Reciprocal Linkage between Self-organizing Processes is Sufficient for Self-reproduction and Evolvability

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Abstract

A simple molecular system ("autocell") is described consisting of the reciprocal linkage between an autocatalytic cycle and a self-assembling encapsulation process where the molecular constituents for the capsule are products of the autocatalysis. In a molecular environment sufficiently rich in the substrates, capsule growth will also occur with high predictability. Growth to closure will be most probable in the vicinity of the most prolific autocatalysis and will thus tend to spontaneously enclose supportive catalysts within the capsule interior. If subsequently disrupted in the presence of new substrates, the released components will initiate production of additional catalytic and capsule components that will spontaneously re-assemble into one or more autocell replicas, thereby reconstituting and sometimes reproducing the original. In a diverse molecular environment, cycles of disruption and enclosure will cause autocells to incidentally encapsulate other molecules as well as reactive substrates. To the extent that any captured molecule can be incorporated into the autocatalytic process by virtue of structural degeneracy of the catalytic binding sites, the altered autocell will incorporate the new type of component into subsequent replications. Such altered autocells will be progenitors of "lineages" with variant characteristics that will differentially propagate with respect to the availability of commonly required substrates. Autocells are susceptible to a limited form of evolution, capable of leading to more efficient, more environmentally fitted, and more complex forms. This provides a simple demonstration of the plausibility of open-ended reproduction and evolvability without self-replicating template molecules (e.g., nucleic acids) or maintenance of persistent nonequilibrium chemistry. This model identifies an intermediate domain between prebiotic and biotic systems and bridges the gap from nonequilibrium thermodynamics to life.

Keywords

artificial life, autocatalysis, nonequilibrium, origins of life, protocell, replicator, self-assembly

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Although there are a number of outstanding theoretical problems to be solved with respect to life's physics and chemistry (such as the determinates of protein folding), most of these have to do with massive analytic complexity and do not stem from uncertainties regarding fundamental laws or principles. Yet despite advances in the realm of basic theoretical biology, there remains considerable uncertainty about the critical steps in the transition from the prebiotic to the biotic chemistry of the simplest molecular systems potentially able to reproduce and evolve. As a result, we still lack a means to approach the theoretical issues involved in formulating what Kauffman (2000) has called a "general biology." The aim of this article is to propose a simple model molecular system that bridges the gap between prebiotic and biotic systems with sufficient simplicity and precision to offer both empirical testability and theoretical insights into the transition from physical chemistry to life.

Definitions of life are notoriously eclectic lists emphasizing different attributes exhibited by known life forms described at various levels of abstraction(see, e.g., comparisons in Schopf 2002). Probably, the most abstract characterization was provided by the philosopher Immanuel Kant who in 1790 defined an organic body as something in which "every part . . . is there for the sake of the other (reciprocally as end, and at the same time, means)." He further argued that "an organized being is then not a mere machine, for that has merely *moving* 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" (Kant 1952/1790). Implicit in Kant's abstract characterization is the fact that organisms are organized so that their organization resists dissolution by virtue of self-repair and self-replication. Rasmussen et al. (2004) provide a typical modern counterpart to Kant's characterization when they argue that "there is general agreement that a localized molecular assemblage should be considered alive if it continually regenerates itself, replicates itself, and is capable of evolving." However, many authors demand more explicit definitions that fill in details of these component processes with additional specifications. For example, Moreno (1998) defines a living organism as "a type of dissipative chemical structure which builds recursively its own molecular structure and internal constraints and manages the fluxes of energy and matter that keep it functioning (by metabolism), thanks to some macromolecular informational registers (DNA, RNA) autonomously interpreted which are generated in a collective and historical process (evolution)."

Although modern accounts can be far more concrete and explicit than Kant's, by virtue of their incorporation of over 200 years of biological science, this knowledge can be a source of distraction, since certain of these criteria may be characteristic of contemporary forms but not of all possible forms of organism. Beyond the general synergistic character of organic dynamics, three additional explicit criteria are common to most modern accounts of life's most basic properties:

1. *Information*. Organisms contain and replicate information, in the form molecular templates that are copied in reproduction and transcribed to determine the structure of crucial functional components.

2. *Metabolism*. Organisms require molecular machinery for obtaining and transforming substrates to support continual maintenance of internal structural integrity as well as for copying and transcribing the molecular information.

3. *Containment*. Organisms are enclosed in structures (e.g., cell membranes and protein capsules) that maintain component proximity and functional linkages and additionally may regulate external and internal concentrations of critical substrate and waste product molecules.

All three of these functional criteria must be met to sustain known life forms, though they need not all be accomplished within a single organism, as in most bacterial and eukaryotic cells, but may also be distributed across interdependent organisms, as in parasites and their hosts or in symbionts. Whether these processes are all necessary to account for the most general features of life—i.e., self-maintenance, self-reproduction, and evolvability—is difficult to determine. One difficulty derives from the absence of any exemplars of extraterrestrial life for comparison, making it difficult to discern essential from incidental features due to environmental conditions and accidents of evolutionary history on this planet. Another difficulty is the absence of forms more primitive than even the simplest contemporary life forms, which are far more complex than could form spontaneously and which have apparently eliminated many stages of simpler precursors. Finally, efforts to produce artificial systems with these properties, but composed of constituents not found in organisms, are still in their infancy. So the range of possible alternative mechanisms is largely unexplored (but see Freitas [2004] for a thorough review of the state of this research). These limiting circumstances make it difficult to deconstruct living organisms for clues about the relative priority and independence of their various attributes, mechanisms, and substrates.

In recent decades, remarkable strides have been made in identifying the minimal components necessary for bacterial cell life. Approaches have generally been characterized as top-down versus bottom-up. Top-down approaches attempt to extrapolate backward, theoretically and experimentally, from current organisms to simpler precursor organisms. Prominent in this paradigm is the attempt to describe and produce "minimal cells" by stripping a simple bacterium of all but its most critical components (Koonin 2000). Though considerably simpler than naturally occurring organisms, these minimal cells still contain hundreds of genes and gene products (Gil et al. 2004) and so turn out to be vastly more complex than even

the most complex spontaneously occurring nonliving chemical systems, implying that they cannot be expected to have formed spontaneously (Szathmáry et al. 2005). The alternative bottom-up approach attempts to generate key system-attributes of life from a minimized set of precursor molecular components. An increasing number of laboratory efforts are underway to combine molecular components salvaged from various organisms and placed into engineered cellular compartments called *protocells* (see recent reviews in Rasmussen et al. 2004; Szathmáry et al. 2005). The intent is to produce an artificial "cell" with the capacity to maintain the molecular processes necessary to enable autonomous replication of the entire system. To accomplish this, protocells must obtain sufficient energy and substrates and contain sufficient molecular machinery to replicate contained nucleic acid molecules and to produce the protein molecules comprising this machinery from these nucleotide sequences, and probably much more (Gil et al. 2004). Though vastly simpler than what is predicted for a minimal bacterial cell, even the most complex protocell systems fall considerably short of the goal of achieving persistent autonomous reproduction even though they incorporate more than a dozen types of complex molecules (e.g., nucleic acids, complex proteins, nucleotides, phospholipids) which are already organized into working complexes (such as ribosomes) by the living systems from which they have been removed. Given that they are composed of cellular components that accomplish the relevant functions in their sources, it is expected that protocell research will accomplish its goal as more complex protocells are constructed. However, even the simplest protocells currently being explored are sufficiently complex to raise doubts that such systems could coalesce spontaneously.

