Lin Y, Mann S, Qiao Y.

- Superstructural ordering in self-sorting coacervate-based protocell networks. *Nat Chem* 16 (2024): 158-167.
11. Ma H, Liu X, Nobbs AH, Mishra A, Patil AJ, Mann S. Protocell Flow Reactors for Enzyme and Whole-Cell Mediated Biocatalysis. *Adv Mater* 36 (2024): e2404607.
  12. Li B, Li, J, Chen, S, Yuan, Q, Fang, C, Gan, W. Monitoring the response of a model protocell to dye and surfactant molecules through second harmonic generation and fluorescence imaging. *Phys Chem Chem Phys* 26 (2024): 8148-8157.
  13. Gaur D, Dubey NC, Tripathi BP. Designing Configurable Soft Microgelsomes as a Smart Biomimetic Protocell. *Biomacromolecules* 25 (2024): 1108-1118.
  14. Esposito J, Kakar J, Khokhar T, Noll-Walker T, Omar F, Christen A, et al. Comparing the complexity of written and molecular symbolic systems. *Biosystems* 244 (2024): 105297.
  15. Cohen ZR, Todd ZR, Maibaum L, Catling DC, Black RA. Stabilization of Prebiotic Vesicles by Peptides Depends on Sequence and Chirality: A Mechanism for Selection of Protocell-Associated Peptides. *Langmuir* 40 (2024): 8971-8980.
  16. Yin Z, Gao N, Xu C, Li M, Mann S. Autonomic Integration in Nested Protocell Communities. *J Am Chem Soc* 145 (2023): 14727-14736.
  17. Katke C, Pedrueza-Villalmanzo E, Spustova K, Ryskulov R, Kaplan CN, Gozen I. Colony-like Protocell Superstructures. *ACS Nano* 17 (2023): 3368-3382.
  18. Grimes PJ, Jenkinson-Finch M, Symons HE, Briscoe WH, Rochat S, Mann S, et al. A Photo-degradable Crosslinker for the Development of Light-responsive Protocell Membranes. *Chemistry* 29 (2023): e202302058.
  19. Gao N, Mann S. Membranized Coacervate Microdroplets: from Versatile Protocell Models to Cytomimetic Materials. *Acc Chem Res* 56 (2023): 297-307.
  20. Dai S, Xie Z, Wang B, Ye R, Ou X, Wang C, et al. An inorganic mineral-based protocell with prebiotic radiation fitness. *Nat Commun* 14 (2023): 7699.
  21. Chen Y, Yan L, Chi Y, Liu Y, Zhao Y. Protocell Self-Assembly Driven by Sodium Trimetaphosphate. *Chemistry* 29 (2023): e202300512.
  22. Chen M, Liu G, Zhang M, Li Y, Hong X, Yang H. Programmatically Dynamic Microcompartmentation in Coacervate-in-Pickering Emulsion Protocell. *Small* 19 (2023): e2206437.
  23. Chen C, Wu S, Wang Y, Cao J, Tian L. Reversible modulation of protocell volume via collective response of functional protein in its membrane. *J Colloid Interface Sci* 651 (2023): 182-190.
  24. Saini B, Mukherjee TK. Synthetic Protocell as Efficient Bioreactor: Enzymatic Superactivity and Ultrasensitive Glucose Sensing in Urine. *ACS Appl Mater Interfaces* 14 (2022): 53462-53474.
  25. De Bari B, Kondepudi DK, Dixon JA. Foraging Dynamics and Entropy Production in a Simulated Proto-Cell. *Entropy (Basel)* 24 (2022).
  26. Holme P, Huss M, Jeong H. Subnetwork hierarchies of biochemical pathways. *Bioinformatics* 19 (2003): 532-538.
  27. Oliveira JS, Bailey CG, Jones-Oliveira JB, Dixon DA. An Algebraic-combinatorial Model for the Identification and Mapping of Biochemical Pathways. *Bulletin of Mathematical Biology* 63 (2001): 1163-1196.
  28. Hackmann TJ. New biochemical pathways for forming short-chain fatty acids during fermentation in rumen bacteria. *JDS Commun* 5 (2024): 230-235.
  29. But SY, Egorova SV, Khmelenina VN, Trotsenko YA. Biochemical Properties and Phylogeny of Hydroxypyruvate Reductases from Methanotrophic Bacteria with Different C (1)-Assimilation Pathways. *Biochemistry (Mosc)* 82 (2017): 1295-1303.
