

Did organs precede organisms in the dawn of life?

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Key-Words: proto-organs, organs, organisms, origin of life, reproduction, molecular evolution

SUMMARY

Evolutionary processes acting on molecule populations and their assemblies preceded the origin of living organisms. These prebiotic world entities were (re)produced; that is, independently produced by the assembly of their components, following an iterative process giving rise to identical entities, recalling the progeny resulting from self-reproduction. Before the dawn of life, natural selection favored the more stable molecular assemblies, some possibly modifying their own structure, or their environment, thereby acquiring some kind of function. In association with others (as when encapsulated together by a vesicle), they found a role when their spatial-temporal coexistence favored the selection of the ensemble. A few successful combinations of those proto-organs, and their maintenance derived from their coded-structural information, might have evolved into self-replication, followed by the extinction of a myriad of looser ensembles. Thus, interactions between encapsulated proto-organs would have had a much higher probability of evolving into organisms than interactions among simpler molecules. Organs might have preceded organisms.

INTRODUCTION: REPRODUCTION AND (RE)PRODUCTION

This hypothesis paper focuses on an alternative view of the processes understood to have resulted in the emergence and evolution of life. What is proposed here implies a different view of the concept of iterative reproduction as the only hallmark of life. In the classic view, reproduction is the process by which (micro- or macro-) organisms replicate themselves, giving rise to a genetically diverse progeny and submitted to Darwinian evolution. Progressing in a top-down analytical direction, we face the epistemological problem of reproduction versus (re)production. Any minimally complex entity can be produced independently and in an iterative manner from the interacting assembly of its heterogeneous components (which we can consider “proto-organs”, see below) in various places and times. This is what we can call “(re)production,” also termed “iterative production” or “iterative evolution,” which would not require a progenitor of the same level of complexity: they are being reproduced, rather than reproducing themselves ^[1]. The resulting higher-level entities emerged by selection; as such, interactive networks evolving through evolutionary transitions can in fact be considered units of selection ^[2]. The independent interaction networks submitted to evolutionary processes have been designed as “evosystems” ^[3]. A (bio)molecule or an ensemble that ensures that a long period of existence will be “naturally selected” against more labile or ephemeral structures. On the other hand, the parts composing a particular ensemble or network might be more protected against degradation toward “non-existence” than if they were elementary independent entities. This concept provides a clue for understanding the role of selection in prebiotic systems. The ultimate role of natural selection is to ensure existence over time, given that the more stable “individuals” will be (re)produced (and, later on, reproduced).

PREBIOTIC NATURAL SELECTION

What precedes the natural selection of living organisms? Why are some molecular assemblies presumably selected against others? The existence of discrete, relatively stable entities is necessarily anti-entropic; thus, it opposes the irreversibility of existence in time. In other words, the existence of such assemblies is due to their self-preservation. Insightfully, the previously introduced term (re)production only means that an entity is *produced* several times. Atom-atom interactions independently *produce*, by Goethean “elective affinities,” particular molecules such as salts, with the same (thermodynamically and kinetically favored) reaction able to be independently (re)produced in various spaces and times. Iterative (either spontaneous or chemically catalyzed) (re)production, such as molecular assembly or polymerization of monomers, creates “order” and favors the prolonged survival of elementary components. The physical processes that give rise to colloids, micelles, or vesicles, among other structures, is also a way of preserving the individual composing molecules. To a certain extent, these are emerging “compartments” that might improve their possibilities of persistence by association with (or encapsulation of) other ordered entities. Indeed, the conceptual core of natural selection is permanence over time: we can say that time itself is sequestered by order, the existential force, or existence-associated energy ^[4].

As noted earlier, natural selection implies individuals (understood as units of selection) embedded in populations of other (more or less similar) individuals. In prebiotic natural selection, driven by stability and (re)production, we can imagine those individuals as molecules^[5] and ensembles of molecules. At these early stages of evolution, individuals evolved at distinct levels of selection; thus, stable “assemblies of molecules” could be considered individuals of higher hierarchical order with respect to the molecules themselves.

