Compartimentation in replicator models

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Abstract. Recently a model formed by self-replicative units with catalytic capabilities evolving in an extended system has been presented. It has been shown that under particular conditions this model exhibits spatial compartimentation without any kind of membrane. In the framework of ALife, we suggest that this model can allow a global growth in the complexity of those models based on the hypothesis of the so-called RNA-world. However, this increase has got a limit defined by the impossibility of expressing the informational potentialities into functional complexity when a unique type of entity is involved in the system.

1 Introduction

Theoretical biology faces the origin of life as a specific problem while Artificial Life (ALife) intends to solve the broader problem of how a living organization could become manifest (no matter where). The main theoretical biology goal is to follow the clues of the origin of a very specific Living Organization (LO), without asking about the generality of this organization or why these components and not others. Biology tries to explain, from the laws of physics and chemistry, the origin of an organization supported by complex molecular components (DNA, RNA, proteins, ...) and, as an intermediate step, the synthesis of these components from simpler forms of organization is investigated.

Most of the work done on the origin of life, in the frame of theoretical biology, is an attempt to explain what kind of process (and from what components) originated the most primitive forms of life (i.e. the terrestrial minimal life [1]) from which all the today's organisms have evolved. It is commonly accepted that in this terrestrial biogenesis there would exist contingent local facts that could differ from those (hypothetically) happening in other places. On the other hand, it is also reasonable to think that some of the processes that took place during the origin of life on the Earth are necessary and, therefore, universal. Then, which of these processes are local and which are universal?

From the ALife perspective the problem of the origin of life is addressed in a different way. It is intended to propose abstract models (that refer to unspecific components) that are able to produce more complex forms. The starting point for these models should be coherent with a set of properties that are always
present in molecular systems, and usually explained by physics and/or chemistry. But apart from this constraint, the biogenesis models in ALife do not restrict to natural kinds of components, in contrast with what happens in the framework of theoretical biology. In fact, the functionalism (predominant in ALife) defends the thesis of the radical separation between the idea of LO and the physical components supporting this organization [2]. Biologists, on the contrary, define the logic of the LO from a set of components that implicitly determine the organization. This has been forgotten in ALife even when the idea of LO is borrowed from theoretical biology. In addition, its claim on the material unspecificity of the primitive components would imply an enormous extension of the definition of LO, along with a change in the scale of the definition of the primitives. Likely, this is one of the most controversial points between biology and ALife. As a matter of fact, biology defines the LO assuming a higher degree of organization implicit in the primitive components. Certainly the situation is a bit different in the theory of the origin of life because in this field, what matter is to get a sequence of abstract and mutually connected stages, which allows the evolution towards progressively complex organizations.

Thus, if it is intended that the two aforementioned research programs converge, two related problems must be solved. On the one hand: what kind of component can support an abstract organization? On the other hand: how must the abstract models define the component characteristics in order to endow them with the capabilities of bringing about more complex organization forms? That is why the more capabilities for complexification the prebiotic ALife models have, the more specifications will have the components of such models for the origin of life.

In theoretical biology, many works and models on the origin of life deal with the so-called R.N.A.-world [3]. This is based on the evidence of combined template and catalytic actions in some RNA molecules [4],[5]. If we agree that evolution is the driving force in the origin of life, the main question to be answered is what are the selective and evolutive features of a population of molecular species under prebiotic conditions. The first theoretical attempt of studying this problem was carried out by M. Eigen two decades ago [6]. He translated the biological problem to a mathematical model, formulating the molecular evolution in terms of differential equations of the different species concentration. Although the model was conceived to deal with RNA-like molecules, it can, in principle, account for any kind of abstract entity holding the assumptions of the model. Eigen's model is based on three important features: two are individual characteristics: self-replication and fitness. The third one is the existence of a constraint imposed by the environment to the whole population.

Can R.N.A.-world based models be reformulated in abstract terms? What are the fundamental assumptions under which a theory of evolution should be developed? Since the original formulation appeared, a lot of work has tried to analyze and generalize this formulation. Following the original idea, we present here a model of a population of species that evolve in a formal world. Components of the system are assumed to be (by simplicity) self-replicative polymers evolving
in a medium where interactions occur by diffusion (e.g., an aqueous medium). We assume also that these polymers are endowed with a basic template capacity, and have got sequence-dependent catalytic capabilities (in accordance with the RNA-world hypothesis in which self-replication is not helped by external catalysts). If, in addition, we add other considerations about physico-chemical constraints, the number of different polymeric species that can be candidates for this kind of models decreases drastically. Therefore, the model we present here can be considered as an abstract RNA-like world.

