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ORIGIN OF LIFE

The Minimal Autopoietic Unit

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Abstract It is argued that closed, cell-like compartments, may have existed in prebiotic time, showing a simplified metabolism which was bringing about a primitive form of stationary state- a kind of homeostasis. The autopoietic primitive cell can be taken as an example and there are preliminary experimental data supporting the possible existence of this primitive form of cell activity.

The genetic code permits, among other things, the continuous self-reproduction of proteins; enzymic proteins permit the synthesis of nucleic acids, and in this way there is a perfect recycling between the two most important classes of biopolymers in our life. On the other hand, the genetic code is a complex machinery, which cannot be posed at the very early time of the origin of life. And the question then arises, whether some form of alternative beginning, prior to the genetic code, would have been possible: and this is the core of the question asked.

Is something with the flavor of early life conceivable, prior to the genetic code?

My answer is positive, although I am too well aware that the term "conceivable" does not mean that this something is easily to be performed experimentally.

To illustrate my answer, I would first go back to the operational description of cellular life as given by the theory of autopoiesis. Accordingly, a living cell is an open system capable of self-maintenance, due to a process of internal self-regeneration of the components, all within a boundary which is itself product from within.

This is a universal code, valid not only for a cell, but for any living macroscopic entity, as no living system exists on Earth which does not obey this principle. In this definition (or better operational description) there is no mention of DNA or genetic code. I added in that definition the term "open system"-which is not present in the primary literature (Varela, et al., 1974) to make clear that every living system is indeed an open system-without this addition, it may seem that with autopoiesis we are dealing with a perpetuum mobile, against the second principle of thermodynamics.

Now consider the following figure (Fig. 1). It represents in a very schematic form a cell, as an open system, with a semipermeable membrane constituted by the chemical S, which

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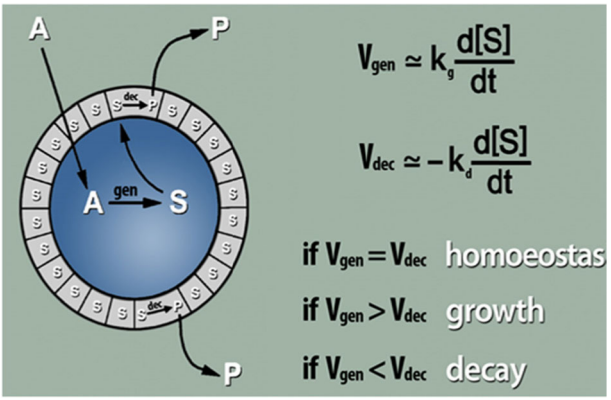

Fig. 1 The minimal autopoietic unit. With two simple reactions, we can model the three major kinetic moods of a living cell. See text for explanations and details

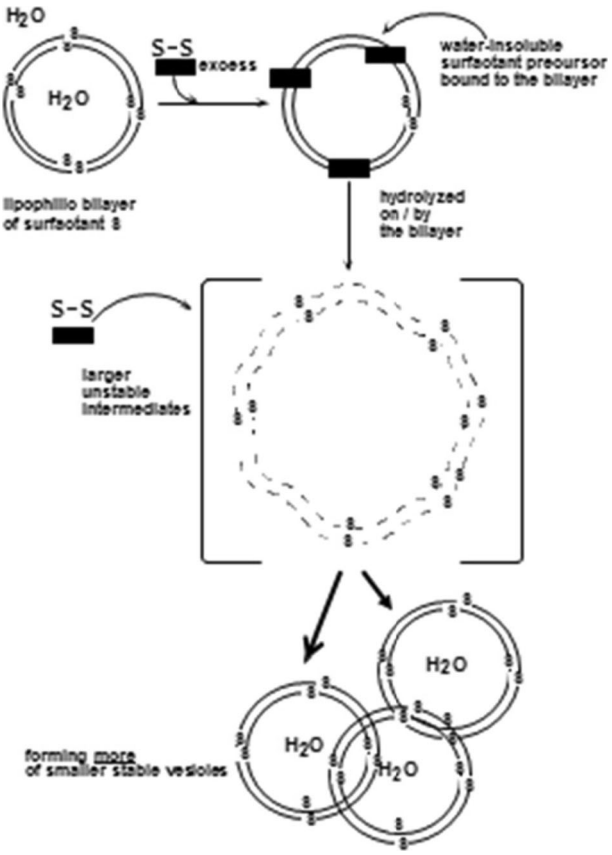

Fig. 2 The binding of the water-insoluble oleic anhydride S-S to oleate vesicles can induce their self-reproduction, due to hydrolysis of S-S into S, the surfactant that makes the vesicle (oleate in our case). An extension of this work is indicated in Fig. 3

permits the entrance of the nutrient A and the elimination of the decay product P. A is transformed inside the cell into S by a chemical reaction characterized by k_{gen}, and S can be transformed into P by the reaction k_{dec}. The two reactions actually may represent two entire families of reaction, in the sense that one can envisage several A and several S and several P.