An implicit assumption of the great majority of these approaches is that replication and transcription of molecular information, as embodied in nucleic acids, is a fundamental requirement for any system capable of autonomous reproduction and evolution. This is a natural assumption since nucleic acid–based template chemistry is the most ubiquitous attribute of all known forms of life. But including this attribute in an artificial cell turns out to be extremely demanding in terms of critical support mechanisms. In order to replicate nucleic acid sequences and transcribe them into protein structure, some of life's most complex multimolecular "machines" are required, and this is as true for protocells as it is in the simplest living organisms. Though some of these complications may be avoided by molecules serving multiple functions, such as the capacity for RNA to also exhibit catalytic functions (Cech 1986), an impressive number of complex molecular structures and interactions must still be provided to support these processes. Thus protocells are valuable test beds for exploring the minimal conditions that are required for life, but leave much unexplained when it comes to the origins of these conditions. As Szathmáry et al. (2005) note: "[I]t is painfully obvious that a great deal of molecular and protocellular evolution preceded the hypothetical 'minimal cell'."

In reaction to the dependence of nucleic acid function on so many supportive processes, many researchers have argued that supportive synthetic and metabolic process must have evolved prior to nucleic acid functions (e.g., Morowitz 1992; Kauffman 1993; de Duve 1996; Anet 2004; Andras and Andras 2005) and that structure-generating nonequilibrium processes may be more basic. Currently, the complicated interdependence between the construction and information functions of life, their relative priority in evolution, and their roles in delimiting units of reproduction and selection have not been resolved, much less the means by which these complex functional relationships might have initially emerged in the earliest stages of biogenesis (Maynard Smith and Szathmáry 1995; Depew and Weber 1995; Hazen 2005).

Resolving the relationship between the informational and material-formative aspects of life has also been an issue for evolutionary theory. Many definitions of evolution such as Mayr's (1988) "change in gene frequencies," and generalizations about natural selection such as Campbell's (1960) "blind variation and selective retention," Dawkins' (1976) "replicator selection," and Hull's (1980) replicator versus interactor distinction ignore the physical requirements of producing new components and assembling them into larger dynamical complexes, focusing only on information replication and selection processes.This abstract informational conception of evolution has become the default definition of a Darwinian process in any system (e.g., Hull et al. 2001).

Recently, computational approaches based on agent-based computer simulations have continued this tradition in studies of selection on reproducing algorithms. This work, broadly described as "artificial life" or A-Life (Langton 1989; Mitchell 1996), traces its roots to the pioneering analysis of self-reproducing automata by the mathematician John von Neumann (1966). His explorations of the logical requirements of self-reproduction followed the insights of the then-new DNA genetics by conceiving of reproduction as an instruction-based process that could be modeled computationally. He argued that a device capable of constructing a complete replica of itself (which also possesses this capability) must include both assembly instructions and an assembly mechanism capable of using these instructions to assemble a replica of itself, including the tokens encoding the instructions. Von Neumann and subsequent researchers explored the formal requirements of self-reproduction almost exclusively via simulation—e.g., in cellular automata (Burks 1970)—because it was quickly recognized that specifying a "kinetic" model of self-reproduction with autonomous means for substrate acquisition and structural assembly adds highly problematic material constraints and energetic demands that rapidly expand the problem into the realms of physics, chemistry, and mechanical design.

Computational simulations of evolutionary processes that explicitly model both reproduction and phenotypic competition also tend to subsume the issues of component production and dynamical organization into abstract cost functions and selection criteria (Holland 1962, 1975; Langton 1989; Ray 1991), as do computational approaches to solving engineering problems (e.g., Fogel 1995).

Because abstract and computational investigations of evolutionary processes can ignore organism embodiment, they risk overlooking critical physicochemical constraints and affordances that lead to competition for resources and differential reproduction among organisms. So, although the abstract logic of natural selection may be multiply realizable (in that it can be exhibited by both living and nonliving systems), selection is dependent upon substrate properties and how they influence form generation. In nature, as opposed to *in silico,* the final measure of selection—variation in reproductive output—is a direct consequence of such material-energetic requirements. In this important respect natural selection is not merely a formal process, but also a thermodynamic one (Fisher 1930/1958; Schrödinger 1944; Prigogine and Stengers 1984; Swenson 1989; Ulanowicz and Wicken, 1989; Eigen and Oswatitsch 1992; Kauffman 1993; Pattee 1996).

The special importance of thermodynamic correlates of living processes was brought into sharp focus in the mid-20th century by the quantum physicist Erwin Schrödinger in his influential monograph *What is Life* (1944). Along with his seminal speculations about an aperiodic crystal-like basis for genetic inheritance, he argued that the ability of organisms, and evolution in general, to resist the effects of the second law of thermodynamics was a fundamental puzzle for physics. While alive, organisms maintain nonequilibrium conditions within their boundaries, countering internal entropy increase by extracting energy from extrinsic sources. Phylogenetic evolution further manages to not only conserve the orderliness embodied in organisms from generation to generation but to also produce ever more structurally complex forms over time. Although these trends are produced at the expense of increased environmental entropy, and globally produce an increase in entropy, their dynamics nevertheless stand in stark contrast to most spontaneous physical processes.

In recent years, much attention has focused on the way that various kinds of spontaneous order-producing dynamics contribute to countering the effects of thermodynamic degradation and increasing the global complexity and orderliness of living systems (e.g., von Bertalanffy 1952; Prigogine and Stengers 1984; Eigen and Oswatitsch 1992; Kauffman 1993). These dynamical tendencies are broadly described as self-organizing processes and contribute to all levels of living systems, from formation of complex multimolecular machines and organelles within cells, to generating complex segmentation and differentiation of embryonic structures, to coordinating complex collective behaviors in social species (Camazine et al. 2001). The ubiquity of self-organizing processes in molecular biology is one of the most distinctive characteristics of life (von Bertalanffy 1952). In the nonliving world, self-organizing processes are comparatively rare and transient in comparison to processes in which features become progressively less organized. They tend to be confined to subregions of larger systems where nonequilibrium conditions transiently persist. But by virtue of the maintenance of nonequilibrium conditions within living cells, self-organization of structure and function is ubiquitous.

