fortune Journals

Perspective Paper

JOURNAL OF BIOINFORMATICS AND SYSTEMS BIOLOGY

ISSN: 2688-5107

What programmed the first genome?

David Lynn Abel

Abstract

All living organisms are controlled, not constrained [1], by programmed genomic commands. First, one of four nucleosides had to have been actively selected at each locus in the programming strings of polynucleotides. Formal rules, not laws, had to be followed to achieve coding. Any attempt to disavow purposeful choice of nucleosides produces one of only two possibilities: 1) stochastic ensembles or 2) nonrandom physicodynamic propensities favoring more ordered polymers such as polyadenosines. In either case, Genomic Prescriptive Information (GPI) and biofunction would have been compromised. A major aspect of genomics also includes other required purposeful choices that control superimposed codings, alternative splicing's, the number of tandem repeats used, methylation sites on DNA, acetylation sites on histones, transcription factor binding sites, and many other choice-based epigenetic controls. Genomes are also actively being algorithmically optimized real-time by Genomically Programmed Rearrangements (GPRs) (transposable elements [TEs] [2-5], long interspersed nuclear elements (LINES) [6-10] and reversible polymorphisms within the same individual) [11-33]. GPRs orchestrate rapid adaptation. Genomic efficacious executable choice commands are ultimately no more physical than Mathematics. They are nonphysical formalisms instantiated into physicality from the far side of the Cybernetic Cut [34-36]. The most critical questions life-origin natural science must address are, 1) "How was the first genome of efficacious executable choice-commands programmed?" and 2) "How were the nano-devices engineered at the same place and time needed to process those choice-commands according to the same formal arbitrary rule conventions? [37, 38].

Keywords: Mundane Proximate Teleology; Choice Causation; Physicalism; Materialism; ProtoBioCybernetics; The Cybernetic Cut; Infogenesis; Chance & Necessity; Synthetic Chemistry; The Definition of Life; Protocellular Metabolomics; Computational Biology; Life origin; abiogenesis; The Universal Determinism Dichotomy (UDD); The Formalism > Physicality (F > P) Principle; Physicodynamic Incompleteness; The Genetic Selection (GS) Principle.

What exactly is Programming?

Linear digital programming typically consists of a string of efficacious executable choice-commands. In material symbol systems (MSSs) [39-41], each purposeful choice is symbolized from an alphabet of physical symbol vehicles, or tokens. When properly processed, these denoted choice-commands are collectively observed to successfully compute and "halt." Turing and Church's famous "halting problem" [42-45] raises the question of how the programmer could know in advance that the computation would

Affiliation:
ProtoBioCybernetics/Protocellular Metabolomics, The Gene Emergence Project, The Origin of Life Science Foundation, Inc USA.

***Corresponding author:**
David Lynn Abel, ProtoBioCybernetics/Protocellular Metabolomics, The Gene Emergence Project, The Origin of Life Science Foundation, Inc USA.

Citation: David Lynn Abel. What programmed the first genome?. Journal of Bioinformatics and Systems Biology. 9 (2026): 108-126.

Received: August 11, 2026
Accepted: August 18, 2026
Published: August 26, 2026

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

successfully complete at the time each individual purposeful pre-function choice was made. Even the finest programmers can't know.

A program is an algorithm—a stepwise procedure of successive choice-commands made at decision nodes that generates desired outcomes. Usefulness; utility; computational success; and formal function of some sort is always sought in any programming process. Programming cannot be accomplished by Chance and/or Necessity. Neither Chance nor Necessity have a goal or the means to pursue a goal. Not even evolution has a goal. Without *purposeful selection* of a certain option from among multiple real options at each decision node, programming is impossible.

The programming must then be processed to be of any value. This is typically accomplished using very well designed and engineered computational "devices." Programming and its processing are both fundamentally formal, not physicodynamic [37, 46-67].

Can Chance Program?

We are not able to identify all of the complex causal factors of "chance events." They have no identifiable aim. No empirical basis exists to justify believing that chance events had any purpose. Thus, it seems reasonable to contend that chance (any amount of random mutations over any amount of time) cannot program a non-trivial computational program. Chance is not a known cause of any non-trivial useful effect. Chance refers to inherent variations from natural fluctuations. The variations are typically small and they even-out over time into a fairly stable pattern of background noise. Noise has never been observed to generate Prescriptive Information (PI). Chance is not a cause of *any* effect. When we talk about "chance," we are usually referring only to a very limited finite *epistemological description* and statistical prediction of the likelihood of future unknown outcomes [68].

Can Necessity Program?

Laws and constraints cannot program any better than chance [41, 69, 70]. If law did the programming, it would produce programs of all "1's," or programs of all "0's"- by law. What makes programming possible is the *freedom of choice* at bona fide *decision nodes*. Almost no Shannon Uncertainty/Possibility would exist to statistically measure if law were the programmer. No Prescriptive Information could possibly have been generated by laws or constraints. Necessity (law) precludes choices. Chance and Necessity are both also blind to usefulness, function and utility [1, 55-59, 62].

Choice Causation alone can program

Three fundamental categories exist in everyday reality, not two: Chance, Necessity and Choice [71-73]. The capabilities of Choice Causation are exhaustless. We contrast Chance and Necessity from Choice Causation for good reason. Programming of any kind requires the freedom of active selection from among multiple options at bona fide decisions nodes. We issue executable commands in hopes of prescribing desired and valued function and computational success. Choice causation is exercised when utility is valued and pursued by agents.

Mutations, whether random or physicodynamically-caused (nonrandom), cannot write programs or genomes [55]. The only other form of nonrandom mutations would be if they are formally directed toward utility by intent. But what in an inanimate environment would steer mutations toward the generation of halting computations? This steering can only be generated by Choice Causation, not Physicodynamic Causation (The Universal Determinism Dichotomy [UDD]) [71]. For mutations to be able to *direct, compute* and *control* homeostatic metabolism, they must be free from necessity, yet non-random. They must manifest functional intent (purposeful polymorphisms).

Evolution not only has no goal; Neo-Darwinian evolution doesn't even exist yet in a prebiotic environment. Nothing is alive yet to differentially survive and reproduce. Molecular/chemical evolution has been shown to require generative active selection, not after-the-fact secondary selection post-function [62]. With molecular evolution, molecules must be chosen prior to any function. Foreknowledge is required to know what active selections will eventually be able to contribute to metabolic and reproductive goals. Again, evolution has no goals.

Is "programming" an accurate description of genomics?

Are "programming," "cybernetic processing of efficacious executable choice-commands," "computations" and "engineered nano-devices" accurate descriptions of genomics and molecular biology? Absolutely.

All known life is programmed and cybernetically processed [53, 57, 74, 75]. Life is an amalgamation of halting computations and highly integrated circuits [50-52, 55, 76]. All of these phenomena are choice-controlled. They depend upon the cell's ability to generate efficacious executable choice-commands (EECCs). And they further depend not only upon the nanodevices to process those commands, but the "voluntary" agreement to abide by formal rule conventions, not laws, of interpretation and performance. This, too, required choice commitments.

What is a gene?

Physicalistic naturalism's traditional definition of a "gene" is "a functional unit of heredity." Immediately the old physicalism has two difficult issues to address: "function" and "heredity". What does metaphysical physicalism know about either? Achieving function and heredity uses physicality

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

the way an engineer uses steel and concrete. But neither function nor heredity is fundamentally physical. They are both abstract, conceptual, nonphysical formalisms, the same as mathematics, logic theory and language.

"Function" has to be defined before "unit of function" can be addressed. What does "function" mean? Defining "function" is impossible without using equally formal terms: utility; usefulness; desire; purpose fulfilment; role; job; formal work (not "work" as defined by physics). Genes do something useful. Genes contribute to pragmatism. They fill a need. Genes *prescribe* function. Genes not only provide instructions, genes issue efficacious executable choice commands at bona fide decision nodes. When cybernetically processed, these choice-commands bring about computational success. They integrate circuits. They determine the starting and reaction conditions that steer and maintain the chemical synthesis of needed metabolites. They direct the transduction of energy and orchestrate metabolic schemes. Some genes perform a lot of different useful functions, especially in view of alternative splicing's[77-80], varying controllable numbers of tandem repeats [81-85], transcription factors [86-90]; epigenetic configurable switch-settings [91-94], etc. Raw physicodynamics on the near side of The Cybernetic Cut [34-36] can achieve none of these formalisms.

The "unit" within the definition of a gene may be physical DNA, but what this unit achieves and how it is used is altogether nonphysical and formal. Both function and heredity, like all formalisms, arose from the far side of The Cybernetic Cut [34-36]. Neither can be generated by physicodynamic causation on the near side of this great ravine.

What is a genome?

Genomes formally prescribe and control living organisms with executable choice commands conveyed using Material Symbol Systems (MSS) [38-41, 95, 96]. This includes active selection of each nucleoside; active selection of nucleotide syntax; transcription; translation; specific pairing of tRNAs with amino acids [97]; previously manufactured specific aminoacyl tRNA synthetase enzymes; start codons; stop codons; enhancers, promotors; 5' UTR's [98-101]; silencers [102-104]; open reading frames; introns; exons; 5' caps [105, 106]; poly-A tails [107-109]; use of various superimposed/ multidimensional codes [48, 110]; highly integrated configurable switch-settings (e.g., DNA methylations; histone acetylations; alternative splicing's of lncRNAs; transcription factors; the setting of tandem repeat numbers; micro RNA silencing; Genomic Programming Rearragements (GPRs) such as TEs and LINEs, Adaptive Pausing Responses, (APRs); Integrated Stress Response (ISR) [144]; many other kinds of transcript variants.

A genome consists of Prescriptive Information (PI) [67, 95, 111] that generates homeostatic metabolism far from equilibrium. PI is Abel's more refined version of Szostak's "functional information" [112-114]. Genomic Prescriptive Information (GPI) [48, 95, 111] consists of Efficacious Executable Choice-Commands (EECC). The ongoing active processing of Efficacious Executable Choice-Command Causation and Control (EECCCC) is the very long-awaited formal definition of life [50, 51, 57].

Genomic Prescriptive Information (GPI) is not just recorded suggestions or instructions of "how to . . . ." That would be hard enough to explain from physicalism alone. Genomic PI consists of actual executable commands. Final function is spatial and tertiary, not just primary or secondary structure. Those linear digital commands incredibly foreknow what the Gibbs minimum-free folding energies of each polynucleotide and polyamino acid mega-peptide (protein) will be. The linear digital commands also know which tertiary structures are needed for chaperone-controlled protein folding and for catalysis of thousands of controlled reactions needed for being and staying alive. How was that achieved using a linear digital representational/symbolic system of recording commands?

