

On Recursive Production and Evolvability of Cells: Catalytic Reaction Network Approach

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Abstract

To unveil the logic of cell from a level of chemical reaction dynamics, we need to clarify how ensemble of chemicals can autonomously produce the set of chemical, without assuming a specific external control mechanism. A cell consists of a huge number of chemical species that catalyze each other. Often the number of each molecule species is not so large, and accordingly the number fluctuations in each molecule species can be large. In the amidst of such diversity and large fluctuations, how can a cell make recursive production? On the other hand, a cell can change its state to evolve to a different type over a longer time span. How are reproduction and evolution compatible? We address these questions, based on several model studies with catalytic reaction network.

In the present survey paper, we first formulate basic questions on the recursiveness and evolvability of a cell, and then state the standpoint of our research to answer the questions, that is termed as 'constructive biology'. Based on this standpoint, we present general strategy of modeling a cell as a chemical reaction network.

At the first part we investigate of the origin of heredity in a cell, by noting that the molecules carrying heredity must be preserved well and control the behavior of a cell. We take a simplified model consisting of two mutually catalyzing molecule species, each of which has catalytically active and inactive types. One of the molecule species is synthesized slowly, and thus is a minority in population. Through the growth and division of this cell, it is shown to reach and remain in a state in which a active, minority molecules are preserved over generations, and control the cell behavior. This minority controlled state is achieved by preserving rare number fluctuations of molecules. The state gives rise to a selection pressure for mechanisms that ensure the transmission of the minority molecule. The minority molecule, thus, carries heredity, and is a candidate for "genetic information". Experimental confirmation of this minority control is also presented.

Next, a protocell model consisting of a large number mutually catalyzing molecule species is studied, in order to investigate how chemical compositions are transferred recursively under replication errors. Depending on the numbers of molecules and species in a cell, and the path rate in the reaction network, three phases are found: fast switching state without recursive production, recursive production, and itinerancy between the above two states. At a recursive production state chemicals are found to form intermingled hypercycle network that consists of core hypercycle and peripheral network that influence each other. How this intermingled network supports the recursive production, and how minority in the core hypercycle gives rise to a switch to other recursive states at the itinerancy phase are elucidated. Evolution of this hypercycle network is also studied, to show the approach to recursive production of cells and switch to more efficient reproduction states. Finally, statistics of the number distributions of each molecule species are studied, to show (i) power-law distribution of fast switching molecules (ii) suppression of fluctuation in the core-network molecule species and (iii) ubiquity of log-normal distribution for most other molecule species. The origin of these statistics are discussed, while suppression of the number fluctuations of a minority molecule that has high catalytic connections with others is clarified, that reinforces the minority control in the replication network.

(Key Words: Minority Control, Heredity, Origin of Life, Constructive Biology Hypercycle, Chemical Reaction Network, Log-normal Distribution, Self-reproduction, Evolution)

1 Basic Question for Recursive Production of a Cell as Reaction Dynamics of Catalytic Network

Question: A cell consists of several replicating molecules that mutually help the synthesis and keep some synchronization for replication. At least a membrane that partly separates a cell from the outside has to be synthesized, keeping some degree of synchronization with the replication of other internal chemicals. How is such recursive production maintained, while keeping diversity of chemicals? Furthermore this recursive production is not complete, and there appears a slow ‘mutational’ change over generations, which leads to evolution. How is evolvability compatible with recursive production?[1]

1.1 Q1: Origin of Heredity

In a cell, among many chemicals, only some chemicals (e.g., DNA) are regarded to carry genetic information. Why do only some specific molecules play the role to carry the genetic information? How has such separation of roles in molecules between genetic information and metabolism progressed? Is it a necessary course of a system with internal degrees and reproduction?

In a cell, however, a variety of chemicals form a complex reaction network to synthesize themselves. Then how such cell with a huge number of components and complex reaction network can sustain reproduction, keeping similar chemical compositions?

To consider this problem, we start from a simple prototype cell that consists of mutually catalyzing molecule species whose growth in number leads to division of the protocell[2]. In this protocell, the molecules that carry the genetic information are not initially specified. The first question we discuss here is how heredity to maintain production of the protocell emerges. Related with the question, we ask if there appears some specific molecules to carry information for heredity, to realize continual reproduction of such protocell. We note that in the present cells, it is generally believed that information is encoded in DNA, which controls the behavior of a cell.

Here, We do not necessarily take a “geno-centric” standpoint, in the sense that gene determines the course of a cell. In fact, even in these cells, proteins and DNA both influence their replication process each other. Still, it cannot be denied that there exists a difference between DNA and protein molecules with regards to the role as information carrier. In spite of this mutual dependence, why is DNA molecule usually regarded as the carrier of heredity? Is there any general rule that some specific molecules play the role of carrier of genetic information so that the recursive production of cells continues?

Now, the origin of genetic information in a replicating system is an important theoretical topic that should be studied, not necessarily as a property of certain molecules, but as a general property of replicating systems. To investigate this problem we need to clarify what “information” really means. In considering information, one often tends to be interested in how several messages are encoded on a molecule. In fact, a hetero-polymer such as DNA would be suited to encode many bits of information. One might point out that DNA molecules would be suited to encode many bits of information, and hence would be selected as an information carrier. Although this ‘combinatorial’ capacity of an information carrier is important, what we are interested here is a basic property that has to be satisfied prior to that, i.e., origin of just “1 bit” information.

As Shannon beautifully demonstrated, information means selection of one branch from several possibilities [3, 4]. Assume that there are two possibilities in an event, each of which can occur with the probability $1/2$. In this case, when one of these possibilities turns out to be true, then this choice of a branch is regarded to have 1 bit information. In this sense, if a specific

cell state is selected from several possible states, this selection process has information, and a molecule to control such process carries information.

Now, a molecule that carries the information is postulated to play the role to control for the choice of cellular state. Furthermore, to play the role to carry the information for heredity, the molecules must be transmitted to next generations relatively faithfully. These two features, i.e., control and preservation are nothing but the problem of heredity.

Let us reconsider what 'heredity' really means. The heredity causes a high correlation in phenotype between ancestor and offspring. Then, for a molecule to carry heredity, we identify the following two features as necessary.

(1) If this molecule is removed or replaced by a mutant, there is a strong influence on the behavior of the cell. We refer to this as the '**control property**'.

(2) Such molecules are preserved well over generations. The number of such molecules exhibits smaller fluctuations than that of other molecules, and their chemical structure (such as polymer sequence) is preserved over a long time span, even under potential changes by fluctuations through the synthesis of these molecules. We refer to this as the '**preservation property**'.