  30. Mandal M, Boese B, Barrick JE, Winkler WC, Breaker RR. Riboswitches control fundamental biochemical pathways in *Bacillus subtilis* and other bacteria. *Cell* 113 (2003): 577-586.
  31. Perry N, Nelson EM, Timp G. Wiring Together Synthetic Bacterial Consortia to Create a Biological Integrated Circuit. *ACS synthetic biology* 5 (2016): 1421-1432.
  32. Mukherjee R, Sinha S, Luker GD, Ghosh, P. Interlinked switch circuits of biological intelligence. *Trends Biochem Sci* 49 (2024): 286-289.
  33. Sun J, Sun C, Wang Z, Wang Y. Biosignals Secure Communication Scheme with Filtering of Active Control Projection Synchronization of Biological Chaotic Circuits with Different Orders Based on DNA Strand Displacement. *IEEE Trans Biomed Circuits Syst* 17 (2023): 470-482.
  34. Giles, J.R, Ngiow, S.F, Manne, S, Baxter, A.E, Khan, O, Wang, P, Staupe, R, Abdel-Hakeem, M.S, Huang, H, Mathew, D, et al. Shared and distinct biological circuits in effector, memory and exhausted CD8(+) T cells revealed by temporal single-cell transcriptomics and epigenetics. *Nat Immunol* 2022, 23, 1600-1613, doi:10.1038/s41590-022-01338-4.

35. Kiwimagi, K.A, Letendre, J.H, Weinberg, B.H, Wang, J, Chen, M, Watanabe, L, Myers, C.J, Beal, J, Wong, W.W, Weiss, R. Quantitative characterization of recombinase-based digitizer circuits enables predictable amplification of biological signals. *Commun Biol* 2021, 4, 875, doi:10.1038/s42003-021-02325-5.
36. English, M.A, Gayet, R.V, Collins, J.J. Designing Biological Circuits: Synthetic Biology Within the Operon Model and Beyond. *Annu Rev Biochem* 2021, 90, 221-244, doi:10.1146/annurev-biochem-013118-111914.
37. Reja, A, Pal, S, Mahato, K, Saha, B, Delle Piane, M, Pavan, G.M, Das, D. Emergence of Photomodulated Protometabolism by Short Peptide-Based Assemblies. *J Am Chem Soc* 2023, 145, 21114-21121, doi:10.1021/jacs.3c08158.
38. Nader, S, Sebastianelli, L, Mansy, S.S. Protometabolism as out-of-equilibrium chemistry. *Philosophical transactions. Series A, Mathematical, physical, and engineering sciences* 2022, 380, 20200423, doi:10.1098/rsta.2020.0423.
39. Monreal Santiago, G, Liu, K, Browne, W.R, Otto, S. Emergence of light-driven protometabolism on recruitment of a photocatalytic cofactor by a self-replicator. *Nat Chem* 2020, 12, 603-607, doi:10.1038/s41557-020-0494-4.
40. Becerra, A.G, Gutiérrez, M, Lahoz-Beltra, R. Computing within bacteria: Programming of bacterial behavior by means of a plasmid encoding a perceptron neural network. *Biosystems* 2022, 213, 104608, doi:https://doi.org/10.1016/j.biosystems.2022.104608.
41. Liu, B, Qian, S.B. Translational reprogramming in cellular stress response. *Wiley Interdiscip Rev RNA* 2013, doi:10.1002/wrna.1212.
42. Kandpal, M, Kalyan, C.M, Samavedham, L. Genetic programming-based approach to elucidate biochemical interaction networks from data. *IET Syst Biol* 2013, 7, 18-25.
43. Abel, D.L., (Ed.) *The First Gene: The Birth of Programming, Messaging and Formal Control*. LongView Press-Academic: Biolog. Res. Div.: New York, NY, 2011; p. 389.
44. Johnson, D.E. *Programming of Life*; Big Mac Publishers: Sylacauga, Alabama, 2010; p. 127.
45. Scalzitti, N, Miralavy, I, Korenchan, D.E, Farrar, C.T, Gilad, A.A, Banzhaf, W. Computational peptide discovery with a genetic programming approach. *J Comput Aided Mol Des* 2024, 38, 17, doi:10.1007/s10822-024-00558-0.
46. Sharov, A.A. Functional Information: Towards Synthesis of Biosemiotics and Cybernetics. *Entropy (Basel)* 2010, 12, 1050-1070, doi:10.3390/e12051050.