THE DAWN OF FUNCTIONS

Order necessarily produces forms or shapes, and forms are a precondition for functions. The classic “FFF” motto, “form follows function” was first conceived and popularized by American architects and artists, such as Horatio Greenough (sculptor, 1805-1852) and Louis Sullivan (architect of the Chicago School, 1856-1924)^[6]. However, the “FFF” notion is reversible, at least in the basic stages of the organization of matter, in which “function follows form.” For some structural features, certain functions are difficult to separate from the forms that produce them: spheres protect, hexagons completely cover flat surfaces, spirals ensure packing, helices bind, and chains endure^[7].

At the early stages of evolutionary processes, non-functional (or “neutral”, in this context) forms are expected to overwhelmingly prevail. However, given the wealth of possible molecular combinations in a virtually unlimited space of interactions, a particular molecular assembly or aggregate might “find” a function. In this sense, functions were not teleologically projected, but were “found” by the molecular assemblies due to a successful combination of monodian chance and necessity. Function is thus any activity associated with a form that is able to change the environment of an evolvable individual in response to an environmental (physicochemical) alteration. Eventually, such a change can result in benefits for the individual molecular entity, such as greater opportunities to be formed, greater stability over time, or greater reactivity. From this point, the emerging functions can provide more efficiently selectable effects for the individual^[8] .

At this prebiotic stage, form and function evolved together, giving rise to more concerted and complex evolutionary dynamics. The progressive development of selectable functional interactions pushed integrated functions into more consistent (robust) ensembles, which were consolidated by the birth of particular complex “forms.” These forms were the ancestors of proto-organs. The notion of proto-organs involves investigating the difference between individualism

(the structure works for itself) and utilitarianism (the structure works for the good of a complex whole) ^[9] . Although the function of proto-organs is only to ensure their individual existence, such an evolutionarily selected function can evolve to work in more complex wholes. At this transition, proto-organs would become organs.

FUNCTIONS AND ORGANS

Etymologically, the word “organ” comes from the Ancient Greek “*οργανον*,” whose original meaning was “something that serves as a tool or instrument.” Therefore, an organ is simply something that performs a function. Applied to biology, “organismic biology” refers to the parts with different but vital functions that make possible the existence of a biological individual, the “organism,” which is composed of the totality of interacting organs. Although the precise definition of organism(s) is still a matter of discussion, it remains a central concept in biology ^[10]. Its seminal conceptualization was proposed in 1919 by the zoologist William E. Ritter, following the track of the evolutionary biologist John S.B. Haldane: “The organism in its totality is as essential to an explanation of its elements as its elements are to an explanation of the organism” ^{[11][12]}. Any organism requires an established, effective, and regulated interaction among its organs, that is, an *organization*. All living multicellular organisms have (more or less complex) organs. In turn, microbes have “organelles,” the equivalent of organs at the sub-cellular level. This concept was probably intuited by Anton van Leeuwenhoek in his first description of microbes as “animalcules” when he observed them under the microscope ^[13], thus assuming the presence of organs within them ^[14]. Later (around 1880), “microorganism” was Louis Pasteur’s preferred denomination for unicellular organisms, based on the term “microscopic organisms” used by the French surgeon, Charles Sédillot ^[15]. In 1884, the German zoologist Karl August Möbius used the terms “organulum” (the diminutive of the Latin “organum”) and the plural “organula” for the first

time, to refer to the various parts of one cell ^[16]. In modern times, “organula” is translated as “organelles.” However, regardless of their size or complexity, organelles and organs are conceptually and ontologically equivalent. Therefore, throughout this work, we will use the term “organ” for both.

THE EVOLUTION OF PROTO-ORGANS PRECEDES THE EVOLUTION OF ORGANS

The origin of proto-organs (as defined above) and the functional interactions among them is currently explored by prebiotic systems chemistry within the field of the origin(s) of life^{[17] [18] [19]}. What we would like to emphasize here is that such primitive functional associations among molecules and molecular assemblies initially created organ-like structures (proto-organs), not true living cells. In any case, it appears that a type of “life-like system with organs but without cells” could have existed, thus progressing in the “evasion from the decay to equilibrium” postulated for living matter by the physicist Erwin Schrödinger^{[20] [21]}.

