The Origin and Evolution of Life by Means of Endo-Exo Circulation

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Most studies on the origin of life have been focused on single self-replicating units : either polymers[1)-7)]or vesicles[8)-10)], but not both. Here, I frame a new theory to attack the origin-of-life problem in two steps. First, I will consider both random polymers and membrane-bounded vesicles. Polymers can be future candidates for self-replicating genetic systems which can help to evolve by natural selection[11)]; while vesicles (or endo-systems[12)]) have their own boundary membranes which can create the micro-environment favorable for such polymers, as these are isolated from the external environment (or exo -world[12)]). Then, I will propose the new paradigm of 'endo-exo circulation' — instead of self-replication — to specify interactive processes between endo -system and exo-world. The endo-exo circulation was possibly driven by cycling environments such as drying-wetting (or dehydration-hydration) cycles in tide pools[13)]. The resulting circulation would make the endo-systems prebiotically evolve[12)14)] without genetic systems, because many different kinds of molecules, supplied by the exo-world, could be subject to weak selection[7)] through intermolecular interactions. If self-replicating polymers arise *de novo* as reliable genetic systems, they would evolve through natural selection. Thereafter, life would begin only when an autonomous system of endo-exo circulation could arise to take over the outside 'drive'. It is one principle of endo -exo circulation that would govern the origin and evolution of life.

To develop a new theory for the origin of life, I assume that life's origin and its evolution would be the continuous complexification of initially non -living — yet highly interacting — entities, and therefore, one principle could govern a great diversity of dynamic phenomena at any instance and level of the highly interacting entities. Conversely, we can identify the unique principle essential to the origin of life by investigating the dynamic organization — involving both structures and processes — typical of present-day life.

Within this framework, I first consider both random polymers and membrane-bounded vesicles as the least hierarchical structures required for the origin of life. Strictly, I assume that there were at least two very different kinds of molecules. One is monomeric molecules that can readily form one-dimensional polymers upon dehydration[15)]. The other is amphipathic molecules — characterized by both hydrophilic 'heads' and hydrophobic 'tails' on the single molecules like phospholipids — that can spontaneously aggregate to form two -dimensional bilayer membranes and to create three-dimensional closed vesi-

