

## The transition from constraint to regulation at the origin of life

Terrence W. Deacon<sup>1</sup>, Alok Srivastava<sup>1</sup>, Joshua Augustus Bacigalupi<sup>1</sup>

<sup>1</sup>*Department of Anthropology, University of California, Berkeley, CA 94720*

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### 1. ABSTRACT

The origin of living dynamics required a local evasion of thermodynamic degradation by maintaining critical dynamical and structural constraints. Scenarios for life's origin that fail to distinguish between constrained chemistry and regulated metabolism do not address the question of how living processes first emerge from simpler constraints on molecular interactions. We describe a molecular model system consisting of coupled reciprocal catalysis and self-assembly in which one of the catalytic bi-products tends to spontaneously self-assemble into a containing shell (analogous to a viral capsule). In this process we call autogenesis self-repair/reconstitution and reproduction are made possible by the fact that each of these linked self-organizing processes generates boundary constraints that promote and limit the other, and because this synergy thereby becomes embodied as a persistent rate-independent substrate-transferrable constraint on the synergy of its component constraint-generating processes. It is proposed that this higher-order formal constraint is necessary and sufficient to constitute regulation as opposed to mere physico-chemical constraint. Two minor elaborations of this model system demonstrate how cybernetic and template-based regulation could emerge from this basic process.

### 2. INTRODUCTION

#### 2.1. Living thermodynamics

Living organisms are thermodynamically and biochemically open physicochemical systems. They constantly exchange matter and energy with their physicochemical environment and yet are constrained within physical boundaries and structures that are maintained through dynamic processes. The physicochemical processes that constitute living organisms tend to persist in states maintained far from thermodynamic and chemical equilibrium, whereas non-living physicochemical processes tend to spontaneously develop toward thermodynamic and chemical equilibrium.

The physical and chemical processes comprising an organism include processes that capture and utilize energy and materials acquired from their environment and utilize these resources to perform the work necessary to remain intact and far from equilibrium. These constructive physicochemical processes are organized into complex cycles and webs of catalyzed reactions that breakdown environmentally acquired molecules and synthesize the bio-molecules that are its critical building blocks. This network of interdependent catalytic interactions enables organisms to efficiently counter the ravages of the Second Law of Thermodynamics by maximizing the probabilities of supportive reactions. This circularity of catalytic interactions can more generally be described as reciprocal catalysis (also termed a collectively autocatalytic set). This theoretical form of molecular dynamics has been the subject of numerous proposals suggesting that it is a defining characteristic of the living process, and a potential precursor to life (1-6) because of its apparent replicative consequences.

Reciprocal catalysis can also occur in non-living systems where its accelerating reaction rates ever more rapidly exports entropy into the surrounding environment reaching maximum rates for the local boundary constraints. Such circularly causal processes are an exemplar of a more general class of processes found in both living and non-living systems that tend to develop toward more highly regular patterns as they multiply only certain relational properties of the collection that get re-entered into the process with each cycle. These kinds of processes often get lumped together under the term self-organizing processes (though both "self" and "organizing" are potentially misleading terms) because they tend to spontaneously simplify local dynamics and/or

amplify local asymmetries of materials and structures in the process of increasing the throughput of energy and the production of entropy. When self-organizing processes are synergistically incorporated into a living system, however, the system as a whole must maintain entropy production at a rate below what these processes would produce in isolation in order to prevent self-destruction (7). Unfortunately, the rates and types of molecular reactions that take place in reciprocally autocatalytic processes—even networks of interconnected autocatalytic processes, as in Eigen and Schuster's (2) hypercycles—are entirely determined by extrinsic factors, such as substrate availability and free energy.

In even the simplest living organisms (excluding viruses) these capabilities involve several types of regulation. Regulation of these processes is a prerequisite for generating structures, controlling metabolism, determining the expression of genetic information, adapting cellular and organ system functions to changes in their immediate environments, repairing and regenerating degraded and damaged structures, and orchestrating reproductive processes.

Non-living dynamical systems open to flows of material and/or energy can evolve increasingly constrained dynamical patterns over time, thus developing toward increasing orderliness. For example, the development of regular eddies in turbulent streams, the formation of hexagonal Rayleigh-Benard convection cells in heated liquid, and the highly regular growth of a snow crystal all exemplify a process of compounding constraints that increases dynamical regularization and the throughput of materials and/or energy. Such a subsystem becomes increasingly constrained over time and eventually reaches a stable dissipation rate where material and/or energy input is matched by the rate of entropy production.

Regulation and constraint are related concepts in that regulation involves the differential imposition and/or removal of constraints affecting some process so that it develops toward or away from some target state. But, constraints are function-neutral restrictions on dynamical and structural variations, whereas regulation is necessarily associated with the normative (i.e. functional/non-functional) organization of some process, whether determined extrinsically or intrinsically. The mere presence of constrained dynamics that contributes to development toward some more ordered state, as in self-organization, does not in itself constitute regulation. Regulation involves the modification of system constraints with respect to changing conditions that would otherwise cause that system to diverge from a specified target state. The classic cybernetic examples of regulation are thermostats and guidance systems organized to use feedback to counter and minimize deviation from a given value. Such systems are designed to constrain such deviations by generating work that is organized to counter each deviation. In other words, regulation is work performed in order to maintain spontaneous change within a constrained range. Regulation is in this sense defined with respect to an extrinsically determined target state, which in the case of designed mechanisms serves a designed function or purpose.

This may, for example, involve the generation of work to contravene a deviation as does the heating unit controlled by a thermostat, or it may involve imposing constraints on some process, as does a centrifugal governor on a steam engine. In these cases, the system is the product of a teleological (purposeful) context in which its design is determined by a human designer. It is also possible that an analogous mechanism could emerge by accident. For example, a geyser like the Old Faithful geyser, which erupts on a highly regular schedule, is also organized in a way that "regulates" its temperature and pressure within a constrained range via a feedback-like mechanism. This cybernetic-like behavior was of course an accident of geology. So calling this a form of "regulation" is largely analogical. But, biological regulation is different. Regulation of blood pressure or body temperature directly contributes to the production and persistence of the system (the organism) that makes this behavior possible. In contrast, neither the geyser's regularity nor the thermostat's maintenance of temperature contributes to the persistence of the particular structures that produce these results. This is a critical clue that there is a fundamental difference between engineered regulation and living regulation.