47. Sharov, A.A. Role of Utility and Inference in the Evolution of Functional Information. *Biosemiotics* 2009, 2, 101-115, doi:10.1007/s12304-008-9032-2.
48. Sharov, A. Role of utility and inference in the evolution of functional information. *Biosemiotics* 2009, 2, 101-115.
49. Hazen, R.M, Griffin, P.L, Carothers, J.M, Szostak, J.W. Functional information and the emergence of biocomplexity. *Proc Natl Acad Sci U S A* 2007, 104 Suppl 1, 8574-8581.
50. McIntosh, A.C. Functional Information and Entropy in living systems. In *Design and Nature III: Comparing Design in Nature with Science and Engineering*, Brebbia CA, Suchrov LJ, P, P., Eds, WIT Press: U.K., 2006.
51. Szostak, J.W. Functional information: Molecular messages. *Nature* 2003, 423, 689.
52. D'Onofrio, D.J, Abel, D.L, Johnson, D.E. Dichotomy in the definition of prescriptive information suggests both prescribed data and prescribed algorithms: biosemiotics applications in genomic systems (Also available at www.DavidAbel.us last accessed 9/2024). *Theor Biol Med Model* 2012, 9, 8, doi:10.1186/1742-4682-9-8.
53. Abel, D.L. Prescriptive Information (PI) [Scirus SciTopic Page] (www.DavidAbel.us Last accessed 9/2024). Available online: www.DavidAbel.us (accessed on
54. Abel, D.L. The biosemiosis of prescriptive information (also available at www.DavidAbel.us Last accessed 9/2024). *Semiotica* 2009, 2009, 1-19, doi:10.1515/semi.2009.026.
55. Cadwallader, L, Mac Gabhann, F, Papin, J, Pitzer, V.E. Advancing code sharing in the computational biology community. *PLoS Comput Biol* 2022, 18, e1010193, doi:10.1371/journal.pcbi.1010193.
56. Mushegian, A. Grand Challenges in Bioinformatics and Computational Biology. *Frontiers in Genetics* 2011, 2, doi:10.3389/fgene.2011.00060.
57. Eisenhaber, F. Discovering biomolecular mechanisms with computational biology; Landes ioscience/Eurekah.com ; Springer Science+Business Media: Georgetown, Tex., New York, 2006.
58. Konopka, A.K. Selected dreams and nightmares about computational biology. *Computational Biology and Chemistry* 2003, 27, 91-92.
59. Doyle, J. Computational biology: Beyond the spherical cow. *NATURE*, 2001, 411, 151-152.



60. Gusfield, D. Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology, Cambridge University Press: Cambridge, 1997.
61. Zaballa, V.D, Hui, E.E. Reducing Uncertainty Through Mutual Information in Structural and Systems Biology. ArXiv 2024.
62. Villalvazo, P, Villavicencio, C, Gonzalez de Rivera, M, Fernandez-Fernandez, B, Ortiz, A. Systems biology and novel biomarkers for the early detection of diabetic kidney disease. Nephron 2024, doi:10.1159/000540307.
63. Sourjik, V, Patil, K.R. Editorial overview: Systems and synthetic biology of microbial cells and communities. Curr Opin Microbiol 2024, 80, 102517, doi:10.1016/j.mib.2024.102517.
64. Luo, Y, Liu, Y, Xue, W, He, W, Lv, D, Zhao, H. Systems biology-based analysis exploring shared biomarkers and pathogenesis of myocardial infarction combined with osteoarthritis. Front Immunol 2024, 15, 1398990, doi:10.3389/fimmu.2024.1398990.
65. Hu, J, Fu, J, Cai, Y, Chen, S, Qu, M, Zhang, L, Fan, W, Wang, Z, Zeng, Q, Zou, J. Bioinformatics and systems biology approach to identify the pathogenetic link of neurological pain and major depressive disorder. Exp Biol Med (Maywood) 2024, 249, 10129, doi:10.3389/ebm.2024.10129.
66. Golebiewski, M, Bader, G, Gleeson, P, Goroehowski, T.E, Keating, S.M, Konig, M, Myers, C.J, Nickerson, D.P, Sommer, B, Waltemath, D, et al. Specifications of standards in systems and synthetic biology: status, developments, and tools in 2024. J Integr Bioinform 2024, 21, doi:10.1515/jib-2024-0015.
