Model of self-replicating cell capable of self-maintenance.

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Abstract. We have constructed a simple model of a proto-cell that simulates stochastic dynamics of abstract chemicals on a two-dimensional lattice. We have assumed that chemicals catalyze their reproduction through interaction with each other, and that repulsion occurs between some chemicals. We have shown that chemicals organize themselves into a cell-like structure that maintains its membranes dynamically. Further, we have obtained cells that can divide themselves automatically into daughter cells.

1 Introduction

The emergence of cells is one of the major transitions in the evolution of life. When primitive self-replicators such as a hypercycle of RNA enzymes evolve into a living cell, they must acquire membranes that will separate them from their noisy environment. It is well known that a hypercycle system can easily be broken down by the occurrence of parasites. Compartmentalization of a hypercycle system is a simplest way to avoid the disaster [2] [14] [15]. At the same time, however, it should be noticed that it is also true that parasites can drive the increase of diversity and complexity of the replicator network [6]. In order to examine the balance between stable reproduction and diversity, we should study a relationship between an internal replication and a cellular structure which enclose it.

Many models of proto-cell structures have been proposed. For example, it is well known that long-chained fatty acids spontaneously form micelles or vesicles when submerged in water. Luisi and his group demonstrated experimentally the self-organization and self-reproduction of liposomes, and showed that such vesicles maintain self-replicating RNA within them [16]. Theoretical models for self-organization and self-reproduction of micelles are studied well [1] [13].

There is another essential feature of cells, that is, self-maintenance. Living cells metabolize and sustain their membrane by themselves, and the boundary of cells are defined by the membrane. This mutual dependence enables the co-evolution of internal chemical networks and the membranes. The coevolution between the two is presumed in the early stages of the cell evolution. With
With respect to this point, Gánti proposed a model for primitive life termed 'the chemoton’, which presents three indispensable functions of the proto-cell: it has a metabolic cycle for assimilation; it maintains its membrane; and it replicate its genetic information. Varela also insisted that the boundary of cells (i.e. the cell membrane) must be organized and maintained by the cell itself. He presented a model on a two-dimensional lattice of an autopoietic cell that can maintain its membrane.

Our purpose in the present study is to demonstrate how such primitive cells can emerge and evolve from a simple set of chemical network. A model of self-maintenance and self-replicating cells in one-dimensional space was proposed by the same author. In the model, we have shown that self-reproduction of the cellular structure emerges spontaneously and there are two distinct processes of replication showing potentially different heredities.

In this paper, we extend our previous model for application to two-dimensional cases and showing that this system has a potential for further evolution.

2 A stochastic particle model

We simulate a discrete space-time dynamics of chemicals in a two-dimensional space, where chemicals catalyze each other’s reactions. Each chemical is given as a particle with/without anisotropic shape that moves around on a triangular lattice. Particles demonstrate two basic motions: hopping to neighbouring sites and rotating at one site. In addition to this behavior, a particle can change its chemical qualities. The former is termed a mobile transition, the latter a chemical transition, and both are determined by the potential energy of the particle.

We assume that there is a repulsive force between some chemicals, thus the physical potential of a chemical $C$ at the site $x$ ($E_C(x)$) is computed by summing up the repulsion potential of all chemicals at the site $x$ and its six neighbouring sites. The mobile transition probability $P_{C}(x, x_0)$ from site $x$ to $x_0$ is computed from the difference in the potential magnitudes as

$$P_{C}(x, x_0) = R_{diff} f (E_C(x_0) - E_C(x)),$$

where $E_C(x)$ gives the potential energy of the particle $C$ at the site $x$. The diffusion parameter $R_{diff}$ is fixed for all particles.