We can imagine a “communal non-cellular life” in which all available functions are present and interact extensively, probably in a stochastic manner, as was presumed by another brilliant physicist, Carl Woese^[22]. Some of these associated functions could have led to the (probably asymmetric) (re)production of the communal, proto-biological system. Then, the more efficient (re)productive pre-biological patches in the communal system could have been selected, probably among those that were more tightly associated with protective abiotic (mineral or metal) surfaces^[23] and progressively evolving to reproduction and interaction. At a critical moment (which could be considered the first “major transition” in evolution, following the concept coined by the theoretical biologist John Maynard Smith), a particularly “lucky association of proto-organs” might have acquired the capability of (probably imperfect) self-reproduction, such as Woese’s “progenote”. Moving from (re)production to reproduction required that a genetic

molecule (in which the information necessary to build all the organism's organs was encoded) and a metabolism (which allowed it to exchange matter and energy with the environment) be combined in the same compartmental system. This combination guaranteed the evolutionary continuity of the organism and, therefore, of the repertoire of organs that proved most successful in each environment^{[17] [18]}.

Given that “nothing in biology makes sense except in the light of evolution”^[24], the history of organelles and organs is mostly based on the evolution of proto-organs. An example is the origin of proto-ribosomes and ribosomes, such as organelles associated with the end of the RNA world and the dawn of the last universal common ancestor, which (ca. 3.8 billion years ago) gave rise to prokaryotic organisms that further diversified the tree of life^[19]. As evolution proceeds across nested and multilevel systems, certain organisms become organs in their turn. The paradigmatic examples are mitochondria, which were prokaryotic organisms (likely alphaproteobacteria) “converted” by endosymbiosis into an essential organ of eukaryotic cells 2.7 billion years ago, as studied in depth by Lynn Margulis^[25].

Also, other organs of some eukaryotic cells (including plastids of photosynthetic algae and plants) originated by endosymbiosis of cyanobacteria^[26]. Additionally, *Buchnera*, an endosymbiotic bacterium of aphids, were independent cells before becoming organs of eukaryotic and animal cells^{[27] [28] [29]}. Lynn Margulis coined the concept “serial endosymbiosis theory,” which proposes that eukaryotic cells originated from symbiotic fusions (symbiogenesis) of various previously independent microorganisms^[30]. Another example is that, in one of the eukaryotic branches of the tree of life in which animals were diversifying, the origins of the liver occurred 520 million years ago, giving rise to the first vertebrates, amphioxii, also known as lancelets. In turn, in the branch that led to mammalian animals, the placenta is an organ that originated probably around 150

million years ago, likely due the intervention of a virus (perhaps a retrovirus), which led to the formation of syncytialized trophoblasts essential in the new organ^[31].

These examples certainly suggest that the “chicken-and-egg” question applies here. Therefore, is there a possibility for the existence of organs and organismal functions without organisms? This question relates to the classic distinction between *individual* “organs” (e.g., parts of an animal body) and *individual* “body parts” (those that perform distinct functions) ^[32]. Taking into consideration the previously discussed etymological origin of the word “organ,” we could approach the question as if in the prebiotic (pre-cellular) world there were “organ or organelle-like functions without organisms,” primarily devoid of any immediate “biological” function or use. In the absence of cellular reproduction processes to guarantee their evolutionary continuity (based on the combination of genome, metabolism, and compartment, as noted above), most of these prebiotic functions were ephemeral, contingency being compensated by their presumably high frequency of emergence and (re)production.

ORGANS WITHOUT ORGANISMS

As mentioned earlier, primitive molecular “individuals” or organs might interact with others, improving the possibility of escape from annihilation (assembly theory). The more complex the ensembles, the higher “individuality” level of the assemblies, so that the individual increases its hierarchy and robustness. The question now is whether this type of organ can perform any “function” outside of its self-preservation, influencing the molecular external environment where it is located. Such a function is exerted in the absence of any organismic integration, thus apparently devoid of any Monodian teleonomy^[33].