67. Barbieri, M. Overview of the fourth special issue in code biology. Biosystems 2024, 235, 105074, doi:10.1016/j.biosystems.2023.105074.
68. Prinz, R. Nothing in evolution makes sense except in the light of code biology. Biosystems 2023, 229, 104907, doi:10.1016/j.biosystems.2023.104907.
69. Petoukhov, S.V. The principle "like begets like" in algebra-matrix genetics and code biology. Biosystems 2023, 105019, doi:10.1016/j.biosystems.2023.105019.
70. Gahrn-Andersen, R, Prinz, R. Ensuring wholeness: Using Code Biology to overcome the autonomy-heteronomy divide. Biosystems 2023, 226, 104874, doi:10.1016/j.biosystems.2023.104874.
71. Zamecnik, L. Causal and non-causal explanations in code biology. Biosystems 2021, 209, 104499, doi:10.1016/j.biosystems.2021.104499.
72. Major, J.C. Archetypes and code biology. Biosystems 2021, 208, 104501, doi:10.1016/j.biosystems.2021.104501.
73. Lacková, E, Faltýnek, D. The lower threshold as a unifying principle between Code Biology and Biosemiotics. Biosystems 2021, 210, 104523, doi:https://doi.org/10.1016/j.biosystems.2021.104523.
74. Gare, A. Code biology and the problem of emergence. Biosystems 2021, 208, 104487, doi:https://doi.org/10.1016/j.biosystems.2021.104487.
75. D'onofrio, D.J, Abel, D.L. Redundancy of the genetic code enables translational pausing (Last accessed 9/2024). Frontiers in Genetics 2014, 5, 140 Open access doi:10.3389/fgene.2014.00140 1 Also at www.DavidAbel.us (Last accessed: 9/2024).
76. Liao, Y, Yin, X, Liu, W, Du, Z, Du, J. Chaperone Copolymer-Assisted Catalytic Hairpin Assembly for Highly Sensitive Detection of Adenosine. Polymers (Basel) 2024, 16, doi:10.3390/polym16152179.
77. Guarra, F, Sciva, C, Bonollo, G, Pasala, C, Chiosis, G, Moroni, E, Colombo, G. Cracking the chaperone code through the computational microscope. Cell Stress Chaperones 2024, doi:10.1016/j.cstres.2024.08.001.
78. Comert, C, Kjaer-Sorensen, K, Hansen, J, Carlsen, J, Just, J, Meaney, B.F, Ostergaard, E, Luo, Y, Oxvig, C, Schmidt-Laursen, L, et al. HSP60 chaperone deficiency disrupts the mitochondrial matrix proteome and dysregulates cholesterol synthesis. Mol Metab 2024, 88, 102009, doi:10.1016/j.molmet.2024.102009.
79. Colomer-Winter, C, Yong, A.M.H, Chong, K.K.L, Veleba, M, Choo, P.Y, Gao, I.H, Matysik, A, Ho, F.K, Chen, S.L, Kline, K.A. The HtrA chaperone monitors sortase-assembled pilus biogenesis in Enterococcus faecalis. PLoS genetics 2024, 20, e1011071, doi:10.1371/journal.pgen.1011071.
80. Vega, F. A Critique of Barbieri's Code Biology Through Rosen's Relational Biology: Reconciling Barbieri's Biosemiotics with Peircean Biosemiotics. Biological Theory 2018, 13, 261–279.
81. Vehkavaara, T, Sharov, A.A. Constructive Aspects of Biosemiotics. Biosemiotics 2017, https://doi.org/10.1007/s12304-017-9304-9.
82. Kull, K. Semiosis stems from logical incompatibility in organic nature: Why biophysics does not see meaning, while biosemiotics does. Prog Biophys Mol Biol 2015, 119, 616-621, doi:10.1016/j.pbiomolbio.2015.08.002.
83. Kull, K. Advancements in biosemiotics: Where we are now in discovering the basic mechanisms of meaning-making. In TARTU SEMIOTICS LIBRARY 11:

- Gatherings in Biosemiotics, Rattasepp, S., Bennett, T., Eds, University of Tartu Press: 2012.
84. Robinson, A, Southgate, C, Deacon, T. Discussion of the Conceptual Basis of Biosemiotics. *Zygon* 2010, 45.
85. Kull, K, Deacon, T, Emmeche, C, Hoffmeyer, J, Stjernfelt, F. Theses on biosemiotics: Prolegomena to a theoretical biology. *Biological Theory* 2009, 4, 167-173.
