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On the Theoretical and Experimental Modeling of Initial Stages of Metabolism Formation in Prebiotic Systems

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Abstract—A concept of the initial stages of chemical prebiotic evolution, which eliminates a number of difficulties in the problem of the origin of life and permits experimental verification, is proposed. According to this concept, a predecessor of living beings has to be sufficiently simple to allow its self-assembly during a geologically short time period. In addition, the predecessor has to possess autocatalytic properties, and an ability for further complication (evolution). A possible scenario of the initial steps of the origin of life in nature and inside an experimental facility is considered. In the scope of the scenario the model of a multivariant oligomeric autocatalyst coupled with phase-separated particles is described. Results of computational simulations of possible initial steps in chemical evolution are presented. The estimates obtained show that the emergence of autocatalytic oligomeric phase-separated systems is possible at reasonable values of kinetics parameters of involved chemical reactions in a small-scale flow reactor.

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INTRODUCTION

According to modern scientific concepts, the probability of spontaneous self-assembly of the simplest living cell of earthly type from organic compounds is practically equal to zero. This means that the mean time necessary for this event is longer in orders of magnitude than the time of the Universe's existence. However, it is known that life on Earth arose almost immediately (on a geological timescale) after water condensation.

This contradiction is eliminated if the following three assumptions are accepted.

(1) Life can exist on different chemical bases, and the earthly life form is only one of a great number of possible realizations.

(2) The origin of the living cell started from the emergence of a certain predecessor of such simple structure that the possibility of its self-assembly was not negligible. Thus, this event could take place within a geologically short time.

(3) A fully fledged living cell is a result of evolution from a simple predecessor driven by natural selection, which already acted at the stage of prebiotic chemical evolution.

These assumptions allow not only the elimination of the above mentioned contradiction, but also to come close to laboratory experiments on the initial stages of chemical evolution. For the specification of experimental conditions, it is necessary first of all to clear up one of the most difficult questions in the problem of the origin of life, namely, how and at what stage of prebiotic chemical evolution cellular metabolism could have emerged. In the present paper, a hypotheses of the establishment of metabolism based on a multivariate oligomeric autocatalyst coupled with the functioning of phase-separated autocatalytic system is proposed and analyzed.

PROPERTIES OF AUTOCATALYSTS, POSSIBLE PREDECESSOR OF LIVING CELLS

An understanding of processes that give rise to the metabolism at a certain stage of prebiotic chemical evolution requires a detailed description of properties of the above-mentioned predecessor. Since the simplest possible variant of the predecessor should be indicated, the properties of the predecessor that are in common with living beings and are necessary for its progressive evolution are to be selected.

An ability to reproduce (autocatalysis) is a necessary, but not sufficient property for chemical evolution of the predecessor. Simple chemical autocatalysts are capable of efficient self-reproduction at the expense of energy and chemicals; however, their chemical structure does not possess sufficient degrees of freedom for producing different variants of autoctalysts. Therefore, simple chemical autocatalysts are not capable of further complication or evolution.

A possible variant of the autocatalytic system capable of evolution is the statistical chemical autocatalytic system (Segre et al., 1998). According to this concept, various catalysts transversely catalyze the synthesis of other catalysts in such a manner that the total effect is the reproduction of all catalysts comprising this system. However, it is not clear how to provide any coordination in this set of diverse catalytic reactions, which is necessary for system stability. In addition, such a system can only appear in the case of simultaneous acquisition of the entire set of these catalysts, which is highly improbable.

The hypothesis that the primary autocatalyst could have been a linear oligomeric molecule capable of catalyzing the polymerization of monomers which composed it seems more grounded. Below, such molecules are named autooligomerase. In this case, only one event of self-assembly is required for starting autocatalytic processes. This event is provided by only one type of chemical reaction, polymerization. Generally, the properties of the linear oligomer depend on the length of chain and the sequence of monomers in it. Under appropriate conditions, a linear oligomerase can synthesize a great number of different linear oligomers, some fraction of which are auto-oligomerases.

Since polymerization of oligomers is under no control (matrix duplication has not emerged yet), any autooligomerase always produce a number of different autooligomerases, and this can initiate chemical evolution at the molecular level. Possible mechanisms of natural selection at the molecular level were proposed and discussed (Parmon, 2001; Bartsev and Mezhevikin, 2003).

In fact, the RNA World concept (Gilbert, 1986) includes the assumption of autooligomerase catalyses. The recent discovery of ligase activity of RNA (Lawrence and Bartel, 2005) gives certain experimental confirmation to this hypothesis. However, attempts to consider the very complex RNA molecule as a primary autooligomerase, and a tendency to explain simultaneously the formation of the genetic code meet a number of difficulties (Segre and Lancet, 2000; Nelson et al., 2000).