A particular macromolecular assembly could have found a function as, for example, a catalyst. Without catalysts, molecular interactions might occur if they are thermodynamically possible, though at an extremely low rate. Catalysts accelerate the interaction over a million-fold, thus reducing the time needed for a reaction from years to fractions of seconds. Given that we are celebrating the centenary of the first work that scientifically addressed the chemical origin of life, by the Russian biochemist Alexander I. Oparin^[34], it is worth remembering that the same author, in a later paper entitled “The Origins of Life and the Origins of Enzymes,” considered enzymes as “instruments” (i.e., organs, in the current proposal) and mentioned the Dixon and Webb statement, “We may surely say of the advent of enzymes... [it] was the most improbable and the most significant event in the history of the Universe”^[35]. Protein catalysts are typical enzymes in current biology; however, the first catalysts were probably not proteins, given that they are too structurally and functionally complex to have been formed spontaneously from the available amino acids. In turn, it is assumed that the first catalysts operating in the precellular world were certain mineral surfaces (e.g., phyllosilicates), followed by catalytic RNAs (ribozymes) and RNA-peptide complexes^{[17] [36] [37]}. As an example, the analysis of sequence-based evolutionary trees has suggested that one of the first protein enzymes, appearing at least 3.6 billion years ago, was adenylate kinase, which is present in every life form on Earth^[38]. The birth of catalysts exponentially accelerated the evolution of macromolecular proto-organs and, ultimately, organ formation in primitive microorganisms. Three examples of key microbial proto-organs with quite distinct functions are presented below: pumps, ribosomes, and nucleic acids.

Proton-pumping ATPases are found in the three domains of life^[39], and they are likely derived from simpler transmembrane pumps. They might have exerted an effect in creating molecular gradients and concentration-based interfaces. This would have required its assembly with multi-

molecular “surfaces” that enhance chemical spatial compartmentation, such as organic hydrogels or lamellar phases formed by amphiphilic molecules (including fatty acids, fatty alcohols, and lipids) that can self-assemble in vesicles, which progressively become functional proto-organs. The results of this function promoted by ATPase/membrane complexes, including the kinetic asymmetry in the concentration of ions or molecules, might facilitate molecular interactions, eventually triggering the stabilization of macromolecular complexes^[40]. Such multimolecular structures have quite different macromolecular origins and likely emerged on several occasions in evolutionary time^[41].

The history of other proto-organs, such as the proto-ribosomes that preceded microbial ribosomes, is currently unknown. However, we can assume that these putative proto-ribosomes could self-assemble by the sequential interaction of a limited number of RNA molecules and proteins, resulting in the successive formation of biomolecular condensates that were progressively refining the peptidyl-transferase function^{[42] [43] [44]}. This nascent architectural process occurs not only inside the cell; it can also be promoted out of the cellular environment^[45], suggesting the possibility of a cell-independent existence of proto-ribosomal particles^[46]. In any case, before the advent of the typical ribosome function (i.e., RNA-based protein synthesis) it is difficult to imagine an evolutionarily preserved function for the various protein-nucleic acid condensates. A possibility is that those complexes that were more tightly assembled could have been more robust to environmental changes with respect to the loose ensembles. However, in the absence of any specific and selectable biochemical function (beyond self-preservation), myriad “robust” RNA-protein condensates could have occurred, whereas only a few among them should be considered proto-ribosomes and, therefore, ancestors of the current ribosomes. This “secondary selection” should be related to the “discovery of a useful organismic function” in cellular life; in this case,

protein synthesis based on the RNA sequence, which was fundamental for genotype-phenotype decoupling.

Concerning the origin of nucleic acids, the canonical hypothesis within the framework of the “RNA world” model (or its current, more plausible version, known as “RNA-peptide” world) is that RNA formed first, and the DNA-RNA-protein world evolved from it. In the field of prebiotic systems chemistry, several pathways have been proposed to produce riboses, nucleobases, ribonucleosides, and ribonucleotides^{[48] [49]}. Also, various heterogeneous mixtures (including the presence of clay minerals, lipid-water, and water-ice interfaces) are currently being tested as prebiotically-plausible scenarios that could have promoted the condensation reactions among (either chemically activated or cyclic) ribonucleotides. This process could have given rise to RNA oligomers^{[17] [50]} that later on originated longer and more functionally complex RNA molecules (e.g., by means of stepwise, ligation-based modular evolution^[51]). In the case of DNA, deoxyribonucleotides can be formed, according to one of the several proposed hypotheses, from the assembly of prebiotic canonical purine and pyrimidine bases, by condensation with acetaldehyde and a sugar-forming precursor, and they could then react with apiose (a branched sugar) to give rise to possible DNA progenitors^{[52] [53] [54]}. As previously mentioned for proto-ribosomes, the number of possible polymers analogous to nucleic acids formed by an immense variety of sugars, nucleobases and linker molecules in the abiotic environment^{[55] [56]} had almost entirely collapsed with the advent of proto-cellularity. Only RNA and DNA were preserved in cells. Among them, RNA was likely maintained thanks to its structural plasticity and functional versatility, whereas the structural robustness of DNA (with two nucleotide-phosphate, helical polymers wrapped around one another) made it a very stable archive of genetic information^{[57] [58]}.