86. Barbieri, M. Biosemiotics: a new understanding of life. *Naturwissenschaften* 2008, 95, 577-599.
87. Pattee, H.H. The necessity of biosemiotics: Matter-symbol complementarity. In *Introduction to Biosemiotics: The New Biological Synthesis*; Springer: Dordrecht, The Netherlands, 2007; pp. 115-132.
88. Zhou, X, Lei, Z, An, P. Post-Translational Modification of WRKY Transcription Factors. *Plants (Basel)* 2024, 13, doi:10.3390/plants13152040.
89. Wang, D, Qiu, Z, Xu, T, Yao, S, Chen, M, Li, Q, Agassin, R.H, Ji, K. Transcriptomic Identification of Potential C2H2 Zinc Finger Protein Transcription Factors in *Pinus massoniana* in Response to Biotic and Abiotic Stresses. *Int J Mol Sci* 2024, 25, doi:10.3390/ijms25158361.
90. Volteras, D, Shahrezaei, V, Thomas, P. Global transcription regulation revealed from dynamical correlations in time-resolved single-cell RNA sequencing. *Cell Syst* 2024, doi:10.1016/j.cels.2024.07.002.
91. Versluis, P, Graham, T.G.W, Eng, V, Ebenezer, J, Darzacq, X, Zipfel, W.R, Lis, J.T. Live-cell imaging of RNA Pol II and elongation factors distinguishes competing mechanisms of transcription regulation. *Mol Cell* 2024, 84, 2856-2869 e2859, doi:10.1016/j.molcel.2024.07.009.
92. Patiyal, S, Tiwari, P, Ghai, M, Dhapola, A, Dhall, A, Raghava, G.P.S. A hybrid approach for predicting transcription factors. *Front Bioinform* 2024, 4, 1425419, doi:10.3389/fbinf.2024.1425419.
93. Teran, D, Zhang, Y, Korostelev, A.A. Endogenous trans-translation structure visualizes the decoding of the first tmRNA alanine codon. *Front Microbiol* 2024, 15, 1369760, doi:10.3389/fmicb.2024.1369760.
94. Sun, J, Hwang, P, Sakkas, E.D, Zhou, Y, Perez, L, Dave, I, Kwon, J.B, McMahan, A.E, Wichman, M, Raval, M, et al. GNN Codon Adjacency Tunes Protein Translation. *Int J Mol Sci* 2024, 25, doi:10.3390/ijms25115914.
95. Gonzalez-Sanchez, A.M, Castellanos-Silva, E.A, Diaz-Figueroa, G, Cate, J.H.D. JUN mRNA translation regulation is mediated by multiple 5' UTR and start codon features. *PLoS One* 2024, 19, e0299779, doi:10.1371/journal.pone.0299779.
96. Barrington, C.L, Galindo, G, Koch, A.L, Horton, E.R, Morrison, E.J, Tisa, S, Stasevich, T.J, Rissland, O.S. Synonymous codon usage regulates translation initiation. *Cell reports* 2023, 42, 113413, doi:10.1016/j.celrep.2023.113413.
97. Chatterjee, S, Yadav, S. The Coevolution of Biomolecules and Prebiotic Information Systems in the Origin of Life: A Visualization Model for Assembling the First Gene. *Life (Basel)* 2022, 12, doi:10.3390/life12060834.
98. Abel, D.L. Complexity, self-organization, and emergence at the edge of chaos in life-origin models (also available from [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Journal of the Washington Academy of Sciences* 2007, 93, 1-20, doi:https://www.jstor.org/stable/24536323.
99. Abel, D.L, Trevors, J.T. Self-Organization vs. Self-Ordering events in life-origin models (also available from [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Physics of Life Reviews* 2006, 3, 211-228, doi:10.1016/j.plrev.2006.07.003.
100. Kok, R.A, Taylor, J.A, Bradley, W.L. A statistical examination of self-ordering of amino acids in proteins. *Origins of life and evolution of the biosphere* 1988, 18, 135-142.
101. Abel, D.L. Moving 'far from equilibrium' in a prebiotic environment: The role of Maxwell's Demon in life origin (<http://DavidAbel.us> Last accessed in 9/2024). In *Genesis - In the Beginning: Precursors of Life, Chemical Models and Early Biological Evolution*, Seckbach, J., Gordon, R., Eds. Seckbach, J., Ed, Springer: Dordrecht, 2012; pp. 219-236.