Maintenance of life's nonequilibrium milieu and construction of its complex structures are dependent on two general classes of self-organizing molecular processes:

1. Autocatalysis: re-entrant cycles of catalytic reactions.

2. Self-assembly: a process resembling crystallization by which aggregate molecular structures spontaneously coalesce.

Autocatalysis occurs whenever each type of molecule in a set of catalysts augments the production of another member of the set in such a way that eventually the formation of each is catalytically enhanced by some other, resulting in a self-reinforcing circle (Kauffman 1986). The interlinked network of catalytic reaction cycles that organize the flow of energy and the synthesis of the critical molecular components in the cell is thus a complex form of autocatalysis. Self-assembly is a special class of molecular aggregation processes that occurs when energetically favored aggregations of molecular components spontaneously grow into large regular structures, sometimes including thousands of individual molecular constituents without external control or manipulation, so long as components are supplied (Crane 1950; Misteli 2001). Of interest for this discussion are self-assembling structures that partition or contain space, such as the wide array of linear, tubular, and sheet structures within living cells. These structures provide compartmentalization, structural scaffolding, motility, and reliable linkages of cells and cell components. This article will focus on a subset of self-assembling molecular structures that enclose space, such as those characteristic of viral capsules and tubular forms.

Both classes of cellular self-organizing molecular processes emerge from biased patterns of molecular interactions that result from allosteric complementarities and hydrogen bonding between large organic molecules. Although most cellular processes depend, to some degree, on contributions from one or both of these self-organizing dynamics, they are commonly considered ancillary to the genetic control of cellular processes. Hence, the possibility that a more fundamental contribution to the logic of life might be found in their interrelationship, irrespective of genetic information, has not been thoroughly explored.

This article calls attention to a complementarity in the dynamics of these two classes of self-organizing processes

that may hold the key to the spontaneous achievement of self-reproduction in simple molecular systems. This complementary relationship will be shown to have the potential to generate more elaborated variants of self-reproduction dynamics, thereby challenging the primacy of molecular information replication as a necessary ingredient in the nonlife-to-life transition.

A Model System

Both autocatalysis and self-assembly can be described as self-organizing processes in a general sense because of their self-reinforcing, form-generating dynamics, though each leads to multiplication of structural regularities (of components and geometry, respectively) via different thermodynamic mechanisms. Thus autocatalysis is a transient nonequilibrium process, whereas self-assembly is an entropy-increasing equilibrium process. Under favorable conditions, autocatalysis can produce a runaway local increase in the molecules comprising the autocatalytic set at the expense of other molecular forms. This increase in the local concentrations of members of this set of molecules briefly counters the normal tendency toward diffusion and admixture. Molecular self-assembly of large regular structures (effectively a special case of crystallization) occurs when component molecules' complementary geometries promote aggregation into lower energy regular tessellations or three-dimensional (3D) forms. Aggregation is self-perpetuating to the extent that the aggregation reduces intrinsic energy, and the symmetry promotes stability and creates structural facets favoring additional component binding. Growth can be open-ended, as in crystalline formations or tubular structures, limited only by substrate availability and structural stability, or it can be self-limiting, as in the case of geometrically closed structures such as the polygonal forms of many viral capsules.

Both autocatalysis and self-assembly contribute to the physical implementation of von Neumann's logical requirements for self-reproduction in cellular molecular systems. Autocatalysis can by itself provide the iterated generation of like components from like components, and self-assembly can result in like components combining into large regular 3D structures independent of extrinsic manipulation. Thus, although instruction and construction processes are widely utilized in living cells, autocatalysis and self-assembly significantly reduce the need for detailed instructional control and dedicated construction mechanisms. But can these be reduced entirely?

Outside of living systems, autocatalysis and self-assembly are inevitably self-limiting and even self-undermining. They continue so long as substrate molecules and free energy are provided in immediate proximity, but they exponentially deplete these conditions. Autocatalysis, in addition, is sensitive to the collective proximity and concentration of all molecules of the autocatalytic set, which will tend to spontaneously diffuse away from each other after synthesis due to normal thermodynamic admixture. Catalysis can also be blocked if catalytic surfaces are occluded by being aggregated with other molecules or if critical substrates are not freely diffusible. So molecular self-assembly can render molecules less catalytically reactive due to immobilization and occlusion of surfaces. (However, it can also facilitate multistage catalytic reactions in the special case where different bound catalysts are spatially organized with respect to specific reaction pathways and with their reactive binding surfaces exposed and aligned.) So these two general classes of molecular processes are to some extent mutually exclusive.

However, autocatalysis produces one condition that is conducive to self-assembly—replenishment of the local concentration of a self-assembling molecule—and self-assembly can produce conditions conducive to autocatalysis—inhibition of the diffusion and dispersal of complementary catalysts.

This reciprocity can be exploited if an autocatalytic cycle synthesizes a product molecule that tends to self-assemble into a closed structure that limits diffusion (e.g., polyhedron, cylinder, etc., analogous to a viral shell). Such a linkage of these dynamics can generate a reliable higher order reciprocity because enclosure formation will be most prolific in the immediate vicinity of a supportive set of autocatalytic molecules. This will increase the probability that such a container will form around the molecules of the set required to make more container molecules. Although by limiting access to new substrates, containment inhibits or blocks catalysis, it also maintains proximity of interdependent catalysts. Thus, even though catalysis is temporarily inhibited, containment increases the probability that the *potential* for autocatalysis will persist, irrespective of temporarily slow reaction rates or local unavailability of substrates, so long as there is some probability of container rupture. When such a structure is disrupted or breached, e.g., by agitation, in the vicinity of new substrate molecules, the contained catalysts are released, autocatalysis recommences, and new catalysts and container-forming molecules are synthesized in close proximity. Reconstitution of the original configuration using some newly synthesized and some old components, or formation of two or more replicas of the original, is likely to result. The decoupling from immediate local dynamics, achieved by containment, results in the intrinsic potentiation of future autocatalysis and, by extension, future container formation. Hence, the reciprocal complementarity of these two self-organizing processes creates the potential for self-repair and even self-reproduction in a minimal form. While it might be argued that the requirement of extrinsic disruption weakens the claim of "self-"reproduction, this process is reliably spontaneous and plays no substantive role in generation of any constituent forms, making it more

autonomous than reproduction in flowering plants that require insect pollinators.

A molecular system with these characteristics can be called an "autocell" because it is self-enclosing and self-reconstituting. Although there are superficial resemblances to the diverse classes of laboratory-generated structures called protocells (see below) and in other respects to "reverse micelles" with extrinsically bound reactive molecules (see Bachmann et al. 1992), it seems useful to distinguish autocells as a separate class of structures based on their combination of three distinguishing criteria, two negative, and one positive: a nonlipid, nonpermeable containment shell, lack of self-replicating template components, and reciprocal cosynthesis of all components. An abstract depiction of the structure of two general classes of autocells is provided in Figure 1. These classes are distinguished by containment geometry, i.e., polyhedral (a) or tubular (b), and are patterned after the forms of viral coats and microtubules. Both are minimally simple autocell systems, composed of only two classes of catalysts, one of which can self-assemble to form a container. A stepwise depiction of the component processes leading to formation of a polyhedral two-component autocell is depicted in Figure 2. More complex autocatalytic sets (including both synthetic and lytic processes) as well as more diverse containment geometries are possible because autocell formation is a *generic molecular system property* that is independent of specific molecular constituents, and only dependent on their relative geometric correspondences. In abstract terms, the key requirement is a complete reciprocal coupling of a spontaneous component production process and a spontaneous proximity-maintenance process that encompasses all essential components. (It is probably also critical for evolvability, discussed below, that this involves a multicomponent structure rather than a single molecule that merely catalyzes the formation of molecules like itself, i.e., a "naked replicator," although I will not defend this logical requirement here.)

