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CONFERENCE REPORT

On Prebiotic Ecology, Supramolecular Selection and Autopoiesis

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The existence of many "worlds" in origin-of-life literature; such as the "lipid world" (Segré et al. 2001), the"iron-sulfur world" (Wächtershäuser 1992), the "aromatic world" (Ehrenfreund et al. 2006) and others, leads to the impression that there are many competing hypothesis for the origin of life. However, if one postulates that a concrete theory for the origin of life should provide a plausible pathway from the stage of prebiotic soup to the stage of life in a series of logical steps, then none of the above mentioned "worlds" comply with this requirement. Most simply provide us with new or alternative ways of making components of the prebiotic soup, whether monomeric or polymeric.

There is only one origin-of-life theory which complies with the above stated requirement: the so called "RNA world" theory (Gilbert 1986). A brief, modern recapitulation of the RNA-world theory goes something like this: On an early Earth there was a prebiotic soup stage in which, in some aqueous environment, there was an abundance of various organic molecules, including nucleotide components. The complex interactions of these molecules, at some point, allowed for the emergence of RNA chains and later on a self-replicating RNA molecule. Once such a molecule was present it made many copies of itself. Due to non-perfect replication, some of the molecules were different and thus behaved differently in the environment (for example they were better replicators), thus paving the way for hereditary features, environmental selection and therefore evolution. Some of these RNAs (namely ribozymes) possessed catalytic activities. RNA molecules which were encapsulated inside lipid vesicles were advantaged over those that were not, principally thanks to protection from the outside environment. Later on those that were able to catalyse synthesis of their own lipid vesicles prevailed over those that could not. At this stage the macromolecular conglomerate started resembling modern cells and the RNA in these "cells" performed both genetic and enzymatic functions. At some point, the RNA protocell "invented" DNA for

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storing genetic information and proteins to perform catalysis with greater efficiency. At this point we arrive at form of life that is ancestral to all modern life on Earth—LUCA.

This scenario could, in principle, happen again (given the right conditions) or be recapitulated in a laboratory experiment. Because of contingent factors we would not expect to recreate in such an experiment exactly the historical LUCA, but something comparable to it: a LUCA-like entity; something that would be equally, unequivocally alive. In this aspect we might say that LUCA-like would be LUCA's lookalike.

At first glance, while seemingly straightforward, the above theory for the origin of life fails in one, crucial aspect: it has not defined "life". However, one could argue that defining life need not be a part of a concrete origin-of-life theory (Szostak 2011), and we may be content if our theoretical considerations result in an entity which, according to most theories at least, would be alive (LUCA-like) without precisely defining the complexification point at which it became alive.

Another crucial feature of an origin-of-life theory should be universality: a general theory of the origin-of-life should describe the transition from inanimate to animate, and must do so independently of any particular chemistry. RNA happened to be important for life on Earth, but if the origin-of-life process happened in different places in the Universe, different genetic molecules may have emerged and different polymers could thus have been used for enzyme-like activity.

Using the RNA-world theory as a starting point to gaze over a larger picture, we can draw up a universal theory for life's origin, in which the "RNA-world" would just be one special case. This "universal replicator" theory for the origin-of-life postulates that, regardless of their chemical nature, replicating molecules may have emerged at different times in different places of the Universe, giving way to alternate "biochemical sets for life" according to different local chemistries.

The RNA world theory has been criticized from many angles, from specific criticism directed at the chemistry (Larralde et al. 1995, Nelson et al. 2000) to deeper rejections of replicator based scenarios (Shapiro 2000, Luisi 2006). However, despite this criticism no alternative theory of similar scope has ever been coined. The various proposed "worlds" mostly limit themselves to the stage of prebiotic soup. The closest alternative theory being that of the so-called "lipid" or "compartmentalistic school". But even here, after reviewing the literature one is left with the impression that "vesicles were important in the origin-of-life" but not with a coherent scenario fulfilling the requirements for an universal origin-of-life theory.