102. Abel, D.L. What utility does order, pattern or complexity prescribe? (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic, Biol. Res. Div.: New York, N.Y., 2011; pp. 75-116.
103. Abel, D.L. The capabilities of chaos and complexity In *Proceedings of the Society for Chaos Theory: Society for Complexity in Psychology and the Life Sciences*, International Conference at Virginia Commonwealth University, Richmond, VA., Aug 8-10, 2008.
104. Durston, K.K, Chiu, D.K, Abel, D.L, Trevors, J.T. Measuring the functional sequence complexity of proteins (Also available from [www.DavidAbel.us](http://www.DavidAbel.us) Last Accessed 7/2024). *Theoretical biology & medical modelling* 2007, 4, 1-14 doi:https://tbimed.biomedcentral.com/track/pdf/10.1186/1742-4682-4-47.pdf

105. Abel, D.L., Trevors, J.T. Three subsets of sequence complexity and their relevance to biopolymeric information. *Theoretical Biology and Medical Modeling* 2005, 2, 29-45 [www.DavidAbel.us](http://www.DavidAbel.us) (Last accessed Nov, 2023), doi:<https://tbiomed.biomedcentral.com/articles/10.1186/1742-4682-2-29>.
106. Abel, D.L. Is Life Reducible to Complexity? In *Proceedings of the Workshop on Life: a satellite meeting before the Millennial World Meeting of University Professors*, Modena, Italy, 2000; pp. 3-4.
107. Abel, D.L. The capabilities of chaos and complexity (Also available at [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Int. J. Mol. Sci.* 2009, 10, 247-291 doi: <https://doi.org/10.3390/ijms10010247>.
108. Lambert, P.A. The Order-Chaos Dynamic of Creativity. *Creativity Research Journal* 2020, 32, 431-446, doi:10.1080/10400419.2020.1821562.
109. Basener, W. Limits of chaos and progress in evolutionary dynamics. In *Biological Information: New Perspectives*, Marks II, R.J., Behe, M.J., Dembski, W.A., Gordon, B.L., Sanford, J.C., Eds, World Scientific: Cornell University Proceedings, 2013; pp. 87-104.
110. Zenil, H. Lee Cronin's Assembly Theory Disputed & Debunked by Dr. Hector Zenil. Available online: <https://www.youtube.com/watch?v=078EXZeS8Y0> (accessed on
111. Uthamacumaran, A, Abrahão, F.S, Kiani, N.A, Zenil, H. On the Salient Limitations of the Methods of Assembly Theory and their Classification of Molecular Biosignatures. arXiv:2210.00901v9 [cs.IT] Cornell U. 2024, [v9] Wed, 17 Apr 2024 00:32:39 UTC (4,841 KB), doi:<https://doi.org/10.48550/arXiv.2210.00901>.
112. Jaeger, J. Assembly Theory: What It Does and What It Does Not Do. *J Mol Evol* 2024, 92, 87-92, doi:10.1007/s00239-024-10163-2.
113. Abel, D.L. "Assembly Theory" in *Life Origin Models*. PrePrints.org 2024.
114. Zenil, H. The 8 Fallacies of Assembly Theory – Medium. Available online: <https://hectorzenil.medium.com/the-8-fallacies-of-assembly-theory-ba54428b0b45> (accessed on
115. Benner, S.A. Assembly Theory and Agnostic Life Finding". *Primordial Scoop*, . e20230324 2023, doi:<https://doi.org/10.52400/APJX5069>.
116. Abel, D.L. Selection in molecular evolution. *Studies in History and Philosophy of Science*, 2024, 107, 54-63, doi:<https://www.sciencedirect.com/science/article/pii/S0039368124001110>.
117. Abel, D.L. Life origin: The role of complexity at the edge of chaos (pdf of PowerPoint available from [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). In *Proceedings of the Washington Academy of Science 2006*, Lecture delivered at the Headquarters of the National Science Foundation, Arlington, VA, 2006.
118. Evans, C.L. *Broad Band: The Untold Story of the Women Who Made the Internet.* ; Portfolio/Penguin. : New York, 2018.
119. Abel, D.L. *Primordial Prescription: The Most Plaguing Problem of Life Origin Science* LongView Press Academic: New York, N. Y., 2015.