The two classes of autocells depicted will have many properties in common, but will tend to differ due to container geometry. The finite regular geometry of polyhedral autocells will determine fixed component numbers (though some polygonal structures, e.g., triangles, can assemble into a number of polyhedral forms) and a corresponding cycle between growth and stasis. Tubular autocells, analogous to microtubules or the tobacco mosaic virus coat, have the potential for continual growth, though mechanical forces will make longer tubes proportionately more fragile.

However, although tubular autocells are not geometrically closed containers, molecular surface forces within the tube will likely impede motion of contained molecules along its length, thus making it an effective barrier to diffusion, and increasingly so with greater length. Both polyhedral and tubular autocells will require extrinsic forces to break them, and thus to reproduce, but this will be less of a disruption of structural integrity for tubules where growth will recommence at the newly exposed ends, with the local release of contained catalysts. The constraints on molecular geometry are also less restrictive for spirally assembled tubes than for polyhedrons, making this form likely easier to achieve in the laboratory as

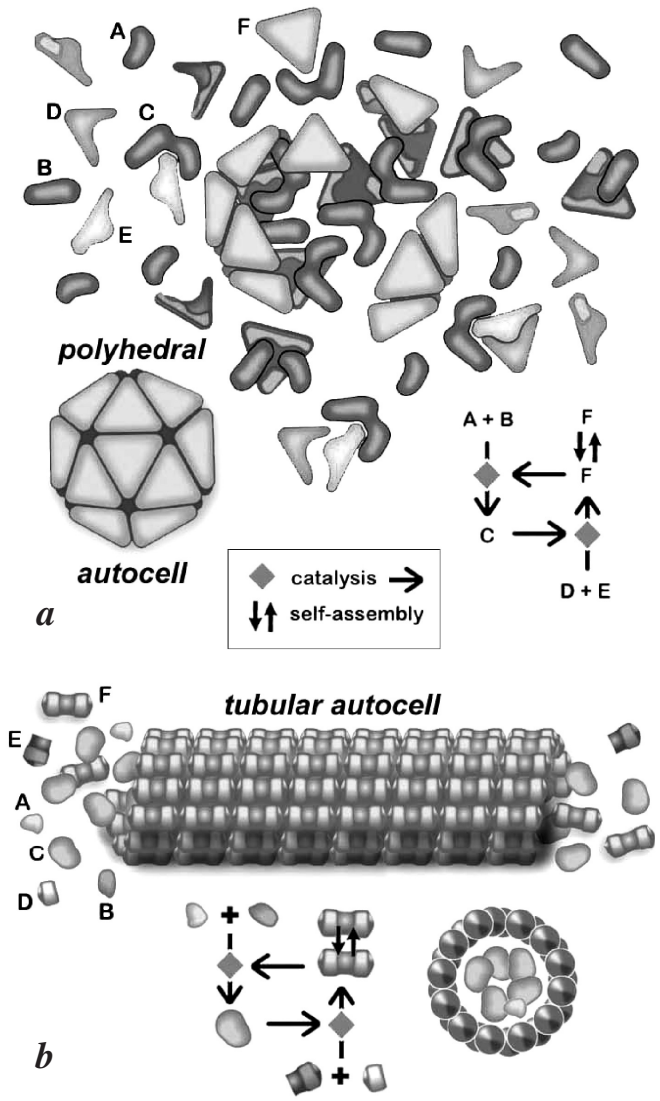

Figure 1.
Two general classes of autocells are depicted as geometric constructions. An autocell produced by polyhedral containment is depicted in (a) and an autocell produced by spirally elongated tubular containment is depicted in (b). Both are minimal autocells to the extent that each is constituted by only two catalysts (C and F in both). Catalysts are also depicted as synthesized from two substrate molecules in each case (A and B and D and E in both), though only in (a) is there any indication of the shape complementarities contributing to catalysis and self-assembly. Autocatalytic cycles are depicted with arrow diagrams for each (using letters in [a] and component shapes in [b]). A polyhedral autocell completely encloses the complementary catalyst and achieves structural closure, allowing no further growth. A tubular autocell does not completely enclose its interior, but contained molecules are retained by viscosity of van der Waals interactions with the inner walls. Tubular autocells also retain the ability for continual elongation. Reproduction in both cases depends on extrinsic forces to break containment.

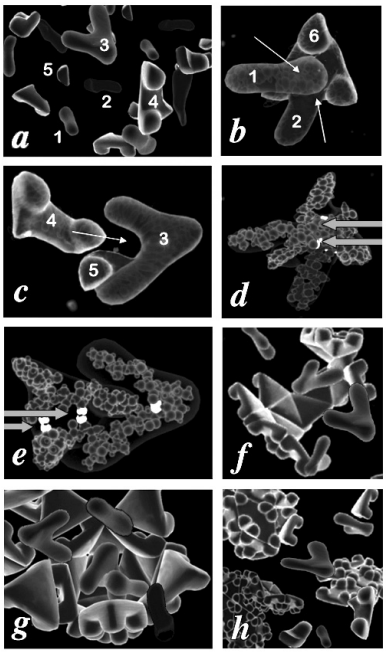

Figure 2.
Idealized depiction of component steps of autocell formation involving a minimum number of catalytic components ($N = 2$) and polyhedral containment. Substrate molecules (1, 2, 4, and 5) are identified in (a) and synthesized catalysts (3 and 6) are identified in (a) and (b). The interactive allosteric shapes of the molecules are abstractly depicted as a generic space-filling shell (shown with a phantom appearance in [d] and [e]). These allosteric relationships are depicted as facilitating covalent bonding (arrows to bright atoms in (d) and (e)) to form autocell catalysts 3 and 6. Self-assembly of molecule 6 into polyhedral shells by edge binding and the encapsulation of nearby catalysts of type 3 ([f] and [g]) creates autocells (h) that are subject to dispersion as discrete units of reproduction and loci of selection.

well as by serendipitous processes in nature. Although tubular autocells will differ in length, and thus are intrinsically more variable, their defining composition will be essentially the same irrespective of length.

Both types of autocell exemplify in molecular terms—and with considerably more simplicity and compactness than previously envisioned—von Neumann's minimal description of self-reproduction: reproducing a replica with the physical capacity to similarly reproduce itself. This is in part possible because they do not include what von Neumann called a "universal constructor" (able to use instructions to build any specified machine), but only a single-product constructor mechanism. Significantly, autocells achieve reproduction of a characteristic unit-form without an instruction component and without the separate instantiation of the construction component of von Neumann's automata. Despite their capacity to self-repair and self-reproduce, however, autocells lack a majority of mechanisms and constituents that are presumed to be essential for living cells or even viruses, and so they do not qualify under any current definition of life. Autocellularity may even be achievable with entirely inorganic constituents.

Although autocell chemistry is currently only speculative, its feasibility should be easily verifiable in the laboratory. The component chemical processes required for autocell formation are all well understood and, despite the combined constraints on molecular symmetries required for both autocatalysis and container self-assembly, the generality of this logic is independent of molecular composition, providing a vast array of possible constituents to choose from. Their practical plausibility warrants consideration of one further extrapolated property: a potential to evolve.