These two conditions are regarded as a fundamental condition for a molecule to establish the heredity. Now, the problem of 'information' at a minimal level, i.e., 1-bit information is nothing but the problem of the origin of heredity. As the origin of heredity, we study how a molecule starts to have the above two properties in a protocell. In other words, we study how 1-bit information starts to be encoded on a single molecule in a replicating cell system. After we answer this basic question, we will then discuss how a protocell with the heredity in the above sense attains incentive to evolve genetic information in today's sense.

To sum up, the first question we address here is restated as follows. Consider a protocell with mutually catalyzing molecules. Then, under what conditions, recursive production continues maintaining catalytic activities? How are recursiveness and diversity in chemicals compatible? How is evolvability of such protocells possible? To answer these questions, are molecules carrying heredity necessary? Under what conditions, does one molecule species begin to satisfy the conditions (1) and (2) so that the molecule carries heredity? We show, under rather general conditions in our model of mutually catalyzing system, that a symmetry breaking between the two kinds of molecules takes place, and through replication and selection, one kind of molecule comes to satisfy the conditions (1) and (2).

1.2 Q2: Recursiveness and Evolvability with Diverse Chemicals

In a cell, the total number of molecules is limited. If there are a huge number of chemical species that catalyze each other, the number of some molecules species may go to zero. Then molecules that are catalyzed by them no longer are synthesized. Then, other molecules that are catalyzed by them cannot be synthesized, either. In this manner, the chemical compositions may vary drastically, and the cell may lose reproduction activity.

Of course, a cell state is not constant, and a cell may not keep on dividing for ever. Still, a cell state is sustained to some degree to keep producing similar offspring cells. We call such condition for reproduction of cell as 'recursive production' or 'recursiveness'. The question we address here is if there are some conditions on distribution of chemicals or structure of reaction network for recursive production.

There are two directions of study. One is with regards to the static aspect of reaction network structure (e.g., topology). The other is the number distribution of chemical species and their dynamics. Of course, one needs to combine the two aspects to fully understand the condition for recursive production of a cell.

Currently there are much interest in the reaction network structure, For example, Jeong et

al.[5] studied the metabolic reaction network, without going into details of the topology. Write down all (known) metabolic reaction equations. Here, the rate of reactions is disregarded, and only if such reaction equation exists in a cell or not is concerned. Then compute how many times a specific molecule species appears in such reaction equations. If this number is large, the molecule species is related with many biochemical reactions. For example H_2O has a large number of connections, since in many reactions it appears either in the left hand or right hand side of the equation. ATP has a relatively high number of connections, too. From these data the histogram $P(n)$ is obtained, as the number of molecules species that appears n times in the equations. From the data, it is shown that $P(n)$ decays with some power of n as $n^{-\alpha}$ [5].

So far, the discussion is limited only to topological structure of the network. In the reaction network dynamics, the number of molecules are distributed. On each 'node' of the network, the abundance of the corresponding molecule species is assigned. Accordingly some path is 'thick' where such reactions occur frequently. Such abundance as well as their fluctuations and dynamics has to be investigated.

In a cell, the number of each molecule changes in time through reaction, and the number, on the average is increased for the cell replication. For this growth to progress effectively, some positive feedback process underlying the replication process should exist, which, then, may lead to amplification of the number fluctuations in molecules. With such large fluctuations and complexity in the reaction network, how is recursive production of cells sustained? Is there any universal statistics in the number distribution of molecules?

2 Brief Historical Survey

2.1 Eigen's Hypercycle

Of course, the problem raised in the last section has been addressed in the study on the origin of life, or origin of replicating system. Here we are not necessarily interested in 'what happened in past', but rather, we intend to unveil the universal logic of cell. Still, it is relevant to review the earlier studies.

To consider the origin of replication system, one needs to discuss how genetic information is faithfully transferred to the next generation. Mills et al.[6] set up an experiment of RNA replication, by using a solution of RNA and enzyme. In this experiment, some enzymes are supplied from outside, and in this sense it is not an autonomous replication system. Still, his group found that RNA molecules with proper sequences are reproduced under some error.

Following this experimental study of Spiegelman on replication of RNA, Eigen's group started theoretical study on the replication of molecules[7]. The replication process of polymer in biochemical reaction is generally carried out with the aid of enzymes. The enzyme is given by a polymer, while its catalytic activity strongly depends on its sequence. For most sequences of the polymers, the catalytic activity is very small, but few of them may have high catalytic activity. Depending on the sequence some polymer has a much higher catalytic activity, and the replication rate of polymers depends on the sequence. As a theoretical argument, consider replication of polymers whose replication rate depends on its sequence. Now, assume that a 'good' sequence has replication rate α times larger than its mutant with a substitution of a monomer from the original sequence. Here, the replication progresses under some error. Without fine machinery for error correction, this error is not negligible. Assume that in each replication process, a monomer is substituted by another monomer with the rate μ . Then the probability that a polymer consisting of N monomers can produce itself is given by $(1 - \mu)^N \approx \exp(-N\mu)$, assuming that μ is small.

Now, let us examine if the good polymer can continue replication, maintaining its sequence, so that the information of this sequence is transferred. The condition that the good sequence

dominates in populations in the ensemble of polymers is given by

$$N < \ln(\alpha)/\mu \tag{1}$$

Here, $\ln(\alpha)$ is typically $O(1)$, while the error rate in the replication of monomer is estimated to be around $0.01 \sim 0.1$, in usual polymer replication process. Then the above condition gives $N < 100$ or so. In other words, information using a polymer with a sequence longer than this threshold N is hardly be sustained. This problem was first posed by Eigen, and is called 'error catastrophe'[7]. On the other hand, information for the replication for a minimal life system must require much larger information. Of course, the error rate could be reduced once some machinery for faithful replication as in the present life emerges. However, such machinery requires much more information to be transmitted by the polymer.

Summing up: For replication to progress, catalysts are necessary, and information on a polymer to replicate itself must be preserved. However, error rate in replication must have been high at a primitive stage of life, and accordingly, it is recognized that the information to carry catalytic activity will be lost within few generations. In other words, faithful replication system requires larger information, while a larger information requires faithful replication system. Thus there appears catch-22 type paradox.

To resolve this problem of inevitable loss of catalytic activities through replication errors, Eigen and Schuster proposed hypercycle[7], where replicating chemicals catalyze each other forming a cycle, as "A catalyzes the synthesis of B, B catalyzes the synthesis of C, C catalyzes the synthesis of A". In this case, each chemical mutually amplifies the synthesis of the corresponding chemical species in this cycle. There occurs a variety of mutations to each species, but this mutant is not generally catalyzed in some other species in the cycle. Then, such mutant is not be catalyzed by C. This is also understood by writing out the rate equation for the increase of the population. In this hypercycle the population increase is given by the product of the populations of molecules such as $N_A \times N_B$, $N_B \times N_C$, $N_C \times N_A$, while the growth of the population of the mutants is linear to each population N_A , N_B , N_C . In the previous estimate for error cascade, the good and mutant sequences increase both linearly to the number. Then the the number of variety of mutants dominates. In the present case, once the populations of the good sequence in the hypercycle is dominated, they can sustain the population, against possible emergence of mutants. With this hypercycle, the original problem of error accumulation is avoided.