120. Abel, D.L. *The Cybernetic Cut: Progressing from Description to Prescription in Systems Theory* [Scirus SciTopic Page] ([www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). Available online: [www.DavidAbel.us](http://www.DavidAbel.us) (accessed on
121. Abel, D.L. *The Cybernetic Cut and Configurable Switch (CS) Bridge* (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic, Biol. Res. Div. 55-74 New York, N.Y., 2011; pp. 55-74
122. Abel, D.L. The three fundamental categories of reality (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic: Biolog. Res. Div.: New York, N.Y., 2011; pp. 19-54.
123. Abel, D.L. What is ProtoBioCybernetics? (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic: Biolog. Res. Div.: New York, N.Y., 2011; pp. 1-18.
124. Abel, D.L. The 'Cybernetic Cut': Progressing from Description to Prescription in Systems Theory (Also available at [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *The Open Cybernetics and Systemics Journal* 2008, 2, 252-262, doi:1874-110X/08.
125. Alberts, B, Bray, D, Lewis, J, Raff, M, Roberts, K, Watson, J.D. *Molecular Biology of the Cell*; Garland Publishing: New York, 1994.
126. Watson, J.D. *The Molecular Biology of the Gene*; Benjamin: New York, 1965.
127. Watson, J.D, Crick, F.H.C. Molecular structure of nucleic acids. *Nature* 1953, 171, 737-738.
128. Watson, J.D, Crick, F.H.C. Genetical implications of the structure of nucleic acids. *Nature* 1953, 171, 964-967.



129. Turing, A.M. The chemical basis of morphogenesis. *Phil. Trans. R. Soc.* 1952, 237, 37.
130. Crick, F. Central Dogma of Molecular Biology. *NATURE*, 1970, 227, 561-563.
131. Crick, F.H.C. *Of Molecules and Man*; University of Washington Press: Seattle, 1968.
132. Crick, F.H.C. The Origin of the Genetic Code. *J. Mol. Biol* 1968, 38, 367-379.
133. Crick, F.H.C. On protein synthesis. In *Proceedings of the Symposia of the Society for Experimental Biology*, New York, 1958; pp. 138-163.
134. Nicolis, G, Prigogine, I. *Exploring Complexity*; Freeman: New York, 1989.
135. Prigogine, I, Stengers, I. *Order Out of Chaos*; Heinemann: London, 285-287, 297-301, 1984.
136. Nicolis, G, Prigogine, I. *Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order Through Fluctuations*, Wiley-Interscience: New York, 1977.
137. Prigogine, I, Nicolis, G. Biological order, structure and instabilities. *Q. Rev. Biophys.* 1971, 4, 107-148.
138. Prigogine, I. *Introduction to Thermodynamics of Irreversible Processes*; John Wiley & Sons: New York, NY, USA, 1967.
139. Prigogine, I. *Introduction to Nonequilibrium Thermodynamics*; Wiley-Interscience: New York, 1962.
140. 140. Abel, D.L. Constraints vs. Controls: Progressing from description to prescription in systems theory (<http://DavidAbel.us> Last accessed 9/2024). *Open Cybernetics and Systemics Journal* 2010, 4, 14-27, doi:10.2174/1874110X01004010014 10.2174/1874110X01004010014.
141. Church, A. An unsolvable problem of elementary number theory. *Am. J. Math* 1936, 58, 345-363.
142. Turing, A.M. On computable numbers, with an application to the entscheidungs problem. *Proc. Roy. Soc. London Mathematical Society* 1936, 42, 230-265 [correction in 243, 544-546].
143. 143. Abel, D.L. Formalism > Physicality (F > P) Principle SciTopic Paper Available online: <http://DavidAbel.us> (accessed on 9/2024).
144. Abel, D.L. The Formalism > Physicality (F > P) Principle (<http://DavidAbel.us> (last accessed 9/2024)). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press Academic: New York, N.Y., 2011; pp. 325-351.
145. Abel, D.L. The Genetic Selection (GS) Principle (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic: New York, N.Y., 2011; pp. 161-188.
146. Abel, D.L. The Genetic Selection (GS) Principle [Scirus SciTopic Page] ([www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). Available online: <http://DavidAbel.us> (accessed on 7/20/2024).
147. Abel, D.L. The GS (Genetic Selection) Principle (Also available at [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Frontiers in Bioscience* 2009, 14, 2959-2969 doi:10.2741/3426.