This disanalogy between living and non-living regulatory processes challenges us to explain the basis for this difference, and thus what makes the persistence of life's far-from-equilibrium thermodynamics possible.

The first question this poses is, "How could processes that arise due to their maximization of entropy production give rise to a form of organization that restrains this tendency?" The second question is, "What difference in dynamical organization is responsible for the shift from a dependence on externally imposed constraints to control by intrinsically generated constraints?" This involves an inside/outside (self/other) distinction that does not have any counterpart in self-organized processes.

This poses a fundamental paradox at the origin of life. This convergence of radically unprecedented thermodynamic features inverts the otherwise ubiquitous tendency characterizing the whole of the nonliving world. Yet, surprisingly, this radical change must have involved extremely simple molecular relationships in order to have arisen spontaneously. These requirements appear almost mutually exclusive, but together they vastly narrow the possible contexts that are relevant to explaining the origin of living thermodynamic processes.

## **2.2. Context-limited versus self-limiting dissipation**

The classical Second Law of Thermodynamics states that physical systems involving large ensembles of interacting components and isolated from the input or output of energy and matter will spontaneously change toward a condition of maximum entropy. This classical formulation was developed and refined during the latter part of the 19th Century to apply to

material-energetic interactions for processes close to equilibrium. But, in the natural world, most physical interactions occur in non-isolated physical systems that are in the process of exchanging both matter and energy with their surrounding environment. This includes cases where extrinsic influences drive the system away from equilibrium as fast or faster than it tends to develop toward equilibrium. Systems that are constantly disturbed by an inflow of material and/or energy can persist far from equilibrium for long periods.

Recognition of this limited application suggested to physical chemists and mathematicians during the first half of the 20th Century that it would be helpful to develop a general rephrasing of the Second Law that applied to both isolated and non-isolated systems, including those maintained far from equilibrium. Probably the most widely cited formulation of this general case was provided by Ilya Prigogine in the late 1940s (8-9). Instead of focusing on the tendency toward global entropy maximization, Prigogine considered the changing entropy relationship between a subsystem and its environment(s). The classical form of the Second Law describes macroscopic dynamical system properties near equilibrium. In order to incorporate far-from-equilibrium processes, it is instead useful to describe the rate and distribution of entropy change between a system and its environment. The critical factors in such cases are the extrinsic perturbation of the subsystem away from equilibrium, the subsystem's tendency to develop toward equilibrium, and the different means by which the subsystem can offload the effects of this perturbation into the environment. These might be described as the system's import and export relationships. Following Prigogine, such local subsystems are described as "dissipative structures" because they can only decrease their internal disequilibrium by offloading this disturbance into their environment.

Of particular interest for this discussion are systems that are being continuously perturbed away from equilibrium. In these cases the disequilibrating effects propagate through the subsystem at a rate that must eventually at least match the rate that they are introduced. Self-organization arises in response to this throughput by decreasing subsystem entropy in a way that increases the rate of global entropy production.

This has often been described as the Maximum Entropy Production (MEP) principle. It is debatable whether MEP is an *extremum* principle in the same sense, as is the Second Law (10-12), but it is generally accepted that a self-organized dissipative system produces entropy at a higher rate than when unorganized. For these conditions, proponents of the MEP principle have variously rephrased the Second Law in terms of the rate of dissipation. Thus, Swenson (13) argues: "[A] system will select the path, or assembly of paths, out of otherwise available paths, that minimize the potential or maximize the entropy at the fastest rate given the constraints." (p. 5) Alternatively, Schneider and Kay (14) focus instead on the perturbation and argue that as a thermodynamic system is "... moved away from equilibrium [it] will utilize all avenues available to counter the applied gradients. As the applied gradients increase, so does the system's ability to oppose further movement from equilibrium." (p. 25) To the extent that living processes are dissipative processes that can be adequately described as constellations of self-organized processes, some version of a rephrased Second Law should apply. Following this line of reasoning, a number of researchers (13-16) have argued that organisms, ecosystems, and the process of evolution all should exemplify the MEP principle.

In these terms, self-organizing processes can be described as doing work to oppose the displacement of the subsystem away from equilibrium. This internal organizing work decreases subsystem entropy but necessarily increases the rate that global entropy is produced. In this respect, self-organized regularities are structured in a way that would otherwise hasten their own destruction should the perturbing effects cease. For this reason, MEP-based self-organization has no capacity for persistence beyond the extrinsically imposed gradients that it develops in response to. In this respect, self-organizing processes are intrinsically self-destroying processes. This calls into question whether self-organization theory is adequate (and thus sufficiently general) to provide a thermodynamic account of living processes.

We believe that, contrary to this view, and irrespective of the validity of the MEP principle, the concept of self-organization is not sufficient to fully account for organism thermodynamics. The concept of self-organization specifically does not appear to explain an organism's capacity to maintain and reproduce its highly structured far-from-equilibrium organization in the face of intrinsic degradation, extrinsically imposed disruption, or loss of supportive resources.

Making thermodynamic sense of this conservative feature of living organisms requires one more step of generalization beyond self-organization and any version of the MEP principle. MEP-based self-organization theory is inadequate for explaining how a living dissipative system can produce constraints able to modify the dissipation process in conditions where external support is modified or temporarily interrupted, so as to resist degradation of its self-organized features.

A hint is provided by dissipative systems that are in some way self-limiting. This self-limiting characteristic can be exhibited by self-organizing processes that grow in scale (e.g. in snow crystal formation) or have fixed upper limits to their composition (such as the self-assembly of viral capsules into polyhedrons with a fixed number of capsid facets). Thus, certain variant forms of self-organizing processes can clearly violate a simple version of the MEP principle and even attain a degree of thermodynamic stability. However, this stability is defined by reaching a basin of thermodynamic equilibrium, and is susceptible to degradation if equilibrium conditions are extrinsically disrupted. Living processes must instead intrinsically limit their dissipative processes in order to preserve their organization across changing conditions.

### 2.3. The autopoietic dilemma

This poses an apparent paradox: Organisms must rely on self-organizing dissipative processes to generate their highly constrained internal chemical and dynamical regularities but these interlinked dissipative processes must in some way be regulated in ways that counter the very conditions that tend to generate them or else organism integrity will fail. This suggests that self-organization due to dissipation may be necessary but not sufficient to account for the constitution of a living organism.