The chemical transition probability $P_{C \rightarrow C'}(x)$ from the state $C$ to $C'$ at the site $x$ is given as

$$P_{C \rightarrow C'}(x) = R_{C \rightarrow C'}(x) f(G_{C'} - G_C + E_{C'}(x) - E_C(x)),$$

where $G_C$ represents the chemical potential of $C$. The reaction parameter $R_{C \rightarrow C'}(x)$ is controlled by a catalyst found on the site $x$. One constraint is given to the form of the function $f$ in order to satisfy the thermal equilibrium condition, as follows:

$$\frac{f(\Delta E)}{f(-\Delta E)} = e^{-\Delta E}$$
We define five different kinds of chemicals, $A; M; W; X$ and $Y$, in a system. Each particle can belong to any one of these chemicals. $W$ plays the role of abstract 'water', and cannot change into any other chemical. $X$ is the material with high chemical potential, though it is not an autocatalytic chemical. $A$ is a unique autocatalytic chemical in the system. Their reaction processes are,

$$A + A \leftrightarrow AA$$

and

$$X + AA \leftrightarrow A + AA.$$  

These chemical reactions only occur among particles that occupy the same site. The forward and backward reactions have an equal reaction parameter, which is given by the following formula:

$$R_{X \rightarrow A}(x) = R_{A \rightarrow X}(x) = B_{X \rightarrow A} + C_A A(x)^2,$$

where $A(x)$ denotes the number of $A$ on the site $x$. In the above equation, $B_{X \rightarrow A}$ and $C_A$ are the base rate and the catalysis coefficient, respectively. As a secondary process, $A$ produces $M$ as a co-product of the total reaction network.

$$X + AA \leftrightarrow M + AA.$$  

The reaction parameters are given by

$$R_{X \rightarrow M}(x) = R_{M \rightarrow X}(x) = B_{X \rightarrow M} + C_M A(x)^2.$$  

In addition to the above reactions, we introduce the natural decay of chemicals into $Y$ where $Y$ has the lowest chemical potential.

Consider that there is a source of material $X$ in this system so that the reaction parameters between $X$ and $Y$ break the pattern of symmetry, as

$$R_{X \rightarrow Y} = B_{X \rightarrow Y}$$

and

$$R_{Y \rightarrow X} = B_{X \rightarrow Y} + S_x$$

where $S_x$ denotes the strength of the source $X$.

We assume there is repulsive force between $M$ and other chemicals like oil in water. In the following simulations, we examine three different kinds of potentials on the chemical $M$. First, $M$ equally repels all the other chemicals around it. Second, $M$ has an anisotropic repulsion regardless of the kinds of chemicals. This feature will be described latter. Third, in addition to the anisotropic repulsion, the repulsion force also depends on the kinds of chemicals.

\footnote{Note that a number of chemicals can occupy each site. In this study, the average is one hundred.}
3 Simulation Results

3.1 Formation of Cells

First, we simulate the case where the repulsion force depends on neither the kinds of chemicals nor the form of \( M \). Starting from the homogeneous initial state which has rich amount of \( A \), a system can maintain replication of \( A \) and reproducing co-product \( M \). Chemicals \( A \) and \( M \) can aggregate to form Turing-like patterns. Figure 1.a shows an example of the pattern generated; the spots of \( M \) are formed among \( W \) and \( A \).

The second case, where the repulsion force depends on the orientation of \( M \) molecule gives different observation. Here \( M \) has an anisotropic potential, illustrated in Fig. 1.b. When these \( M \)'s are placed on a triangular lattice, the 'head' can be aligned in any of three directions (e.g. 0, \( \pi/3 \) and 2\( \pi/3 \)). We assume that it can change its direction stochastically, with the transition probability given by,

\[
P_{MM'}(x) = R_{\text{rot}} f(EM(x) - E'_{M}(x)),
\]

where \( M' \) denotes \( M \) which has another orientation.

Figure 1.b shows the repulsion potential generated by \( M \) for other chemicals \( A, W, X \) and \( Y \). The repulsion force from \( M \) becomes strongest when \( M \) and other chemicals are on the same site (indicated by black in Fig. 1.b). The repulsion is the second strongest at the front of or behind \( M \) (dark gray sites) and relatively weaker at the other four side-sites (light gray). We also assume there is repulsion between \( M \)'s when their directions are different. Thus, the \( M \) molecule tends to take the same direction as neighbouring \( M \)'s.

When \( M \) has this kind of anisotropic repulsive force, the clusters are organized differently than they are in the isotropic cases. The clusters of \( M \) become thin films that we simply name 'membrane' (see Fig. 1.c). The difference in the repulsion potential between front- and side-sites of \( M \) affects the thickness of membrane. Also, when the repulsion between \( M \) with different direction is stronger, the membranes tend to run straighter. These effects allow us to get membranes that have various degrees of flexibility.