Since the proposal of hypercycle, population dynamics of molecules for such catalytic networks have been developed. However, the hypercycle itself turned out to be weak against parasitic molecules, i.e., those which replicate, catalyzed by a molecule in the cycle, but do not catalyze those in the cycle. In contrast to the previous mutant, the growth rate of the population of these molecules is again the product of the populations of two species, and such parasitic molecules can invade.

Although the hypercycle itself may be weak against parasitic molecules, i.e., those which are catalyzed but do not catalyze others, it is then discussed that compartmentalization by a cell structure may suppress the invasion of parasitic molecules, or that the reaction-diffusion system at spatially extended system resolves this parasite problem[8]. As chemistry of lipid, it is not so surprising that a compartment structure is formed. Still, as the origin of life, this means that more complexity and diversity in chemicals are required other than a set of information carrying molecules (e.g., RNA).

2.2 Dyson's Loose Reproduction System

If initially there is a variety of chemicals that form a complex network of mutual catalyzation, this system may be robust against the invasion of parasitic molecules. Such idea resembles stability of ecosystem, where complex network of several species may resist to invasion of external species.

Hence we need to study if replication of complex reaction network can be sustained. In this case, from the beginning, there are many molecule species that mutually catalyze, allowing for the existence of many parasitic molecules. Here, complete replication of the system is probably difficult. Then the question we have to address is if such complex network can maintain molecules that catalyze the synthesis of the network species. This question was addressed by Dyson[9], as a possibility of loose reproduction system.

Dyson, noting the experiment of Oparin on the formation of cell-like structure, considered a collection of molecules with proteins and others. These molecules cannot replicate themselves like DNA or RNA. They, on the other hand, can have enzyme activities, and catalyze the synthesis of other molecules albeit not faithful reproduction they may be. Still, they may keep similar compositions. Although accurate replication of such variety of chemicals is not possible, chemicals, as a set, may continue reproducing themselves loosely, while keeping catalytic activity. Indeed, the accurate replication must be difficult at the early stage of life, but loose reproduction could be easier. However, if this collection of molecules can keep catalytic activity through reproduction is not evident.

Dyson obtained a condition for the sustainment of catalytic activities in these collection of molecules, by taking an abstract model. For simplicity he classified molecules into two states depending on if they have catalytic activity or not. Furthermore, he assumed that the ratio of the synthesis of catalytic molecules is amplified as the fraction of catalytic molecules is larger, i.e., a positive feedback process is assumed. This model is mapped to a kind of Ising model. With the aid of mean-field analysis in statistical physics, he showed that the catalytic activities can be sustained depending on the number of molecules and their species. Although his model is abstract, the result he obtained probably can be applied to any system with a set of catalytic molecules, be it protein, lipids, or other polymers.

It is important to study if such loose reproduction as a set is possible in a mutually catalytic reaction network (also see e.g.[10, 11]). If this is possible, and if these chemicals also include molecules forming a membrane for compartmentalization, reproduction of a primitive cell will become possible. In fact, from chemical nature of lipid molecules, it is not so surprising that a compartment structure is formed.

Still, in this reproduction system, any particular molecules carrying information for reproduction do not exist, in contrast to the present cell which has specific molecules (DNA) for it. As for a transition from early loose reproduction to later accurate replication with genetic information, Dyson did not give an explicit answer. He only referred to 'genetic take-over' that was originally proposed by Cairns-Smith[12], who discussed that a precise replication system by nucleic acids took over the original loose reproduction system by clay. Indeed, Dyson wrote that his idea is based on 'Cairns-Smith theory minus clay'. However, the logic for this "take over" is not unveiled.

Considering these theoretical studies so far, it is important to study how recursive production of a cell is possible, with the appearance of some molecules to play a specific role for heredity.

3 Constructive Biology

3.1 Standpoint of constructive biology

Before describing our theoretical model and explaining the numerical results, it is relevant to briefly summarize our basic standpoint in the study of biology, termed as "constructive biology" [1, 13]¹. Here we are interested not in details of specific biological function but in universal features of a biological system. Accordingly we need to study some features that are not influenced by the details of complicated biological processes. The present organisms, however,

¹ One can skip this subsection, if one is not much interested in general standpoint in the study of biology.

include detailed elaborated processes that are captured through the history of evolution. Then, for our purpose, it is desirable to set up a minimal biological system, to understand universal logic that organisms necessarily should obey. Hence, the approach that should be taken will be 'constructive' in nature. This constructive approach is carried out both experimentally and theoretically.

Our 'constructive biology' consists of the following steps of studies. (i) construct a model system by combining procedures; (ii) clarify universal class of phenomena through the constructed model(s); (iii) reveal the universal logic underlying the class of phenomena and extract logic that the life process should obey; (iv) provide a new look at data on the present organisms from our discovered logic.

There are three levels, to perform these steps: (1)gedanken experiment (logic) (2)computer model, and (3)real experiment. The first one is theoretical study, revealing a logic underlying universal features in life processes, essential to understand the logic of 'what is life'.

Still, life system has a complex relationship among many parts, which constitute the characteristic feature as a whole, which then influences the process of each part. We have not gained sufficient theoretical intuition to such complex system. Then it is also relevant to make computer experiments and heuristically find some logic that cannot be easily reached by logical reasoning only. This is the second approach mentioned above, i.e., construction of artificial world in a computer. Here we combine well-defined simple procedures, to extract a general logic therein [2, 14, 15, 16, 17].

Still, in a system with potentially huge degrees of freedom like life, the construction in a computer may miss some essential factors. Hence, we need the third experimental approach, i.e., construction in a laboratory. In this case again, one constructs a possible biology world in laboratory, by combining several procedures. For example, this experimental constructive biology has been pursued by Yomo and his collaborators (see e.g., [18, 19, 20, 21] at the levels of biochemical reaction, cell, and ensembles of cells.)

Taking this standpoint of constructive biology, we have been working problems listed in the table both theoretically and experimentally. The first two items in the table are related with the construction of a replicating system with compartment, raised in the questions in §1. Of course, this problem is essential to consider the origin of a cellular life. However, we do not intend to reproduce what has occurred in the earth. We do not try to guess the environmental condition of the past earth. Rather we try to construct such replication system from complex reaction network under a condition preset up by us. For example, by constructing a protocell, in the present paper, we ask the condition for the heredity, or universal features of the reaction dynamics to support the recursive production of cells.