In the following, we will comment the main characteristics of those models of populations formed by general self-replicative species, and we will suggest that diffusion can be the cause of spatial compartmentation. We will discuss also the implications of this compartmentation in the origin of life. We hope that this discussion may help to bridge the gap between biology, together with its standard works on the origin of life, and those that ALife has begun to develop.

2 Replicator models

Self-reproduction is an essential characteristics of the living beings. Without this capacity there is no way to maintain indefinitely the LO and, at the same time, explore new possibilities. Whereas reproduction involves the creation of a new organization, replication is referred to the process by which a structure (e.g., a molecule) is copied. Here we are concerned with the latter. In this context, self-replication is the process from which a given entity creates a new entity similar to the former one. Although the limits of this similarity are not totally specified, we will say that self-replication occurs when there is a way to relate the offspring with the original entity. Notice that following this definition self-replication is intrinsically error-prone, allowing the emergence of new entities and, therefore, evolution.

Every abstract entity that can replicate itself will be referred to as a replicator [7]. Obviously, many different entities satisfy this generic definition. It can be proven rigorously that the evolution laws of these systems are equivalent under some general conditions [8]. For instance, the temporal evolution of an ecosystem when rabbits and foxes coexist can be similar to the evolution of a population formed by RNA-like molecules evolving in a tank reactor if an error-free self-replication is assumed. The description of such replicator models depends on important aspects that decide the subsequent development of the theory. What are the basic characteristics of a model conceived to explain the temporal evolution of a population of formal replicators evolving in a hypothetic prebiotic scenario? Let us enumerate and comment the most relevant:

(i) The macroscopic observable must be described. Concentration is the macroscopic observable that is studied usually in chemical kinetics. That was also the variable M. Eigen uses in his original formulation [6]. Thus, generally, replicator models describe the temporal evolution of the concentration of every replicator in the system. If, as remarked in the previous section, replicators are thought to be polymeric chains built up from different types
of digits, the number of different replicators that could be present simultaneously in the system can be enormous (e.g., if the chain length is about 100, and the different types of digits are 4, as occurs in present day nucleic acids, this number is astronomical: $4^{100} \approx 10^{60}$). This characteristic, and the fact that the dimensionality of the system changes with time (appearance or extinction of a replicator) imposes serious limitations to the treatment of these models.

(ii) The physical mechanisms that take place during the process of self-replication. There is a great controversy about this point. On the one hand, we observe that the most simple way self-replication occurs in Nature is via a template. Hence, we will assume here that our abstract polymers self-replicate via a template: a particular component of the chain reacts preferably with another component (its complement). E.g., in current RNA, guanine (G) reacts with larger probability with citosine (C), and uracil (U) with timine (T). Notice that the reaction among not complementary pairs is also allowed. On the other hand, when we have relatively complex structures self-replication is a template process that involves catalytic action. However, the RNA-world hypothesis discards the existence of any kind of external catalyzer working during self-replication. The matter is that replication is a catalyzed process, but must be made without contribution of any external catalyzer, so it must be internal. The only way to solve this paradoxical situation seems to assume that replicators have got catalytic activity. Then, it is necessary that replicators play both template and catalytic role. The discovery of the catalytic activity of some current RNA, the so-called ribozymes [4], [5], has offered a plausible answer to this problem. In summary, self-replication must be necessarily carried out through the catalytic help of other replicators, giving rise to a catalytic network (see an example in figure 1).