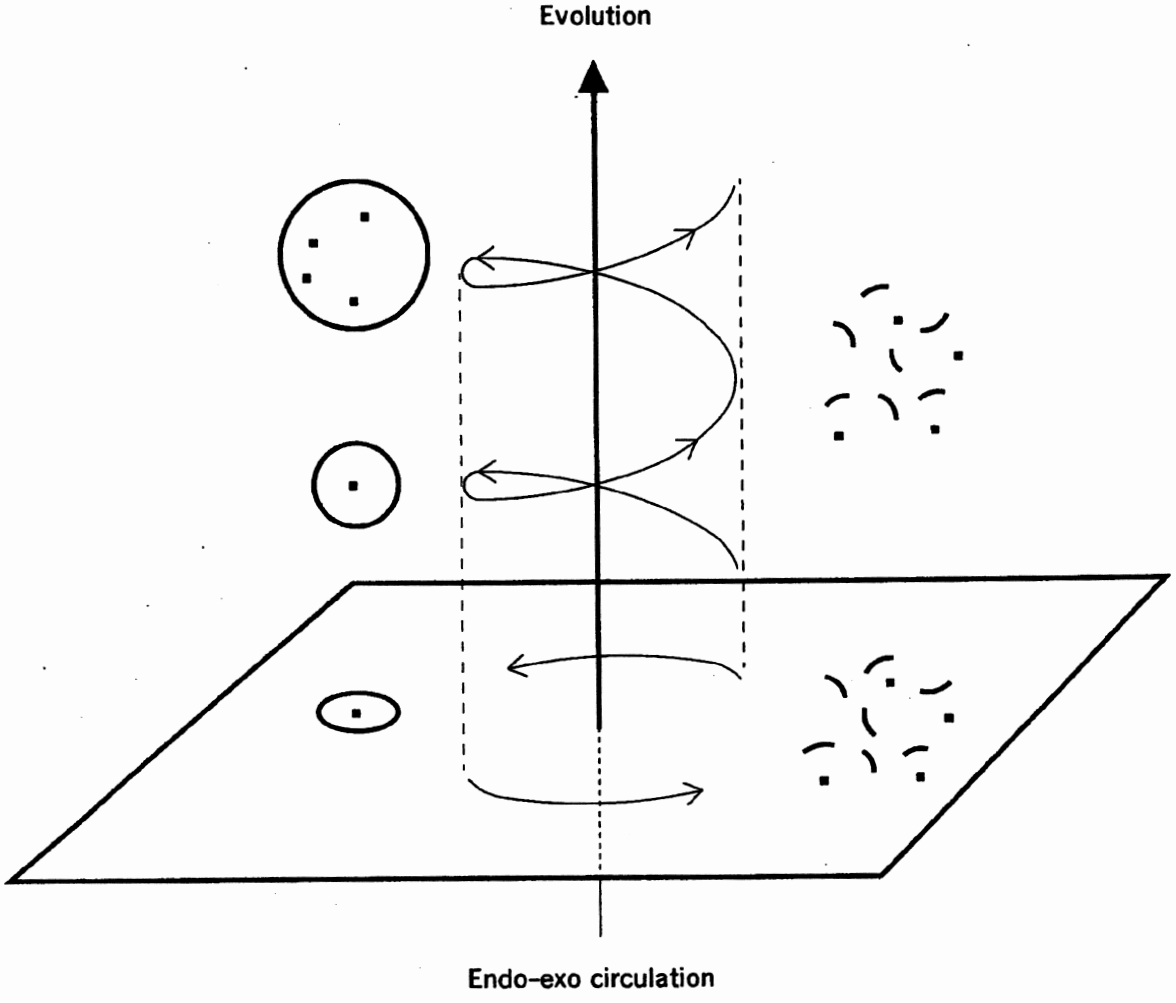

FIG. 1 The new paradigm of endo-exo circulation. A closed vesicle (or an endo-system) can keep its identity as it has the boundary membranes which isolate the micro-environment from the exo-world. Suppose that such a closed vesicle is subject to assembly-disassembly cycles (see the lower panel) — that is, the boundary membranes are broken, allowing entry of molecules from the exo-world (as called encaptulation[13),24)]), and resealed. (Here fragments of membranes and individual molecules are indicated by arcs and dots, respectively.) At each cycle, the vesicle could not retain the same composition as it was before, but instead 'evolve' in a spiral way (see the upper panel) : indeed, it can create new combinations of molecules involved which might be subject to weak selection through intermolecular interactions, and therefore, it can reach beyond the boundaries of its identity (as called self-transcendence[14)]). In addition, the enclosed micro-environment can provide a basis for open evolution, because an almost infinite number of molecules are supplied by the exo-world at every cycle. I refer such interactive processes between endo-system and exo-world as endo-exo circulation. Note that the endo-exo circulation can link different levels of the hierarchy such as individual molecules, polymers, membranes and vesicles. As a result, the endo-system can undergo continuous complexification with the emergence of new levels of the hierarchy.

cles (or liposomes) in an aqueous solution[16)17)]. The two different kinds of molecules thus frame quite different degrees of freedom or different levels of hierarchy, and hence, it is easy to create the division of labor among the molecules: linear polymers are plausible candidates for genetic systems, bilayer membranes of a closed vesicle are interfaces between the inside and the outside, and the closed vesicle provides the micro-environment as a chemical reactor where nutrient molecules and energy are constantly supplied by the external environment. Both polymers and vesicles, therefore, must be the *least* hierarchical structures required for the origin of life.

Despite this requirement, most studies have traditionally been focused on either polymers or vesicles with emphasis on the process of self-replication, and so, many difficulties remained to be solved. Three of the major difficulties are: (i) self-replicating polymers[1)-7)] alone never evolve *de novo* out of random polymers without other pre-evolving systems[18)-20)] nor the bounded complex system required for autocatalysis[6)]; (ii) self-replicating vesicles[8)-10)] alone never evolve by natural selection, because they lack stored information in a stable way based on self-replicating polymers[21)]; and (iii) even if there are self-replicating polymers along with vesicles, protocells would not originate without any dynamic process between the two units, because bilayer membranes are effective barriers to ionic solutes, hydrophilic metabolites and many other molecules[22)-24)]. Considering all the difficulties as a whole, we are faced with one serious dilemma: without evolving processes no evolving units (e. g., self-replicating polymers and protocells) could arise, but without evolving units no evolutionary processes could begin. There must be some key process other than self-replication which could link different levels of the hierarchy, leading to life's origin and its evolution.