Genomes prescribe and propagate useful biofunction with a holism that includes highly integrated circuits. [50, 51, 55-57, 62]. Genomes, like gaming software, are programmed with extraordinary "degrees of end-user freedom" [55, 57, 62, 115]. No human programming can hold a candle to the sophistication and ingenuity of life's programming and cybernetic processing. This is true even of the simplest known life forms (e.g., *Mycoplasma genitalium and mycoides*). To believe that such final function was generated by anything other than efficacious formal choice-commands is the real fanatical "blind belief."

The bottom line of GPI is purposeful choice commands at bona fide decision nodes instantiated into physicality using a material symbol system. The fact that life emanates only from purposeful choices is a major reason physicalistic naturalism has never been able to explain abiogenesis. It is also the reason that physicalism is not a viable worldview [76]. Physicodynamics cannot make purposeful choices at bona fide decision nodes. Physicodynamics does not recognize, nor can it pursue function, usefulness or utility. Yet all of the life sciences are forced to deal with the reality of Mundane Proximate Teleology (MPT) [49, 76] on a daily basis. All known life is programmed and cybernetically processed to achieve the ultimate in sophisticated function. Life is controlled, not merely constrained, by GPI. Life could only have arisen out of purposeful choices. Whether we like it or not, that's what programming is. Purposeful choices are life's very essence. Algorithmic optimization is about improving those choices to achieve better computational efficiency, fittest genomes, and only secondarily fittest phenotypes.

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

We are never going to understand the meaning of this text if we limit our study to molecules of ink on molecules of paper, or focus merely on "physical" electrons. Genes have their meaning in the symbolized executable choice commands that orchestrate biofunction and life, not just physico-chemistry or even microscopic physics. Alternative splicing and methylations of DNA have formal functional consequences, not just physicodynamic effects. What genes do is purposeful and in the pursuit of utility. Invariably this requires Choice Causation at bona fide decisions nodes—choosing from among real alternatives with the intent of prescribing usefulness. The commands are proven to be efficacious by virtue of eventual computational halting with maximum efficiency. This computational halting is the homeostatic metabolism far from equilibrium that programming choices alone produce and optimize. But this effect is not realized at the time the active choices have to be made. How did inanimate protolife outsmart the Turing problem to generate life?

Heredity

Heredity is a form of function. Heredity makes possible the passing on to future generations of these "functional units," or modules, of programmed efficacious executable choice commands.

Metabolism is not replicated in heredity. Recorded, symbolized, efficacious executable commands are inherited. The representational formal "rule systems" and devices to process those commands must also be inherited. These systems are not like mere thermodynamic or weather-front pseudo "systems." The latter two are not even formal true "systems." Metabolism is an abstract, conceptual, steered, formal, pragmatic system to which physicodynamics is blind. Life processes have to be pragmatically directed.

What enabled chemistry to fashion formal gene function? How was heredity conceived and accomplished? Physical symbol vehicles *represent* meaning. Representationalism is formal, not physical. Symbols and symbol-sequences can be replicated and passed on to new generations by highly refined formally functional replicative systems. They even have very sophisticated error correction mechanisms [116, 117]. But the devices needed to process these inherited commands must also be prescribed and manufactured [118, 119]. Heredity is a formal process of recuring formal effects, the same as everyday engineering.

Symmetry/Reversibility cannot explain genomic programming

No symmetry exists in genomics. Choice Causation and the Prescriptive Information of genomics are invariably time-irreversible. Choice causation operates only within the dimension of the time arrow. The effects of choice causation cannot be reversed without new contravening choices being made. The physical laws are technically not causes of effects, anyway. They are just measurement equalities expressed in nonphysical mathematical equations.

The symmetry of natural law knows nothing of pragmatic benefit. Reversibility knows nothing about vectors through time of progressive algorithmic optimization. One bad choice can produce a fatal blue screen with, "Does not compute!" The only mulligans in programming involve starting over with better choices. To reverse a prior choice, a new choice must be issued that supplants the first one. The first choice cannot go backwards. It does not ever reverse itself. Mulligans require new and different choices. In this sense, genomic PI (GPI) is not determinative in the sense of equational laws. GPI is causative in time.

What good is programming without processing?

In addition to needing explanation for the phenomenon of programming, the New Naturalism [49, 76] must also address the cause of highly engineered nanocomputers and incredible molecular machines needed to process choice-command syntax. For either programming or devices to be of any value, they both must be produced at the same relative place and time obeying shared arbitrary conventional rules, not laws. Rules are chosen. They are nonphysical, abstract, conceptual and formal. They are not just physicodynamically constrained. Where did these engineered devices come from, especially at the same time and place as the string of programming commands? We immediately encounter still another of the usual chicken-and-egg paradoxes of abiogenesis science. We can't have devices without life. We can't have life without nano-devices.

The processing of a program either has to be accomplished directly by an agent, or by "devices" designed and engineered by agents. The devices would be what NASA calls "biosignatures," that is, products that are uniquely produced only by "life." Life itself is a biosignature of life—another chicken and egg paradox. Life is a product that only the agency of life could have produced, because it requires purposeful choices at bona fide decision nodes in order to generate non-trivial efficacious executable choice commands and controls. This is something that physicodynamics on the near side of the Cybernetic Cut cannot do. So, what could have caused life? "All life must come from previously existing life." Could it be that pre-exiting life existed on the far side of The Cybernetic Cut prior to its instantiation into the near physicodynamic side?

What is life?

For centuries we have struggled to formally define life. The best we could ever do was to provide descriptive lists of typical attributes of life [53, 120-136]. Gecow [47, 137] appeals to half chaos and half order that progresses in biological evolution. But formal organization must be

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

distinguished from mere order [138]. And evolution did not exist in a prebiotic environment [58]. In his promotion of "unintentional purposeful information," Gecow attempts to distinguish the concept of "purpose" from subjective intention. Yet empirical evidence of physicodynamics having any sense of purpose seems nonexistent. The best potential model to evaluate "self-organization" and "emergence" claims would be in an abiotic environment where nothing exists but inanimate physicodynamics. Logic dictates that such an environment could only be sterile.

As already defined above, life is the active ongoing Processing of Efficacious Executable Choice-Command Causation and Control (PEECCCC). This is a potentially falsifiable definition [50, 51, 54, 55]. This formal definition of life is applicable to all forms and kingdoms of life. It is applicable to non-evolving lifeforms and to suspended animation. It is even usable by NASA. This definition of life can only be called programming and computation. Our problem is that physicodynamics cannot program or process such computations. The cybernetic processing of nucleotide syntax, along with a lot of other formally-controlled biological processes, proves the reality of those efficacious executable commands. Life consists of innumerable integrated, successful "halting's" of programmed computations. These computations don't just happen. They are not physicodynamically caused. They are certainly not random events. Whether we are willing to admit it or not, they are caused by efficacious Choice Causation [71] arising from the far side of The Cybernetic Cut [34-36] These commands cannot be explained by Chance and/or Necessity.

The only known cause of Efficacious Executable Choice Commands (EECCs) is active selection at bona fide decision nodes. For the old physicalistic naturalism to be foundational to science, it must be able to explain this phenomenon in purely physicodynamic terms. If it cannot, physicalistic naturalism as a metaphysical worldview has no place in natural science as its most foundational axiom. Einstein's warning to minimize metaphysics in natural science is justified and affirmed.

Life's PI also includes epigenomic switching controls, lncRNA alternative splicing, transcription factors, variable tandem repeat number controls, etc. But all of these controls depend upon active selection prior to the realization of any computational halting or biofunction. Particularly when we examine the question of the very first genomic programming, the programing choices and their syntax would have had to precede any biofunction at all. Resistance to this statement usually centers on autocatalytic RNAs. The many serious problems with self-replicative RNAs are usually ignored, but have been the subject of scores of previous papers and books [58, 115, 139-158].

Life is not reducible to physico-chemistry

Purposeful choices produce real effects that are one-way only: nonsymmetrical and time-irreversible. This is very different from microscopic physics, especially. Wang [159] in 2025 demonstrated that life cannot be reduced to chemistry. Life requires a prescriptive information role. Wang showed that objects are linked to representational symbols in coding and decoding functions. He defines biological information in terms of the decoding process. Molecular machines such as membrane receptors and ribosomes connect signs to physical objects. He argues that the unidirectional flow of genomic prescriptive information (GPI) through molecular machines and nanocomputers violates the microscopic time-reversal symmetry of physical laws mentioned in Section 2.4. Irreversibility in chemistry forces acknowledgement of a prescriptive informational contribution to life's processes. Molecular machines provide specific mechanisms to unidirectionally connect extracellular signals to intracellular second messengers in signal transduction. Extracellular signals unidirectionally flow to intracellular second-tier messengers. The role of nucleotide triplets in translation depends on their position in mRNA. No chemical basis exists for amino acids to flow to specific triplet codons. No reversibility exists. Wang contends that biological information is non-physicochemical and differs ontologically from physical chemistry. An arrow of time is manifest in life that is not apparent in inanimate nature [159]. Wang contends that the unidirectionality and irreversibility of biological information violates the (microscopic) time-reversal symmetry in physical laws and the principle of microscopic reversibility in chemistry.

The Undeniable purposeful choices of subcellular life

Each nucleoside must be purposefully chosen from among four options at every locus in the programming string. The belief that this active nucleoside selection is nothing more than happenstantial becomes rapidly more statistically prohibitive with each addition to the long functional polynucleotide chain. Each nucleoside choice matters, as proven by the fact that only one wrong nucleotide choice out of 3 billion choices can cause sickle cell anemia, achondroplasia (dwarfism), and scores of other genetic diseases.

Spin selectivity must be chosen: right handed sugars only; left-handed amino acids only. No physicochemical basis for this choice exists without investigator involvement in experimental design used to steer events toward homochirality. Pure populations of reagents generated from already existing life must be purchased to model homochiral proto-metabolism. Even when steered, handedness is only partial, never absolute as life requires [160-164].

The sequencing—meaningful syntax—of nucleoside selections needed for the polynucleotide to prescribe specific

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

formal biofunctions has to be purposefully chosen. Although genomics is ultimately four dimensional, the linear digital sequencing of nucleotides effectively determines minimum Gibbs-free energy conformations and molecular functionality. Wrong nucleoside choices prevent proper protein folding which in turn prevents proper protein function, whether structural or catalytic. Chaperones themselves must also be prescribed with linear digital code.

