Origin of Life

Diversified World: Drive to Life's Origin?!**

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What is decisive for the origin of life? Here we do not want to delve into the chemical details but attempt to look at the fundamental motivation which leads to the remarkable process of self-organization to simplest forms of life. That should be useful to stimulate experimentation. It is often assumed that in principle life can arise in a homogeneous medium or at a reactive interface by intrinsic necessity (see, for example, reference [1]). Processes of this type are known, but is it really possible that such a process can lead to a machine as intricate as the genetic apparatus of biosystems? The idea that life arises slowly in a chaos of lifeless matter is fascinating, but is life's emergence not a process dfferent in principle? Are not quite special highly diversified environmental conditions changing periodically in a particular way required as the driving force for the formation of increasingly more complex forms, evolving to forms of early life?

Model Pathway

To establish the plausibility of a theory of the origin of life a tangible and detailed sequence of hypothetical physical-chemical processes which leads to the basic machinery of life must be proposed. Each step would have to be as simple as possible, however, to understand the fundamentals of this type of processes. But it cannot be expected from such a way to go that a genetic apparatus as complex as that which actually exists in the biosystem will be achieved, but a less intricate apparatus with the same functional properties. Such a model pathway would have to be constantly improved on the basis of new experiments and knowledge. A description of the historical pathway is not aspired. The process should demonstrate how systems with lifelike properties are formed as well as chemically totally differently constructed supramolecular systems, or systems that could arise at suitable locations everywhere in the universe.

The extremely important questions currently of special interest in connection with the origin of life (what role do RNA, DNA, peptides, thioesters, pyrite, etc. play? And where did the process take place, in the depths of the ocean, at a volcano, on Mars, or elsewhere? How was the beginning of a replication process possible? Which enzyme-free metabolic processes were required to synthesize the building blocks of a first replica-producing system and to exploit an energy source?[2]) are not considered here. We attempt to contribute to finding answers to questions concerning further evolution of a replicating molecule toward the genetic machine by developing theoretical models. Which principle requirements, independent of the special chemistry, must be fulfilled to initiate and drive forward this process? What are the demands placed on the building blocks of the evolving systems and the environment? How can these demands be fulfilled with the resources of chemistry? Can in this way a plausible model pathway to systems with a genetic apparatus be found? In a recent publication[3] some critical steps of a simple model pathway suggested in reference [4] are simulated on a computer. The model pathway assumes that quite specific external influences are fundamentally important for the origin of life. The proposed hypothetical steps lead to a simple translation device, to a plausible explanation of the basic transformations (transition from RNA to DNA as carrier of genetic information), and to the development of the genetic code of biosystems in detail. Here we focus on general aspects of the process.

The Beginning

It is assumed that amongst the enormous diversity of regions with different properties on the prebiotic Earth there exists, by chance, somewhere a small, singular region with the following important properties:

1) the presence of certain, energy-rich monomers which were formed by fortuitously prevailing conditions and are continuously replenished. In the thought experiment two mutually complementary monomer types are assumed to be available;
2) unique, temporal-spatial environmental properties which allow the continual formation of short strands by condensation of the monomers;
3) occasionally, in a very seldom step, a short strand is formed by chance in which the monomers are connected in such a waythat the strand can act as a template for the formation of the complementary strand;

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4) replica formation starts and continues under the prevailing conditions, and by accidental copying errors strands are formed with different monomer sequences which display different folding structures, and selection occurs (for example, by different hydrolysis sensitivities of differently folded strands).

Despite considerable efforts it has hitherto not been possible to realize a plausible initial reproduction process experimentally,[5] although more recent approaches [6,7] are encouraging. Very diverse possibilities have been suggested as the starting point of life's origin on Earth, including processes on mineral surfaces. The question is not under discussion here, but each proposal should be substantiated by giving a plausible pathway to a system of self-replicating RNA-like chains.[8] According to the model[4] such a replicating system presumes the formation of a homochiral template strand so that the fitting together of template and the developing strand is guaranteed. Such a template is formed by chance in a racemic solution of monomers. In this accidental, initiating process is seen the origin of the homochirality of biological systems. The formation of such a symmetry break has been realized experimentally in reference [6]. The experiments in reference [7] support the idea of a complex temporal-spatial structure as fundamental already for the initial process.