This situation seems paradoxical because self-organization in the form of the reciprocal co-production of each of the component molecules, structures, and processes of an organism has long been recognized as one of the most ubiquitous and distinctive characteristics of life. Indeed, the first modern statement of this principle can probably be attributed to Immanuel Kant's effort to define the apparently intrinsic teleology of living beings. In his 1790 Critique of Teleological Judgment (17) he distinguishes organisms from mere machines in terms of their reciprocal productive power as follows: "An organized being is then not a mere machine, for that has merely motive power, but it possesses in itself formative power of a self-propagating kind which it communicates to its materials though they have it not of themselves." (p. 558) and "... every part ... is there for the sake of the other (reciprocally as end, and at the same time, means)." (p. 557) In a striking parallel, the evolutionary biologist J. B. S. Haldane (18) gave the following definition of life in 1929: "A simple organism must consist of parts A, B, C, D, and so on, each of which can multiply only in the presence of all, or almost all, of the others." (p. 245)

This circular component production logic has been the focus of many modern efforts to characterize what makes an organism distinctive from other forms of physico-chemical processes. Probably the most commonly cited modern characterization of this co-productive characteristic of organism dynamics is Maturana and Varela's (19) concept of *autopoiesis*, or "self-production." The term distinguishes the dynamics of living organisms from dynamical systems whose organization is externally imposed and thus *allopoietic*. They define an autopoietic system as one that "constitutes itself ... as a concrete unity ... by specifying the topological domain of its realization ..." So an "autopoietic machine" is one that collectively produces its material components as well as the network of relations between them that constitutes their unity in a discrete physical location. These latter properties are not attributed to any separate and distinctive mechanism over and above the closed co-production of components and yet are essential defining attributes. Indeed, this organization is described as the "fundamental variable which it maintains constant" (19, p. 79).

These characterizations highlight but do not provide an explanation of how this organizational unity is generated and maintained. In simple terms, the autopoietic account merely assumes the presence of some means of maintaining this co-productive unity of interdependent components. This unspecified factor is presumed to regulate these co-productive relationships with respect to one another so that their synergistic interdependence is preserved. The requirement for an additional controlling influence is well exemplified by reciprocally catalytic chemical processes. Though each molecular species comprising a collectively autocatalytic set is a product of the interactions among other members of the set, their collective reciprocity is only an extrinsically observed descriptive property. In a solution containing such a set of catalysts, exhaustion of substrates and molecular diffusion will spontaneously decrease the rate of autocatalysis as the system approaches equilibrium and inverse reactions will come to balance catalyst production. There is no intrinsic unity to this probability of collective co-production, and nothing that insures this collective property across changing conditions. But, maintaining unity of the network of co-production is critical for organisms. So although component co-production is an important attribute of living organization, it is the maintenance of this network of dynamical interdependencies that is what most demands an explanation.

The most common solution offered to counter this absence of a unifying influence is to imagine enclosing a set of reciprocally catalytic molecules within a container analogous to a living cell (19-21). But, confinement isn't unity, only proximity. Physical confinement doesn't guarantee persistent unity or self-similarity of organization across time and with respect to damage or thermodynamic degradation. Catalytic co-production will also cease in a container that prevents penetration. So, persistence of this dynamical organization requires that new substrates are able to enter to be catalyzed and waste products are able to leave. In addition, unless these two diffusion processes are regulated so that only appropriate molecules can enter and exit at controlled rates, consistent with the rate of catalytic production, the organization will progressively degrade. Even just the generation of new components will be problematic. Unregulated growth can only be sustained if the container itself enlarges at an appropriate rate. Container components must therefore be produced at a rate that is regulated to roughly compensate for surface to volume differences (i.e. surface growth should roughly approximate the 2/3 power of internal component production). In addition, even if differential component production rates are controlled, constant growth can only persist if non-destructive fission and re-annealing of the contained system is probable. Thus autopoiesis, at least as understood in these terms, must assume the existence of a number of the very regulatory relationships it is supposed to explain.

A final critical shortcoming of this general approach to organism dynamics is its failure to consider any of the thermodynamic requirements and constraints involved. Organism thermodynamics necessarily diverges from both near-equilibrium thermodynamics and far-from-equilibrium self-organized thermodynamics. Critical to achieving these thermodynamic ends is a means for maintaining organizational integrity of the interdependent component processes. The thermodynamic agnosticism of autopoietic theories renders them insufficient to explain these critical distinctions between living and non-living thermodynamic systems.

## 2.4. The formal versus physical logic of biological regulation

It would thus appear that the organizational unity of even the simplest precursor to an organism requires something in addition to reciprocal generation of components in order to maintain its dynamical self-similarity across material change. This “something in addition” is the fundamental regulatory principle that requires explanation. It must provide a regulatory influence over all component interactions with respect to each other and their immediate environment. It must also stabilize and persistently reconstitute their co-dependent organization. And, it must in some way be independent from the dynamics it regulates; otherwise, it will be susceptible to modification and corruption along with this dynamics. Consequently, it must operate something like a representation or a model of this global synergistic organization, and be able to impose the constraints implicit in this model upon the dynamical relations among system components. This is a tall order.

Robert Rosen (22) and Francisco Varela (23) have each argued that living organization is constituted by a formal principle over and above its physico-chemical composition. They further argue that this formal property involves a logical circularity that resembles a logical type violation (24), i.e. analogous to the way that the referential circularity of whole represented by a part characterizes the liar's paradox: e.g. “This statement is false.” In other words, there must be something contained within each organism that in some way represents the whole of which it is a part. This formal non-reducible feature of life's logic is described as an “impredicate” relationship by Rosen (22) because it defies analytic reduction. And Varela (23) explicitly invokes the logic of self-referential distinctions (as developed by George Spencer Brown 25) to describe this property. They each use this to argue that life has an irreducible quality.

In his discussion of self-reproducing machines, John Von Neumann (26) may have been the first to recognize the requirement for maintaining “instructions” independent of the construction processes. An analogous separation of the genetic “information” and metabolic processes has become implicit in the now standard dogma of the genotype/phenotype distinction. It is taken for granted by the interpretation of genetics on the analogy of a “code” and of DNA functioning as a source of “algorithmic” control over cellular-molecular processes. But defining the concept of organism in these terms implicitly presumes a sort of biological dualism. It suggests that the respective formal and material aspects of life are somehow intrinsic properties of the different classes of molecules that assume these functions in living cells. It should not be surprising, then, that models of the simplest precursors to living cells (e.g. protocells) simply assume that the regulation of metabolic and reproductive processes will automatically arise by combining nucleic acids and the molecules involved in their replication within lipid vesicles.