We are certain that the molecular composition and structure of current pumps, ribosomes, or nucleic acids in the current biosphere is simply the result of an extremely stringent series of bottlenecks exerted on proto-organs. From an incommensurable number of possible existing proto-organs in the pre-cellular environment, very few survived the extremely narrow selective pressures of natural selection and were maintained once cellular life originated. In opposition to most eukaryotic cells, many types of bacterial and archaeal microorganisms have distinct arrays of organs (including those mentioned above, as well as magnetosomes and protein-shelled carboxysomes, for example), which suggests that a number of macromolecular assemblies might have been captured by primitive vesicles ^[59].

PROTO-CELLULARITY AND ORGANS' EVOLUTIONARY MATURATION

The random capture of various abiotic proto-organs at various concentrations and compositions by primordial vesicles (spontaneously formed in the same water environment) was probably a critical step in the history of life. The first self-assembled membranes were composed of amphiphilic compounds such as fatty acids and fatty alcohols, leading to the formation of micelles and closed membranous vesicles^[60]. The resulting compartmentation of random ensembles of proto-organs in vesicles provided a heterogeneous combinatorial material for the selection of the more fit (i.e., robust or interactive) prebiotic assemblies. In these compartmented molecular landscapes, the proto-cells, “molecules that stay together, evolve together,” according to Orgel’s postulate^[61]. A few of these proto-cells might be considered the “uterus of life,” thus initiating an evolutionary-developmental (Evo-Devo) process based on the benefits of the interactions among proto-organ functions. This process might have led to proto-organ maturation, functional exaptation, coevolution, or cellular biogenesis through “attractor dynamics,” ultimately giving rise to a particularly successful composition, a kind of internal composome ^{[62] [63] [64] [65]}. The self-

replication of vesicles with their composition of proto-organs, following graded autocatalysis, and the complexification of some of them (as well as the proto-organ interactions) by fusion processes are conceivable in this prebiotic scenario^[66]. Although the vesicles containing proto-organs are still “infrabiological” lacking both genetic information and metabolism^{[17] [67]}, those processes should lead to significant increases in system information concerning time (e.g., rates of synthesis and degradation of molecules or their aggregates), space (e.g., proximity, attractiveness, shape complementarity), energy (e.g., charge differences), and in more complex systems, control (e.g., regulation)^[68]. Once self-replication began in a single or a few particular vesicles containing proto-organs, a new, strong natural selection process of the fittest primitive organisms could be initiated, with the consequence of massive extinction (abortion) of all other existing combinations of pre-organs. However, some proto-organs could also evolve to a “new function” (exaptation) by synergistic associations with others, as has been observed in living organisms. For example, the precipitation of iron nanoparticles in association with organic material could have found a function as a mechanism able to mitigate the damaging effect of reactive oxygen species on primitive macromolecular structures^[69].

EMERGING FUNCTIONS AND THE ARCHEOLOGY OF LIFE

Although we have focused this hypothesis paper on the origin of the first organisms based on the meaningful assembly of prebiotic proto-organs, we should mention that current research in molecular evolution and genetics associated with the origin of life is inspired by other evolving systems, as proposed in the emerging field of “RNA archaeology”^[70]. Following experimental work on ancestral, functional RNA molecules and their progressive integration in coding RNA polymers (which would lead to the building of the first genomes operating in the RNA world),

most of these primordial elements or “tools” (including ribozymes) likely lost their original function and are thus considered the “forgotten” or the “losers” in the evolutionary process^[71]. In archeo-anthropology, early “tools” used by non-human primates were natural objects without any anthropogenic function, such as stones, shells, or fallen tree branches. These objects “found a function” in the context of human evolutionary development, as hammer stones, cutting shells, or sticks^[72]. Note that “tools” or “instruments” can again be considered a type of “extracorporeal proto-organ” providing new functions to the evolving humans. Later, the sequential assembly of these proto-organs (such as a stick with a stone at the end) could have led to more complex “organismal” functions. Similarly, a critical advance in human evolution was the origin and evolution of language, a topic already treated by Darwin in his book, “The Descent of Man”^[73]. Language function probably followed spontaneous (non-communicative) individuals’ signs and sounds, which “found a social function” in early communities and exponentially increased their semiotic significance when signs and sounds were sequentially and deliberately associated^[74] to provide meaningful information. Therefore, sequential molecular assemblies opening the way to complex biomolecules, genetic polymers, and organs could also be interpreted as primitive elements (signs), allowing future communication strategies in the biological language(s)^[71].