Now, we need paradigm shifts in the key process of adaptive evolution from self-replication to endo-exo circulation. Figure 1 illustrates how a closed vesicle (or endo-system[12)]) not only shows identity in contrast with the open environment (or exo-world[12)]), but also undergoes prebiotic evolution through variation and weak selection in the context of a combination of molecules involved. Traditionally, identity and evolution have been ascribed to the same self-replicating polymers or genetic systems, because such polymers maintain identity by self-replication and yet undergo Darwinian evolution through variation and natural selection. Recent studies on present-day cells, however, suggest that the membrane processes—such as the growth, budding and fusion of plasma membranes and vesicles, together with the membrane transport and membrane transduction—are not directly controlled by genetic systems, and still they are essential for adaptive behavior of cells, biogenesis of intracellular organelles and many other functions[25)-26)]. Of course, such present-day membrane processes are ascribed to endo-exo circulation rather than self-replica-

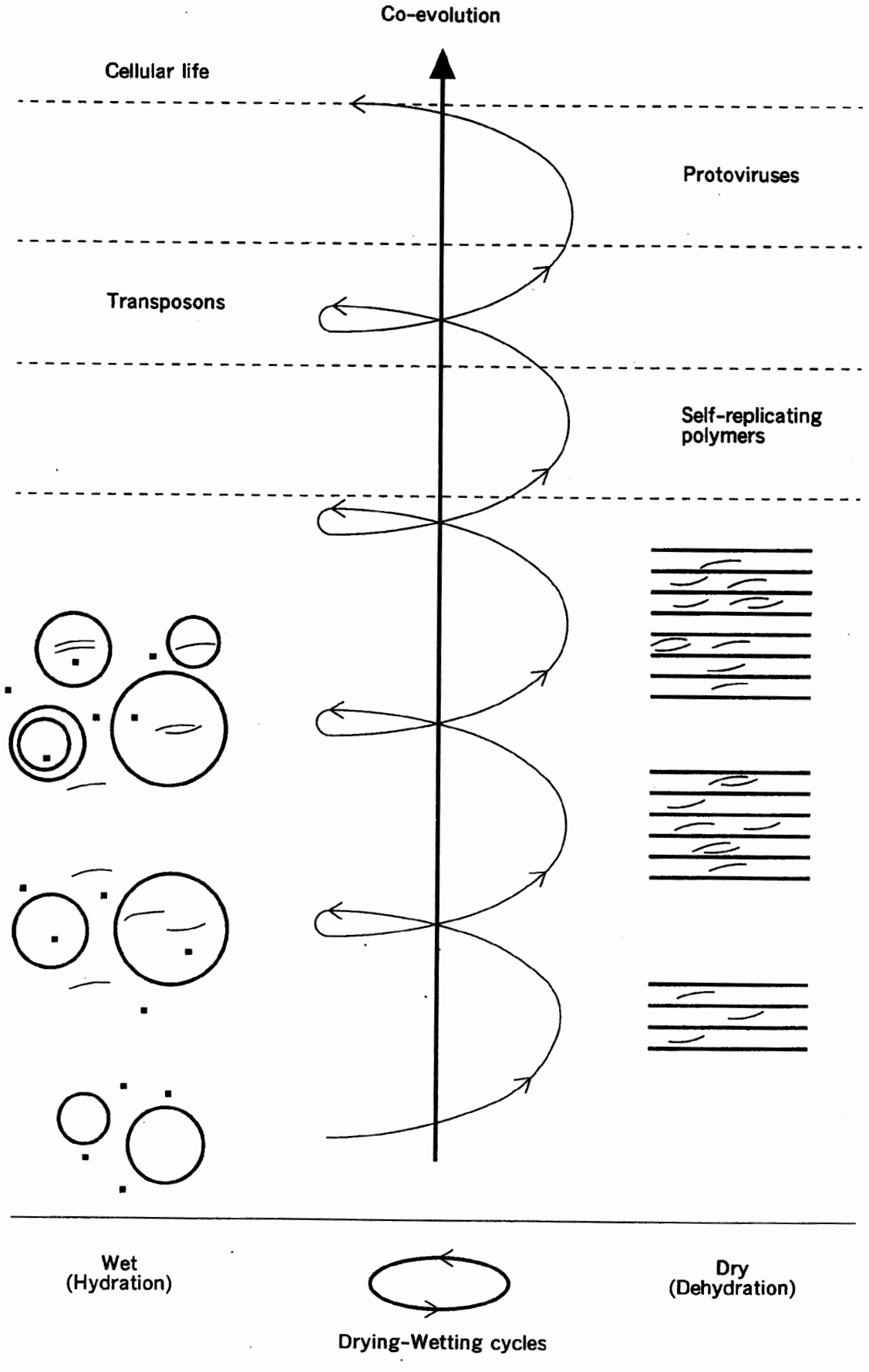
Co-evolution
Cellular life
Protoviruses
Transposons
Self-replicating polymers
Wet (Hydration)
Dry (Dehydration)
Drying-Wetting cycles