The idea that the core organizing feature of life is a formal rather than a physical property has been systematically explored by Howard Pattee (27-29). Pattee describes this distinction separating the physico-chemical dynamics of the organism from what he calls “semiotic controls” as an “epistemic cut.” He has emphasized that quite special physical conditions are required for these abstract relations to be realized. Specifically, they critically depend upon the presence and maintenance of formal controls that are physically instantiated as “nonintegrable constraints, energy degenerate states, and temporal incoherence” (29). These properties segregate organizational control from dynamics and thereby prevent critical organizing constraints on organism dynamics from being corrupted by the very physico-chemical processes they control.

Putting these critiques and requirements together we can now clearly identify the apparent paradox that life poses to physics. Although self-organized dissipative processes can emerge in far-from-equilibrium conditions as subsystems develop toward more efficient reduction of energetic and/or material gradients, their organization is structured to oppose the effects of these gradients. Were organisms just complex self-organizing systems they would therefore be inherently self-eliminating. Living processes are, in contrast, intrinsically self-sustaining. This requires the presence and persistence of some intrinsic source of constraint that limits these dissipative processes irrespective of their physical and chemical details.

## 3. AUTOGENESIS

### 3.1. Constraints on constraint-production

Although under persistent far from equilibrium conditions local self-organizing constraints can be internally-generated, they are entirely dependent on extrinsic perturbation. These constraints can be dynamical or structural. An eddy in a stream is dynamically generated and maintained. Its form persists only so long as the flow of water remains constant and the obstruction that perturbs this flow away from linear remain constant. Snow crystals exemplify a link between both dynamical and structural constraints. Snow crystals grow into highly regular complex hexagonally symmetric patterns as a result of many converging constraints. First there is the constraint of ice lattice formation which tends toward only a very few regular patterns that correlate with differences in temperature, humidity, and pressure. Second, there is the complex thermodynamics of the phase change from vapor to solid and the heat energy this liberates into the growing crystal lattice. This heat is dissipated to the surrounding air through the structured lattice and plays a role in equalizing growth and melting patterns throughout the crystal. Third, there is the structure that has been laid down at earlier stages of growth the limits the positions at which new growth is most probable. Thus, the dissipative dynamics of crystal growth leaves a structural trace of its developmental history, which constrains each subsequent stage of growth. This allows structural constraints to compound upon one another, and is partially responsible for the complex symmetries that result, even though accretion of new water molecules is also an effect of random Brownian motion. In this respect a snow crystal is a sort of palimpsest of the brief history of the differing atmospheric conditions through which it fell. In many respects, then, its structure is a form of memory.

As argued above, some form of constraint memory is required to maintain and regulate the interdependent network dynamical processes that constitute a living organism. To explore how constraint generation processes might be organized to preserve these constraints so that (unlike a snow crystal) they can be persistently reused Deacon (7, 30, 31) has proposed a model system called an autogen (also called an autocell in 30 and 31). An autogen consists of two synergistically linked self-organizing processes (illustrated in Figure 1): a collectively autocatalytic set of molecules that generate byproduct molecules which tend to self-assemble into a container, similar to a viral capsule. Though only conceptual, this type of molecular complex is probably empirically realizable, because both molecular processes have been widely observed in nature and are well understood. As we will demonstrate below, such a system should be able to repair itself if damaged and potentially reproduce. Because of the linkage between the two component processes, wherever reciprocal catalysis is most rapid there will also be a growing concentration of self-assembling molecules. This will result in a high probability of forming a self-assembling container that encloses the very catalysts that generate its components.

Two possible variants of this autogenic relationship are illustrated in Figure 1: a polyhedral and a tubular form of autogenic process. Just as the products of each catalytic process (products C and F in Figure 1) serve as reciprocal catalyst, each for the other, one of the products (F in Figure 1) is a component of a self-assembling shell structure—analogue to a capsid molecule in a viral shell. It is via this process that one self-organizing process, the shell structure, limits the other process, autocatalysis, from completely dissipating the co-locality of catalytic materials and the structure necessary to maintain that locality, which is itself a product of the catalysis.

This simple configuration results in the tendency to generate, preserve, and reconstitute three forms of constraint. The first two are (1) the local gradient of catalyst and capsid concentration produced by reciprocal catalysis and (2) the generation of a boundary to diffusion that results from self-assembly of a container. The first two forms of physical and chemical constraint mutually promote and limit one another. The critical boundary constraint on reciprocal catalysis is proximity of the catalysts of the set to each other (i.e. relatively high local concentration of these molecules). Typically, products of such a reaction will diffuse away as soon as they are generated. However, enclosure in an autogenic shell will maintain catalysts in local proximity to one another, so that even when catalysis eventually ceases within its interior, the full set of catalysts will be maintained in “formal” disequilibrium with respect to their external surroundings. Conversely, the critical boundary constraint on capsule self-assembly is a high local concentration of capsid molecules. The process of self-assembly increasingly depletes the local region of these molecules as they are incorporated into the growing shell. Self-assembly will be facilitated by catalytic processes that locally replenish the supply of these molecules. Local reciprocal catalytic production of these molecules provides this boundary constraint.

As a result of this reciprocity of constraint production, there is a high probability that the same boundary constraints for each process will be maintained even when the complex closes and chemical dynamics ceases. This potential reciprocity of constraints will be remembered, so to speak, even in an inert state. Moreover, if the structural integrity of this inert molecular complex is in some way disrupted (e.g. by thermal agitation) in the presence of new catalytic substrate molecules the release of these catalysts will immediately re-initiate both processes. What were previously only potential boundary constraints while inert will again become dynamically expressed. In this way the integrity of a disrupted autogen can be reconstituted—a form of self-repair. In addition, it is also possible that a significantly disrupted complex will re-reform into two or more new replicas of the original—a form of self-reproduction.