(iii) The existence of some kind of restriction in the accessibility of the phase space, i.e., the macroscopic variables cannot get all the possible values. The influence of constraints on a population was pointed out by Darwin more than hundred years ago. Whereas in the absence of a restriction the total population increases indefinitely, any limitation in the sources yields necessarily to the selection of one or several types of replicators. Thus, any model about the origin of life should include some kind of restriction. There are several ways this selective process can be implemented [9]. For example, one possibility is to have a closed system in which only energy can be interchanged with the surroundings [10]. In this context, the total mass must be conserved and the only way to keep the system out of equilibrium is maintaining the affinity of the reactions different from zero by controlling the external flux of energy. As it will be discussed below, this can be done through the reaction of the regeneration of active or rich-energy monomers (the building blocks from which the replicators are built up). This is a characteristic endergonic process where inactive monomers are regenerated with a finite velocity using the external supply of energy, by means of any kind of primitive transduction process. For instance, Skulachev [11] has proposed a plausible mechanism for
a primitive use of UV radiation as a primary source of energy for monomer activation. Conclusions about the dynamics of catalytic networks evolving under this constraint have been obtained recently \[10, 12\].

(iv) *The particular boundary conditions under which the system is forced to evolve.* Related with the previous point is the problem of defining the boundary conditions of the system: the relation with the environment and the spatial geometry. For example, if, as stated before, a closed system is assumed, then there is no flux of matter through its borders. The choice of one or other topology depends on the nature of the problem (e.g., it can be assumed one, two, or three dimensional spaces, and considering periodic or non-periodic boundary conditions). The influence of boundary conditions on the system dynamics can be critical, i.e., slight environment disturbances can cause important changes in the system behavior. Although this point is considered of secondary importance in many studies, it could contain the explanation for relevant aspects of the theory of molecular evolution.

![Figure 1](image-url)  

**Figure 1.** Schematic example of catalytic network. Replicator $I_k$ ($k = 1, 2, 3, 4$) can react with the catalytic help of other replicators $I_j$ ($j \neq k$) to produce a copy similar to itself. In addition, replicators have got a lifetime. Then, they can degrade producing energy-poor monomers (process not shown in the figure).

According to these points, mathematical models have been developed within the framework of theoretical biology. From these models, the general behavior of catalytic networks has been extensively analysed during the last two decades and many relevant properties has been derived (see, for example, the recent study \[13\], and references therein).

In his pioneer work, Eigen and Schuster studied with special emphasis a particular network architecture, the *hypercycle*, in a continuous stirring tank reactor.
(i.e., a homogeneous medium) [14]. A hypercycle is a catalytic network formed by replicators that are cyclically linked. Contrary to what happens in populations of replicators without catalytic capabilities [15], hypercycles step toward diversity, allowing the coexistence of different replicators through cooperation. But, the strong selective properties of hypercycles prevent their later evolution and growth (by increasing the number of replicators involved in the organization). Moreover, it has been proved that highly membered hypercycles become very sensitive to fluctuations and they are eventually unstable [16].

Due to unspecificity, in a prebiotic scenario, general catalytic networks are certainly more realistic than hypercycles. However, they are also unstable. It can be proven that coexistence among all the replicators is favored when the catalytic interactions are symmetric and self-catalysis is not allowed [17]. If catalytic constants are different enough from each other, the state of coexistence of all the replicators involved in the network becomes unstable, and the system evolves towards a less membered network (maybe by losing more than one element). Therefore, any mutation that affects the catalytic efficiency of replicators can eventually destroy the network. This fact limits seriously the possibility of evolution of catalytic nets. The question then is how to solve the limitations of these models to increase the information content and therefore, explain more complex organizations?

3 The role of diffusion

There is an aspect, included in the previous assumptions, that must be more deeply taken into account. That is the diffusive forces acting on all the species present in the system. As it was previously stated, models based in the RNA-world hypothesis must consider populations of replicators evolving on an extended environment (that eventually could be inhomogeneous). Indeed, replicators are diluted in a liquid medium where, without any physical constraint, the diffusion through it is possible. Thus, in principle, diffusive forces should be considered in the study of evolving populations in prebiotic conditions. Nevertheless, many replicator models are analysed assuming that the population evolves in experimental devices with any kind of artificial mechanism of homogenization, e.g., the Continuous Stirring Tank Reactor (CSTR) models [9]. Therefore, the conclusions obtained from them (as those about catalytic networks remarked above) are only valid in the homogeneous limit.

Diffusion tends to homogenize the medium when acting on the replicators as a single force. Therefore, intuitively, one would say that systems under diffusion will approach asymptotically to a homogeneous state (and then, the diffusive terms could be removed from the theoretical description). However, in replicator models diffusion is coupled with a local reaction field, dependent on the replicator properties. Then, a direct question arises: is this coupling between local reactions and diffusion able to cause symmetry breaking and spatial pattern formation?