The thought experiment[4] as described rests on the assumption that an appropriate self-replicating system will be realized experimentally, since fundamentally nothing speaks against it. The real puzzling feature in the origin of life emanates from the subsequent processes. How can such a system develop into an entity with a genetic apparatus?

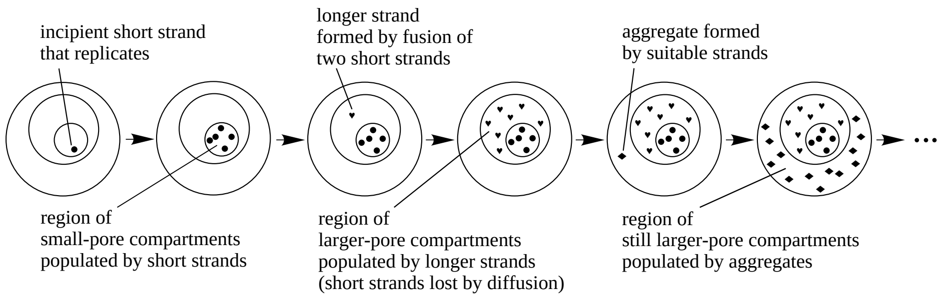

Figure 1. Highly diversified world: driving force for increase in complexity by colonizing increasingly less favorable regions. Only short strands emerge spontaneously, the occurrence of longer replica-forming strands is much too improbable. After short strands have multiplied, longer strands can easily occur by fusion. These strands may form folding structures. Aggregate-forming strands may appear.

Structural Diversity of the Environment:

Stimulus for Continuous Complexity Increase

According to the model the critical factor in the origin of life is that in the small region under consideration where multiplication of strands and selection takes place, a strand is formed fortuitously by a copying error which can survive and multiply in a neighboring region with slightly different properties, in contrast to the hitherto existing strands. The process is ongoing (Figure 1); increasingly less favorable regions are occupied with replicable forms. This requires the occurrence of increasingly more complex and more intricate systems. In this way the systems thus formed become increasingly independent upon the quite special, restrictive conditions in the region in which the process has begun. The fact that an enormous number of regions with different properties existed on the prebiotic Earth plays a central role in the model. The multiformity is the stimulus for the continuous increase in complexity. In this view of a beginning in a most particular region, sequences of very different processes (many kinds of chemical reactions, concentration and separation processes) led to building blocks for a replicating system. This view should stimulate the search for many different possibilities to obtain such building blocks.

Periodicity and Compartmentalization

Living systems are complex aggregates of mutually compatible molecules. Thus even for the first steps suitable conditions must be found which lead to the aggregates of mutually compatible molecules and to the evolution of increasingly more complex and intricate aggregates. In addition to the structural diversity, temporal periodicity and spatial compartmentalization (e.g. day–night cycle and small pores in a rock) are fundamentally important conditions.

A periodic change between totally different environmental influences, for example different temperatures, is important: aggregates must be formed through the interdiffusion and interlocking of individual molecules: these aggregates are subjected to a selection process; the aggregates must then disintegrate again into individual molecules which are replicated; and a new cycle must begin. The process continues, driven by the given periodicity.Compartmentalization is important to avoid the individual molecules diffusing apart, enabling the molecules to come together for reconstitution. The compartments must be somewhat porous so that copies of the newly produced favorable form within a compartment can gradually spread over the whole region.These general considerations are important in the search for a detailed model pathway[4] and for the determination of the parameters for computer simulation[3]. Two fundamental facts should be taken into account when considering the evolution of increasingly complex aggregates:

1) A prerequisite for aggregates of interlocking strands to be formed is that template strand and replicate are antiparallel in the double strand. Only in this case the single strands obtained after separating template and replicate can form compact folding structures required to build aggregates. Indeed, the postulated