The triplet codon table is representational and formal. Each nucleoside choice affects the coding. While some flexibility exists in the triplet codon table, good programming reasons have been discovered on many levels for this flexibility. The flexibility is nonrandom, and highly specific and purposeful [110]. It is not just "degenerative" [110]. The sextet translational pausing code superimposed on the triplet codon code is just one of the reasons for the triplet code flexibility. Proper folding of the translated polyamino-acid into needed proteins is controlled by the superimposed translational pausing code [110]. Nucleoside selection is critical to the translational pausing code just as it is to the triplet codon code. For both superimposed codes to accomplish their tasks, flexibility is required in the triple codon scheme.

Table 1: Undeniable subcellular purposeful choices

1. Nucleoside active selection at each locus in the forming programming string
2. Spin selectivity choice for sugars and amino acids
3. Chosen nucleotide sequencing that produces syntactical programming
4. Triplet codon table representationalism requires choice of certain triads of nucleotides
5. Superimposed Sextet Translational Pausing coding requires choice of certain nucleotides [165]
6. Alternative splicing choices, especially of lncRNAs, determine multiple functions [166, 167]
7. Transcription factors require choice of where to bind DNA to achieve needed utility
8. Purposeful choices of methylation sites on DNA determine functions
9. Purposeful choices of acetylation sites on histone proteins determine DNA coiling and function
10. Other kinds of epigenetic switches require purposeful choices to set.
11. Purposeful choices of the number of tandem repeats determine biofunctions and adaptation [82, 84, 85, 168-171]
12. Operons
13. Promotors
14. 5' UTR's [98-101]
15. Silencers [102-104]
16. Open reading frames/exons
17. Introns
18. 5' caps [105, 106]
19. Enhancers [172, 173]
20. Repressors [174-176]
21. Specific pairing of tRNAs with amino acids [97]
22. Previously manufactured specific aminoacyl tRNA synthetase enzymes
23. Start codons
24. Stop codons
25. Poly-A tails [107-109]
26. Use of various superimposed/multidimensional codes [48, 110]
27. Many other kinds of highly integrated configurable switch-settings [91, 93, 177, 178]
28. Adaptive pausing response (APR) (ribosome stalling at translation initiation codons) [179]
29. Integrated Stress Response (ISR) signaling that permits resumption of growth and reversal of mitochondria fragmentation [180]
30. microRNAs (miRNAs) silencing of other RNAs and their post-transcriptional regulation of gene expression [181]
31. The shifting around of transposable elements (TEs) [182]
32. Large scale structural variations (LINEs) to achieve rapid adaptation [2-4, 7],
33. Transcript variants [183] of eukaryotic genes that each express many varied mature mRNAs

All of these capabilities demonstrate the efficacious executable programming commands and controls of life.

Choice-control commands and their processing are unique to life [37, 50-52, 54-58, 61-63, 65, 95, 115, 120, 184]. Genomic Prescriptive Information (GPI) [48, 95, 111] doesn't just instruct. GPI directs, controls and executes life's activities.

Life is formal more than physical

The programming and computation in subcellular life is extraordinarily sophisticated. Our finest human programmers cannot out-smart the Turing and Church's "halting problem" [42, 44, 45]. How did prebiotic nature? How did Chance and Necessity? The inability to answer this question has effectively dethroned physicalistic naturalism as the official metaphysical worldview of natural science [49-52, 153].

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

Synthetic chemistry and all of the biological sciences, especially, have affirmed the wisdom of Einstein's warning to minimize such metaphysics [185-188]. We thought we had done this when we prohibited any discussion of Choice Causation from natural science. Choice was defined presuppositionally as being too metaphysical. The purely formal mathematical laws of physics and chemistry received no such negative prejudicial treatment. We incorporated this glaring inconsistency into our very definition of "science" as its most fundamental axiom: "Physicodynamics is all there is; physicodynamics is sufficient to explain all of reality." No axiom could be more purely metaphysical, dogmatic, absolutist, blindly faith-based, and unsound.

We need to seriously consider the following questions that may threaten our current lifelong worldview:

1) How does differential phenotypic survival and reproduction improve the active selection of each nucleoside and polynucleotide syntactical programming?
2) Was it Chance or was it Necessity that advanced the genomic and epigenomic programming of an insect to that of a cow?
3) Is mere time a cause of effects?
4) Will eons of time *program* computational halting and algorithmically optimize genomes?
5) Exactly what is it that mutates [55]?
6) If Genomic Prescriptive Information [GPI] is what mutates, what caused GPI?
7) How did the very first genome get programmed *prior to* its mutation?
8) Do typographical errors write PhD theses?
9) Why are so many mutations now being proven to be non-random [189-193]?

Many lower animal choices conform to rules they are not equipped to question. Bacteria *choose* to approach food sources. The unspoken rule is that food sources must be approached to provide benefit. Bacteria *choose* to avoid noxious stimuli. The unspoken rule is that survival depends upon choosing to leave the area of poison. Because of the exercise of purposeful choice, bacteria are technically "agents." Their survival depends upon their very real choices. Natural science cannot continue to "shove under the rug" this reality. It must address the "How?" of Choice Causation and Mundane Proximate Teleology (MPT). Teleonomy fails miserably when it attempts to redefine purpose and choice into a purely physicalistic framework.

Even before discussing life, the physical Laws are all formal, not physical. Both mass and velocity in law equations are *formal measurements*. The quantity of motion consists of formal representations, not physical entities. Momentum cannot be conceived in physics outside of measurement and mathematical formulation. What is conserved is the vector parameter of motion "p" called "Momentum." It is calculated by multiplying the object's measured mass times its measured velocity and direction. Momentum's direction is the same as the direction of the object's velocity. As the object increases in mass or velocity, it is harder to change its direction or to slow or stop it with some external force. A vector quantity is a formal representational measurement.

Thus, both laws and rules are formal rather than physical. The *relationships* within those equalities are formal rather than physical. Our manipulation of equations is formal. The application of laws in problem-solving is formal. Should we be surprised that Mundane Proximate Teleology (MPT) is formal? Should the fact that MPT is formal rather than physical disqualify it from natural science investigation? We don't disqualify mathematics and equalities of measurements from natural science.

Even if we finally came up with one parsimonious unifying equation for reality, it would still be a nonphysical formalism and mathematical equality originating from the far side of The Cybernetic Cut. And that equation of everything would still not in and of itself identify Cause. The determinism would arise from mathematical equality constraints within the equation, not from an explanation of what actually caused the purposeful choices that in turn caused the effect of the cosmic formalism (e.g., the mathematical laws; logic theory) that describe physicality. The Formalism > Physicality [F > P] Principle [67, 194] points to the governance of formalism over physicodynamics.

Then, we have the problem of synthetic chemistry needing formal steering at every turn. Both initial and operative conditions must be chosen and controlled. Otherwise, only useless black tar results.

The genome is a formal effect in addition to being a formal cause.

We tend to think of the genome as the cause of biological formal organization, orchestration and controls. But the genome also must be viewed/considered as an effect rather than a cause. Something caused the effect of the programmed genome. Most researchers conduct their investigation into what caused the genome with nothing but macroscopic and microscopic naturalistic physics. Their metaphysical presuppositions of physicalism blind them to the logical impossibility of explaining formal orchestration with nothing but physical interactions. Quilici et al [195] , for example, emphasize the increasing role of computational quantum chemistry in trying to understand the chemical pathways that may have led to life's origin. But physicodynamics is on the near side of The Cybernetic Cut [34-36]. Formalisms involve Choice Causation and invariably arise on the far side

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

of this great ravine. In addition, "computational" anything is formal, not physical. If computation has to be used to figure out the cause, we have already violated the starting purely metaphysical presupposition of physicalism. We cannot "argue our case" for physicalism without employing formal contentions.

Not only is Genomic Prescriptive Information (GPI) part of every-day down-to-earth reality, so is mathematical physics and synthetic chemistry. To fully investigate everyday intra-cosmic reality, the natural sciences must shift to the methodology of The New Naturalism [49]. The New Naturalism explores Choice Causation in addition to Physicodynamic Causation. The New Naturalism acknowledges that the majority of significant real physical effects in everyday reality are caused by purposeful choices. Programmed four-dimensional genomes is just one of these innumerable rationally steered effects. Science cannot fulfill its mission studying only physicodynamic causation. Doing so would preclude justification of the scientific method itself.

Decision nodes cannot be reduced to mere "bifurcation points." A phase space of mere possibilities and Shannon statistical Uncertainty has never been observed to spontaneously produce refined engineering-like utility. We never cease imagining the latter. But we have zero empirical basis for such a supposition. It's just that we HAVE to given our metaphysical persuasions. No other possibility exists other than self-organization of highly refined formal orchestration and device engineering. "It HAD to have happened, because here we are!" That is a conclusion forced only by prior purely metaphysical presupposition—something Einstein specifically warned against [187, 188]. The physicalist is forced to believe against all reason that the genome HAD to have just emerged. We incorporated this blind-belief metaphysic into our very definition of science. Physicodynamics was all we had to work with, and all that was allowed. Even if the genome really is a program of efficacious executable choice-commands, inanimate nature *had* to have issued them given our physicalistic presuppositions. One or more of the four known forces *had to have done* the programming. Was it the force of gravity? Was it the electromagnetic force that did the programming? Was it the strong or weak nuclear force? Whatever the cause of the effect known as the programmed genome, we confidently believed it just happened given enough time. Never mind that no amount of time is a cause of any effect. Yet we believed the genome just self-organized itself into existence, pathetically pointing to eons of time as the cause. You know, it just "emerged." This is what the former physicalistic naturalism sold as "science" [37, 52, 55, 56, 76, 153, 155-157, 196-198]

Fittest phenotypes secondarily survive and reproduce best only because the genomes that prescribed and computed them are fittest [57]. This is the Genetic Selection (GS) Principle [184]. Phenotypes didn't just "emerge." Living phenotypes cannot "self-organize" themselves into existence. Neither can the genomic programming that prescribes them.

Genomic prescription of multi-step function (e.g., the Krebs cycle and reverse Krebs cycle) could not have been produced by trial and error tinkering. The number of permutations quickly rises to insurmountable odds, and becomes a statistically prohibitive achievement by noise. Many fail to realize that "tinkering" and "trial-and-error" searches are still searches. Inanimate nature does not conduct searches. Tinkering, crude though it may be, is still an active search and selection process. Not even evolution conducts trial-and-error *searches*. Evolution has no goal. Evolution searches for nothing. There is NO "so that . . . " and NO "in order to . . . " in evolution. Yet these purposeful concepts are repeatedly used in paper after paper as the mechanism of "natural selection." In legitimate evolution theory, evolution cannot pursue goals or program genomes. It is altogether secondary. Evolution is only phenotypic. It does not purposefully tinker with or algorithmically optimize genomes. No basis for iterative engineering processes exists in natural selection. No such process has ever been observed to just spontaneously "emerge" or "self-organize" from inanimate nature. Natural selection is always after the fact of algorithmic optimization at the genomic level. First, genomic prescription must arise using a linear digital symbol system to prescribe efficacious executable choice commands (The Genetic Selection (GS) Principle [184].