FIG. 2 The co-evolution of polymers and vesicles through endo-exo circulation, driven by drying-wetting cycles. Such cycling environments are initially required as the outside 'drive' (see the bottom panel). During dehydration, polymerization reactions are driven; and vesicles tend to fuse into multilayered structures that could trap solutes within single membranes or between alternating membranes, thereby bringing a variety of molecules into close contact with one another (see the middle panel). Here, membranes are indicated by circles (on the left side) or straight lines (on the right side). Polymers and monomers are represented by curves and dots, respectively. Through intermolecular interactions, the molecules might be weakly selected at any instance. Upon hydration, many kinds of polymers and vesicles would be produced. Some vesicles could encaptulate nearby solutes, including polymers. There may, of course, be some amount of truncation selection removing vesicles that develop too weak membrane structures to maintain themselves. In this sense, selection would occur at any level of the hierarchy. During another round of dehydration, the encaptulated pre-existing polymers would have an ordering effect on other encaptulated monomers, because they could serve as 'templates' to direct replication effectively in a narrow space of multilayered structures[13]. Upon rehydration, many different vesicles are formed again from multilayered structures, some of which would enclose the solute molecules including original templates and several copies. The first self-replicating polymers, transposable elements, and protoviruses would be driven to co-evolve before the autonomous cellular life (see the top panel). Note that self-replication is the derived character of the endo-exo circulation. The origin of autonomous cellular life can be defined by the events that an autonomous system of endo-exo circulation would arise to take over the outside 'drive'.

tion, because vesicles, organelles or cells are individually viewed as endo-systems that are undergoing variation with respect to combinations of molecules.

What mechanisms initially drive the endo-exo circulation on the prebiotic Earth ? Note that there were two very different kinds of molecules : monomeric molecules readily forming linear polymers upon dehydration[15] and amphipathic molecules spontaneously aggregating to create closed vesicles upon hydration[16),17]. Thus, dehydration-hydration cycles[13] can be one of the plausible mechanisms of the endo-exo circulation, by which many different kinds of polymers and vesicles are alternately generated and degenerated. Such drying-wetting cycles must have occurred in the prebiotic environment, particularly at intertidal zones, just as today[24]. Although emphasis was placed on the encaptulation of various solutes by closed vesicles[13], this evidence suggests that the dehydration-hydration cycles would drive the endo-exo circulation.

Since selection upon pre-existing variability implies evolution, polymers and vesicles would prebiotically co-evolve through endo-exo circulation, if there are two events in a cycle : (i) formation of a great diversity at all levels of the hierarchy such as individual molecules, linear polymers, bilayer membranes and closed vesicles ; and (ii) selection at all levels of the hierarchy through intermolecular interactions (see Fig. 2). The enclosed micro-environment can be a chemical reactor where many different kinds of molecules are supplied by the exo-world, thereby providing a chemical basis for 'the RNA world'[3], involving ribozymes[27),28]. The first self-replicating polymers could arise in the RNA world, and thereafter they could evolve through natural selection. In this sense, self-replication, typical of genetic polymers, can be the emergent property of the endo-exo circulation. If, in addition, self-splicing (or inversely self-inserting) introns evolve in the RNA world, they could create new combinations of polymers, like transposable elements. Such 'selfish' elements would become genetic parasites or infectious viruses when encaptulated by protective coats. Traditionally, it seems likely that viruses must have evolved after cells, as they depend on their host cells for biosynthesis. The present theory, however, suggests alternative possibility : no cellular life could originate without an autonomous system of endo-exo circulation, but yet encaptulated 'selfish' elements or protoviruses could arise *de novo* as long as the outside 'drive' persists. The origin of life is then defined by the events that some autonomous system of endo-exo circulation would arise to take over the outside 'drive'. Whereas endo-exo circulation links different levels of the hierarchy, leading to the origin of protocells ; self-replication has no such effects, although it can undergo Darwinian evolution through natural selection. Only the principle of endo-exo circulation, therefore, determines the continuous complexification with the emergence of new levels of organization in the hierarchy, resulting in the diversity of life.

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