Autocell systems also fulfill the three abstract criteria for evolvability (even if not natural selection in the strictest neo-Darwinian sense):

1. *Self-reproduction with fidelity.* Autocells are capable of continuous self-reproduction, and so are potential progenitors of lineages. The necessary synergies between components guarantee a high degree of fidelity in this process even without template replication. Because of the holistic character of autocell reproduction, however, fidelity will likely be increasingly difficult to maintain as autocell complexity increases, and may serve as a constraint on complexity. An autocell lineage will increase in numbers so long as there are sufficient substrate molecules in the surrounding environment, energy to drive catalysis, and conditions that periodically disrupt autocell integrity (e.g., agitation).

2. *Competition for resources.* Lineage propagation will result in competition between lineages for the substrate molecules required for reproduction. Autocell lineages that arise from the same ancestor or otherwise share similar chemical properties (e.g., due to arising from similar initial conditions) will propagate at rates correlated with their relative success at garnering the same (or catalytically similar) substrate molecules from a finite pool.

3. *Heritable variation.* Although autocells tend to re-establish the molecular configurations predisposed by the molecules inherited from progenitors, this must occur via partial breakup and re-enclosure. This makes incorporation of other molecules from the local environment a high probability. Autocell components are thus susceptible to substitution by catalytically similar molecules and are capable of propagating this change to a future lineage so long as appropriate substrates continue to be available. Incidentally, incorporated molecules that exhibit catalytic interaction with existing components so as to become insinuated into the cycle of autocatalysis will be regularly synthesized. To the extent that these heritable structural variations augment reproduction they will produce lineage-specific propagation advantages. Differential lineage propagation will be a function of correspondences between the requirements for reproduction and features of the surrounding molecular and energetic environment.

These features qualify autocell lineage evolution as a generic form of natural selection, despite the absence of

separately transferred information-bearing units, and even though this blurs the distinction between Weismannian and Lamarckian inheritance. So, even though autocells lack many presumed core attributes of life, they satisfy both the material and the logical conditions for self-reproduction and evolution in a minimal sense. Autocell dynamics demonstrate that these fundamental attributes of life can emerge without the presumptive critical and ubiquitous role of separate information-bearing molecules; for example, nucleic acid polymers functioning as templates. But it may also provide a new context for exploring the origins of these functions. For example, tradeoffs between replication fidelity and complexity, while limiting autocell evolvability, may contribute the most significant selection pressures favoring transition to template-based processes. This creates a context for asking how template-based information functions might have evolved from functionally distinct antecedents, i.e., in an autocell ecology. If autocell evolvability is sufficient to reach this level of complexity then other properties of nucleic acid components (e.g., the phosphate accumulation and transfer roles of nucleotides, or polymerization as a means of energy storage, etc.), which could contribute to autocell evolvability, become important clues to the evolution of molecular information functions (see discussion below).

Discussion

Comparison with Other Protolife Models

The autocell model exhibits similarities with previous systems invoked to explore the origins of life. Probably the most comparable model systems were described by the Hungarian chemist Tibor Gánti in 1971 (although his work became available in English only in 2003). Gánti's purpose was to outline a theoretical chemical logic for defining life. He described a theoretical chemical system, which he called a "chemoton," that he believed embodied the minimal conditions for an entity described as living. A chemoton is an autocatalytic system composed of three coupled autocatalytic cycles: one that captures energy, one that produces a cell membrane, and one that replicates molecular information in a template-code molecule (for specifying the other parts of the system). Like the autocell, Gánti's chemoton is a theoretical chemical system. But it is considerably more complicated than an autocell, involving a large number of different types of molecules all arranged into complicated interdependent chemical reaction cycles. This complexity is the result of requiring that the chemoton mechanism include semipermeable containment, continual metabolism, and information replication, in order to abstractly model life in its current forms. Because the autocell model does not attempt to exemplify the necessary and sufficient conditions for life in general, only those sufficient for self-reproduction, each of these three criteria is potentially dispensable.

Gánti's chemoton is more similar to an autocell than a protocell (see below), however, in that emphasis is given on the reciprocity and synergistic coupling of the chemical processes involved rather than on any specific substrate, reaction, or combination of elements. Yet, although the chemoton model does not necessarily require the equivalent of DNA replication and template function, it does assume that some form of molecular information transmission is involved. In contrast, the autocell model demonstrates that reproduction and self-maintenance can be achieved at least in minimal form without a separate information replication cycle. Although a distinct replication of an encoded representation of the essential structural–functional relationships may augment replication fidelity and evolvability, it is not a necessary prerequisite for these properties. Gánti considered the incorporation of an information replication cycle as an "absolute life criterion" because it was deemed necessary for "unlimited inheritance." But although the holistic replication of autocell structure affords only limited inheritance, this limitation is ultimately merely definitional. If autocell evolvability is sufficient to achieve the level of complexity sufficient for the emergence of template-supported replication, it is justifiable to argue that autocell lineages have the potential to achieve unlimited inheritance.

Gánti explored this issue by contrasting the chemoton to a simpler model chemical system that is more closely analogous to autocells. Gánti called it a "self-reproducing spherule." It consists of an autocatalytic cycle that produces an enclosing lipid membrane. He assumed that the membrane would need to be semipermeable in order to support ongoing catalysis, that the spherule would continually grow, adding catalysts and lipid molecules, and that reproduction would occur via growth and subdivision by virtue of the rapid overproduction of membrane molecules producing structural instability. These properties are significantly more elaborate and impose considerable obstacles to spherule design in comparison to autocells. This is because achieving autonomous lipid synthesis and providing mechanisms for membrane growth and especially selective membrane permeability do not have obvious prebiotic solutions. Also lipid membrane containment is structurally amorphous and lipid vesicle subdivision is not coupled with systematic distribution of contents to "offspring" (so what constitutes an individual's identity is unclear). These features are effectively forced on Gánti's model by two design criteria. The first is his assumption that autocatalysis would need to be continuous, whereas the autocell cycles between catalysis in the disrupted state and inertness in the enclosed state. The second is the relatively passive role of the lipid membrane container with respect to component replication, spherule division, and re-assembly; whereas autocell containment molecules and containers are coformed along with supportive catalysts. As in the autocell, catalysis in the spherule provides morphological constraints on incorporation of variant components across

reproductions, but lipid membrane formation is primarily a function of hydrophobic polarity, and is only minimally constrained by stereochemical binding geometry. In a commentary included with the English translation of Gánti's work, Eörs Száthmary (2003) points out that cell membranes are capable of a form of "structural inheritance" of acquired characteristics (Jablonka and Lamb 1995) where atypical molecules incorporated into the membrane can be passed to daughter cells (analogous to inheritance of membrane modifications in Paramecium). Since neither membrane components nor membrane structures are directly involved in the structural replication of these spherules, inheritance of structural defects in membrane form is not productive and new replicas of these variants are not reproduced. Such passively inherited structural variants are subject to rapid diminution in the lineage, and are thus of finitely limited heredity. These features follow from the fact that the enclosing lipid membrane is formed from side-products of the autocatalytic synthetic processes and do not contribute to reproduction of other components.