In his pioneer work, and much to the surprise of the scientific community, Turing proved that this coupling can bring about the formation of spatial structures
for a particular choice of the local field [18]. Since then, the analysis of many models describing physical and chemical systems has demonstrated that self-organization is not as an rare event as was thought several decades ago [19].

A similar reasoning might guide Boerlijst and Hogeweg [20] to discover that replicator models can suffer also self-organization when evolving in an extended system. Essentially, they showed that a local reaction based in self-replication coupled with diffusive forces can produce pattern formation. In particular, they studied a hypercycle formulated using cellular automata techniques, and they proved that diffusion induces the formation of spiral patterns. Perhaps, from an evolutive point of view, the main consequence is that under diffusion hypercycles are more resistant to parasites (i.e., any replicator which takes advantage of being a member of the network without favouring any of the network elements) (a recent discussion about that can be found in [21]). This fact revived the hypercycle organization as a relevant concept to evolutionary biology. However, the importance of their work on the rest of selective and evolutive features of replicator models has not been studied in its total extent.

Can other network architectures form spatial patterns? What kind of patterns? In the next section we will present a model that exhibit pattern formation. This patterns could be directly related with a compartmentmentation process during the origin of Life.

4 Clustering by diffusion

Chacón and Nuño have presented a model of a population of replicators evolving in a closed extended system [22]. The model is designed accordingly with a previously proposed theoretical scheme [10]. It addresses the temporal evolution of a population of replicators in a closed system. In agreement with the assumptions stated in section 2, the following reactions can take place:

\[
I_i + I_j + \mu^* \xrightarrow{k_{ij}} 2I_i + I_j \\
I_i \xrightarrow{\delta_i} \mu \\
\mu \xrightarrow{\gamma} \mu^*
\]

Each replicator \(I_i\), in the presence of the activated monomer \(\mu^*\), can self-replicate with the catalytic help of \(I_j\) with rate \(k_{ij}\) (1). Replicators can degrade producing inactivated monomers \(\mu\) with a rate \(\delta_i\), (2), and this byproduct can be recyclated in \(\mu^*\), with a rate \(\gamma\) (3).

Replicators and monomers are embedded in a medium, where they diffuse with diffusion coefficients \(D\) and \(d\), respectively. In a first approach, the probability of mutation is set to be zero. Reaction (3) maintains the system far from equilibrium by means of an endergonic reaction (for example, by taking energy from the environment).
According with the above reaction scheme, the time evolution of the species concentration is governed by the following system of partial differential equations:

\[
\dot{x}_i(r) = x_i(r)\left[a(r) \sum_{j=1}^{n} k_{ij} x_j(r) - b_i + \gamma x_i(r) + \delta_i\right] + D \nabla^2 x_i(r)
\]

\[
\dot{a}(r) = \gamma b(r) - [a(r) \sum_{j=1}^{n} k_{ji} x_i(r) x_j(r)] + d \nabla^2 a(r)
\]

\[
\dot{b}(r) = \sum_{i=1}^{n} \delta_i x_i(r) - \gamma b(r) + d \nabla^2 b(r)
\]

where \(x_i\), \(a\) and \(b\) are the concentrations of the replicators and activated and inactivated monomers, respectively. Clearly, the structure of the equations maintains the total concentration \(\sum_{i=1}^{n} x_i + a + b\) constant within the system.

Under particular conditions, system (4) presents inhomogeneous solutions that account for pattern formation [22]. But, contrary to the hypercycle model, the patterns are radically different. Instead of spirals, consequence of the cyclic coupling among the members of the network, symmetrical or almost symmetrical stationary clusters appear for a particular choice of the parameters. These clusters are regions with high concentration of the total amount of replicators and low concentration of their constituents (monomers) separated by areas highly populated by monomers. This pattern remains stable although monomers can move over the whole space. An example of these structures is shown in figure 2.

It is worthy to mention that, as occurs in hypercycle models, a minimum number of replicators (four) is needed for the system to exhibit pattern formation. Moreover, the network architecture and the catalytic weights have a high influence on the system dynamics: even for catalytic networks formed by four replicators only special choices of the catalytic constants allow pattern formation. This fact may be a consequence of the local dynamics: the formation of clusters seems to be possible only when the dynamics for the species concentrations is chaotic [28], [27]. Similar behavior has been reported in Coupled Map Lattice models [23].