Reality is fundamentally formal. Physicality is secondary. Physicality is only an effect, not the primary cause. Ultimately, everything formally controlled emanates from the far side of The Cybernetic Cut [34-36], including the Mundane Proximate Teleology (MPT) [49, 76] that is instantiated into the near side of the Cybernetic Cut secondarily. Physicodynamics was never primary. It was always a secondary product—a temporary materialization and instantiation of formal prescription. And that formal prescription in life comes in the form of Efficacious Executable Choice-Command Causation and Control (EECCCC), the formal definition of life [50, 51, 54-58])

Even AI has to be programmed. The only way AI can "make choices of its own" and "learn" is if it has been programmed to do so by agency. No inanimate "it" will ever be able to choose or learn on its own. It must be steered and programmed to learn and choose "on its own." It must be taught and commanded to do its own thing with impressive *programmed* end-user freedom.

Vo et al [183] studied eukaryotic genes that each express many varied mature mRNAs. These are defined as transcript variants. Alternative transcription start sites are chosen. Alternative post transcriptional processing is purposefully selected. These transcript variants prescribe proteins in

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

distinct functional domains. Even noncoding RNAs are selectively generated. Each has highly tailored metabolic roles. All of these prescriptions are non-random. They are directed by efficacious executable commands. Many of these commands do not arise from Crick's Central Dogma, but from unknown, peptide, protein, long noncoding RNAs and other RNAs, Methyl groups, acetyl groups, the selected number of tandem repeats and a whole slew of other causative factors. Increasingly, epigenetic configurable switch-settings seem to play even bigger choice-command control role than the genes themselves. The prescriptions are cell-type specific. They vary with developmental stages, aging processes, and pathogenesis of diseases.

There is no getting around programming choices, purpose, and teleology, as Oxford physiologist Dennis Nobel contends [199, 200]. RNA sequencing (RNA-Seq) is becoming increasingly more important in identifying purposeful transcript variants that *control* life, not constrain life.

Life pursues staying alive in its every molecular biological and biochemical activity. Life manifests purpose at every turn. The only way "mutations" are going to explain efficacious executable choice-commands is if they are purposefully chosen—"directed," as we would call it.

Genomically Programmed Rearrangements (GPRs) are reversible polymorphisms within the same individual that orchestrate rapid adaptation. [11-33]. GPRs, like the initial genome, require Choice Causation to efficaciously re-program the genome on the fly. This reprogramming (GPRs) cannot appropriately be referred to as mutations in the traditional sense. These polymorphisms are chosen. Choice Causation is real in genomics and molecular biology [56]. This purposeful steering begs intra-cosmic explanation [54, 55, 57, 58, 61, 115]. It cannot be conveniently compartmentalized into metaphysics, and then ignored. Real intra-cosmic causes of real physical effects must be addressed by natural science. This constitutes The New Naturalism [49, 76]. For nonrandom, non-physicodynamically caused mutations to be considered GPRs, Mundane Proximate Teleology (MPT) is required [49, 76]. MPT is very different from questions of metaphysical ultimate transcendent teleology. The latter has nothing to do with every-day down-to-earth Choice Causation. We observe Choice Causation of real physical effects a hundred times per day in all directions. Science cannot ignore such obvious empiricism.

Also chosen are epigenetic switch-settings. De Carvalho et al [25] found that the interplay of epigenetic and genetic variation influences population divergence and potentially contributes to speciation. DNA methylation was associated with regions exhibiting accentuated genetic differentiation between populations of *Timema cristinae* stick insects. Epigenetics has to be included within the programming concept of genomics. Methylations and acetylations are methods of achieving Efficacious Executable Choice Command and Control (EECCCC), the processing of which is the defining element of life vs. nonlife [50, 51, 54-57, 61].

Medical geneticists recognize genomic programming for what it is.

The fact that all known life is programmed and cybernetically processed seems well accepted by most geneticists and molecular biologists at this point [53, 54, 201-203]. All of the medically related biosciences make liberal use of life's programming model in seeking treatments. Innumerable abnormalities are attributable to programming "bugs." Many of these "bugs" consist of nothing more than one aberrant single nucleotide polymorphism (SNP) [204]. Achondroplasia, sickle cell anemia, cystic fibrosis, hemophilia, Huntington's disease and many autoimmune diseases are just a few examples of just one "typographical error" adversely affecting the entire coded program.

No programming choices known to natural science are more efficacious than the programming choices of non-diseased genomics. Disease most often comes in the form of only one deleterious SNP typographical error in what *was* 3 billion good choices in coding.

We have always known that 'programming by random mutations" was an embarrassing model to have to dogmatically preach and defend. But given our purely metaphysical presupposition that "Physicality is all there is," we had no choice but to preach it. As it became more and more evident that many mutations are nonrandom [189-193, 205], the notion of macroscopic genomic causation shifted from Chance to Necessity. The problem then became that Necessity precludes Prescriptive Infogenesis. Law not only cannot program, law precludes programming. Law allows for no freedom and flexibility. PI requires active selection from among real options. The latter is the key to refined function. Necessity eliminates the freedom to choose at each decision node. Outcomes are fixed with probabilities very near 1.0. Results are pre-determined by Necessity. Thus, programming choices and controls become impossible. Prescriptive Information can only be generated out of freedom from necessity. Without Shannon Uncertainty, infogenesis becomes impossible. Law would eliminate almost all uncertainty. Fixed law kills freedom. A hoped-for parsimonious equation of everything would make it impossible to explain most anything. The majority of what is really interesting in this world is what was generated by the freedom of Choice Causation at bona fide decision nodes, not highly-ordered, redundant, boring , parsimonious order determined by Physicodynamic Causation [49, 76].

Undecidability?

Is the source of these initial protocellular choice-commands "undecidable" by science? If so, physicalistic

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

naturalism just disqualified its claim to exclusive explanatory knowledge. It just admitted it's failure to establish exclusivity of understanding using nothing but physicodynamic physicalism. The second is says, "It cannot be determined," physicalistic naturalism cannot simultaneously argue that "Chance and Necessity are sufficient to understand all of reality."

Elucidating the cause of the first genome is a perfectly reasonable "How?" question of natural science inquiry. As long as natural science continues to contend that life-origin is purely physicodynamic, it cannot simultaneously argue that the cause of the first genome is "undecidable" (metaphysical—beyond physics to ascertain). Natural science is obligated to fully explore what caused initial Genomic Prescriptive Information (GPI) in the first gene [37, 38]. PI cannot mutate unless it first exists [55]. What produced PI in the first place? What chose the commands recorded in *the template* that then educated and enlightened the stochastic ensembles of RNA analogs? It accomplishes nothing to keep talking about "templates" if the templates themselves contain no PI. What was the source of the template's efficacious executable commands? How did the template know what to prescribe? Without an answer to this question of the source of the template's GPI, there remains no point to studying replication of the template. Even if the template got replicated, the question would remain, "So what?"

Nothing is more "natural" in this world than life. In every direction we look we see extremophiles. If life's origin is unexplainable by physicalistic naturalism, physicalistic naturalism is dead as the foundational axiom of science. It can no longer remain a respectable metaphysical worldview, either. Life is too prevalent and central to reality. It is a bankrupt perspective that cannot measure up to its reputation.

Probably the most difficult problem of all is to explain the "How?" and origin of down-to-earth Mundane Proximate Teleology (MPT) [49, 76]. There's no problem with admitting, "We don't know what programmed the first genome. It's a great mystery." We are simply admitting that naturalistic science doesn't know everything it has always claimed to know in its physicalistic dogma.

Self-Organization and Emergence

Stochastic ensembles of RNA and RNA analogs have never been observed to "self-organize" or to "emerge" into anything better than stochastic ensembles. Zero empirical evidence exists of nontrivial function "self-organizing" out of physicodynamics alone. It is a logical impossibility for anything to organize itself into existence. It would have to already exist to do any organizing. No concept more ridiculous has ever become so entrenched into mainstream peer-reviewed literature than the notion of "self-organization." It is nothing more than fairy tale pipe dream. The notion was made necessary by being forced into a corner with the bankrupt presupposition of physicalism. Formal organization requires purposeful steering which requires purposeful choices. Formal organization and orchestration must be distinguished from Prigogine's mere self-ordering of dissipative structures [138, 206-208]

Decision nodes are not mere "bifurcation points." Choices (active purposeful selections) produce very real physical effects not explainable by metaphysical physicalism. Innumerable "end-around runs" of explanation of "controls" have been attempted, but without success [209-212]. Constraints are not controls unless those constraints are purposefully chosen. An example is the choice of initial conditions and environmental constraints of ongoing reactions in experimental designs. We are often blind to such "investigator involvement," drawing false naturalistic conclusions as a result.

Mundane Proximate Teleology had to have programmed life

No one has ever observed a non-trivial program arise from nothing but happenstantial pseudo "choices," whether random or non-random. Goal-less "programming" "does not compute."

Formal organization, orchestration, programming, and algorithmic optimization all require purposeful choices. If physicality cannot make purposeful choices, physicalism as an explanation for abiogenesis is a dead-end. No purely physicodynamic model of abiogenesis ever published has succeeded in explaining the programming of life, its processing, or the engineering of the nanodevices required to process that subcellular programming. When the Universal Plausibility Metric (UPM) is calculated for any of these life-origin papers, ξ is invariably less than 1.0. The Universal Plausibility Principle [213-215] requires peer review and editorial rejection of all these models for lack of scientific plausibility. They should never have been published in peer-reviewed scientific literature. They are nothing more than run-away imagination—pipe dreams. They are science fiction at best.

Naturalism and Natural Science must be redefined to include the study of Choice Causation and Mundane Proximate Teleology (MPT). Yes, MPT must be carefully distinguished from questions of metaphysical ultimate transcendent teleology. MPT is simply the study of undeniable everyday down-to-earth intra-cosmic Choice Causation. Choice Causation and Engineering science should never have been divorced from "natural science" in the first place. This form of causation is every bit as legitimate a subject of scientific investigation as Physicodynamic Causation. Both components of the Universal Determinism Dichotomy (UDD) [71] are mundane proximate causes of real physical

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

effects in the real world. The "How's?" of both forms of causation are legitimate subjects of natural science.