It is natural to suppose that the primary metabolism was based on more simple molecules than RNA and protein (Segre and Lancet, 2000). There is a protocell assembling project where peptide nucleic acids (PNA) play the role of matrix molecules instead of RNA (Rasmussen et al., 2002).

It seems logical to go further and to suppose that the existence and evolution of the predecessor of living systems was based on molecules of a simple chemical nature and nongenomic inheritance. This removes the need from autocatalytic systems for the implementation of a very complex function of matrix duplication at the initial stage of chemical evolution. A variant of nongenomic inheritance was proposed by Pohorille and Deamer (2001). However, comparatively complex molecules—polypeptides—are considered as autocatalysts in the present paper.

It is known that substances of various natures can demonstrate various catalytic activity. As examples it is possible to mention very short peptides (dipeptides and tripeptides), ribozymes, lipozymes, PNA, and various minerals (Gilbert, 1986; Laszlo, 1999; Ferris et al., 1996; Segre et al., 2001; Carny and Gazit, 2005). There are no grounds to deny possible catalytic activity of short linear hetero-oligomers, which can consist of very simple monomers.

It can be assumed that natural selection at the level of autocatalytic molecules was an important stage on the way to the formation of the living cell. However, the origin and evolution of metabolism are impossible without phase separation. Many types of phase-separated particles (PSP) that are capable of self-organizing in the course of different physical processes are known (Fox and Dose, 1972).

PSP of micellar type can be used for modeling the stage of the metabolism origin. Such particles in the course of their growth can reach specific size, and then, due to mechanical instability, will be divided, i.e., demonstrate primitive self-reproduction. It was shown that the particles themselves can operate as autocatalytic systems (Segre et al., 2001).

At the initial stage of chemical evolution, the membrane could have been assembled from amphiphiles presented in the environment of PSP. Due to phase effects, such PSP can accumulate different substances: gases, inorganic and organic compounds. As appropriate monomers are accumulated inside them, various linear molecules with oligomerase activity can be assembled. In the absence of matrix duplication, oligomerases inevitably produce a great variety of oligomers capable of different catalytic activity. If oligomers capable of synthesizing appropriate amphiphiles are present in this pool of oligomers, then a phase-separated system (PSS) possessing primitive metabolism can emerge.

The addressing to oligomers of the simplest chemical nature and the abandonment of the necessity of considering matrix duplication at the initial stages of chemical evolution allows us to come to simple and very probable scenarios of probiont metabolism origin. This provides the possibility to pose the problem of experimental modeling of the initial stages of evolution. In turn, experimental verification of the hypotheses for the origin of life poses questions of optimum conditions providing maximum acceleration of these experiments.

HYPOTHESIS OF THE ORIGIN OF PRIMITIVE METABOLISM AT THE STAGE OF CHEMICAL PREBIOTIC EVOLUTION

The hypothesis considered develops the earlier proposed concept of the origin of life (Bartsev et al., 2001; Bartsev and Mezhevikin, 2003, 2005) and agrees with the above assumptions. The hypothesis includes two postulates supplemented by a set of necessary conditions providing chemical prebiotic evolution. These

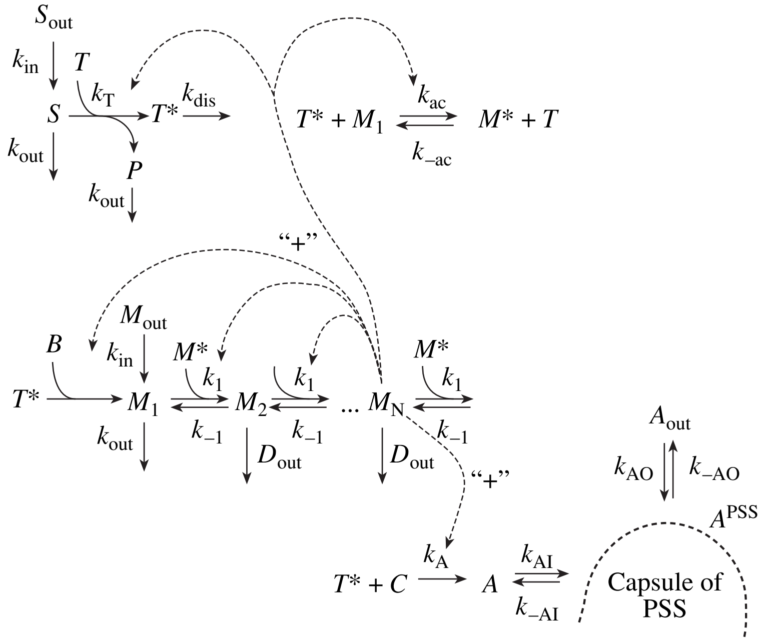

Fig. 1. Reactions inside the zone of origin, but outside of PSS. Designations: (D) flow rate; (S_0) initial concentration of high-energy substrate; (S) concentration of the substrate inside the reactor; (T) concentration of the carrier; (O^*) concentration of the activated carrier; (M_0) initial concentration of the monomer; (M_1) concentration of the monomer inside the reactor; (M^*) concentration of the activated monomer; (M_i) concentration of the oligomer of ith length; (A_0) initial concentration of amphiphiles; (A) concentration of amphiphiles inside the reactor; (A_i) concentration of the aggregate consisting of i amphiphiles; (A, N) concentrations of some non-organic and simple organic compounds which can be used for the synthesis of monomers and amphiphiles; and (k_{dis}) constant of dissipation. Broken curves designate activation.