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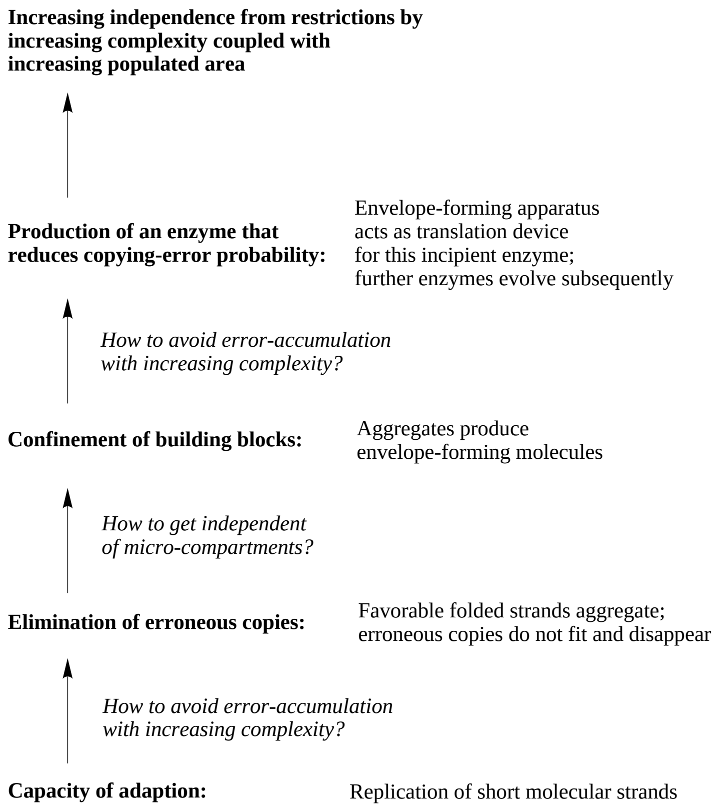

Figure 2. Early stages in the evolution of life in the thought experiment: logical steps, barriers, and their surmounting.

antiparallelity is realized in living forms.

2) A basic question is how to overcome the difficulty that evolution comes to an end at a certain level of complexity because of copying errors accumulation. This requirement is achieved automatically in the model by the formation of aggregates of mutually compatible molecules: molecules which have a changed folding through reproduction errors do not, in general, integrate and disappear. With increasing complexity of the aggregating forms the mechanism is always determinative and of fundamental importance in the evolution of increasingly intricate systems.

The first steps resulting from these considerations are given in Figure 2. They lead to a simple genetic apparatus.

Computer Simulation

Each cycle in this simulation consists of a

1) construction phase (simulation of the formation of functional aggregates by diffusion and joining together of molecular strands);
2) selection phase (aggregates—according to a feasibility parameter which determines their survival probability—are randomly selected. This parameter is held in a library for each aggregate form which is regarded as a possibility to occur in any phase in the evolution process;
3) Replication phase (aggregates break down into individual strands which serve as tempates for a replica formation after which template and replica strand separate).

The calculation results[3] underpin critical breakthroughs in the first stages of the hypothetical model (for example, the formation of an aggregate such as in Figure 3 that functions as a simple translation apparatus).

Basic Idea and Procedure

The basic principle of the model (continuous increase in complexity, associated with the colonization of increasingly less favorable regions) represents an extension of the Darwin Theory according to which during biological evolution increasingly more complex systems are formed through new ecological niches being populated. Previously empty regions are increasingly occupied. Later the creation of ecological niches by gradual expulsion of competitors becomes important.[9] The basic procedure (the search for an unbroken chain of hypothetical, physical-chemical process which leads to a genetic apparatus) represents an extension of Darwin's way to go. In the search for the mechanism of the origin of life