THE ODDS OF LIFE

The probability that current microbial organisms originate as a result of a successful combination of an unaccountable *number* of independent, prebiotic molecules captured by primitive vesicles is impossible to determine; however, this probability is extremely low. Our proposal is based on the assumption that the *number* of macromolecular “proto-organs” that originated along a process of (still non-biotic) natural selection and captured by vesicles is necessarily much, much lower. Even in this case, our hypothesis implies that many (most) proto-organs have been “lost forever” during

the process, perhaps because the membrane compartments never captured them, or, if they did, because their structural requirements or their function was incompatible with those of other proto-organs present in the vesicle. Only for probabilistic reasons should these elementary proto-organs and organs precede organisms (Figure 1). This view suggests the possibility of many alternative “forms of life” and precludes the search for other living entities (either artificial or extraterrestrial) only based on similitudes with the (extinct or extant) organisms we know. Therefore, our proposal could also be of interest in the fields of synthetic biology and astrobiology.

HYPOTHESIS SHOULD BE TESTED

The hypothesis championed in this work, focused on the transition from prebiotic chemistry to the first organisms, appears intuitively and probabilistically sound; however, the question is whether it is experimentally testable. Hypotheses should be tested, not only championed. Approaches to this goal could come from prebiotic systems chemistry, including studies in dynamic combinatorial chemistry, self-assembly and self-organization, chemical selection, and autocatalytic systems ^[17] ^[75]. Also, clues to test this hypothesis could derive from technological advances in the chemical construction of new molecules^[76], in chemo-informatics including machine learning applied to combinatorial polymer chemistry, as well as in computational chemistry for predictive insights into chemical interactions ^[77]. The final goal is the investigation of associative networks of interacting molecules and their aggregates, at various hierarchical levels, to give rise to emergent functions in compartmented media ^[78]. A relevant hurdle to be crossed is the study of the compatibility between the physicochemical principles that control the natural selection operating in these material systems with the genotype-phenotype interdependence that drives Darwinian evolution^[79]. The later steps in this process would be the construction of synthetic (artificial) bacteria-like vesicles, able to reproduce and evolve (thus, true living beings), though not

necessarily mimicking the known forms of life ^[80] ^[81]. However, even the most promising scenarios for the in-vitro development of vesicle populations would face tremendous bottlenecks in terms of preserving the complexity that, occasionally, might come out of their underlying chemistry that could somehow self-produce, grow, and reproduce, transferring various properties to the offspring^[17] ^[82]. In any case, we trust that advancing and future research lines could be useful to provide data in support of our hypothesis. The role of modern science is to overcome the challenge of complexity.

ACKNOWLEDGEMENTS

This work is dedicated to the memory of our (FB and CB) friend Lynn Margulis (1938-2011), whose passion for science and epistemological freethought was an instrumental inspiration for our work.