conditions have to be implemented in the experiments on the initial stages of chemical evolution modeling.

Postulate 1. There exists a wide set of linear oligomer chains manifesting variable catalytic activity, where the same catalytic function can be performed by oligomers of different length of chain and of different sequence of monomers.

Postulate 2. The potential predecessor of living cell is phase-separated autocatalytic system capable of further complication (evolution) due to the functioning of autocatalytic core of primordial metabolism. The role of the initial core is performed by a linear oligomer molecule capable of catalyzing polymerization of monomers from which they are assembled.

Condition 1. The reaction medium has to contain inorganic and simple organic compounds, including monomers, as well as high-energy substances for thermodynamic and kinetic admissibility of polymerization. At the first stages of chemical evolution on the Earth, high-energy substances were provided by geochemical cycles.

Condition 2. The reaction medium has to contain the simplest amphiphiles for assembling PSP of micellar type. PSP provides overcoming of thermodynamic and kinetic barriers of polymerization, and local increase of reactant concentrations.

Note that the optimum conditions for selection and identification of oligomers possessing auto-oligomerase activity are implemented in flow reactor of ideal mixing with a controllable rate of reaction medium exchange.

According to this hypothesis, the first key step is the experimental detection of auto-oligomerase activity. Therefore, the final goal of the research consists in a theoretical estimation of necessary experimental conditions of the most probable and fast emergence of elementary autocatalytic oligomeric molecular systems.

DESCRIPTION OF COMPUTER MODEL

Complete schemes of reactions inside and outside of PSS are presented in Figs. 1 and 2. Extended explanation of these schemes and assumptions are considered below.

(1) There is *a zone of origin* where high-energy substances, various inorganic substances, and minor amounts of amphiphiles and monomers are supplied. The zone of origin is organized as flow reactor of ideal mixing.

(2) High-energy substrate transfers energy to a carrier, which provides chemical activation of monomers.

(3) Amphiphiles are capable of spontaneous and reversible binding with each other. PSS is formed when

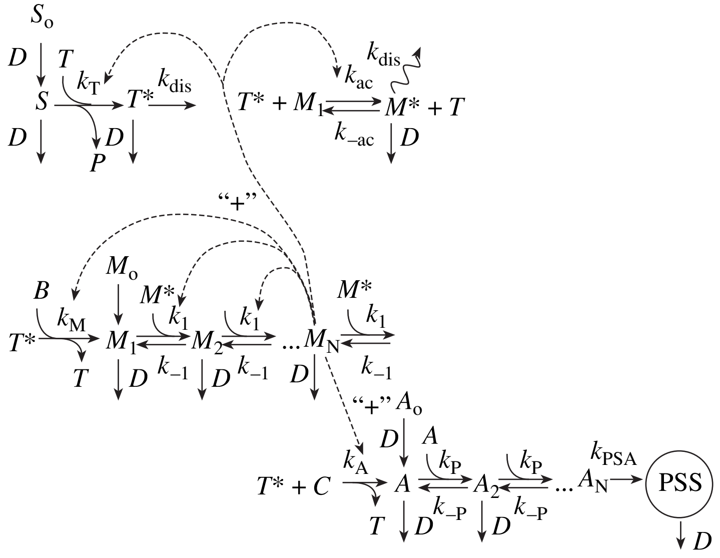

Fig. 2. Reactions inside PSS. Designations: (S_{out}) concentration of high-energy substrate outside the PSS; (S) concentration of the substrate inside the PSS; (T) concentration of the carrier; (O*) concentration of the activated carrier; (M_{out}) concentration of the monomer outside the PSS; (M_1) concentration of the monomer inside the reactor; (M^*) concentration of the activated monomer; (M_i) concentration of the oligomer of *i*th length; (A_{out}) concentration of amphiphiles outside PSS; (A) concentration of amphiphiles inside PSS; (A_{PSS}) amount of amphiphiles in the PSS capsule; (A, N) concentrations of some nonorganic and simple organic compounds which can be used for the synthesis of monomers and amphiphiles; (k_{dis}) constant of dissipation, (k_{in}) constant rate of the substrate incoming from outside; (k_{out}) constant rate of the substrate leakage from PSS; (D_{out}) constant rate of the oligomer leakage due to temporary disintegration of the PSS's capsule.