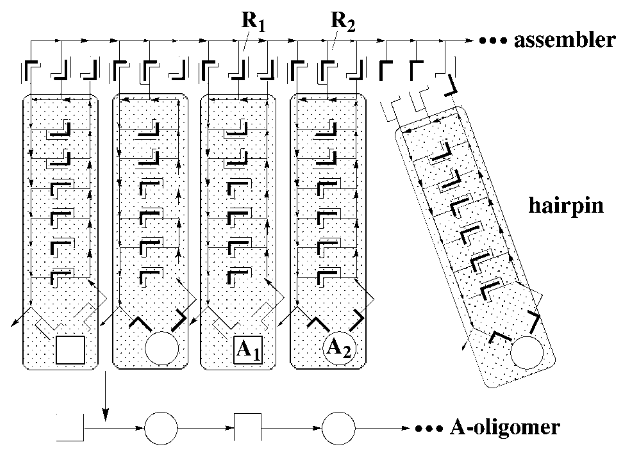

Figure 3. Translation apparatus for a binary code. Important stage in the model pathway in the computer simulation: assembler and hairpin strands of *R* monomers (R_1 and R_2). Cohesive alignment of hairpins by means of the reading frame. A-monomers (A_1 and A_2) are bound to the open end of the hairpins. A binary code relating the sequence of R_1 and R_2 in the assembler with the sequence of A_1 and A_2, which are linking to form the A-oligomer. The A-oligomer acts as an enzyme. R and A are reminiscent of a ribonucleotide and an amino acid in biosystems.

the method described should be immediately plausible by its relation to Darwin's basic ideas.

Origin of Life: Self-Organization by Intrinsic Necessity or by the Necessity to Increase Complexity with Extending Populated World?

A diversified environment, the drive to life in the present view, plays no role in the theories which are based on the assumption that the essential process in the origin of life can be considered, in principle, as a self-organization in a homogeneous phase by intrinsic necessity. It is interesting to inquire after the causes for the great fascination and the broad acceptance of this idea.Up to the beginning of the 1970s it was frequently thought that the origin of life was inconsistent with thermodynamics, but then the thermodynamic conditions for processes of self-organization in a homogeneous medium in the steady state were given.[10] Thus the described statement was considered to be disproved, the gap between physics and biology bridged, and the basic laws of a theory of the origin of life discovered. However, the fact that structures form in a homogeneous medium by self-organization does not allow one to conclude that this type of self-organization can actually lead to living systems.

Thermodynamics and the Origin of Life

The idea that the origin of life is inconsistent with thermodynamics cannot be refuted, in our view, without giving a plausible model pathway, and all the more the more detailed the pathway is. The problem of the origin of life is therefore finding such a pathway and not a question of thermodynamics since every physical-chemical process is consistent with thermodynamics.

Gradual or Sudden Manifestation of Life?

In the conception that within an in principle homogeneous phase increasingly more complex forms evolve slowly, life originates gradually. A different situation is given if in contrast we start from the concept that in a region with singular properties a clearly orientated process is set in motion: through replication, variation, and selection a development is instantaneously initiated which (jointly with an increasing expansion of the populated region) leads to increasingly complex forms. In this explosive process a property of matter emerges all of a sudden which was not previously manifest. It is useful to define physical-chemical systems with this singular behavior as living organisms even life in common sense appears much later. Thus life originates suddenly with the appearance of the first self-replicating molecule which is variable through errors in the copying process.

Genetic Information

The special feature of living organisms is that they carry information as certain sequences of building blocks, the recipe for the construction of copies (genetic information). The evolutionary process and therefore the genetic information can only be seen in connection with the given environment. The genetic information carried by the evolving forms should not be confused with the observer's information required to characterize the environment of these forms. The genetic information, quantified by the number of bits, is transferred from one generation to the next. In the described portrayal of a sudden change from the lifeless to the living, genetic information is produced with the appearance of the first self-replicating molecule. The carrier of the information (the recipe for the construction of copies) is the molecule itself. With the advance of evolution the genetically transferred information grows (measured by the number of bits), and the carrier of the information itself changes at certain stages of evolution.[8] The information grows with the extension in the information-bearing chain, and its significance increases (measured by the minimum number of bits which must be produced and rejected in order to achieve the observed evolution stage). As described above, there are very different conceptions on the nature of the initial information carrier, exemplifying the presented scenario (sudden appearance of an initial information-carrying, physical object and continuous complexity increase).[11] Genetic information is clearly defined other than in scenarios where the origin of life is considered as gradual change from the lifeless to the living.

Outlook

The driving forces inducing the emergence of life are sought by theoretical modeling. It is attempted to see motivations that lead to this process which must also be valid anywhere in the cosmos under quite different but extremely specific chemical and spatiotemporal conditions. To achieve advances in our understanding of the origin of life model pathways must be improved by an increasingly detailed determination of the environmental conditions and an ever better preparative chemical underpinning. The concept that the process begins in a particular region should stimulate a broad search for experimental possibilities.