Many unanswered questions remain:

1. Did *any* intra-cosmic pre-biotic cause ever manifest intent?
2. If such a cause did manifest intent, what caused and mediated that intent?
3. Did any intra-cosmic pre-biotic cause manifest an appreciation of usefulness/utility/function?
4. Where did mathematical formalisms like π, the speed of light, invariances and symmetries come from?
5. How did physicality produce mathematics?
6. Did Prescriptive Information (PI) have a cause?"
7. Are efficacious executable choice commands possible without intent?
8. Could life exist without Genomic PI (GPI)?
9. Did inanimate nature "select for" life before it was programmed? How? Why?
10. How could inanimate physicodynamics have programmed anything?

Can a metaphysical physicalist answer any of these questions above? If not, how can physicalists possibly be so arrogant and absolutist as to pontificate that "physicodynamics is all there is, or that physicodynamics is sufficient"?

85% of earthly reality strongly resembles human engineering choices. Look in any direction. Only 15% of what we see on land, at least, is nothing but inanimate "nature." Most of what we observe is, or is derived from life. Biosignatures prevail in all directions. They are the most prominent part of everyday reality.

All known life is programmed and cybernetically processed. Both require purposeful choices. No boundary should exist around engineering-like choices that would preclude scientific exploration of intra-cosmic reality. Choice Causation is no less real and normal than Physicodynamic Causation. Most everything any cell does is directed by the active ongoing Processing of Efficacious Executable Choice-Controlled Causation and Control (PEECCCC). Homeostatic metabolism isn't organized and orchestrated by mere physical forces, laws and constraints. Biochemical pathways have to lead somewhere useful. A thirteen-step Krebs cycle is useless until the final step [198, 216-220]. What motivated the process of all the prior nonfunctional steps? What steered the Krebs cycle to its final efficacious step? What function was there for the environment to select until the final step? But the environment doesn't select for function, anyway. Environmental selection selects only for the fittest already-programmed, already-cybernetically processed, already-living organisms [49, 51, 54-58, 62, 63, 76, 115].

It is the word "*WHAT?*" that trips us up in the title of this paper

Life's programming and cybernetic processing are undeniable. Forces, laws and constraints are inanimate "things"—"its." We know that never in the history of human observation has an inanimate thing programmed a nontrivial formal computation or algorithm. Programming is a biosignature—a product of already existing life. We are not accustomed to inanimate "things" achieving integrated circuits and efficacious epigenetic configurable switch-settings. The question asked by this paper seems strange because it is utterly unempirical. It conforms only to our bankrupt metaphysical worldview of physicalism. But no one has ever observed an inanimate thing make programming choices that successfully compute and halt. Programming requires active selections from among real options at bona fide decision nodes. The size of phase spaces of possibilities, probabilities and eons of time are irrelevant. Only living "agents" can choose with intent. Inanimate "its" cannot. Nothing is left in the question that titles this paper that would cause us pause other than the word *"WHAT?"* "What" describes an inanimate thing, an "it," rather than an agent. "*WHAT* caused life's programming?" is an inapplicable, inappropriate and inept question specifically because of the use of the word "*WHAT?*" in the question.

Only life programs. But no already-existing life existed on earth in a prebiotic environment. The same is true of an astrobiological/exobiological perspective of life origin. Abiogenesis *by definition* could not have been caused by intra-cosmic life or an intra-cosmic biosignature. It had to have been caused by life from the far side of The Cybernetic Cut [34-36], outside of physicodynamics.

How could physicality have done *any* computations? Programming and computations are abstract, conceptual and formal, not physical. But we have defined into the scientific method itself the purely metaphysical axiom that, "Physicodynamics is ultimately all there is," and "Physicodynamics is sufficient to explain everything." How were these religious "articles of faith" established scientifically? The fanatical dogma of so-called "natural science" all along has been that "Inanimate Nature is sufficient to explain everything, including life-origin." Even methodological naturalism functionally requires operating under this repressive purely metaphysical pre-assumption. This presupposition is the source of the use of the word "*WHAT*" in the question of this paper's title. The question as worded makes no sense. Is not programming a biosignature—a product only of life? If so, the question posed by this paper points to a faulty presupposition. Worse yet, it points to a fundamental axiom of science that is untenable. The axiom of physicalistic naturalism as the basis for science has been essentially falsified by modern molecular biology and genomics, by synthetic chemistry,

Abel DL., J Bioinform Syst Biol 2026
DOI:10.26502/jbsb.5107115

and by the mathematical nature of the physical laws. All known life is programmed and cybernetically processed by very sophisticated nanocomputers and molecular machines. This is the reason The First Law of Biology pronounced by Virchow and Pasteur has never been falsified. This is the reason why "All life must come from previously existing life." Only agents can program.

Genomic programming is ever so much more conceptually complex than human cybernetics. Many interrelated and conditional controls cooperate. Neighboring genes have increased influence on each other. Operons and enhancers compound the already conceptually complex computational potential. But the fundamental principle still holds, that programmed effects do not precede in time the choices that cause and control those effects. More importantly, a certain configurable switch-setting *causes* the gene to be turned on or off. A certain alternate splicing *causes* a different gene function.

Conclusion

Genes and genomes don't just instruct function. That formalism would be hard enough for metaphysical physicalism to explain (technically, logically impossible). Genes issue efficacious executable choice-commands at bona fide decision nodes. When cybernetically processed, these choice-commands actually execute formal computational success. They integrate circuits. They determine the starting and reaction conditions that steer and maintain the chemical synthesis of needed metabolites. They direct the transduction of energy and orchestrate multi-step, overlapping, error-correcting metabolic schemes. They are purely abstract, conceptual and as formal as mathematics, logic theory, language and the scientific method itself. Raw physicodynamics on the near side of The Cybernetic Cut [34-36] can achieve none of these formal tasks and goals.

Physicodynamics cannot generate engineered cybernetic "nano-devices" like ribosomes and such incredibly ingenious molecular machines needed to process genomic and epigenetic commands. This dilemma alone is sufficient to proclaim physicalism not only to be on life support, but to declare it already expired [49, 76].

Life simply could not have come into existence without Choice Causation and Mundane Proximate Teleology (MPT) [49, 76], whether our metaphysical worldview likes it or not. Our definition of what is "natural" in "natural science" must change. We cannot allow metaphysical physicalism to interfere with scientific discovery. We will never elucidate how the first genome was programmed if we disallow active selection with intent. That is the very key to life and its formal definition [50].

What programmed the first genome? Not "What?" but "Who?" Only agents can make purposeful choices. Only an agent, therefore, could have programmed computational programs and engineered such sophisticated "devices."

But who is the "who"?" The short answer: *Maxwell's demon*. But isn't Maxwell's demon just a "thought experiment" and a cartoon character? *Natural* science can't possibly take the demon seriously, can it? "That would be unscientific." Natural science and the New Naturalism [49, 76] had better take the demon seriously, because all of the biological natural sciences emanate from Choice Causation and manifest Mundane Proximate Teleology at every turn [49-52, 54-59, 61-63, 76, 115]. In addition, most of synthetic chemistry requires purposeful setting of precisely *chosen* and enforced initial and operational conditions. All of the force constants are incredibly fine-tuned to make physical reality and life possible. The periodic table is formally organized. The determinism of physics depends upon equalities of mathematical measurements (formal representations of physicality, not physicality itself).

Life is controlled, not constrained. Controls require purposeful choices. Life pursues function. Forces, mass, energy, thermodynamics, undirected chemical reactions know nothing of function. Physicalistic Naturalism is a failed fanatical purely metaphysical belief system that should never have been adopted as the most fundamental axiom of science. Choice Causation and intra-cosmic Mundane Proximate Teleology must be included in natural science's investigations.

The Formalism > Physicality (F > P) Principle clearly governs physical reality. Natural science has no choice but to acknowledge and study formal causes emanating from the far side of The Cybernetic Cut [34-36]. This is The New Naturalism [49, 76]. Maxwell's demon is an Agent wearing much bigger britches than we were ever willing to admit. He is a "demon" only in his opposition to the bankrupt metaphysic of physicalism. Otherwise, the demon wears a white cowboy hat.

References

1. Abel DL. *Constraints vs. Controls: Progressing from description to prescription in systems theory.* Open Cybernetics and Systemics Journal 4 (2010): 14–27.

2. Fuentes-Iglesias A, R Garcia-Vilchez and D Guallar. *Transposable elements in aging: From biomarkers to effectors.* Adv Genet 116 (2026): 189–244.

3. Docavo Garcia A and JW Jachowicz. *Shaping mammalian genomes: The regulation and co-option of transposable elements in early development and gametogenesis.* Adv Genet 116 (2026): 55–100.

4. Bida L and K Kashkush. *Large-scale structural variations induced by transposable elements promote population-specific divergence in Triticum turgidum ssp. dicoccoides.* BMC Plant Biol (2026).

5. Stanek TJ, et al. *Complex determinants of R-loop formation at transposable elements and major DNA satellites.* Genetics 229 (2025).

6. Li J, et al. *In vitro fertilization-conceived offspring exhibit altered Long Interspersed Nuclear Elements-1 retrotransposition dynamics associated with long-term disease risks.* Am J Obstet Gynecol (2026).

7. Godden AM, BT Rix and S Immler. *Diverging transposon activity among polar bear sub-populations inhabiting different climate zones.* Mob DNA 16 (2025): 47.

8. Toda T, et al. *Long interspersed nuclear elements safeguard neural progenitors from precocious differentiation.* Cell Rep 43 (2024): 113774.

9. Kuriyama Y, et al. *The differential expression of long interspersed nuclear elements-1 as a marker for hypomethylation in Merkel cell carcinoma.* Clin Exp Dermatol 47 (2022): 1726–1728.

10. Marston JL, et al. *SARS-CoV-2 infection mediates differential expression of human endogenous retroviruses and long interspersed nuclear elements.* JCI Insight 6 (2021).

11. Rey C, et al. *Programmed DNA elimination in Mesorhabditis nematodes.* Curr Biol 33 (2023): 3711–3721.

12. Zagoskin MV, et al. *Argonautes and small RNAs associated with nematode programmed DNA elimination.* bioRxiv (2025).

13. Stefanov BA and M Nowacki. *Functions and mechanisms of eukaryotic RNA-guided programmed DNA elimination.* Biochem Soc Trans 53 (2025): 473–85.

14. Simmons JR, et al. *Spatial genome reorganization is associated with chromosomal breakage regions and karyotype changes induced by programmed DNA elimination.* bioRxiv (2025).