The third to sixth items are related with the construction of multicellular organisms with developmental process. When cells are aggregated, they start to form differentiation of roles, and then from a single cell, robust developmental process to form organized structure of differentiated cells is generated. This developmental process to form a cell aggregate is transferred to the next generation. An experimental construction of multi-cellular organisms (with cell differentiation) from bacteria is one target. Here again, we do not try to imitate the process of the present multi-cellular organisms. For example, by putting bacteria cells into some artificial condition, we study if the cells can differentiate into distinct types or form some robust distribution of cells. Also, in-vitro construction of morphogenesis from undifferentiated cells has been possible by putting cells into some given conditions[22]. With these studies, we can establish a viewpoint of universal dynamics underlying development rather than the conventional picture as finely tuned-up process for it[15, 16].

The seventh item is construction of evolution, in particular speciation process, that is how a species splits into two distinct groups different both in phenotype and genotype[17].

To carry out this plan experimentally we need a system to design a life system controlled as

we like. Such controlled experiments are now possible by recent advances in technology, such as flow-cytometry, imaging techniques, microarray to measure gene expressions, while advances in nanotechnology provide a powerful tool in constructing a system to regulate and observe behaviors of a single cell or multiple cells, in a well controlled situation.

Here this construction is interesting by itself, but our goal is not the construction itself. Rather we try to extract general features that a life system should satisfy, and set up general questions. For example, as posed in §1, we set up a question if there are some ‘information molecules’ that control the replication system. Then we answer the question by setting up a theory. For each item, we set up general questions, and make model simulations, and set up a general theory to answer the question. This theoretical part is carried out in tight collaboration with the experiment.

Table I: examples of constructive biology under current investigation:

construction of	experiment	theory	question to be addressed
replicating system	in-vitro replicating system with several enzymes	minority control	origin of information
cell system	replicating liposome with internal reaction network	dynamic bottleneck in autocatalytic reaction system	evolvability and recursiveness for growth
multicellular system	interaction-induced differentiation of an ensemble of cells	isologous diversification in inter-intra dynamics	robustness in development
developmental process (I)	controlled differentiation from undifferentiated cells	emergence of differentiation rule	irreversibility in development
developmental process (II)	activin-controlled construction of tissues formation	self-consistency between pattern and dynamics	origin of positional information
generation	germ-line segregation from ensemble of cells	higher-level recursiveness	origin of recursive individuality
evolution	interaction-dependent evolution of E Coli	symbiotic sympatric speciation	genetic fixation of phenotypic differentiation

To close this subsection, we give a brief remark on the study of the so called Artificial Life (AL). Indeed, our approach may have something in common with AL[23]. In the AL study people intended to construct life-as-it-could-be, not restricted to the present organisms. Originally, in the study of AL, they have been interested in logic of life that all possible biological system should obey, be it on this earth or in other conditions in the universe.

Indeed, there are some important studies on the origin of replicating structure from the side of computation (e.g., [24]). However, the conventional AL study often tended to imitate life, and could not propose basic concepts to understand ‘what is life’. Also, the conventional AL study was often biased into the study in a computer. It often assumes a combination of logical processes with manipulation of symbols like the study of artificial intelligence.

Our approach is distinct from the conventional artificial life study in the two points. First, we do not take such symbol-based approach, but rather we use dynamical systems approach. Second, tight collaboration between experiment and theory is essential. Note, however, this collaboration is not of the type to ‘fit the data’ by some theoretical expression, but rather at a conceptual level. We will see an example of such collaboration in §4.

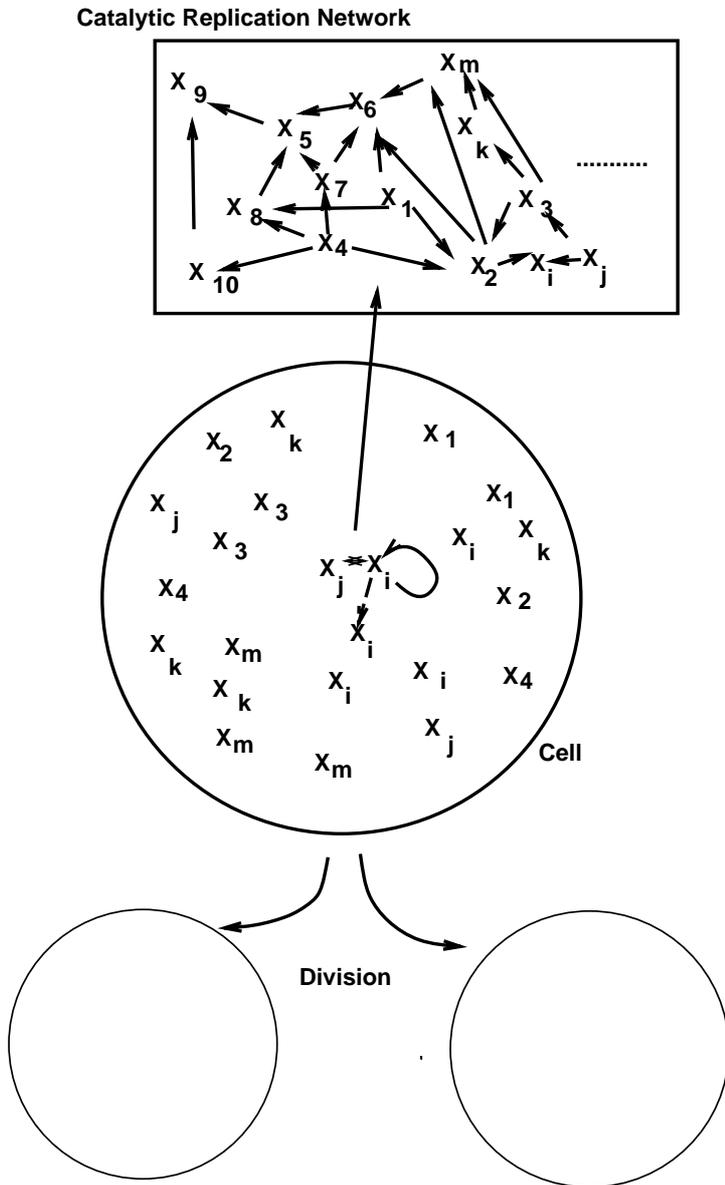


Figure 1: Schematic representation of our modeling strategy of a cell

3.2 Modeling strategy for the chemical reaction networks

Now, we discuss a standpoint in modeling cell, based on the standpoint of the last section. Then, what type of a model is best suited for a cell to answer the question in §1? With all the current biochemical knowledge, we can say that one could write down several types of intended models. Due to the complexity of a cell, there is a tendency of building a complicated model in trying to capture the essence of a cell. However, doing so only makes one difficult to extract new concepts, although simulation of the model may produce similar phenomena as those in living cells. Therefore, to avoid such failures, it may be more appropriate to start with a simple model that encompasses only the essential factors of living cells. Simple models may not produce all the observed natural phenomena, but are comprehensive enough to bring us new thoughts on the course of events taken in nature.