5 Discussion

In the light of what has been said in the previous section, one is tempted to establish a straightforward relation between the formation of spatial clusters and the origin of a permanent compartmentation in the system. Nevertheless, the permanence of dissipative structures needs of a constant influx of energy into the system. In the previous model an energy contribution is required during the conversion of poor-energy monomers into rich-energy monomers. The mechanism is similar to that described by Sagan and Ponamperuma for the formation of ATP, CTP, GTP and UTP from inactivated monomers [24]. This process could
Figure 2. Snapshot of the total concentration of a four-membered catalytic network evolving in a bidimensional domain with non-flux boundary conditions. The diffusion coefficients are $D = 10^{-2}$ and $d = 1$. The matrix of catalytic constants is:

$$
\begin{pmatrix}
0.5 & 1.6 & 0 & 2.2 \\
1.5 & 0 & 2.0 & 0 \\
0.5 & 0 & 0.6 & 0.4 \\
0.1 & 0 & 0 & 0
\end{pmatrix}
$$

The values of the rest of the parameters are: $\delta_i = 0.1$ for $i = 1, 2, 3, 4$ and $\gamma = 1$. White represents areas with a high amount of replicators, whereas dark grey represents areas with low concentration. Notice that the system has not reached a stationary state (some of the clusters are still splitting to get a quasisymmetric disposition).

be thought as a first step for the fixing of a metabolism dedicated to create the activated units needed for self-replication of molecules. It is well known that present day cells take advantage of energy by means of a mechanism coupled with the membrane (during the process of transduction carried out by ATPases)[23], a so complex mechanism that is hard to imagine that it could appear during the prebiotic stage. However, it turns out even more risky to formulate the question about how it could go further, from these structures, towards the origin of a biological membrane.
The interest of this compartmentation process is that it presents some of the functional advantages of cellular systems, without requiring the relatively complex structure of a membrane. The appearance of a membrane in simple molecular systems is not a rare phenomenon. There are models for which the construction of the membrane in very simple systems is a result of the metabolic activity of the own system [26]. But for such very simple systems, their isolation means an obstacle for a possible increase in their complexity (since there is no information content inside the system). The main problem when considering the process of compartmentation with a membrane is that as the complexity of the encapsulated systems increases, the set of functional conditions that the membrane should fulfill increases too. Already, for relatively low-complexity systems, the functional requirements for the membrane to act as an interface unit are very high (mechanisms for selective permeability and transduction of energy). Accordingly, the origin of a membrane with these functional characteristics requires that the replicators could translate the information in specifying the construction of a sufficiently complex metabolic network. Hence, when a too simple system is enclosed within a membrane, it will not have any chance to evolve towards the complexity needed in a prebiotic scenario.

That is why the possibility of compartmentation without membrane is very interesting for molecular systems of an intermediate complexity. Contrary to other models that explain the emergence of heterogeneous structures that have not functional consequences for the system, the appearance of a compartmentation can play a casual role in the behavior of the whole system. Although this question might be investigated with some detail, our conjecture is that the compartmentation could have allowed the replicators to increase their informational content.

Let us comment briefly some consequences that spatial compartmentation could have on the subsequent evolution of population of replicators. The searching efficiency of a replicator model depends on the diversity of the system. Thus, during the process of evolution, having many different testing banks will increase the possibility of appearance of a useful combination. This can be solved in two different ways: (a) simultaneous coevolution of many networks in different spatial scenarios, without intercommunication; or (b) evolution of a single network that self-compartmentates in different patches within the same extended system. Both solutions (a) and (b) are not mutually exclusive, but (b) certainly looks more realistic and attractive since it allows both evolution and communication, being the latter an aspect that could become very important to generate higher order organization among sufficiently differentiated patches of the same system.

On the other hand, the selective features can be also altered, as the following example shows. Assume that each replicator develops a specific way of regenerating the rich-energy monomers. Thus, in a medium without compartimentation, all the members of the population would take advantage of a larger production of activated units developed by a particular replicator. On the contrary, if compartimentation takes place, and eventually one replicator is linked to a
metabolic activity greater than the average within a compartment, only those replicators belonging to this compartment will exploit this selective advantage, to the detriment of the rest of the population. Work along this line is currently in progress.

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