In contrast, all components of an autocell's catalytic and self-assembly processes are directly involved in replicating its global form. Because neither the unbound contained catalysts nor the bound catalysts constituting the container are outside the synthetic process, all acquired substitutions are potentially reproducible and not merely by passive structural inheritance. This provides a primitive precursor to the information that maintains organizational identity across replications in living cells, by providing reciprocal replication of any potential component. So even though inheritance is still structurally constrained, there is no theoretical limit to alteration of these features over the course of lineage evolution. The temporarily inert state of a closed autocell further aids in the maintenance of structural identity across reproductions, by limiting the potential dissipating effects of side reactions in autocatalysis, since enclosure stops catalysis, maintains catalytic set proximity, and maximizes content homogeneity due to the collocation of the highest catalyst concentrations and most rapid container formation.

So despite the considerably more complex requirements for creating a self-reproducing spherule, Gánti's spherules would still have more limited inheritance than autocells and their "progeny" would be far less consistent in structure. Autocell dynamics, in contrast, demonstrates that not all of Gánti's "absolute criteria for life" are essential for either open-ended self-replication or the potential of open-ended heritable modification that evolution requires. In this way, the autocell model provides a further simplification that fills an important gap in theories of the emergence of life.

The autocell model is even more divergent from most protocell models. Though some authors apply the term protocell generically to any protolife system, this obscures many important distinctions. The architectures of the various protocell systems are based on a backward extrapolation from existing living systems. Morris (2002) defines protocells as "Darwinian liposomes-bilayer vesicles with mutable on-board replicases linked to phenotypes." Most exemplars include four characteristics, presumed essential, that distinguish them from autocells: (1) replication of nucleic acid molecules (or related molecules with analogous function); (2) mechanisms to facilitate their replication; (3) containment within a lipid vesicle; (4) growth and fissioning of the enclosing vesicle in a way that distributes replicated nucleic acid molecules and replicative mechanisms to the daughter vesicles (Rasmussen et al. 2004). Simple "protocells"have been synthesized in the laboratory and are currently being explored for their potential to self-replicate (Szostak et al. 2001). One of many critical remaining challenges includes supplying protocells with energy to drive contained synthetic and replication reactions. Both energy and substrates must be continuously available if continual open-ended reproduction is to be possible, because protocells are conceived as maintaining a continuous nonequilibrium state. Clearing this last hurdle adds considerable difficulty and complexity. In most current protocell models, molecular information replication is presumed to be a critical requirement while reciprocal interdependence between information replication, component production, and reproduction-enclosure processes is bracketed from consideration and often must be extrinsically regulated. This incomplete coupling distinguishes the design logic of protocells from both chemoton and autocell models.

Although the autocell model also focuses on containment and molecular replication, it is their dynamical interdependence that defines it. Autocell self-repair, self-reproduction, and structural conservation require no special class of replicator molecules and are not dependent on additional qualifications on containment, such as the capacity for selective transport of substrates and waste products, or the capacity for continual growth and correlated fission (though these latter two features may be a spontaneous attribute of tubular autocells). The comparative simplicity of the autocell cycle is aided by the inertness of the completed structure, which does not require substrates for self-maintenance or possible self-reproduction unless disrupted, and then only transiently. The requirement for gaining open-ended access to substrates is accomplished by alternation between inert closed and catalytically active open phases. In terms of both information replication and metabolism, autocells are not alive, although analogies to viruses and bacterial spores suggest themselves. Moreover, even reproduction must be extrinsically initiated, even though the potential to compensate for structural disruption and to produce replicas that maintain their structural and dynamical identity are intrinsic properties. Autocells are for this reason somewhat intermediate between passive equilibrium-seeking crystalline growth processes and living processes. They counter spontaneous degradation by

spontaneous reconstitution, replication, and stabilization of a configuration that embodies these capacities. Rather than maintaining themselves in a persistent nonequilibrium state they cycle between brief phases of nonequilibrium dynamics and extended phases of inert potential; providing a ratchet-like preservation of the consequences of self-organization. And rather than depending on molecular templates for component replication and structural memory across reproductions, they take advantage of the stereochemical specificity of catalysis and the geometric specificity of self-assembly, as well as from the attractor dynamics of these two self-organizing processes, to maintain and replicate structural identity.

Constraints on Spontaneous Autocell Formation

Because of its relative simplicity the autocell model suggests a much wider range of approaches to the mystery of the emergence of life, extending insights suggested by complex systems approaches(Kauffman 1993; Depew and Weber 1995). These approaches have shown that, for example, the probability of spontaneous autocatalysis is non-negligible in environments containing a sufficient diversity of catalytically interactive molecules (Farmer et al. 1987). The autocell model additionally shows how some of the barriers to sustained autocatalysis (e.g., catalytic set diffusion and set degeneration due to side reactions) may be partially mitigated by alternation between a brief catalytic phase and a contained inert phase. In general, self-assembly dynamics is possible in a wide variety of molecular systems, and the special variants that could lead to self-assembly of simple molecular enclosures are therefore not likely to be highly improbable. Indeed, many forms of self-assembling molecular enclosure mechanisms have been explored by chemists interested in nanotechnology applications of these processes (see, e.g., Padilla et al. 2001), and could potentially lead to laboratory-based autocell systems. The fact that these two classes of chemical processes are neither exceedingly rare, chemically complex, nor confined to a very limited class of molecular types makes their spontaneous linked coincidence a plausible scenario for the emergence of protolife, from a cosmic perspective.

But although autocell evolution is potentially unlimited, it is highly constrained. Because the repair and replication of the global organization of an autocell is accomplished entirely by virtue of molecular structure complementarities, evolvability is limited in comparison to living cells or protocells that synthesize their components from simpler building blocks (e.g., amino acids) by way of template molecules. Lacking template guidance of polymerization, autocells will be highly environment-specific, depending on a highly limited class of specific substrate molecules of sufficient size and structural complexity to be catalytically active. More significantly, the spontaneous emergence of autocellularity in a prebiotic environment likely requires three unusual conditions: (1) the presence of significant quantities and concentrations of large polymers; (2) some considerable degree of structural similarity among these molecules; and (3) sufficient variety and degeneracy of their stereochemical properties to support spontaneous autocatalysis and self-assembly. The spontaneous nonbiogenic production of large numbers of structurally similar molecules of appropriate size for effective catalysis is presumed to be unlikely on the prebiotic earth, even if not an issue in the laboratory. Nor is it easy to determine how wide a range of conditions might be conducive to spontaneous autocell formation, because of the vast range of possible molecular forms susceptible to both catalytic interaction and self-assembly processes and the nonlinear interdependence of the geometric and energetic conditions enabling reciprocity of both processes. However, because of their relative simplicity, these requirements for the emergence of autocells are almost certainly far less constraining than for the spontaneous formation of even the simplest self-reproducing protocells, or even Gánti's self-reproducing spherules.