15. Ruiz-Ruano FJ, et al. *Programmed DNA elimination drives rapid genomic innovation in two thirds of all bird species.* bioRxiv (2025).

16. Dedukh D, et al. *Programmed DNA elimination occurs during early gametogenesis in hybridogenetic hybrids from Hexagrammos genusdagger.* Biol Reprod 113 (2025): 605–614.

17. Simmons JR, et al. *Chromosome fusion and programmed DNA elimination shape karyotypes of nematodes.* Curr Biol 34 (2024): 2147–2161 e5.

18. Mochizuki K. *Programmed DNA elimination.* Curr Biol 34 (2024): R843–R847.

19. Estrem B, RE Davis and J Wang. *End resection and telomere healing of DNA double-strand breaks during nematode programmed DNA elimination.* Nucleic Acids Res 52 (2024): 8913–8929.

20. Rzeszutek I, XX Maurer-Alcalá and M Nowacki. *Programmed genome rearrangements in ciliates.* Cell Mol Life Sci 77 (2020): 4615–4629.

21. Chen X, et al. *The architecture of a scrambled genome reveals massive levels of genomic rearrangement during development.* Cell 158 (2014): 1187–1198.

22. Swart ECB, John R. Magrini Vincent et al. *The Oxytricha trifallax Macronuclear Genome: A Complex Eukaryotic Genome with 16,000 Tiny Chromosomes.* PLoS Biol (2013).

23. Kissmer B and Z Gompert. *Chromosomal Rearrangements Might Play a Central Role in Adaptation.* Mol Ecol 34 (2025): e70159.

24. Gompert Z, et al. *Adaptation repeatedly uses complex structural genomic variation.* Science 388 (2025): eadp3745.

25. de Carvalho CF, et al. *Linking DNA Methylation to Localised Genetic Differentiation in Timema cristinae Stick Insects.* Mol Ecol 34 (2025): e70049.

26. Montejo-Kovacevich G, et al. *Exploring context dependency in eco-evolutionary patterns with the stick insect Timema cristinae.* Ecol Evol 10 (2020): 8197–8209.

27. Lucek K, Z Gompert and P Nosil. *The role of structural genomic variants in population differentiation and ecotype formation in Timema cristinae walking sticks.* Mol Ecol 28 (2019): 1224–1237.

28. An X, et al. *Genomic structural variation is associated with hypoxia adaptation in high-altitude zokors.* Nat Ecol Evol 8 (2024): 339–351.

29. Liang X, et al. *Genomic structural variation contributes to evolved changes in gene expression in high-altitude Tibetan sheep.* Proc Natl Acad Sci USA 121 (2024): e2322291121.

30. Chi X, Y Li and X Qiu. *V(D)J recombination, somatic hypermutation and class switch recombination of immunoglobulins: mechanism and regulation.* Immunology 160 (2020): 233–247.

31. Melamed D, et al. *De novo mutation rates at the single-mutation resolution in a human HBB gene region associated with adaptation and genetic disease.* Genome Res 32 (2022): 488–498.

32. Melamed D, et al. *De novo rates of a Trypanosoma-resistant mutation in two human populations.* Proc Natl Acad Sci USA 122 (2025): e2424538122.

33. Tomkins JP. *Engineered Genomic Changes in Adaptation.* Acts and Facts 55 (2026): 14–17.

34. Abel DL. *The 'Cybernetic Cut': Progressing from Description to Prescription in Systems Theory.* The Open Cybernetics and Systemics Journal 2 (2008): 252–262.

35. Abel DL. *The Cybernetic Cut and Configurable Switch (CS) Bridge*, in *The First Gene: The Birth of Programming, Messaging and Formal Control*, D.L. Abel, Editor (2011): 55-74.

36. Abel DL. *The Cybernetic Cut: Progressing from Description to Prescription in Systems Theory* (2008).

37. Abel DL. *Primordial Prescription: The Most Plaguing Problem of Life Origin Science* (2015).

38. Abel DL, ed. *The First Gene: The Birth of Programming, Messaging and Formal Control* (2011).

39. Rocha LM. *Evolution with material symbol systems.* Biosystems 60 (2001): 95–121.

40. Abel DL and JT Trevors. *More than Metaphor: Genomes are Objective Sign Systems*, in *BioSemiotic Research Trends*, M. Barbieri, Editor (2007): 1-15.

41. Abel DL and JT Trevors. *More than metaphor: Genomes are objective sign systems.* Journal of BioSemiotics 1 (2006): 253–267.

42. Turing AM. *On computable numbers, with an application to the entscheidungs problem.* Proc. Roy. Soc. London Mathematical Society 42 (1936): 230–265.

43. Church A. *An unsolvable problem of elementary number theory.* Am. J. Math 58 (1936): 345–363.

44. Davis MD. *Computability and Unsolvability (The real source of "The halting problem", not Turing's 1936 paper)* (1958).

45. Chaitin GJ. *Leibniz, randomness & the halting probability.* Mathematics Today 40 (204): 138–139.

46. Guarra F and G Colombo. *Computational Methods in Immunology and Vaccinology: Design and Development of Antibodies and Immunogens.* Journal of Chemical Theory and Computation 19 (2023): 5315–5333.

47. Gecow A. *Way to operationalization of the life process definition 'from purposeful information' resulting from Abel's proposal; mechanisms of evolutionary progress.* BioSystems (2026): 105889.

48. D'Onofrio DJ and G An. *A comparative approach for the investigation of biological information processing: An examination of the structure and function of computer hard drives and DNA.* Theoretical Biology and Medical Modeling 7 (2010): 3.

49. Abel DL. *The New Naturalism.* Journal of Bioinformatics and Systems Biology 9 (2026): 83 –95.

50. Abel DL. *Defining "Life".* Journal of Bioinformatics and Systems Biology 9 (2026): 1–10.

51. Abel DL. *The Life/Non-Life Dichotomy.* Journal of Bioinformatics and Systems Biology 9 (2026): 1–17.

52. Wesół B. *How Naturalism Refutes Itself: Pragmatist Challenges for Naturalism (William James and Charles Sanders Peirce).* Studia Philosophiae Christianae 60 (2025): 77–90.

53. Arcas BAy. *What Is Intelligence? Lessons from AI About Evolution, Computing, and Minds*. Could be #19634, ed. Antikythera (2025): 624.

54. Abel DL. *Life is Programmed Computation.* Journal of Bioinformatics and Systems Biology 8 (2025): 08–16.

55. Abel DL. *Mutations of WHAT?* Journal of Bioinformatics and Systems Biology 8 (2025): 83–98.

56. Abel DL. *Spontaneous Mutations vs. Prescribed Polymorphisms.* Journal of Bioinformatics and Systems Biology 8 (2025): 68–82.

57. Abel DL. *The Common Denominator of All Known Lifeforms.* Journal of Bioinformatics and Systems Biology 8 (2025): 29–35.

58. Abel DL. *"Assembly Theory" in life-origin models: A critical review.* BioSystems 247 (2025): 105378.

59. Abel DL. *Physicodynamic Incompleteness Updated in 2025 from 2009*. Scirus Sci-Topic Paper (2025).

60. Tamang SaA, Sagar. *Codon Chart: Table, Amino Acids & RNA Wheel Explained* (2024).

61. Abel DL. *What is Life?* Archives of Microbiology and Immunology 8 (2024): 428–43.

62. Abel DL, *Selection in molecular evolution.* Studies in History and Philosophy of Science 107 (2024): 54–63.

63. Plantinga A. *The evolutionary argument against naturalism*, J. Stiller, Editor (2021).

64. Veritasium. *Molecular machines walking on two legs video: molecular machines walking on two legs video* (2017).

65. Johnson D. *Biocybernetics and Biosemiosis* (2013).

66. Abel DL. *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*, J. Seckbach, Editor (2012): 219–236.

67. Abel DL. *Formalism > Physicality (F > P) Principle SciTopic Paper*. 2012 3/15/2026].

68. Trevors JT and Abel, David Lynn *Chance and Necessity Do Not Explain the Origin of Life.* Cell Biology International 28 (2004): 729–739.

69. Abel DL. *The capabilities of chaos and complexity*, in

Society for Chaos Theory: Society for Complexity in Psychology and the Life Sciences (2008).

70. Abel DL. *Complexity, self-organization, and emergence at the edge of chaos in life-origin models.* Journal of the Washington Academy of Sciences 93 (2007): 1–20.

71. Abel DL. *The Universal Determinism Dichotomy (UDD): Physicodynamic Determinism (PD) vs Choice Determinism (CD).* Scopus Sci Topic Paper (2005).

72. Abel DL. *The three fundamental categories of reality*, in *The First Gene: The Birth of Programming, Messaging and Formal Control*, D.L. Abel, Editor (2011): 19–54.

73. Abel DL and JT Trevors. *Three subsets of sequence complexity and their relevance to biopolymeric information.* Theoretical Biology and Medical Modeling 2 (2005): 29–45.

74. Abel DL. *Life is Programmed Computation.* Journal of Bioinformatics and Systems Biology 8 (2025): 1–16.

75. Abel DL. *What is Life?* Archives of Microbiology and Immunology 8 (2024): 428–443.

76. Abel DL. *Is Naturalism on Life Support?* Journal of Bioinformatics and Systems Biology 9 (2026): 43–72.

77. Song Y, et al. *Predicting the structural impact of human alternative splicing.* Genome Biology 26 (2025): 283.

78. Haltenhof T, M Preussner and F Heyd. *Thermoregulated transcriptomics: the molecular basis and biological significance of temperature-dependent alternative splicing.* Biochem J 481 (2024): 999–1013.

79. Black AJ, JR Gamarra and J Giudice. *More than a messenger: Alternative splicing as a therapeutic target.* Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms 1862 (2019): 194395.

80. Wang Y, et al. *Mechanism of alternative splicing and its regulation.* Biomed Rep 3 (2015): 152–158.

81. Tomkins JP. *Genomic Tandem Repeats: Where Repetition is Purposely Adaptive.* Acts and Facts 54 (2025): 14–17.

82. Lujumba I, et al. *A practical guide to identifying associations between tandem repeats and complex human traits using consensus genotypes from multiple tools.* Nat Protoc (2025).

83. Homma K, et al. *Longer internal exons tend to have more tandem repeats and more frequently experience insertions and deletions.* Life Sci Alliance 8 (2025).

84. Ershova ES, et al. *Variation in the Content of Three Tandem Repeats of the Human Genome (Ribosomal, Satellite III, and Telomere) in Peripheral Blood Leukocyte DNA of People of Different Ages (5-101 Years).* J Aging Res (2025): 8847073.