When we start from a single 'cell', that is, a spot of \( A \) enveloped by membranes as shown Fig. 1.d, this structure can maintain itself stably because \( A \) within the cell keep reproducing themselves and sustain the membranes by supplying \( M \); simultaneously, the membranes keep \( A \) from diffusing outward. Note that this structure collapses when the membranes are broken (see Fig. 1.e). Chemical \( A \) cannot sustain reproduction because they leak away through the defect in the membrane. In the absence of a supply by \( A \), the membranes decay and disappear.

3.2 Cell division

Living cells are not closed systems. They must ingest nutrients and excrete wastes through their membranes. In this section, we study the case where \( M \) shows
selective repulsion depending on the kind of molecules. We assume that the repulsion between $M$ and two chemicals $X$ and $Y$ is much weaker than that of the other chemicals.

In this case, $X$ and $Y$ can permeate through the membranes at a rate proportional to the gradient of their density. Because there are more $X$ in the environment than on the inside of the cell, the cells can absorb the external chemical $X$ and grows gradually. When the cell reaches a certain size at which it has outgrown its stability, it begins to generate a new membrane inside. This finally divides the mother cell into daughter cells (see Fig. 2). These new cells repeat the process of growing and dividing. Sometimes a cell fails to sustain its membrane structure and dies, due to a shortage of materials or to interference from other cells.
We can change the flexibility of the membranes by altering the repulsion strength between $M$s. This has the result of varying the division dynamics of cells. Examples are presented in Fig. 3. A strong repulsion between $M$ results in the formation of stiff membranes, and the shape of cells becomes more regular (Fig. 3.a and 3.b). On the other hand, Fig. 3.c represents a cell with more flexible membranes, which form in the presence of low repulsion values for $M$. These cells divide themselves irregularly at some narrow part.

![Fig. 2. Snapshots of cell division. The cell grows by ingesting $X$. Next, the membrane grows inward. Finally, the mother cell divides into five daughter cells.](image)

### 4 Discussion

We have demonstrated the model of a self-maintaining cell. The cell has an internal autocatalytic cycle of chemicals, which maintains the membrane by itself and the membrane keeps the cell from collapse. We have also shown that the self-maintaining cell can replicate itself spontaneously; a transition is made from molecular reproduction to cellular reproduction.

In real life, the earliest membranes may have been simpler and rougher than the phospholipid membranes. The marigranule [5] represents an example of a
Fig. 3. The variations of the cell. The shapes of cells and their manner of division depend on the values of repulsion between $M$. Pictures (a) and (b) show cells with stiff membranes. Picture (c) shows cells with flexible membranes.

primitive cell. It has rough shell and can ingest amino acids from the environment. Though the materials of which marigranules consist are very elementary molecules, there is no linkage between the organization of shells and its internal dynamics. If such structure established a symbiotic relationship between its embedded chemical network and its membrane, the membranes could become the targets of the Darwinian selection and evolve into more complex structures.

In this study, we have shown that the cell divides in a different manner according to variation in the interaction strength between $M$s. It is also true that we can change some properties of biological membranes by varying their components. For example, unsaturated fatty acids components soften the membrane and cholesterols do the opposite.

Self-replicating spots in the two-dimensional reaction-diffusion system [12][8] have been well studied. However, the kinds of replicating pattern cannot be as diverse as the patterns generated by cells with membranes. The cellular membrane can function as a boundary condition to the internal chemical network, and conversely, the internal reactions determine the cell shape. In this sense, the chemical reactions within cell membranes can be richer than those without membranes. The compartmentalization of chemicals will allow cells to be regarded as units of evolution, because it maintains the identity of their contents during reproduction.

Koch previously discussed the division mechanisms of phospholipid vesicles by considering the property of mechanical energy [7]. Our model demonstrates an analogous dynamic division mechanism.

The evolution of selective permeability of the membrane must be considered in future studies. Cell membranes determine how cells communicate with the environment, including other cells. Cells selectively receive stimuli from the environment and from other cells, and respond to these stimuli. Our cell model provides several possible approaches by which to observe the formation and
evolution of membrane functions, and of how the interaction between cells is generated by each cell’s own internal dynamics.

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