Even so, the requirements for spontaneous autocell formation are significant. If these conditions are not spontaneously achievable in at least some abiotic conditions, an autocell scenario for the origins of life (or protolife) is not plausible. Indeed, the prior availability of suitable macromolecules has long been considered a serious stumbling block for all theories of the origins of life. Even the spontaneous prebiotic synthesis of the component monomers of the most important of life's molecules—amino acids, sugars, nucleotides, phospholipids—has been difficult to explain. Classic experiments provided evidence that some amino acid synthesis could be achieved spontaneously from simpler precursors, such as water, methane, ammonia, and carbon dioxide, presumed at the time to be components of the primitive earth atmosphere (e.g., Miller 1953; Oparin 1961; Miller and Urey 1959). But many other relevant building blocks remain difficult to explain, and an abiotic mechanism for polymerization of amino acids into peptides is believed to be unlikely in the prebiotic earth environment (Maynard Smith and Szathmáry 1995).

Extraterrestrial Sources of Autocell Constituents

If we are willing to look beyond the context of the prebiotic earth, however, we may find that certain of these limiting conditions may not be so unlikely. For example, there may be an alternative to the amino acid polymerization problem. There is evidence that in quite different extraterrestrial environments (such as the gaseous surface of gas giants like Jupiter), polymers of cyanide (e.g., HCN polymers such as polyamadines) may be formed by spontaneous dehydration reactions (Matthews 1975, 1997). Given the scale of this environment this might provide vast quantities of large polymers. If catalytic interactions are possible in Jovian-like atmospheres, autocell evolution could be occurring extraterrestrially on a

massive scale. More importantly, significant amounts of Jovian polymers could have been transported (e.g., via cometary transport) to rocky planets of the inner solar system where aqueous conditions would be available (like Mars or Earth). This is important, since HCN polymers have been shown to spontaneously hydrolyze to form heterologous peptides in aqueous environments (Mathews 1975). This lends renewed support to a "polymers first" scenario for prebiotic chemical evolution that would be suitable for the emergence of autocells.

Such prebiotic peptides would likely deviate from those produced by contemporary organisms in many respects. For instance, without template coding favoring linear polymerization, the polymers formed under such conditions would likely be more structurally diverse and irregular, even if not as large as organic proteins, because of the presence of branched rather than predominantly linear architectures. Also, without template-guided constraints on polymerization, intrinsic chemical reaction biases would play a much more prominent role in determining molecular structure. This would result in far more homogeneity in the general size and structure of these polymers than is found in organic proteins. These are potentially advantageous biases. An environment supplied with modest concentrations of structurally similar 3D complex peptide-like polymers would be ideal for autocell formation and evolution. It even suggests the possibility that lytic rather than synthetic reactions (such as those modeled above) could have been the basis for the first stages of autocellularity—a condition that would also be energetically more favorable. Thus, polymeric molecules in sufficient concentrations, diversity, and catalytic capacity might have been available on the prebiotic Earth and Mars to initiate and sustain autocell evolution. Additionally, transport to an inner rocky planet would expose these molecular systems to minerals and metals like iron, phosphorus, sulfur, and so on, which would provide significant aid for energy-demanding catalytic reactions.

So despite these potential caveats, autocell formation should be possible in conditions that are far more variable than those of ancient or modern earthly environments. More importantly, it may be realizable using molecular substrates radically unlike peptide polymers. Assuming that the coincidence of reciprocal coupling of the few stereochemical relationships necessary to support autocell formation is even minimally probable in some naturally occurring conditions, the substrate-independent realizability of autocellularity should make this form of molecular organization far more prevalent throughout the universe than anything resembling earth-based life. Given the probability that the formation of other planetary systems will follow similar rules in similar galactic conditions, planetary systems with similar stratified organization of planets and chemical compositions should be common. Thus, if spontaneous autocell formation is even weakly probable in such conditions we should expect that highly similar autocell forms could arise independently in vastly separated star systems.

Implications for General Biology

The probability of spontaneous autocell formation in this or any solar system is, in an important sense, irrelevant to deciding whether this form of molecular system is comparable in some way to living organisms. Even if spontaneous autocell formation turns out to be so unlikely that its production is confined to the highly controlled conditions obtainable only in laboratory settings, the self-repair and self-propagating properties of such synthesized autocells will still make them far more comparable to organisms than to all other forms of abiotic chemistry.

This functional affinity warrants the designation of a superordinate classification scheme that would recognize the affinity of autocells with organisms. To designate the entire class of self-reproducing chemical systems susceptible of evolution (including autocells, living organisms, and possibly other forms with these features) I propose the term *Autaea* (named for their bounded autonomy and self-supportive dynamics). This would serve as a grand classification of forms defining the basic units of a general biology.

But a classification that recognizes an autocell-life affinity should not be confused with phylogenetic taxonomies based on common ancestry. It is a classification based on analogous functional organization. As such it would not be an alternative to lineage-based taxonomies, but an orthogonal classification scheme. Thus, similarly organized forms arising in causally and chemically isolated contexts (such as in separate star systems or laboratories) may be distinguishable into distinct parallel grades of functional organization. Although such a classification may not appear to offer an immediately useful scheme for organizing life forms, it may nonetheless help to highlight nonphyletic formative principles that may illuminate aspects of biological organization that would otherwise go unnoticed.

The intermediate status of autocells between life and nonlife suggests an important organizational dichotomy that can be recruited for further classification purposes: mode of structural reproduction. Autocell functional-continuance and reproduction is maintained solely by the highly constrained morphological limitations of the stereochemistry that enables the whole ensemble of components to converge to a highly limited stable structure. This form of reproduction can be characterized as holistic, ensemble-, and attractor-based, in the terms of the classification of replication processes proposed by Szathmáry (1999, 2000). All modern organisms (including viruses), and hence presumably also their common ancestor, are organized around indirect template-based specification of functional components and the template-code substrate is sequestered from other phenotypic interactor roles. This provides coded reproducers with unlimited heredity. So, while there

may be many plausible variations on the logic of reproduction, probably the most critical feature separating autocell-like systems from life involves the presence or absence of template coding for form-producing processes.

In this regard, we can describe autocell repair and proliferation as "morphological reproduction" and coded synthesis of components from a replicated template as "coded reproduction." Morphological reproduction is distinct from mere "structural inheritance" (see Jablonka and Lamb 1995) in that it is actively replicated in autocell reproduction rather than passively inherited as are, for example, membrane abnormalities when cells divide. The distinction between morphological and coded reproduction is not categorical, however. While autocell reproduction is directly dependent on morphological correspondence relationships between molecules, coded reproduction is ultimately just a more complex and indirect version of this. The nucleotide code relationship of living systems can be decomposed into a number of reciprocally linked morphological reproduction processes. Both DNA–DNA replication and DNA–RNA replication can be described as morphologically based replication in which complementary molecular geometries constrain precise molecular interrelationships. Likewise, the ribosomal process that maps mRNA sequence morphology to amino acid sequence morphology is also dependent on linked morphological matching relationships: that between mRNA and tRNAs. Finally, the polar orientation of the amine and acid poles of amino acids that are conducive to peptide bonding, irrespective of other residues, completes the insulation of one form-form matching process from another so that a code-like arbitrarity is possible.