85. Cho ST and ES Wright. *Accurate detection of tandem repeats exposes ubiquitous reuse of biological sequences.* Nucleic Acids Res 53 (2025).

86. Yang M, et al. *WRKY Transcription Factors: Epigenetic and Post-Translational Regulation of Plant Immunity and Growth-Environment Adaptation.* Plant Cell Environ (2025).

87. Yang H, et al. *Global analysis of transcription factors using both the reference genome and the multi-transcriptome of Akebia trifoliata reveals a sophisticated functional strategy.* Front Plant Sci 16 (2025): 1529326.

88. Xiufeng G, H Zhiping and W Jingzhi. *Advantages and Possibility of Transcription Factors FOXOs in HCC.* Cell Biochem Funct 43 (2025): e70126.

89. Porter DF, et al. *Disease-linked regulatory DNA variants and homeostatic transcription factors in epidermis.* Nat Commun 16 (2025): 8387.

90. Zhou X, Z Lei and P An. *Post-Translational Modification of WRKY Transcription Factors.* Plants (Basel) 13 (2024).

91. Zhao X, et al. *Chronic heart failure and GPX3 promoter methylation: A clinical-epigenetic analysis.* Heart Lung 78 (2026): 102750.

92. Jalaludin J, NF Suhaimi and S Abubakar. *DNA methylation as an epigenetic marker of children's exposure to traffic-related air pollution in the Klang Valley, Malaysia.* Int Arch Occup Environ Health 99 (2026).

93. Hafner A, et al. *Intragenic methylation repatterning is associated with alternative splicing and unique epigenetic phenotypes.* bioRxiv (2026).

94. Chindea T, et al. *Diet-Driven Epigenetic Alterations in Colorectal Cancer: From DNA Methylation and microRNA Expression to Liquid Biopsy Readouts.* Biomedicines 14 (2026).

95. Abel DL. *The biosemiosis of prescriptive information.* Semiotica 174 (2009): 1–19.

96. Arcas Bay. *Is Life a Form of Computation? Alan Turing and John von Neumann saw it early: the logic of life and the logic of code may be one and the same* (2025).

97. Pawłowski PH and P Zielenkiewicz. *Determining the Identity Nucleotides and the Energy of Binding of tRNAs to Their Aminoacyl-tRNA Synthetases Using a Simple Logistic Model.* Life 14 (2024): 1328.

98. Zhan Y, et al. *Specific RNA structures and elements in the 5'-UTR of the SARS-CoV-2 genome and subgenomic RNA are critical for its infection.* Genes Dis 13 (2026): 102030.

99. Ossevoort T, et al. *40S ribosomal subunits move along*

the 5′ UTR through an eIF4A-independent mechanism in higher eukaryotes. bioRxiv (2026).

100. Mazunina EP, et al. *Identification of novel 5′ UTR variants for enhanced mRNA translation and vaccine immunogenicity.* Sci Rep (2026).

101. Glenet M, et al. *EV-B 3D polymerase remodels viral populations through 5'UTR recombination to subvert cardiac antiviral innate immunity.* PLoS Pathog 22 (2026): e1014441.

102. Delihas N. *Diverse Processes Drive the Origination and Maturation of an Array of Enhancers and Silencers During a Vast Evolutionary Timescale of a Bicistronic Gene.* Genes (Basel) 17 (2026).

103. Badia Roige B, E Pfeifer and J Frunzke. *Control of foreign DNA: emerging roles of xenogeneic silencers.* Curr Opin Microbiol 93 (2026): 102800.

104. Aimo A, et al. *Therapy of amyloidosis: stabilizers and silencers.* Eur Heart J Suppl 28 (2026): v100–v105.

105. Zips N, E Kulko and S Kath-Schorr. *Click to Translate: Synthesis of Trans-Cyclooctene Modified 5′ mRNA Caps for Bioorthogonal Activation.* Chembiochem 27 (2026): e70420.

106. Locherer C, et al. *Staphylococcus aureus Small RNAs Possess Dephospho-CoA 5′-Caps, but No CoAlation Marks.* Noncoding RNA 8 (2022).

107. Zhang YY, JP Zhang and XB Zhang *Engineering the poly(A) tail for therapeutic mRNA: from expression control to manufacturing robustness.* Front Bioeng Biotechnol 14 (2026): 1838589.

108. Krog TF, IS Haukland and GT Haugland. *Nucleoside Modifications and Poly(A) Tail Length Greatly Influence Protein Expression from In Vitro-Transcribed mRNA in a Salmonid Cell Line.* Vaccines (Basel) 14 (2026).

109. Guan WL. *Beyond the Poly(A) Tail: The Expanding Functional Landscape of PABPN1 and Its Dysregulation in OPMD and Cancer.* Wiley Interdiscip Rev RNA 17 (2026): e70052.

110. D'onofrio DJ and DL Abel. *Redundancy of the genetic code enables translational pausing.* Frontiers in Genetics 5 (2014): 140.

111. Abel DL. *Prescriptive Information (PI) [Scirus SciTopic Page]* (2009).

112. Szostak JW. *Functional information: Molecular messages.* Nature 423 (2003): 689–689.

113. Hazen RM, et al. *Functional information and the emergence of biocomplexity.* Proc Natl Acad Sci USA 104 (2007): 8574–81.

114. McIntosh AC. *Functional Information and Entropy in living systems*, in *Design and Nature III: Comparing Design in Nature with Science and Engineering*, Brebbia CA, Suchrov LJ, and PP, Editors (2006).

115. Abel DL. *Why is Abiogenesis Such a Tough Nut to Crack?* Archives of Microbiology and Immunology 8 (2024): 338–364.

116. Barak P, D Gibney and C Jain. *Haplotype-aware long-read error correction.* Algorithms Mol Biol (2026).

117. Alberts B JA. Lewis J, et al. *DNA Repair* in *Molecular Biology of the Cell. 4th edition* (2002).

118. Wang B and Y Lu. *Collective Molecular Machines: Multidimensionality and Reconfigurability.* Nanomicro Lett 16 (2024): 155.

119. Weirich P. *Decision Space: Multidimensional Utility Analysis* (2001).

120. Abel DL. *Is life unique?* Life 2 (2011): 106–134.

121. Chatterjee S, *Defining Life*, in *From Stardust to First Cells: The Origin and Evolution of Early Life*. Springer International Publishing: Cham (2023): 9-14.

122. Nekludoff A A. *Life as a Filtered Outcome: Filtered Configuration Framework.* Zenodo (2026).

123. Kordium V A. *Defining life and evolution: Essay on the origin, expansion, and evolution of living matter.* Biosystems 209 **(**2021): 104500.

124. Periyasamy S, A Gray, and P Kille. *The bottom-up approach to defining life: deciphering the functional organization of biological cells via multi-objective representation of biological complexity from molecules to cells.* Front Physiol 4 **(**2013): 369.

125. Tsokolov S. *A Theory of Circular Organization and Negative Feedback: Defining Life in a Cybernetic Context.* Astrobiology 10 (2010): 1031-1042.

126. Ruiz-Mirazo K, J Pereto and A Moreno. *Defining life or bringing biology to life.* Origins of Life and Evolution of the Biosphere 40 (2010): 203-213.

127. Benner S A. *Defining Life.* Astrobiology 10 (2010): 1021-1030.

128. Bitbol M and P L Luisi. *Autopoiesis with or without cognition: defining life at its edge.* Journal of the Royal Society, Interface [electronic resource] / the Royal Society 1 (2004): 99-107.

129. Emmeche C. *Defining life as a semioitic phenomenon.* Cybernetics and Human Knowing 5 (1998): 3-17.

130. Rizzotti M. ed. *Defining Life: The Central Problem in Theoretical Biology*. University of Padova Press: Padova 208 (1996).

131. Tsokolov S A. *Why Is the Definition of Life So Elusive? . Epistemological Considerations* 9 (2009).

132. Korzeniewski B. *Confrontation of the cybernetic definition of a living individual with the real world.* Acta Biotheor 53 (2005): 1-28.

133. Ruiz-Mirazo K, J Pereto and A Moreno. *A universal definition of life: autonomy and open-ended evolution.* Orig Life Evol Biosph 34 (2004): 323-46.

134. Korzeniewski B. *Cybernetic Formulation of the Definition of Life.* Journal of Theoretical Biology 209 (2001): 275-286.

135. Luisi P L. *About various definitions of life.* Orig Life Evol Biosph 28 (1998): 613-622.

136. Losee R M. *A disicpline independent definition of information.* J. of the American Society for Information Science 48 (1997): 254-269.

137. Gecow A. *Two coherent definitions of the life process derived from the half-chaos theory and the (unintentional) purposeful information theory.* BioSystems 256 (2025): 105533.

138. Abel D L and J T Trevors. *Self-Organization vs. Self-Ordering events in life-origin models.* Physics of Life Reviews 3 (2006): 211-228.

139. Shapiro R. *Prebiotic cytosine synthesis: a critical analysis and implications for the origin of life.* Proc Natl Acad Sci U S A 96 (1999): 4396-4401.

140. Shapiro R. *Prebiotic ribose synthesis: a critical analysis.* Orig Life Evol Biosph 18 (1988): 71-85.

141. Shapiro R. *Origins: A Skeptic's Guide to the Creation of Life on Earth*. New York: Bantam (1987).

142. Shapiro,R. *The improbability of prebiotic nucleic acid synthesis.* Orig Life 14 (1984): 565-570.

143. Eschenmoser A. *Question 1: Commentary.* Origins of Life and Evolution of Biospheres 37 (2007): 309-314.

144. Eschenmoser A. *The search for the chemistry of life's origin.* Tetrahedron 63 (2007): 12821-12844.

145. Chen I A, K Salehi-Ashtiani and J W Szostak. *RNA catalysis in model protocell vesicles.* J Am Chem Soc 127 (2005): 13213-13219.

146. Lilley D. *The origins of RNA catalysis in ribozymes.* Trends Biochem Sci 28 (2003): 495-501.

147. Fedor M. *The role of metal ions in RNA catalysis.* Curr Opin Struct Biol 12 (2002): 289-295.

148. Lilley DM. *Origins of RNA catalysis in the hairpin ribozyme.* Chembiochem 2 (2001): 729-733.

149. Zhuang X, et al. *A single-molecule study of RNA catalysis and folding.* Science 288 (2000): 2048-2051.

150. Wang J F. W D Downs and T R Cech. *Movement of the guide sequence during RNA catalysis by a group I ribozyme.* Science 260 (1993): 504-508.