However, it is the author's opinion that such a theory can, in reality, be assembled from published work in the compartmentalistic school. Let us begin with an introduction of the notion of *prebiotic ecology*. In the prebiotic soup thousands of different molecular species where interacting with each other forming all sorts of aggregates, polymers, and amphiphilic assemblies (Hunding et al. 2006) which interacted in various ways with one another. We can say that prebiotic ecology is a situation of systems chemistry from an early Earth, and we make the assumption that what would emerge from such a milieu is *supramolecular selection*—a situation in which certain assemblies of molecules are selected by the environment over others. The important factor here is that supramolecular selection is a mechanism that spontaneously arises in prebiotic ecology.

Let us consider prebiotic ecology by looking at three different experimental works in which supramolecular selection spontaneously arises from experimental models (thus giving credence to our assumption).

In an experiment paper by Thomas and Luisi (2005), the authors investigated interactions between two supramolecular structures, namely tRNA and liposomes. When present together in the same test tube these structures interact and tRNA causes large liposomes to aggregate; tRNA does not however exhibit this effect on small liposomes (Fig. 1a). The

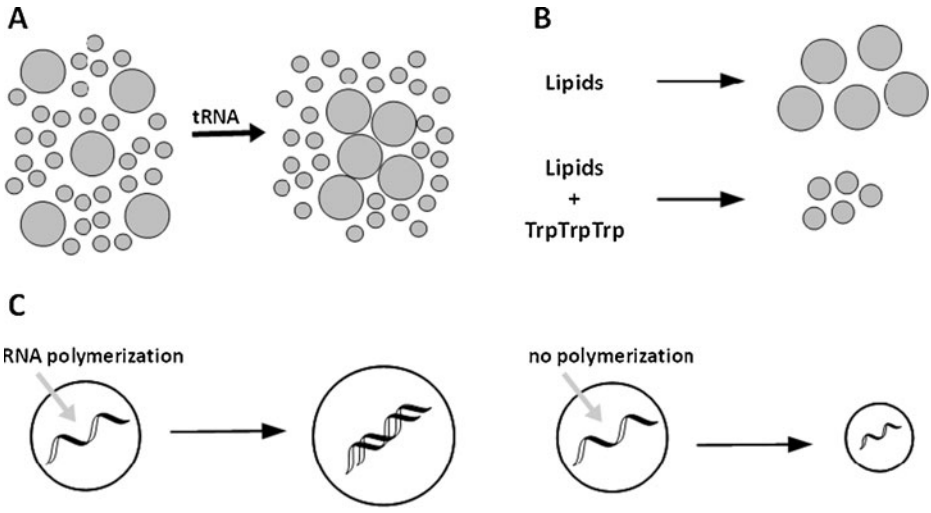

Fig. 1 Examples of supramolecular selection

next experimental example comes from a paper by Stano et al. (2005) in which the authors investigated interactions of tryptophan oligomers in the process of liposome formation. These authors found that the size distribution of newly formed liposomes differs according to the presence of various tryptophan-rich peptides. If these peptides are not present, larger liposomes are formed than in their absence (Fig. 1b). In the third experiment by Chen et al. (2004), two different populations of fatty acid vesicles containing a single strand of RNA were placed in an environment containing activated RNA monomers. Because the membrane components of the two populations differed, one was able to take up RNA monomers from the environment while the other was not. Incoming RNA monomers polymerise on the complementary RNA strand within the up-taking vesicles. This newly formed RNA oligomer cannot diffuse from the vesicles, thus increases the osmotic pressure inside the vesicle. This in turn results in one vesicle population growing at the expense of the second population (Fig. 1c). In each of the above experiments, different supramolecular assemblies had different fates which were not directly related to any thermodynamic stability but dependent on contingent factors at play in a given environment at a given time.