The morphological modifications of nucleotide sequences (e.g., via point mutation) are consequently subject to chemical and functional constraints that have little in common with linked morpho-functional chemical properties of protein shape. The resulting chemical arbitrarity of linking morphological reproduction mechanisms provides considerable advantages for evolvability. This hierarchic dependence suggests that direct morphological replication is ultimately primitive while indirect coded replication is evolutionarily derived from it. The priority of morphological component reproduction is also exemplified by the fact that all living cells and viruses depend on morphologically reproduced components in addition to nucleic acid based syntheses. Prion protein reproduction is the only entirely morphologically based replication process known associated with living systems. But a prion is not only entirely parasitic on the neuronal synthesis of specific precursor preprion proteins, it only imposes its morphology on these precursor molecules and contributes nothing in the way of new components.

The logic of this hierarchic dependence of forms of replication can be summed up by noting the obvious generalization that information replication inevitably entails form replication. A similar point is made by Szathmáry (2000) when he argues that evolution tends to develop from holistic to modular and phenotypic to genotypic replication, and so on. Therefore, some form of morphologically based reproduction of components is a logical requirement that must be operationalized at some level even in A-Life simulations.

Using these criteria, then, we can delineate a superordinate classification of possible forms of life-like systems and their probable simpler antecedents. Two major organizational grades can be distinguished based on mode of reproduction. I propose the term *Semeota* (from *seme,* sign; named for the semiotic basis of organism replication and identity) for the class of all organisms that use molecular coding in order to synthesize components and reproduce, as do all terrestrial organisms and viruses. I propose the term *Morphota* (morphology-based systems) for the class of organisms that is generated and reproduced by way of the constraints of molecular morphology alone. As the above analysis suggests, *Semeota* will inevitably be a derived offshoot from *Morphota* in a given planetary context. But by virtue of the vastly increased evolvability of *Semeota*, and their capacity to break down and reconstruct molecules to suit their needs rather than rely on their abiotically synthesized availability, the evolution of template coding is expected to create conditions that eliminate most *Morphota*. Nevertheless, *Morphota* might continue to predominate in harsh conditions owing to their relative simplicity and reduced environmental constraints.

Of course, if a form of autocell evolution is possible, the autocell forms described here are only the simplest types of *Morphota*. Many more complex forms of noncoded reproducers are likely possible, which may incorporate semipermeable membranes, continual exchange of substrates and waste products, separation of energy capturing and energy utilizing chemical processes, and continual maintenance of nonequilibrium chemical dynamics. In other words, there may be considerable room for intermediate evolutionary stages between simple autocellular *Morphota* and *Semeota*. More importantly, given that template-based coded reproduction (such as in terrestrial organisms) is composed of reciprocally interdependent morphological reproduction processes (as described above), an evolutionary pathway from simple morphological reproduction to coded reproduction is effectively a logical requirement that must be realized in any evolutionary sequence leading to coding. This offers a research program within which we can begin to explore the evolution of coded reproduction systems and the origins of the complex heteropolymers (e.g., nucleic acids) that serve as templates.

A speculative scenario can illustrate this possibility. In living cells, for example, nucleotides serve a dual role as energy-ferrying molecules and template building blocks. This duality might reflect an antecedent form of *Morphota* in which various forms of nucleotides provide energetic support

for catalytic reactions, and where nucleotide polymerization serves as a means of "storing" deactivated nucleotides during "dormant" phases. Such relatively unreactive nucleotide polymers would thus be available for subsequent exaptation as templates. The origins of nucleic acid chemistry could thus turn out to involve a complex evolutionary sequence of stages both before and after the advent of template functions. Laboratory exploration of autocellular systems could thus be a critical tool for exploring this currently ubiquitous informational character of life.

The possibility of autocell forms incorporating nucleic acid polymers, even if not involved in template functions, opens the door to some potentially radical possibilities for the origins of cellular versus viral forms of *Semeota*. It is generally assumed that viral forms evolved as fractionated derivatives of cellular systems, because of their dependence on cellular metabolism for production of viral constituents from viral nucleic acid templates. But it is possible that this dependence could have evolved subsequently and that some viral forms could trace their ancestry to *Morphota* that did not originally have a coding link between their nucleic acid polymers and encapsulation molecules. The absence of autocatalytic formation of components in known viruses argues against this scenario, but a plausible argument could also be made for subsequent loss of this function to far more efficient cellular alternatives due to parasitism. So we cannot conclude that all remnants of such a prebiotic evolutionary phase are extinct.

There are also obvious implications for astrobiology. The multiple realizability of this molecular organizational logic, and the wide range of planetary conditions likely conducive to formation and persistence of *Morphota,* but not *Semeota*, suggests that astrobiologists might consider looking for the very different chemical and structural signatures that would be left by *Morphota*. These might include anomalous concentrations of highly similar polymers and microfossils of viral dimensions and with regular molecular structures that are characterized by enclosed volumes. The discovery of traces of morphotic evolution on other planets in our solar system would radically reorient thinking about prebiotic terrestrial chemistry.

Finally, the simplicity and generality of the autocell mechanism also offers a new class of laboratory model systems that can be exploited for their special life-like properties. Laboratory synthesized autocells would not necessarily be limited to forms related to life or composed of organic molecules. Given the highly generic criteria that must be met to achieve this result, engineered autocell-like systems can probably be composed of highly diverse substrates arranged in combinations that could never occur spontaneously. For example, autocells formed of inorganic molecular substrates could combine autocellular self-assembly, self-repair, and self-reproduction properties with other electrical, chemical, or even nuclear properties of these materials to produce functions quite different than anything found in life. These life-like behaviors are also of considerable relevance for practical applications in the growing field of nanotechnology. Molecular containers that can be induced to spontaneously replicate and encapsulate surrounding molecules and then release them again under controllable conditions could have numerous uses, from molecular cleanup and storage to targeted drug delivery. However, the most intriguing property of engineered autocell systems would undoubtedly be the potential to develop special variant forms by directed evolution. Achieving a nanodesign strategy that, instead of prespecifying its products, directed their evolution by the controlled modification of their environment—perhaps incrementally converging toward a target application context—would be the Holy Grail of nanotechnology.

Conclusions

Although no autocell has been produced in the laboratory or identified in nature, and many chemical kinematic issues have been overlooked which could make their physical realization quite difficult to achieve, they offer a useful model system for exploring the minimal physical requirements for self-repair, self-reproduction, and evolution. Their plausibility and simplicity demonstrates that these core attributes of life likely derive solely from a reciprocal coupling of mutually reinforcing self-organizing dynamics. In abstract terms, this involves a reciprocal coupling between a component production process (autocatalysis) and a component proximity-maintenance process (enclosure self-assembly). These criteria can likely be achieved in diverse ways besides those presented here. It is the higher order synergy of these processes—not mere enclosure of self-replicating entities—that creates the necessary and sufficient conditions for the emergence of these fundamental biological properties. This insight fills in a missing link joining nonequilibrium thermodynamic processes to self-reproduction and evolutionary processes. The basic principles involved should be capable of further extension to systems well beyond the molecular chemistry of life.

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