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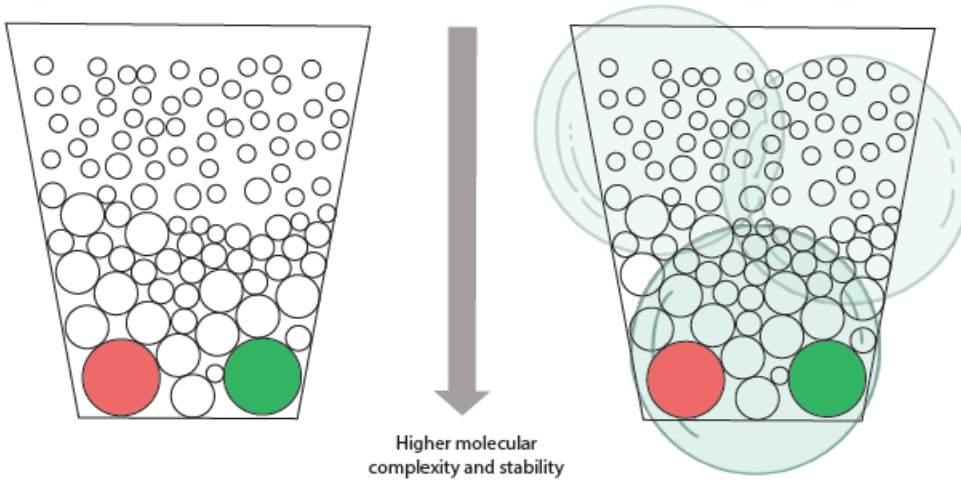
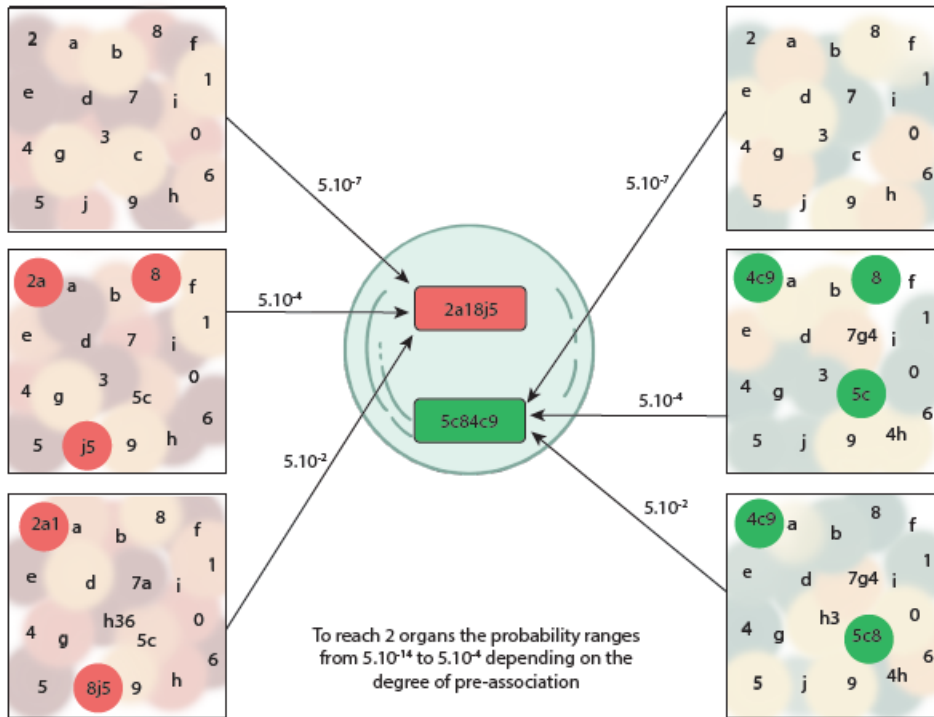


Figure 1. A highly simplified scheme showing how vesicles (in light blue) capture simple entities or more complex pre-formed ensembles (red and green small circles) that should have emerged from molecular entities with lower levels of complexity. In the upper panel, in different prebiotic environments (squares), some of these entities composed of 1, 2, or 3 members (represented by numbers and letters) will become part of self-constructed, more complex 6-membered shaped ensembles, combining numbers and letters. Such ensembles might acquire some primitive function, as ensuring their permanence in time, or altering the environment, and are considered proto-organs (red and green rectangles). The possibility that by capturing only simpler entities, a proto-organ will develop inside a vesicle should be extremely low. In the center of the upper panel, a vesicle captures with the same probability various simple molecules or relatively complex proto-organs components. The larger the number of captured proto-organs components, the higher the probability of the emergence inside a vesicle of a 6-member proto-organ. The possibility of having two or more different proto-organs in the same vesicle, and the resulting interactions between them will contribute to the organ functional maturation. and the vesicle will evolve as a proto-organism. In the lower panel, the larger associations (proto-organs) tend to cluster in space and time, depending on their stability in particular environments, in such a way increasing their possibility of being captured by the same vesicle (forming big red or green circles, proto-organisms). The shown probabilities apply only to the number of elements in this schematic figure, and are presented only as an illustration: in the natural world, the differences in probability should be much larger in favor of the capture of proto-organs by vesicles, in the way to become proto-organisms.