In setting up a theoretical model here, we do not put many conditions to imitate the life process. Rather we impose the postulates as minimum as possible, and study universal properties

in such system. For example, as a minimal condition for a cell, we consider a system consisting of chemicals separated by a membrane. The chemicals are synthesized through catalytic reactions, and accordingly the amount of chemicals increases, including the membrane component. As the volume of this system is larger, the surface tension for the membrane can no longer sustain the system, and it will divide. After the division of this protocell systems, they should interact with each other, since they share resource chemicals. Under such minimum setup as will be discussed later, we study the condition for the recursive growth of a cell, as well as differentiation of the cell.

Let us start from simple argument for a biochemical process that a cell that grows must at least satisfy. In a cell, there are a huge number of chemicals that catalyze each other and form a complex network. These molecules are spatially arranged in a cell, and in some problems such spatial arrangement is very important, while for some others, the discussion on just the composition of chemicals in a cell is sufficient to determine a state of a cell. Hence, for the starting point we disregard the spatial structure within a cell, and consider just the composition of chemicals in a cell. Hence, if there are k chemical species in a cell, the cell state is characterized by the number of molecules of each species as N_1, N_2, \dots, N_k . These molecules change their number through reaction among these molecules. Since most reactions are catalyzed by some other molecules, the reaction dynamics consist of a catalytic reaction network.

Through membrane, some chemicals may flow in, which are successively transformed to other chemicals through this catalytic reaction network. For a cell to grow recursively, a set of chemicals has to be synthesized for the next generation. As the number of molecules is large enough, the membrane is no longer sustained, even just due to the constraint of surface tension. Then, when the number of molecules is larger than some value, it is expected to divided. Hence, the basic picture for a simple toy cell we take is given as in Fig.1.

Of course, it is impossible to include all possible chemicals in a model. As our constructive biology is aimed at neither making complicated realistic model for a cell, nor imitating specific cellular function, we set up a minimal model with reaction network, to answer the questions raised in §1. Now, there are several levels for the modeling depending on what question we try to answer.

(0) By taking reversible two-body reactions, including all levels of reactions, ranging from metabolites, proteins, nucleic acids, and so forth. For example, to answer the general question, how non-equilibrium condition is sustained in a cell, such level of model is desirable[25].

(1) Assuming that some reaction process are fast, they can be adiabatically eliminated. Also, most of fast reversible reactions can be eliminated by assuming that they are already balanced. Then we need to discuss only the concentration (number) of molecules species, that change relatively slowly. For example by assuming that enzyme is synthesized and decomposed fast, the concentrations can be eliminated, to give catalytic reaction network dynamics consisting of the reactions with



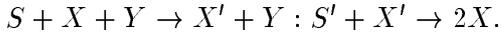
where X_j catalyzes the reaction[15, 26]. If the catalysis progresses through several steps, this process is replace by



leading to higher order catalysis[16].

For a cell to grow, some resource chemicals must be supplied through membrane. Through the above catalytic reaction network, the resource chemicals are transformed to others, and as a result, cell grows. Indeed, this class of model is adopted to study the condition for cell growth, to unveil universal statistics for such cells, and also as a model for cell differentiation.

(2) Model focusing on the dynamics of replicating units (e.g.. Hypercycle): For a cell to grow effectively, there should be some positive feedback process to amplify the number of each molecule species. Such positive feedback process leads to autocatalytic process to synthesize each molecule species. For reproduction of a cell, (almost) all molecule species are somehow synthesized. Then, it would be possible to take a replication reaction from the beginning as a model. For example, consider a reaction



Then as a total, the reaction is represented as

$S + S' + X + Y \rightarrow 2X + Y$. Assuming the resources S and S' are constantly supplied, we can consider the replication reaction



catalyzed by Y . At this level, we can take a unit of replicator, and consider a replication reaction network. This model was first discussed in the hypercycle by Eigen and Schuster discussed in §2.1.

(3) coarse-grained (phenomenological) level: Some other reduced model is adopted for the study of gene expression or signal transduction network. The modeling at this level is relevant to understand specific function of a cell.

In the present paper we mainly use the modeling of the level (2). This class of model can be obtained by reducing from the level-(1) model, by restricting our interest only to take into account of replicating units. In this sense, the model is a bit simpler than the level-(1) model. On the other hand, it may not be suitable to discuss the condition for cell growth, since at the level-(2) model, the supply of resource chemicals is automatically assumed, and one cannot discuss how transported chemicals are transformed into others. In the present paper, we briefly refer to the level-(1) model only at the end of §5.4, to demonstrate the universality of our result, but for details, see the original papers [15, 26] on the level-(1) modeling .

To sum up, we envision a (proto)cell containing molecules. With a supply of chemicals available to the cell, these molecules replicate through catalytic reactions, so that their numbers within a cell increase. When the total number of molecules exceeds a given threshold, the cell divides into two, with each daughter cell inheriting half of the molecules of the mother, chosen randomly. Regarding the choice of chemical species and the reaction, we discuss later for specific models. (see Fig.1 for schematic representation).

4 Minority Control Hypothesis for the Origin of Genetic Information

In the present section we propose an answer to the question raised in §1.1, by taking a simple model of a cell with replicating molecules, and proposing a novel concept on minority control, and providing corresponding experimental results.

4.1 Model

As discussed in §3.2, we start from consideration of a prototype of cell, consisting of molecules that catalyze each other. As the reaction progresses, the number of molecules in this protocell will increase. Then, this cell will be divided, when its volume (the total number of molecules) is beyond some threshold. Then the molecules split into two ‘daughter cells’. Then our question in §1 is restated as follows: How are the chemical compositions transferred to the offspring cells? Do some specific molecules start to carry heredity in the sense of control and preservation, so that the reproduction continues?

Before considering the specific model, it may be relevant to recall the difference of roles between DNA (or RNA) and protein. According to the present understanding of molecular biology[27], changes undergone by DNA molecules are believed to exercise stronger influences on the behavior of cells than other chemicals. Also, a DNA molecule is transferred to offspring cells relatively accurately, compared with other constituents of the cell. Hence a DNA molecule satisfies (at least) the "preservation" and "control" properties (1) and (2) in §1.1.