Keywords Minimal cell · Autopoiesis · Origin of life · Genetic code · Primitive metabolism

The important point is that, depending on the numerical values of the two reaction velocities, the system can be in homeostasis, or can grow-which eventually can bring to self-reproduction-or can decay and eventually die. Thus, this simple system represents the three kinetic modes of a living cell- growth with reproduction, homeostasis, and death.

Again, for all that there would be no need, at this stage, to invoke DNA or the genetic code. In other words, such a minimal cell can be in principle realized with chemistry alone, without the help of molecular biology.

Can one such system be realized experimentally as a concrete system operating in solution? And would that make sense as a possible precursor of biological cells?

One attempt to realize experimentally one such a system in a simplified version was published by our group several years ago. It was based on oleate vesicles, to which oleic anhydride S-S would bind as the substance A. In Fig. 2, is schematized how this process can lead to self-reproduction of vesicles, as documented in the literature (Walde, et al., 1994). However, as already stated, this is only one of the kinetic pathways. If internally there is a reaction which destroys S-S, then the process of growth and self-reproduction can be kept in balance. In fact, one such system has been produced experimentally by Zepik et al. (Zepik, et al., 2001), several years ago.

In this case, while hydrolysis on the membrane would afford S, an oxidizing agent would attack the double bond of the oleate, destroying S into P (refer to Fig. 1). The hydrolysis is a process catalyzed by the OH- localized in the hydrophobic bilayer. By balancing the relative concentrations of the reagents, it was possible to obtain all three kinetic modes (homeostasis, self-reproduction, and death of the system (Zepik, et al., 2001) as illustrated in this next Fig. 3.

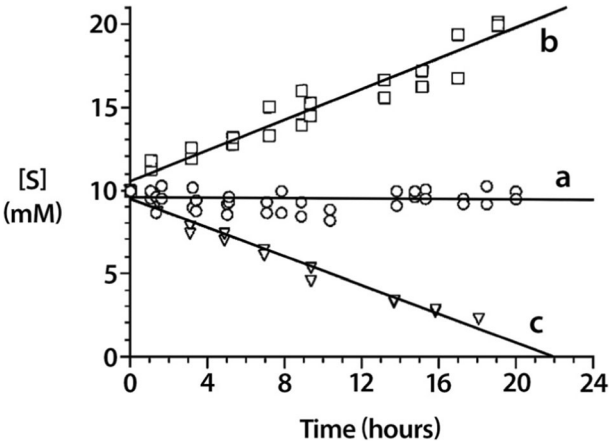

Fig. 3 The time course of oleic acid generation in the Zepik et al. system. **a**) Hydrolysis and oxidation: the velocity of hydrolysis and the velocity of oxidation are numerically equal. **b**) Only hydrolysis: the velocity of oleate production (and therefore the formation of vesicles) is predominant. **c**) Only oxidation (!): the decay velocity (the rate of oleate oxidation and breakdown) is predominant, which leads to the destruction (death) of the whole system

Generally, in this kind of experiments where the water insoluble oleate anhydride is binding to the oleate bilayer, we have self-reproduction of vesicles (Zepik, et al., 2001). However, in the experiment described by Zepik et al., there is a competitive reaction, an oxidation reaction which destroys oleate.

The oxidation reaction is the OsO_4-catalyzed cis hydroxylation of olefins with the hexacyanoiron (iii) ion as a cooxidant. Osmium tetroxide reacts first with the olefin to give a cyclic diester, which is then hydrolyzed to the diol and osmate (OsO_4). The latter is continuously regenerated to OsO_4 by an excess of K_3 [Fe (CN) $_6$]. The oxidation affords 9,10-dihydroxystearic acid, which does not form vesicles.

Self-reproduction arises following the accumulation of excess S at the internal surface of the membrane. I should add that this paper has been barely cited in the literature, and one Referee actually asked why I had done all that. I say this to make the point that indeed our question number 8 has never been taken seriously in the literature.

The weakness of this work by Zepik et al., is that there is no independent internal metabolism- all takes place at the membrane surfaces. One should add that the idea to have a "metabolism-first" has been advocated by Morowitz since the early 90.ies (Morowitz, et al., 2000), the idea namely that enzymes may have come out later, to accelerate a metabolism which was already there.

I would like to end the description of this system with an invitation and a challenge: can one obtain such a Zepik' system, and more in general the system of Fig. 1, with other kind of organic chemistry reactions, and possibly in a way that an internal mechanism-more than reactions at the bilayer- are involved? Realizing experimentally a form of metabolism into a cell-like compartment would indeed be a great chemical achievement. Not yet at hand. And not clear whether this, although conceivable, would be relevant for the origin of life.

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