The implicit reciprocity constraint between these two physico-chemical processes is a higher order form of constraint. This reciprocity constitutes is neither a physical nor a chemical constraint. It consists in the inter-dependent synergy between “types” of physico-chemical constraint-generating processes. The tendency for an autogenic complex to reconstitute its unity if disrupted is thus a consequence of a formal relationship. Because it is not a physico-chemical constraint it is persistently present through all phases of the autogenic process: inert or dynamical, potential or expressed. This higher-order constraint is effectively a self-reconstituting boundary condition for promoting its own persistence. It is this feature that creates the foundation upon which abiogenesis, and eventually information, can find a foothold.

By reconstituting itself if disrupted this dynamical process also effectively completes a work cycle. Stuart Kauffman (32) points out that completion of a work cycle is a necessary property of what he characterizes as autonomous agency: the “capacity to act on its own behalf.” Completion of self-reconstitution, resets the system so that it is capable of initiating the same dynamical process again and again. In this way autogen closure doesn’t just reconstitute a physical structure, it reconstitutes the capacity for self-reconstitution.

### **3.2. From synergistic constraint generation to regulation**

In general terms we can define regulation as a behavior generated in order to constrain some dynamical system variable to a range that supports persistence or prevents degradation of that system and/or its functions. Typical examples of regulation (as discussed above) are negative feedback mechanisms like thermostats and autopilots. These negative feedback systems are designed to behave in a way that converges toward a predetermined target state irrespective of how they are perturbed away from

this state. But this cybernetic behavior does not constitute regulation in itself. In a man-made regulator, this target state or range of variation is imposed by design processes that are independent of and outside of the operation of that system.

In contrast, if analogous cybernetic behavior happens to occur by chance in inorganic nature, like the maintenance of pressure and temperature in the Old Faithful geyser, we could only describe it as “regulation” in a metaphorical sense because achieving this cybernetic pattern of behavior has nothing to do with producing or maintaining its specific organization, and therefore has no intrinsic function.

In recent decades, many such feedback processes have been identified in living organisms. They are often analogized to man-made cybernetic systems. Though biologists recognize that these systems were not designed, in the sense that engineered systems are, it is commonly said that chance variation and selective preservation by natural selection has played an analogous role to purposeful design in the evolution of organism regulatory mechanisms. The problem with this seemingly reasonable analogy is that it merely passes the buck, so to speak. Organism adaptation and reproduction are quintessential regulatory processes themselves. How did this regulation ultimately arise if not from prior regulation? And if inorganic processes can only be described as regulatory if serving an extrinsically imposed function, how could regulatory processes ever have spontaneously emerged from inorganic processes alone?

This is where the logic of autogenesis can contribute some critical insights. Neither a geyser nor a thermostat generate dynamics that maintain, repair, or reproduce the physical systems that produce these dynamics. The constraints that constitute a geyser’s oscillatory expulsions will degrade if either the heat needed to fuel them dissipates or the constrained volume of the geyser is eroded by the repeated passage of water. Similarly, the thermostat, if left alone by human attention, will eventually fall prey to increasing entropy as components wear out. Dynamics inherent within these cybernetic systems is imposed and maintained only by extrinsic means. In the case of the geyser, such extrinsic impositions are naturally occurring terrestrial processes; whereas, for the thermostat, both its improbable structure and its ultimate function are determined by human designers and users.

The intent of this paper is to consider the possibility of the spontaneous emergence of regulation from particular inter-dependencies among intrinsic physico-chemical constraints. The autogenic logic described above provides an exemplary system in which the co-constraints of inter-dependent self-organizing processes are sufficient to maintain, repair, and reproduce their own critical collective boundary constraints. An autogen thus regulates the conditions that contribute to its own integrity by generating processes that counter forces tending to disrupt this integrity. This is a minimal form of regulation that preserves “self” in a literal physical sense. This formal reciprocity constraint organizes the component physico-chemical constraint-generating processes that are its origin. And yet, as a formal constraint, it is not any specific physico-chemical property.

This satisfies a requirement that Howard Pattee (discussed above) has repeatedly argued must be a fundamental feature of life: the regulation of organism dynamics by rate-independent non-integrable constraints. The higher-order synergy constraint is rate independent because it persists whether or not the system is inert or in the process of dynamically reconstituting itself. So its regulatory influence persists independent of the autogen’s dynamical state or the shuffling of its specific individual molecular constituents. Moreover, it is even capable of being reproduced with entirely new constituents. It is a form of self-regulation that is literally constituted by the relationships between the *forms* of the constituent dynamical processes irrespective of their molecular constitution. In this respect, there is no physical discontinuity required to produce this “epistemic cut” between physico-chemical dynamics and the formal source of regulation. The synergy constraint is an intrinsic emergent property of the whole and yet not tied to any specific substrate. The “epistemic cut” is produced by this indifference to specific physical embodiment (i.e. its multiple realizability), which enables this formal constraint to “remember” and “represent” the form of the autogen despite changing dynamical and material conditions.

One obvious clue that this form of organization crosses the boundary from constraint to regulation and out of the domain of merely physico-chemical processes is that regulation can succeed or fail. Physico-chemical constraints are present or absent. Certain processes will either occur or not as a result. Constraints per se, can neither fail nor succeed. They merely exist, because, for continuously dynamic inorganic processes there is no arbitrary “set point” or preferred state other than equilibrium. The autogen, however, illustrates just such a “set point” which simultaneously embodies the capacity to persist despite perturbation. This set point is effectively its completed inert form. An autogen can persist in this inert state indefinitely, unless sufficiently perturbed, at which time its preserved reconstitutive potential will tend to return it to that initial state, thereby preserving this potential. This set point is “remembered” even when environmental conditions are not conducive to its dynamical reconstitution. So an autogen is like a cybernetic regulator in this one respect: there is a target state that defines the target state toward which it tends to develop. Like a cybernetic regulator, an autogen’s set point is maintained irrespective of the system’s dynamical state. But unlike a designed cybernetic system, if an autogen is dissociated in a context lacking sufficient substrates or energy to drive its catalytic processes, this self-regulatory capacity will fail to be regenerated. Or if there has been an accidental molecular substitution in one of the component processes, the self-regulatory capacity may be degraded. Thus, an autogenic process is regulatory in a more complex self-directed way than is a designed cybernetic regulator. Its regulatory function is intrinsic to its very constitution.