151. Orgel L E. *RNA catalysis and the origins of life.* J Theor Biol 123 (1986): 127-149.

152. Pace N R and T L Marsh. *RNA catalysis and the origin of life.* Orig Life Evol Biosph 16 (1985): 97-116.

153. Tour J M, Parker M C, Jeynes C. *Thermodynamic limitations on the natural emergence of long chain molecules: implications for origin of life.* Biocosmos 1 (2025): 64-71

154. Ewert W and D D Axe. *RNA Sequence-to-Structure Mapping has Limited Evolutionary Benefit.* BioComplexity Journal 2026 (2026): 1-13.

155. Meyer S C. *Darwin's Doubt*. New York, NY: Harper Collins (2013).

156. Meyer S and P Nelson. *Can the origin of the genetic code be explained by direct DNA templating?* BIO-Complexity 2011 (2011): 1-10.

157. Meyer S C. *Signature in the Cell*. Harper One (2010).

158. Tan CL A E. *Revising the Central Dogma: Regulated, Dynamic, and System-Dependent. BIO-Complexity 2024 (3):1-21. doi:10.5048/BIO-C.2024.3.* BIO-Complexity 2024 (2024): 1-23.

159. Wang R L. *Life is chemistry plus information.* BBA Advances 7 (2025): 100162.

160. Tour J M, Parker M, Jeynes C. *Thermodynamic limitations on the natural emergence of long chain molecules: implications for origin of life.* BioCosmos 1 (2025): 64-71.

161. Zenil H and J Tour. *Harvard debate between James Tour and Lee Cronin with Hector Zenil critique (2024)*.

162. Tour J. *Public challenge to Jack Szostak and 9 other abiogensist specialists to answer any one of five questions* (2024).

163. Tour J. *The Origin of Life Has Not Been Explained* (2020).

164. Thaxton CB, Bradley Walter L, et al. *The Mystery of Life's Origin*. 2020: Discovery Institute.

165. D'Onofrio, D.J. and D.L. Abel, *Redundancy of the genetic code enables translational pausing.* Front Genet 5 (2014): 140.

166. Karlebach G, et al. *Betacoronavirus-specific alternate splicing.* Genomics 114 (2022): 110270.

167. Mvubu N E, B Pillay and M Pillay. *Infection of*

pulmonary epithelial cells by clinical strains of M. tuberculosis induces alternate splicing events. Gene 750 (2020): 144755.

168. Tomkins J P. *Genomic Tandem Repeats: Where Repitition is Purposely Adaptive.* Acts & Facts 54 (2025): 14-17.

169. Reinar W B, et al. *Length Variation in Short Tandem Repeats Affects Gene Expression in Natural Populations of Arabidopsis thaliana.* Plant Cell 33 (2021): 2221-2234.

170. Reinar W B, et al. *Length variation in short tandem repeats affects gene expression in natural populations of Arabidopsis thaliana.* The Plant Cell 33 (2021): 2221-2234.

171. Sawaya S, et al. *Microsatellite tandem repeats are abundant in human promoters and are associated with regulatory elements.* PLoS ONE 8 (2013).

172. Lv J, et al. *3D-super-enhancers are condensate-associated cis-regulatory communities.* Nucleic Acids Res 54 (2026).

173. Esvald E E, et al. *Making of BDNF: role of promoters, enhancers, and untranslated regions.* Trends Neurosci (2026).

174. Niu J, et al. *OsHMGB1 functions as a transcriptional repressor of OsNRT2.2 in rice: Calcium-regulation and additive function with OsCCA1.* Int J Biol Macromol (2026): 153918.

175. Cao L, et al. *[Study on cellular repressor of E1A-stimulated genes regulating autophagy and polarization of alveolar macrophages in sepsis-induced acute respiratory distress syndrome and its clinical value].* Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 38 (2026): 641-647.

176. Alvarez-Rodriguez M G, et al. *Citrullination in proteins of the polycomb repressor complex 1.* Arch Biochem Biophys 785 (2026): 110955.

177. Zhong Y, et al. *Exercise and Epigenetic Regulation in COPD: Current Evidence and Potential Mechanistic Pathways.* Int J Mol Sci 26 (2025).

178. Sun S, et al. *Beyond the genome: epigenetic regulation of immune responses and T cells in brain tumors.* Front Immunol 16 (2025): 1690552.

179. Jobava R, et al. *Adaptive translational pausing is a hallmark of the cellular response to severe environmental stress.* Mol Cell 81 (2021): 4191-4208.

180. Jobava R, et al. *Adaptive translational pausing is a hallmark of the cellular response to severe environmental stress.* Molecular Cell 81 (2021): 4191-4208.e8.

181. Walsh C J, et al. *Discovering MicroRNA-Regulatory Modules in Multi-Dimensional Cancer Genomic Data: A Survey of Computational Methods.* Cancer Informatics (2016): 25-42.

182. Ten things you should know about transposabl elements (2026).

183. Vo K, et al. *Detection of mRNA Transcript Variants.* Genes (Basel) 16 (2025).

184. Abel D L. *The Genetic Selection (GS) Principle*, in *The First Gene: The Birth of Programming, Messaging and Formal Control*, D.L. Abel, Editor. 2011, LongView Press--Academic: New York, N.Y (2026): 161-188.

185. Einstein A. *Remarks on Russell's theory of knowledge*, in *The Philosophy of Bertrand Russell*, P.A. Schlipp, Editor. Tudor: New York (1944): 277–291.

186. Einstein A, B Podolsky and W Rosen. *Can quantum mechanical description of physical reality be considered complete?* Phys. Rev 47 (1935): 777-780.

187. Einstein A. *Sidelights on Relativity*. An address delivered on May 5th at the University of Leyden. Mineola, N.Y. Dover (1920).

188. Einstein A. *Einstein Portal A Database of Albert Einstein's Collected Works* (1905).

189. Yao X F, et al. *Non-Random Distribution of EMS-Induced Mutations Reveals Preference for Open Chromatin and Expressed Genes in Rice.* Adv Sci (Weinh) 12 (2025): e10034.

190. Retnakumar R J, et al. *Genome-wide accumulations of non-random adaptive point mutations drive westward evolution of Helicobacter pylori.* BMC Microbiol 25 (2025): 229.

191. Pessino S, et al. *Diploid aposporous sunflower forms triploid BIII progeny displaying increased apospory levels and non-random genetic mutations.* Sci Rep 15 (2025): 4808.

192. Fu J, et al. *Non-Random Distribution of G-Quadruplex Structures Reveals Regulatory and Ecological Adaptations in Bacterial Genomes.* Int J Mol Sci 26 (2025).

193. Matsushita T and T Kano-Sueoka. *Non-random Codon Usage of Synonymous and Non-synonymous Mutations in the Human HLA-A Gene.* J Mol Evol 91 (2023): 169-191.

194. Abel D L. *The Formalism > Physicality (F > P) Principle*, in *The First Gene: The Birth of Programming, Messaging and Formal Control*, D.L. Abel, Editor. 2011, LongView Press Academic: New York, N.Y (2026): 325-351.

195. Quilici A L, M V P De Sousa and A A C A Braga. *Chemistry of the origins of life: how prebiotic chemistry can be approached by computational quantum methods.* Frontiers in Astronomy and Space Sciences 13 (2026).

196. Gordon B and W Dembski, eds. *The Nature of Nature: Examining the Role of Naturalism in Science*. Intercollegiate Studies Institute (2011).

197. Meyer S C. *The origin of biological information and the higher taxonomic categories.* Proceedings of the Biological Society of Washington 117 (2004): 213-239.

198. Behe M J, W Dembski and S C Meyer. *Science and Evidence for Design in the Universe*. San Francisco, CA: Ignatius Press (2000).

199. Noble D and R Noble. *Understanding Living Systems*: Cambridge University Press (2023).

200. Noble D. *The Music of Life: Biology Beyond Genes*: Oxford University Press (2008).

201. Scalzitti N, et al. *Computational peptide discovery with a genetic programming approach.* J Comput Aided Mol Des 38 (2024): 17.

202. Scalzitti N, et al. *Computational Peptide Discovery with a Genetic Programming Approach.* Res Sq, (2023).

203. Marks R J. *Non-Computable You: What You Do That Artificial Intelligence Never Will*: Discovery Institute. Kindle Edition (2022).

204. Bell J I. *Single nucleotide polymorphisms and disease gene mapping.* Arthritis Res 3 (2002): 273-278.

205. Sun M X, et al. *A female patient carrying a novel DMD mutation with non-random X-chromosome inactivation from a DMD family.* BMC Med Genomics17 (2024): 46.

206. Prigogine I. *The End of Certainty*. New York The Free Press (1997): 161-162.

207. Nicolis G and I Prigogine. *Exploring Complexity*. New York: Freeman (1989).

208. Prigogine I and I Stengers. *Order Out of Chaos*. London, Heinemann (1984): 285-287, 297-301.

209. Endres R G. *The unreasonable likelihood of being: origin of life, terraforming, and AI.* npj Systems Biology and Applications (2026).

210. Pazuki R H and R G Endres. *Robustness of Turing models and gene regulatory networks with a sweet spot.* Phys Rev E 109 (2024): 064305.

211. Matas-Gil A and R G Endres. *Unraveling biochemical spatial patterns: Machine learning approaches to the inverse problem of stationary Turing patterns.* iScience 27 (2024): 109822.

212. Cook J, S Pawar and R G Endres. *Thermodynamic constraints on the assembly and diversity of microbial ecosystems are different near to and far from equilibrium.* PLoS Comput Biol 17 (2021): e1009643.

213. Abel D L. *The Universal Plausibility Metric (UPM) & Principle (UPP).* Theoretical Biology and Medical Modelling 6 (2009): 27.

214. Abel D L. *The Universal Plausibility Metric and Principle (UPP)*, in *The First Gene*, D.L. Abel, Editor. LopngView Press-Academic Division: New York, NY (2011): 305-322.

215. Abel D L. *The Universal Plausibility Metric (UPM) & Principle (UPP) (2010).*

216. Behe M J, *Darwin Devolves. The New Science About DNA That Challenges Evolution*. 2019: HarperOne (352).

217. Marks II R J, et al. eds. *Biological Information: New Perspectives*. World Scientific: Cornell University Proceedings (2013).

218. Behe M. *Experimental Evolution, Loss-of-Function Mutations, and "The First Rule of Adaptive Evolution".* The Quarterly Review of Biology 85 (2010).

219. Behe M J and D W Snoke. *Simulating evolution by gene duplication of protein features that require multiple amino acid residues.* Protein Science 13 (2004): 2651-2664.

220. Behe M J. *Darwin's Black Box*. New York: Simon & Shuster: The Free Press (1996).