The second premise of the theory outlined in this work is that supramolecular selection in a prebiotic environment can result in the formation of a supramolecular assembly which exhibits autopoiesis—an *autopoietic entity* (AE). An autopoietic entity is a defined structure that is able to self-produce from within itself (Luisi 2003), thus maintaining its existence through time. Chemical models of autopoiesis have been achieved experimentally in micelles and vesicles (Bachmann et al. 1992, Wick et al. 1995). In these experiments, it has been observed that the process of self-production of an AE is under constant challenge from various environmental factors that disrupt it. This constant environmental pressure can result in one of three fates: in the first, a steady state of preservation in the current form of AE is reached; in the second, if self-production cannot match the environmental factors, the AE slowly diminishes with ultimate cessation of its existence; in the third case, when self-production outpaces environmental factors, the AE grows in size (Fig. 2).

A growing AE (for example growing self-producing vesicle) will become unstable and divide into two or more vesicles of more stable size. At this point we witness the emergence of *structural heredity*. Daughter vesicles will inherit characteristics of their parents, thus

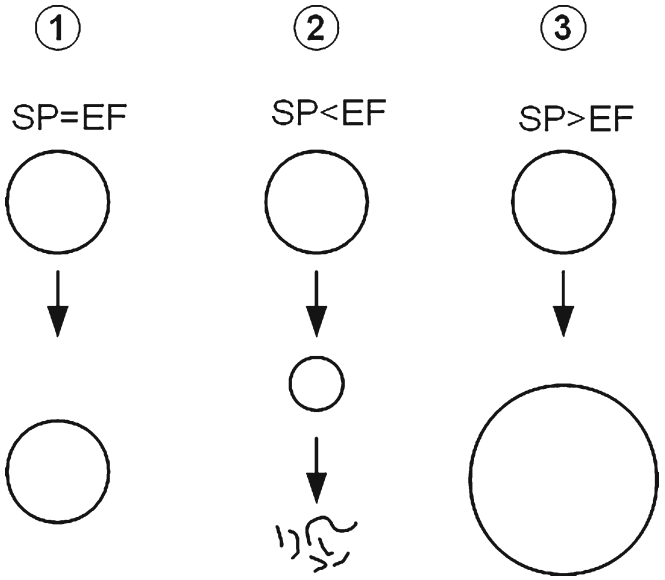

Fig. 2 Three fates of autopoietic entities. *SP* self-production, *EF* environmental factors

obtaining the property of autopoiesis from parent vesicles. If the self-production of AE is a complex process involving more than one reaction, it is likely that not all daughter "cells" will inherit autopoietic properties.

However, those that do will carry on this feature giving rise to *hereditary evolution* (with structural heredity being the chief mechanism at play). Parent's features will be passed on to progeny and the progeny will in turn compete with each other, and in this scenario, the first thing that would evolve in a biological-like manner (through hereditary evolution) is ordered division (Fig. 3). At this point, the principal driving force for further complexification would pass from supramolecular selection to structural heredity and this would, in turn, enable autopoietic entities to evolve.

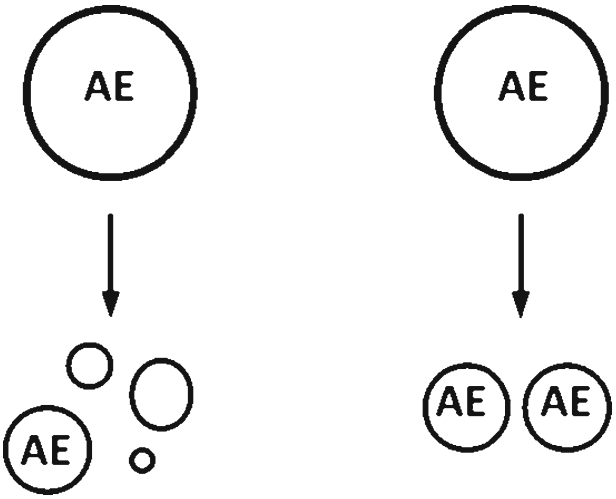

Fig. 3 Ordered division will be first feature to evolve

AEs will undergo evolution towards better adaptation to survive in their environment. It is expected that, at some point, evolving autopoietic entities would invent *genetic heredity* as a superior way to pass on features. Once AEs with genetic heredity come around, these will quickly out-compete other AEs.