We argue that this hierarchically organized constraint relationship provides a plausibility proof for the emergence of *telos* (a form of Aristotelian “final causality”) from mere physico-dynamic processes (Aristotelian “efficient causality”). Regulation has no meaning without the existence of *telos*, and *telos* has no meaning without the existence of a “self” for which one end (preservation) is “preferred” over another (destruction). It is the self that persists or not depending on the outcome that is the beneficiary or casualty. In contrast, in the non-living world outcomes are irrelevant to any given dissipative physico-dynamical process. All mere physico-dynamical constraints will spontaneously change until they reach maximum entropy and equilibrium. This fate, however, is not inevitable for living organisms whose lineages may potentially propagate their regulation of constraints and far from equilibrium condition indefinitely.

Although, the origins of life might conceivably have involved a very different chemical constitution, we hypothesize that it necessarily must have involved something analogous to autogenic logic. If so, then the origin of life is coincident with the origin of self-reconstituting formal constraint. It is both a plausibility argument for the emergence of self-regulated end-directed dynamics and for abiogenesis.

Of course, as with life in general, there will inevitably be changes in the environment that tend to undermine the preservation of any lineage with these characteristics. The capacity to reproduce and therefore provide a sort of lineage memory of this higher-order regulatory logic is the necessary basis for evolvability and the ground with respect to which new adaptations can be acquired. A core dynamic that self-regulates the processes that work against degradation becomes a sort of magnet for any additional variants that contribute to this self-maintaining capacity. This minimal form of evolvability can emerge despite the lack of specific molecular replication and inheritance mechanisms (but see below). This is what makes the evolution of higher-order more complex forms of regulation possible (as will be discussed below).

## 4. CONDITIONAL AUTOGENESIS

### 4.1. The emergence of cybernetic regulation

As describe above, cybernetic forms of regulation are organized to use feedback from the environment to control processes that minimize deviations from some preferred value of a system variable. In living systems, the preferred value of its critical functional variables is set by internally generated mechanisms, not extrinsically as in engineered regulators. Maintaining these values within critical tolerances is the very essence of adaptation and is critical for maintaining the structures and processes that generate these same regulatory mechanisms. For a lineage of organisms to persist and evolve, however, it must include the possibility of exhibiting diverse variants of these mechanisms. On one hand, this requires a form of memory to preserve the organizational constraints that have sustained individuals in past environments. On the other hand, each generation must be tolerant of variations on this mnemonic theme in order to accumulate new adaptations suited to changing environments.

In a simple autogenic system, functional variation might arise via the periodic incorporation of different molecules into its catalytic network during a dynamical re-closure phase. To the extent that this new molecule can insinuate itself into one of the component processes and interact to support the appropriate catalytic interaction, it may itself become incorporated in the global autogenic dynamic and passed to future replicas. So long as the core self-regulatory capacity remains intact across future replications this new variant will persist as well. This is the basis upon which higher-order complex forms of regulation can evolve.

The probability that a simple autogen will be disrupted and reconstituted is entirely independent of whether substrates are or are not present in the environment at that time. In general, as reactants are consumed from the environment during autogen formation, the local environment will become progressively less supportive. If an autogen completes the formation of its shell and becomes temporarily inert, it can persist even in environments that are poor in available catalytic substrates. So, despite the fact that autogen formation decreases the local concentration of substrates, this inert phase will enable diffusion processes to re-equilibrate this local asymmetry of concentration. Inert autogens will also tend to diffuse to other locales.

Consider a possible variation of autogen structure in which shell molecules are structured so that catalytic substrate molecules free floating in the external environment will tend to reversibly bind to them. If the shell tends to become increasingly unstable as the number of bound substrates increases, an adaptive consequence can follow. An autogen with a surface that is sensitive to the presence and concentration of substrates (see Figure 2A) will be less likely to be disrupted in the absence of supportive substrates and more likely to do so in their presence. This context-sensitive biasing of the constraint on shell fragility can thus serve as an adaptation that improves the probability of successful reproduction. Consequently, an autogen lineage with this added capacity will tend to out-reproduce autogen lineages that are insensitive to this relevant environmental factor.

A correlation between structural fragility of a molecular structure and the presence of a particular molecule in its environment would be irrelevant in the absence of the autogenic capacity. But, in the context of autogenesis, this correlation becomes a further yet higher-order form of regulation. The autogenic process now does something more than just regulate the synergy between constraint-generation processes. It also regulates an additional synergistic relationship between the activation of these processes and an environment that promotes their function in preserving the system’s capacities. The extent of surface-bound substrates effectively becomes an “indication” of the favorable or unfavorable state of the environment with respect to the probability of repair or reproduction. In other words, it provides “information” about the environment with respect to the self-



regulation of processes that depend on that environment. One might even be justified in claiming that the resulting change in autogen fragility interprets this state of the environment as useful or not by virtue of its correlation with the difference in probability of successfully propagating the autogenic form.

This is analogous to cybernetic regulation to the extent that the system responds differently with respect to environmental change in a way that maximizes the probability of reproduction. This regulation of integrity—regulation with respect to the value of a particular environmental variable—is thus second-order regulation over and above the formal regulation of internal reciprocities, and is a step closer to biological control. This provides plausibility to the hypothesis that intrinsic cybernetic regulation can emerge spontaneously, but only as it is dependent on this more fundamental form of self-regulation. In this respect, autogenic dynamics provides a base platform upon which secondary forms of regulation can be built.

This suggests a two-part hypothesis: (1) Autonomous regulation (i.e. regulation not imposed from outside the system) can emerge in systems that embody a self-regulatory integrity-maintaining capacity as their core formal dynamical tendency; and (2) this capacity is dependent on a prior reciprocal self-reconstituting synergy of constraint-generating processes.

#### **4.2. Template regulated autogenesis: an imaginative scenario**

We are now in a position to address the question of the emergence of “semiotic” control, which Pattee (28, 29) proposes as the defining feature of organism dynamics. We have shown (above) that the self-regulation that characterizes autogenesis is itself a formal rate-independent constraint that can thereby be maintained and reproduced irrespective of specific substrates or dynamical/inert status. But in an autogen this regulation of self-integrity is embodied holistically, so to speak, in the distributed relationships between component processes. In all living organisms, and even viruses, the critical rate-independent self-determining constraints are embodied in specialized molecules: DNA and RNA. This poses the problem of explaining how information about the self-regulating dynamics of an organism and critical to its generation can become off-loaded onto the physical structure of a specialized molecule.