In addition, a DNA molecule is stable, and the time scale for the change of DNA, e.g., its replication process as well as its decomposition process, is much slower. Because of this relatively slow replication, the number of DNA molecules is smaller than the number of protein molecules. At each generation of cells, single replication of each DNA molecule typically occurs, while other molecules undergo more replications (and decompositions).

With these natures of DNA in mind, while without assuming the detailed biochemical properties of DNA, we seek a general condition for the differentiation of the roles of molecules in a cell and study the origin of the control and preservation of some specific molecules.

Now, we consider a very simple protocell system[2], consisting of two species of replicating molecules that catalyze each other (see Fig.2). assuming that only two kinds of molecules X and Y exist in this protocell, and they catalyze each other for the synthesis of the molecules.



Here, this "catalytic reaction" is not necessarily a single reaction. In general there can be several intermediate processes for each "reaction". The model simply states that there are two molecules that help the synthesis of the other, directly or indirectly. In general, the catalytic activities as well as the synthesis speeds differ by types of molecules. Without losing generality one can assume that X is synthesized faster than Y .

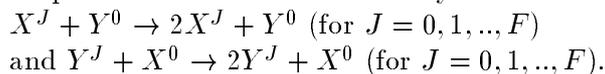
With this synthesis of molecules, the total number of molecules in the protocell will increase, until it divides into two. As long as the molecules catalyze each other, this synthesis continues, as well as the division (reproduction) of protocell. However, some structural changes in molecules can occur through replication ('replication error'). These structural changes in each kind of molecules may result in the loss of catalytic activity. Indeed, the molecules with catalytic activity are not so common. On the other hand, molecules without catalytic activity can grow their number, if they are catalyzed by other catalytic molecules. Then, as discussed in §2.1, the maintenance of reproduction is not so easy.

Following the above discussion, we consider the following model, as a first step in answering the question posed §1.1[2].

(i) There are two species of molecules, X and Y , which are mutually catalyzing.

(ii) For each species, there are active and inactive ("I") types. Considering that the active molecule type is rather rare. There are F types of inactive molecules per active type. For most simulations, we consider the case in which there is only one type of active molecules for each species.

Active types are denoted as X^0 and Y^0 , while there are inactive types X^I and Y^I with $I = 1, 2, \dots, F$. The active type has the ability to catalyze the replication of both types of the other species of molecules. The catalytic reactions for replication are assumed to take the form



(iii) The rates of synthesis (or catalytic activity) of the molecules X and Y differ. We stipulate that the rate of the above replication process for Y , γ_y , is much smaller than that for X , γ_x . This difference in the rates may also be caused by a difference in catalytic activities between the two molecule species.

(iv) In the replication process, there may occur structural changes that alter the activity of molecules. Therefore the type (active or inactive) of a daughter molecule can differ from that of

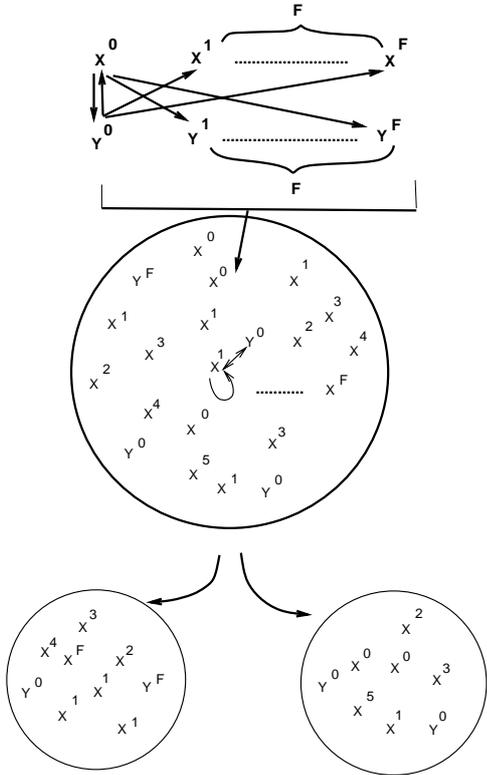


Figure 2: Schematic representation of our model

the mother. The rate of such structural change is given by μ , which is not necessarily small, due to thermodynamic fluctuations. This change can consist of the alternation of a sequence in a polymer or other conformational change, and may be regarded as replication ‘error’. Note that the probability for the loss of activity is F times greater than for its gain, since there are F times more types of inactive molecules than active molecules. Hence, there are processes described by

$$\begin{aligned}
 & X^I \rightarrow X^0; \text{ and } Y^I \rightarrow Y^0 \text{ (with rate } \mu) \\
 & X^0 \rightarrow X^I; \text{ and } Y^0 \rightarrow Y^I \text{ (with rate } \mu \text{ for each),} \\
 & \text{resulting from structural change.}
 \end{aligned}$$

(v) When the total number of molecules in a protocell exceeds a given value $2N$, it divides into two, and the chemicals therein are distributed into the two daughter cells randomly, with N molecules going to each. Subsequently, the total number of molecules in each daughter cell increases from N to $2N$, at which point these divide.

(vii) To include competition, we assume that there is a constant total number M_{tot} of protocells, so that one protocell, randomly chosen, is removed whenever a (different) protocell divides into two.

With the above described process, we have basically four sets of parameters: the ratio of synthesis rates γ_y/γ_x , the error rate μ , the fraction of active molecules $1/F$, and the number of molecules N . (The number M_{tot} is not important, as long as it is not too small).

We carried out simulation of this model, according to the following procedure. First, a pair of molecules is chosen randomly. If these molecules are of different species, then if the X molecule is active, a new Y molecule is produced with the probability γ_y , and if the Y molecule is active, a new X molecule is produced with the probability γ_x . Such replications occur with the error rates given above. All the simulations were thus carried out stochastically, in this manner.

We consider a stochastic model rather than the corresponding rate equation, which is valid for large N , since we are interested in the case with relatively small N . This follows from the

fact that in a cell, often the number of molecules of a given species is not large, and thus the continuum limit implied in the rate equation approach is not necessarily justified [28].

Furthermore, it has recently been found that the discrete nature of a molecule population leads to qualitatively different behavior than in the continuum case in a simple autocatalytic reaction network [29]. In a simple autocatalytic reaction system with a small number of molecules, a novel steady state is found when the number of molecules is small, that is not described by a continuum rate equation of chemical concentrations. This novel state is first found by stochastic particle simulations. The mechanism is now understood in terms of fluctuation and discreteness in molecular numbers. Indeed, some state with extinction of specific molecule species shows a qualitatively different behavior from that with very low concentration of the molecule. This difference leads to a transition to a novel state, termed as discreteness-induced-transition. This phase transition appears by decreasing the system size or flow to the system, and is analyzed from the stochastic process, where a single-molecule switch changes the distributions of molecules drastically.