148. Tour, J. Public challenge to Jack Szostak and 9 other abiogenesis specialists to answer any one of five questions. Available online: <https://www.youtube.com/drjamestour> (accessed on 9/2024).
149. Tour, J. The Origin of Life Has Not Been Explained. Available online: <https://video.search.yahoo.com/search/video?p=james+tour+origin+of+life#id=5&vid=dd4103fe43753599738257330ef375ad&action=view> (accessed on 5/1/2024).
150. Thaxton, C.B., Bradley, Walter L, Olsen, Roger L, Tour, James, et al. *The Mystery of Life's Origin* Discovery Institute: 2020.
151. Manino, E, Bessa, I, Cordeiro, L.C. Towards global neural network abstractions with locally-exact reconstruction. *Neural Netw* 2023, 165, 344-357, doi:10.1016/j.neunet.2023.06.002.
152. Kim, J.K, Ahn, B.H, Kinzer, S, Ghodrati, S, Mahapatra, R, Yatham, B, Wang, S.T, Kim, D, Sarikhani, P, Mahmoudi, B, et al. Yin-Yang: Programming Abstractions for Cross-Domain Multi-Acceleration. *IEEE Micro* 2022, 42, 89-98, doi:10.1109/mm.2022.3189416.
153. Trevors, J.T, Abel, D.L. Chance and necessity do not explain the origin of life (Also available at [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Cell Biol Int* 2004, 28, 729-739, doi:S1065-6995(04)00141-6.
154. Abel, D.L. Linear Digital Material Symbol Systems (MSS) (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic, Biol. Res. Div.: New York, N.Y., 2011; pp. 135-160.
155. Rocha, L.M. Evolution with material symbol systems. *Biosystems* 2001, 60, 95-121.
156. Abel, D.L, Trevors, J.T. More than Metaphor: Genomes are Objective Sign Systems. In *BioSemiotic Research*

- Trends, Barbieri, M., Ed, Nova Science Publishers: New York, 2007; pp. 1-15 Downloadable from <http://DavidAbel.us> (Last accessed 19/2024).
157. D'Onofrio, D.J, An, G. A comparative approach for the investigation of biological information processing: an examination of the structure and function of computer hard drives and DNA. *Theor Biol Med Model* 2010, 7, 3, doi:10.1186/1742-4682-7-3.
  158. Abel, D.L, Trevors, J.T. More than metaphor: Genomes are objective sign systems (also available from [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Journal of BioSemiotics* 2006, 1, 253-267.
  159. Abel, D.L. The Universal Plausibility Metric (UPM) & Principle (UPP) (also available at [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). *Theor Biol Med Model* 2009, 6, 27
  160. Abel, D.L. The Universal Plausibility Metric and Principle (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic: New York, N.Y., 2011; pp. 305-324 <http://DavidAbel.us> (last accessed in 309/2024)
  161. Abel, D.L. The Universal Plausibility Metric (UPM) & Principle (UPP) [Scirus SciTopic Page] ([www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). Available online: <http://DavidAbel.us> (accessed on 7/20/2024).
  162. Abel, D.L. Physicodynamic Incompleteness. Scirus Sci-Topic Paper (<http://DavidAbel.us> (last accessed 7/2024) 2022.
  163. Abel, D.L. Physicodynamic Incompleteness (Scirus SciTopics Page) (also available from [www.DavidAbel.us](http://www.DavidAbel.us) Last accessed 9/2024). Available online: <http://DavidAbel.us> (accessed on 7/20/2024).
  164. Chaitin, G.J. Information, randomness & incompleteness : papers on algorithmic information theory, 2nd ed, World Scientific: Singapore ; New Jersey, 1990; pp. v, 320 p.
  165. Popper, K.R. Scientific Reduction and the Essential Incompleteness of All Science. In *Studies in the Philosophy of Biology: Reduction and Related Problems*, F. J. Ayala, a.T.D., Ed, Berkeley: University of California Press: 1974; pp. 259–284.
  166. Abel, D.L. Why is Abiogenesis Such a Tough Nut to Crack? *Archives of Microbiology and Immunology* 2024, 8, 338-364.
  167. Abel, D.L. The Birth of Protocells (<http://DavidAbel.us> Last accessed in 9/2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed, LongView Press--Academic, Biol. Res. Div.: New York, N.Y., 2011; pp. 189-230.
  168. Kuhn, T.S. *The Structure of Scientific Revolutions*, 2nd 1970 ed, The University of Chicago Press: Chicago, 1970.