Here we arrive at a situation where our supramolecular assembly may possess all the properties which made LUCA unequivocally alive, and, in a similar manner to that used in the RNA-world theory, we can call these AEs with genetic heredity, LUCA-like.

As with the RNA-world theory, the theory discussed above does not provide any specific definition of life. However it has outlined a scenario which took us from the prebiotic soup to a LUCA-like. This theory also complies with the requirement of being universal, since no specific chemistry is required: the emergence of DNA as the genetic material is largely based on contingent factors. This whole scenario could, in theory, happen somewhere else in the Universe at different time or be recapitulated in a laboratory experiment.

The RNA-world theory suggests many experiments, such as those dealing with nonenzymatic RNA polymerization, the investigation of the function of rybozymes and the prebiotic synthesis of nucleotides, and these research directions have largely shaped the origin-of-life field in the last decades.

The theory outlined in this work puts forth a new, innovative pathway for future origin-of-life research, paved with experiments such as prebiotic synthesis of lipid precursors (for example fatty acid anhydrides), the demonstration of evolution in autopoietic populations and a mileu of experiments along the lines of supramolecular selection. It is the author's hope that future research will encompass those directions as means of testing the alternative theory.

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Comments on Prebiotic Ecology, Supramolecular Selection and Autopoiesis

Pier Luigi Luisi

I find it very good that Rafal, as representant of the new generation of scientists in our field, takes up the basic question, on how we go from a macromolecular assembly to life. He also introduces something relatively new, like the notion of ecology—a vision that departs from the detailed mechanisms of single reactions, to embrace a more systemic view. Also in my group, we have recently shifted the interest of research from the analysis of individual cells to the analysis of "colonies", with the argument that cooperation among different chemical entities might better contribute to the difficult jump from non-life to life (see Carrara et al., 2012).

All this being very good, I question the jump by which Rafal's arguments bring us from the macromolecular assembly to LUCA. To me, what is in between is indeed the most difficult of the issues in our field. LUCA being already a full-fledged cell-with genome and metabolism etc.—the question which is painfully open, is : what is the structure/function of the protocells (if we like to call it this way) preceding LUCA?

I have been stumbling with this question for the last many years, and I remember the discussion with Francisco Varela about it, when I, as a simple-minded chemist, wanted to construct in the laboratory a compartment endowed with autopoiesis—a project which I never completed. Such a compartment would be self-maintaining due to an internal organization (this comes from the basic definition of autopoiesis, as mentioned by Rafal). In other terms, it would be a protocell displaying a kind of metabolism, and therefore also an interaction with the environment (the simplest form of cognition—see the other contributions on the matter).

But: nobody has been able to construct a protocell of this kind, and it is not easy to conceive how this could be done. This is very difficult not only from the technical point of view, but is completely elusive also from the theoretical point of view. Try to make one such system on paper, if you can…

And going on with suppositions: Suppose you have made a protocell with inside the Krebs cycle, (or any other metabolic cycle), with a compartment permeable enough to be alimented from the outside. To make something like that would be, I believe, a major achievement—but still does not solve our problem of the origin of life, namely of making a protocell that leads us to LUCA. In fact, in an origin-of-life scenario, the enzymes of the cycle would soon disappear (decay, oxidation, whatever…), and the whole structure would collapse—unless there is a self-replicating mechanism inside for the proteins themselves. But this would be a cell with a kind of genome: we would be already well advanced in our pathway to the origin of life.

So, can we have a protocell (something that has a relatively long homeostasis time course) without a self-replicating mechanism? And one which would eventually lead to a protocell that acquires the genetic inheritance, as Rafal mentions?

To say yes is not enough: to me, as an experimentalist, the answer should be given with a scheme that can be experimentally implemented. I haven't seen any of these on paper. And I take then this nice contribution by Rafal as an invitation to think about this basic, open question: what is the structure/function of protocells prior to the invention of the genetic code and the corresponding self-replication mechanism?

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