In [29], given are examples in which a discreteness in molecule number leads to a novel phase that is not observed from a continuous rate equation of chemical reaction. In a cell, since the number of some molecules species is very small, we need to seriously consider the possibility that the discreteness in molecule numbers may lead to a novel behavior distinct from the continuum description.

4.2 Result

If N is very large, the above described stochastic model can be replaced by a continuous model given by the rate equation. Let us represent the total number of inactive molecules for each of X and Y as

$$N_x^I = \sum_{j=1}^F N_x^j; N_y^I = \sum_{j=1}^F N_y^j$$

Then the growth dynamics of the number of molecules N_x^J and N_y^J is described by the rate equations, using the total number of molecules N^t ,

$$dN_x^j/dt = \gamma_x N_x^j N_y^0 / N^t; dN_y^j/dt = \gamma_y N_x^0 N_y^j / N^t. \quad (6)$$

From these equations, under repeated divisions, it is expected that the relations $\frac{N_x^0}{N_y^0} = \frac{\gamma_x}{\gamma_y}$, $\frac{N_x^0}{N_x^I} = \frac{1}{F}$, and $\frac{N_y^0}{N_y^I} = \frac{1}{F}$ are eventually satisfied. Indeed, even with our stochastic simulation, this number distribution is approached as N is increased.

However, when N is small, and with the selection process, there appears a significant deviation from the above distribution[2]. In Fig.3, we have plotted the average numbers $\langle N_x^0 \rangle$, $\langle N_x^I \rangle$, $\langle N_y^0 \rangle$, and $\langle N_y^I \rangle$. Here, each molecule number is computed for a cell just prior to the division, when the total number of molecules is $2N$, while the average $\langle \dots \rangle$ is taken over all cells that divided throughout the simulation. (Accordingly, a cell removed without division does not contribute to the average). As shown in the figure, there appears a state satisfying $\langle N_y^0 \rangle \approx 2 - 10$, $\langle N_y^I \rangle \approx 0$. Since $F \gg 1$, such a state with $\frac{\langle N_y^0 \rangle}{\langle N_y^I \rangle} > 1$ is not expected from the rate equation (6). Indeed, for the X - species, the number of inactive molecules is much larger than the number of active ones. Hence, we have found a novel state that can be realized due to the smallness of the number of molecules and the selection process.

For the dependence of $\{ \langle N_x^0 \rangle, \langle N_x^I \rangle, \langle N_y^0 \rangle, \langle N_y^I \rangle \}$ on these parameters, see also figures of the paper of [2]. From these numerical results, it is shown that the above mentioned state with $\langle N_y^0 \rangle \approx 2 - 10$, $\langle N_y^I \rangle < 1$ is reached and sustained when γ_y/γ_x is small and F is sufficiently large. In fact, for most dividing cells, N_y^I is exactly 0, while there appear a few cells with $N_y^I > 1$ from time to time. It should be noted that the state with almost no inactive Y molecules appears

in the case of larger F , i.e., in the case of a larger possible variety of inactive molecules. This suppression of Y^I for large F contrasts with the behavior found in the continuum limit (the rate equation). In Fig.4, we have plotted $\frac{\langle N_y^0 \rangle}{\langle N_y^I \rangle}$ as a function of F . Up to some value of F , the proportion of active Y molecules decreases, in agreement with the naive expectation provided by Eq. (6), but this proportion increases with further increase of F , in the case that γ_y/γ_x is small ($\lesssim .02$) and N is small.

This behavior of the molecular populations can be understood from the viewpoint of selection: In a system with mutual catalysis, both X^0 and Y^0 are necessary for the replication of protocells to continue. The number of Y molecules is rather small, since their synthesis speed is much slower than that of X molecules. Indeed, the fixed point distribution given by the continuum limit equations possesses a rather small N_y^0 . However, in a system with mutual catalysis, both X^0 and Y^0 must be present for replication of protocells to continue. Note, for the replication of X molecules to continue, at least a single active Y molecule is necessary. Hence, if N_y^0 vanishes, only the replication of inactive Y molecules occurs, and divisions from this cell cannot proceed indefinitely, because the number of X^0 molecules is cut in half at each division. Furthermore, a cell with $N_y^0 = 1$, only one of its daughter cells can have an active Y molecule. Summing up, under the presence of selection, protocells with $N_y^0 > 1$ are selected.

On the other hand, the total number of Y molecules is limited to small values, due to their slow synthesis speed. This implies that a cell that suppresses the number of Y^I molecules to be as small as possible is preferable under selection, so that there is a room for Y^0 molecules. Hence, a state with almost no Y^I molecules and a few Y^0 molecules, once realized through fluctuations, is expected to be selected through competition for survival (see Fig.5 for schematic representation).

Of course, the probability for such rare fluctuations decrease quite rapidly as the total molecule number increases, and for sufficiently large numbers, the continuum description of the rate equation is valid. Clearly then, a state of the type described above is selected only when the total number of molecules within a protocell is not too large. In fact, a state with very small N_Y^I appears only if the total number N is smaller than some threshold value depending on F and γ_y . In other words, too large cell is not favorable, because the fluctuation is too small to produce such rare state.

4.3 Minority Controlled State

We showed that in a mutually catalyzing replication system, the selected state is one in which the number of inactive molecules of the slower replicating species, Y , is drastically suppressed. In this section, we first show that the fluctuations of the number of active Y molecules is smaller than those of active X molecules in this state. Next, we show that the molecule species Y (the minority species) becomes dominant in determining the growth speed of the protocell system. Then, considering a model with several active molecule types, the control of chemical composition through specificity symmetry breaking is discussed.

4.3.1 Preservation of minority molecule

First, we computed the time evolution of the number of active X and Y molecules, to see if the selection process acts more strongly to control the number of one or the other. We computed N_x^0 and N_y^0 at every division to obtain the histograms of cells with given numbers of active molecules.