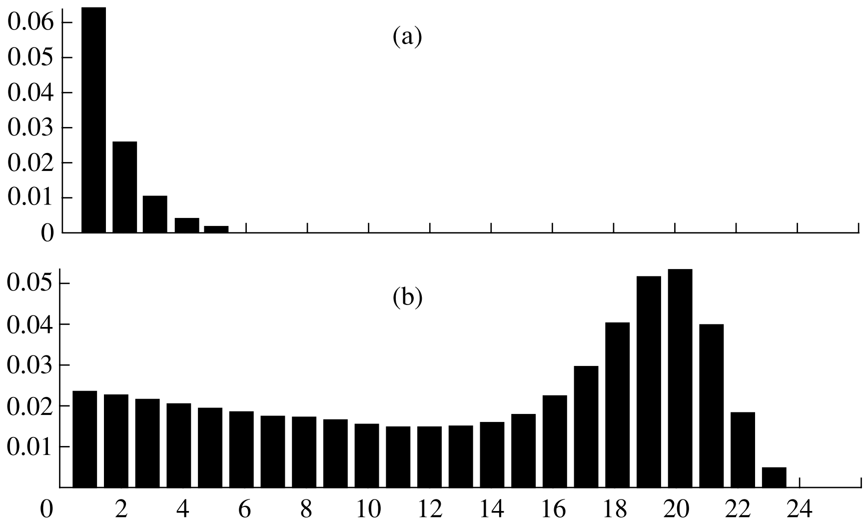

Fig. 3. Computer simulation of steady state oligomer distribution with respect to their length: (a) inside the flow reactor and (b) inside the phase-separated system compartment.

the amount of bounded amphiphiles exceeds a certain critical value. The capsule of PSS is in dynamic balance with external concentration of amphiphiles.

(4) Activated monomers are capable of spontaneous and reversible binding with each other, forming linear oligomers. Some fraction of these oligomers after achievement of certain length is capable of catalyzing the synthesis of amphiphiles from simple substances. Another fraction is capable of monomer synthesis. And some fraction of oligomers are auto-oligomerases.

(5) The concentration of monomers inside PSS is higher than outside due to the interphases redistribution. Inside PSS, the balance of polymerization reaction is shifted to oligomer synthesis.

(6) The increase in PSS sizes occurs due to the embedding of amphiphiles both synthesized inside PSS

and coming from the outside. The growth of PSS results in the dilution of reactants inside it. If the concentration of some substances for which the capsule of PSS is impenetrable exceeds some limiting level, the integrity of the capsule is broken and at some time an outflow of the internal contents of PSS takes place. Then the capsule of PSS is restored.

(7) In this model, a compartment representation is used. This means the dynamics of substances in the zone of origin, averaged dynamics of PSS capsule growth, and averaged concentration of substances inside PSS are actually considered. The total amount of amphiphiles included in PSS capsules is considered as one of the basic variables. It is supposed that after achievement of the certain critical size, PSS is divided into two PSSs; therefore, in the model, the total area of the surface and the total volume are proportional to the amount of amphiphiles in the capsule. The flows of substances into and out of PSS are proportional to the area of the PSS surface.

Some results of computer simulation of the this model are shown in Fig. 3. The figure demonstrates a hump in the distribution of oligomer lengths inside PSS. This means that an autocatalytic process inside PSS takes place. This simulation was conducted at reasonable parameters of reaction rates and flow in the reactor. This result illustrates a principle possibility of the formation of phase-separated autocatalytic systems in the course of chemical evolution under conditions of real experiment.

CONCLUSIONS

The hypothesis proposed for the origin of prebiotic metabolism allows experimental verification. The key stage of its verification is primarily based on the detection of auto-oligomerase activity of linear molecules that appear as a result of polymerization of monomers of simple chemical structure under the experimental conditions described.

The model considered allows a preliminary estimation of necessary parameters of autocatalytic synthesis of oligomers, and coupling synthesis of phase-separated systems. The preliminary estimations show that the formation of autocatalytic oligomeric PSS is possible at reasonable values of kinetic parameters of the chemical reactions involved in the flow reactor process. The signature of auto-oligomerase reaction is the presence of a hump on the distribution of oligomers with respect to the length of their chains.

It is important to note that, as auto-oligomerases of small chain length are taken as a predecessor of living beings, the problem of overcoming the threshold of biological complexity becomes substantially less acute (Avetisov and Gol'danskii, 1996).

In the context of the primary autocatalytic system, the problem of the genetic code retreats into the background. At the same time, note that there is quite realistic scenario of the formation of genetic code (Altshtein, 1987), which is in a good agreement with a hypothetical final stage of metabolism with nongenomic inheritance.

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