[1] D. Segré, D. Lancet, *EMBO Rep.* **2000**, *1*, 217–222; A. D. Miller, *ChemBioChem.* **2002**, *3*, 45–46.

[2] N. Lahav, *Biogenesis: Theories of Life's Origin,* Oxford University Press, New York, **1999**; A. Brack, *The Molecular Origins of Life: Assembling the Pieces of the Puzzle,* Cambridge University Press, New York, **1998**; C. Wills, J. Bada, *The Spark of Life. Darwin and the Primeval Soup,* Oxford University Press, Oxford, **2001**; G. Wächtershäuser, *Prog. Biophys. Mol. Biol.* **1992**, *58*, 85–201; C. de Duve, *Blueprint for a Cell: The Nature and Origin of Life,* Patterson, Burlington, **1991**; I. Fry, *The Emergence of Life on Earth,* Rudgers University Press, New Brunswick, **2000**; G. F. Joyce, *Nature*, **2002**, *418*, 214—221; *Frontiers of Life, Vol. 1, The Origin of Life* (Eds.: D. Baltimore, R. Dulbecco, F. Jacob, R. Levi-Motalcini), Academic Press, San Diego, **2000**

[3] C. Kuhn, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 8620–8626.

[4] H. Kuhn, H.-D. Försterling, *Principles of Physical Chemistry. Understanding Molecules, Molecular Assemblies, Supramolecular Machines,* Wiley, New York,

2000; H. Kuhn, J. Waser in *Lock-and-key principle* (Ed.: J.-P. Behr), Wiley, New York, **1994**, p. 247 – 306; H. Kuhn, J. Waser in *Biophysics* (Eds.: W. Hoppe W. Lohmann, H. Markl, H. Ziegler), Springer, Berlin, **1983** p. 830 – 874; H. Kuhn, *Angew. Chem.* **1972**, *84*, 838 – 862; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 798 – 820; H. Kuhn, *Naturwissenschaften* **1976**, *63*, 68 – 80; H. Kuhn, J. Waser, *Angew. Chem.* **1981**, *93*, 495 – 515; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 500 – 520.

[5] L. E. Orgel, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 12503 – 12504.

[6] A. Eschenmoser, *Science* **1999**, *284*, 2118 – 2123; M. Bolli, R. Micura, A. Eschenmoser, *Chem. Biol.* **1997**, *4*, 309 – 320.

[7] A. Luther, R. Brandsch, G. von Kiedrowski, *Nature* **1998**, *396*, 245 – 248.

[8] For example, the first self-reproducing molecule can be a short strand similar to pyranosyl-RNA. In this case base pairing is more stable and selective than is the case with natural furanosyl-RNA.[6] This is of advantage for the start of evolution. Later, when a certain degree of complexity has been achieved that correct fitting together of the components is guaranteed, a more rapidly functioning machine built up from furanosyl-RNA would be more advantageous. But how could such a conversion come about? A genetic apparatus of a certain complexity based upon pyranosyl-RNA produces an enzyme which allows the formation of a furanosyl-RNA replica. This leads to a symbiosis until the furanosyl-RNA based system is no longer dependent upon pyranosyl-RNA system which then disappears.

[9] Darwin did not suppose, however, that his theory of the origin of the species is the way to approach the problem of the origin of life, as his famous picture of the start in a "warm little pond", which stimulated the later concept of an primeval soup, shows.

[10] M. Eigen, Naturwissenschaften **1971**, *58*, 465 – 523; I. Prigogine, D. Glansdorff, *Thermodynamic Theory of Structure, Stability and Fluctuations*, Wiley-Interscience, New York, **1971**.

[11] The frequenly posed question "what first, metabolism or genetic apparatus?" is not relevant in this context. In the given model (life beginning in a most partcular region where chains of reactions lead to a replicating system) the former case is assumed: metabolism present in the beginning, improved and developed during the evolution of the genetic apparatus by stepwise inclusion of enzymes.