Though not totally implausible or magical, the following scenario involves thoroughly imaginative molecular interactions that are at most place-holders for generic types of processes. Our point is not to offer this as a proposal for the evolutionary origins of nucleic acid molecules, but rather to demonstrate the general principle by which the self-reconstituting constraints of an autogenic process can become offloaded onto a molecular structure. Indeed, it is likely that the first informational molecules in the precursor stages leading to modern organism forms were quite unlike the polynucleotides that serve this function today. We leave the search for this precursor chemistry to future theorists and chemists. Our intention is only to exemplify a general principle.

As a preface to this scenario, consider a curious coincidence exemplified by two core features of the molecular biology of living cells. The first is that the energetic functions of cell metabolism depend on one general class of energy-ferrying molecules: nucleotides like cAMP, ATP, GDP and their relatives. The second is that the information-bearing molecules within living cells, such as DNA and RNA are also composed of nucleotide residues strung together as polymers. The scenario we propose assumes that the energetic function of nucleotides preceded the evolution of the information template function of nucleotide polymers.

We begin this fanciful scenario by simply positing the existence of a molecular mechanism for the autogenic synthesis of diverse nucleotides, and an autogenic process in which these nucleotides serve to capture environmentally available pyrophosphates (such as might be generated near volcanic vents) and use this energy to drive catalytic activity (Figure 2B). This mechanism for energetically driving the catalysis could provide more rapid autogen reconstitution and drive chemical reactions that are otherwise very improbable. This can provide an evolutionary advantage for this form of autogen. In the inert state, however, the presence of these energetic molecules is irrelevant, and might even be potentially damaging. But autogen closure might also facilitate polymerization of the free nucleotides (e.g. by the exclusion of water) into a randomly ordered polymer analogous to DNA or RNA (Figure 2C).

The resulting randomly assembled polymer could provide a three-dimensional structure on which catalysts can align via various forms of reversible non-covalent bonds. Because of stereochemical coincidences between catalyst structure and nucleotide polymer structure the relative binding proximity of different catalysts will be determined by nucleotide order within the polymer (Figure 2D). This can provide a sort of template. The differential proximity of catalysts could potentially play a role in their likelihood of interacting with one another, because those nearby each other will be more likely to be released from this polymer chain in close temporal succession with one another. In this way template structure can provide a biasing constraint on catalytic interactions. With only a very few catalysts this would probably not make any significant difference in autogen reconstitution, but as the number of interdependent catalysts increases in evolution selective biasing of catalytic interactions will become increasingly important. The more interacting types of molecules the more possibilities for molecular interactions that are not conducive to autogenic reconstitution. The “combinatorial explosion” of these possible compromising reactions will thus pose a severe complexity limit on unregulated autogenic systems. Template biasing in some form will be essential for the evolution of autogenic complexity.

Though nucleotide sequence order may begin in a random state, selection on the relative efficiency of reproduction due to minimization of costly side reactions in a population of autogens will provide a source of natural selection favoring convergence toward a sequence order that maximizes their reproductive effect. This should yield a template structure that embodies in its physical structure a representation of the specific abstract dynamical organization that constitutes autogenic identity. For this template scenario to work, two additional conditions need to be met: the template needs to be replicated in daughter autogens and there needs to be the possibility for small variations in the replicated templates (analogous to DNA point mutations). Of course, these assumptions are also required for any polynucleotide replication theory of life's origins. For the purpose of this scenario they are merely assumed.

This somewhat fanciful scenario is a stand-in for any template evolution process that could provide some degree of biasing of molecular interactions in an autogenic context. Though quite primitive in comparison with the DNA sequence determination of amino acid sequence order constituting a protein, it nevertheless demonstrates how complex global regulation of a many-component molecular network of interactions can come to be regulated by the structure of a molecule. This has many advantages over the holistically distributed global self-regulation of the simple autogenic process, though it ultimately derives this functional capability from this more basic form of regulation. The resulting template molecule has effectively offloaded constraints that previously were necessarily embodied holistically in the entire autogenic organization and the specific stereochemical complementarities between interacting molecules. Template-based constraint reduces constraints on the specific molecular details required to make autogenesis possible. Incidental modifications of template structure can now provide an indirect means for alternative catalytic interaction patterns to be generated and tested by natural selection.

The general principle that these two scenarios illustrate shows how implicit Cartesian assumptions about physical and semiotic constraints can be avoided. It suggests that the “epistemic cut” distinguishing physical and semiotic processes is not unbridgeable. Regulation is a form of constraint that is formal. It is extrinsic to the physical and chemical processes it regulates, and yet emerges from and depends on it.

## 5. CONCLUSION

In this paper, we have provided a conceptual model of a molecular system (an autogen) that demonstrates how physico-chemical constraints can spontaneously give rise to formal “semiotic” constraints and how this constitutes genuine regulation.

All dynamical processes, whether close to or far from equilibrium, are structured so that they dissipate any labile gradients and promote development toward ever-higher global states of entropy. Self-organizing processes are special cases that increase the rate of gradient dissipation by developing increasingly more direct and therefore regular pathways for gradient reduction to occur. This local regularization is critical to generating order in living systems but it is also the most efficient way to undermine the very conditions that produce it. In contrast, life must accomplish the opposite. It must be organized so that it preserves and reconstitutes the intrinsic and extrinsic conditions that support it, even in the face of influences that tend to undermine its continued existence.

Autogenesis emerges from the synergy between the physico-chemical constraint-generating processes that together actively maintain their synergy. The anti-entropic self-rectifying character of the whole warrants describing the constituent processes in autogenesis as “functions” and describing the higher-order constraint of the whole as a form of intrinsic regulation. Because this higher order constraint regulates system integrity and unity, it also constitutes the locus of autonomous agency, or self. The higher-order formal constraint constituting autogenic self can persist irrespective of the system's changing components and dynamical status. Because this autonomous agency is ultimately dependent on persistence of a formal constraint it is irreducible to its component physico-chemical constituents or their interactions.

In addition to demonstrating the plausible emergence of intrinsic regulation from physico-chemical constraint relationships, we believe that autogenesis provides a platform from which (and based upon which) all secondary forms of regulation can arise. This is exemplified by demonstrating how it can provide scaffolding for two higher-order forms of regulation, which we describe as cybernetic and template-based regulation, respectively. Though these conclusions are derived from conceptual models not organisms, these models are based on well-understood physico-chemical principles, which makes these hypotheses empirically testable.

If such systems are even remotely realistic (and even if they have nothing to do with the origins of life as we know it), they demonstrate the plausibility of a bridge from physico-chemical constraints to biological regulation.

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**Key Words:** Self-Organization, Autogenesis, Autopoiesis, Maximum Entropy Principle, Autocatalysis, Self-Assembly, Abiogenesis, Review

**Send correspondence to:** Terrence W. Deacon, Department of Anthropology, University of California, Kroeber 232, Berkeley, CA 94720, Tel: 510 691-9332, Fax: 510 643-8557, E-mail: [deacon@berkeley.edu](mailto:deacon@berkeley.edu)

**Figure 1.** Two possible forms of autogenic molecular complexes: A is a polyhedral form with a self-assembling capsule analogous to a polyhedral virus, whereas B is a tubular form with a self-assembling capsule analogous to that exhibited by microtubules. Modified with permission from (30).

**Figure 2.** Panel A depicts an autogenic complex with a capsule that is made increasingly fragile by the binding of catalytic substrate molecules from the environment. Besides catalysts and substrates the image also depicts nucleotides and phosphates (+) which can serve as a means for capturing environmentally available free energy to aid catalysis. Panel B depicts the differential binding of catalysts to a polynucleotide formed during the closed inert phase of autogenesis. Panel C depicts the way that differential proximity of catalytic binding on a polynucleotide polymer might bias catalytic interactions by releasing them in a preferential order. Panel D depicts a corresponding catalytic network of interactions between the set of catalysts and substrates that has the highest probability of achieving autogenic self-reconstitution and which could be favorably biased by template-based sequential release thereby minimizing the probability that other potential interactions could interfere with completion of the autogenic work cycle Modified with permission from (7).

**Running title:** From constraint to regulation

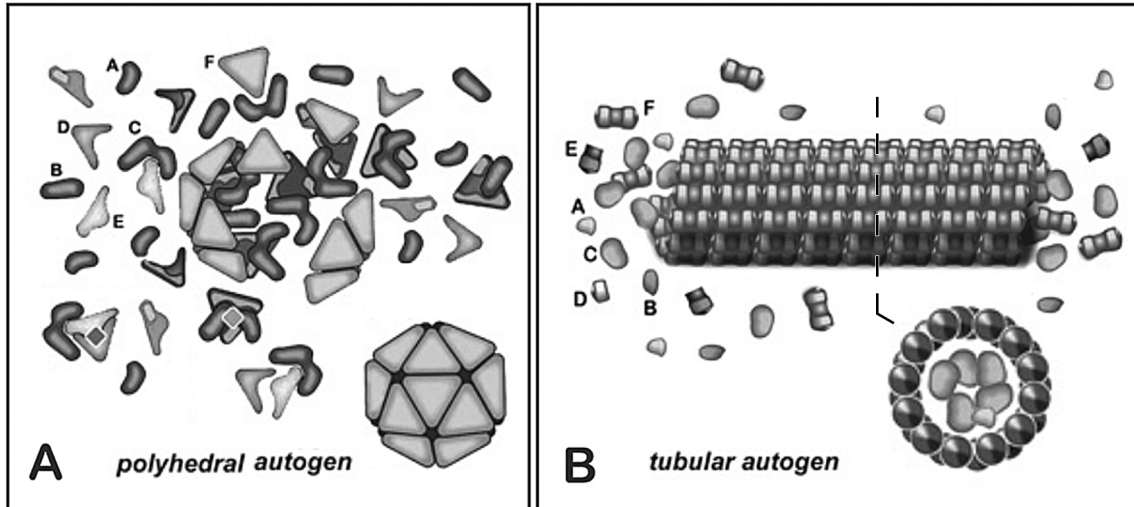


fig1

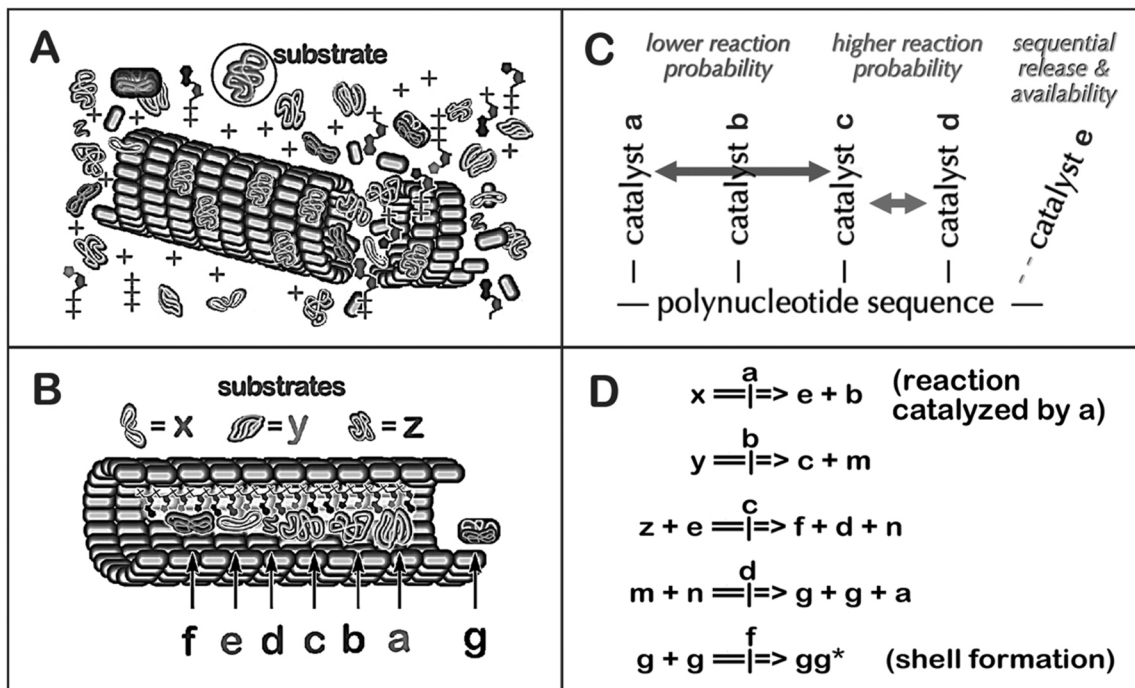


fig2