The fluctuations in the value of N_y^0 are found to be much smaller than those of N_x^0 . The selection process discriminates more strongly between different concentrations of active Y molecules

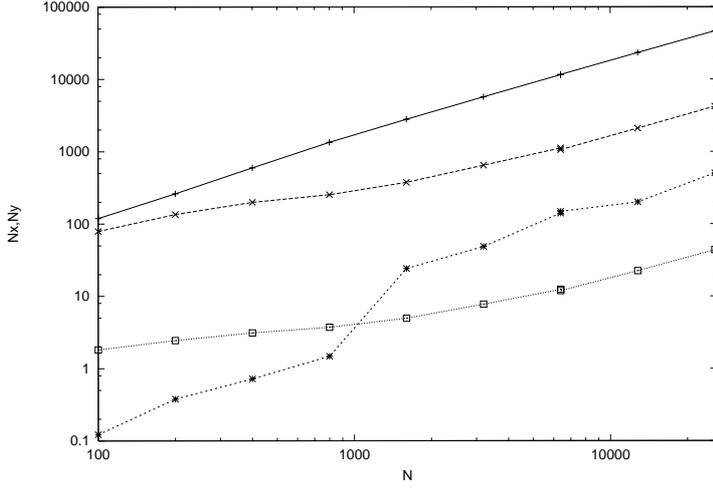


Figure 3: Dependence of $\langle N_x^0 \rangle$ (\times), $\langle N_x^I \rangle$ ($+$), $\langle N_y^0 \rangle$ (\square), and $\langle N_y^I \rangle$ ($*$) on N . The parameters were fixed as $\gamma_x = 1$, $\gamma_y = 0.01$, and $\mu = .05$. Plotted are the averages of N_x^0 , N_x^I , N_y^0 , and N_y^I at the division event, and thus their sum is $2N$. We use $M_{tot} = 100$, and the sampling for the averages were taken over $10^5 - 3 \times 10^5$ steps, where the number of divisions ranges from 10^4 to 10^5 , depending on the parameters. Reproduced from [2].

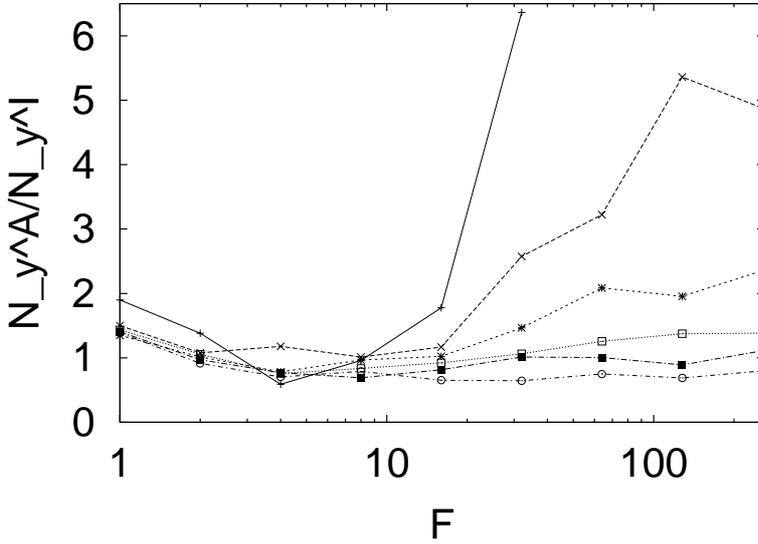


Figure 4: Dependence of the active-to-inactive ratio, $\frac{\langle N_y^0 \rangle}{\langle N_y^I \rangle}$, on F . The parameters were fixed as $\gamma_x = 1$, $\gamma_y = .01$, $\mu = .05$, and $F = 128$. Plots for $\gamma_y = .005$ (\diamond), $.01$ ($+$), $.015$ (\square), 0.02 (\times), 0.025 (\triangle), and 0.03 ($*$) are overlaid. Plotted are the averages of N_x^0 , N_x^I , N_y^0 , and N_y^I at the division event. Reproduced from [2].

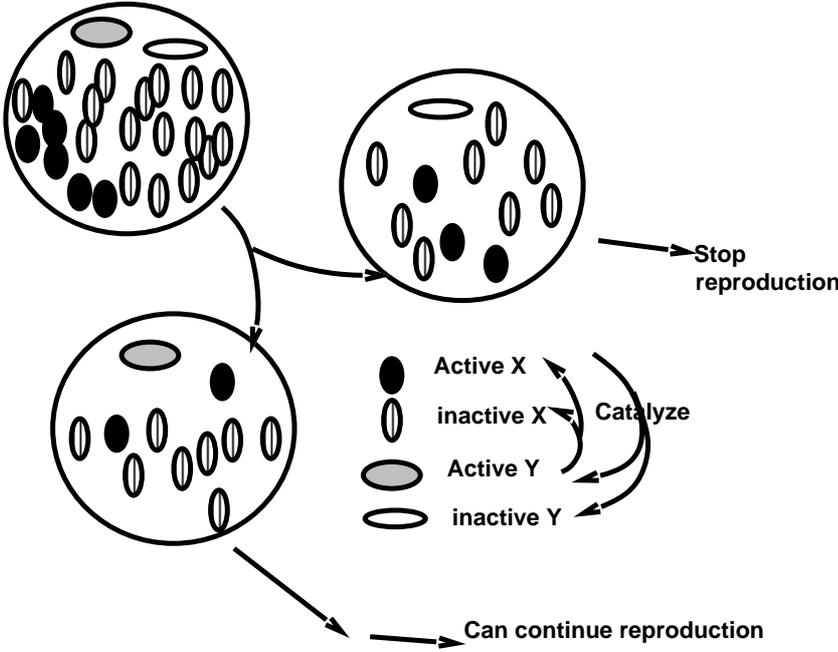


Figure 5: Schematic representation of our logic. Once an active molecule of each molecule species is lost, the reproduction does not continue.

than between those of active X molecules. Hence the active Y molecules are well preserved with relatively smaller fluctuations in the number.

4.3.2 Control of the growth speed

Now, it is expected that the growth speed of our protocell has a stronger dependence on the number of active Y molecules than the number of active X molecules. We have found that the division time is a much more rapidly decreasing function of N_y^0 than of N_x^0 . Even a slight change in the number of active Y molecules has a strong influence on the division time of the cell. Of course, the growth rate also depends on N_x^0 , but this dependence is much weaker. Hence, the growth speed is controlled mainly by the number of active Y molecules.

4.3.3 Control of chemical composition by the minority molecule

As another demonstration of control, we study a model in which there is more specific catalysis of molecule synthesis. Here, instead of single active molecule types for X and Y , we consider a system with k types of active X and Y molecules, X^{0i} and Y^{0i} ($i = 1, 2, \dots, k$). In this model, each active molecule type catalyzes the synthesis of only a few types ($m < k$) of the other species of molecules. Here we assume that both X and Y molecules have the same “specificity” (i.e., the same value of m) and study how this symmetry is broken.

As already shown, when N , γ_y and F satisfy the conditions necessary for realization of a state in which N_y^I is sufficiently small, the surviving cell type contains only a few active Y molecules, while the number of inactive ones vanishes or is very small. Our simulations show that in the present model with several active molecule types, only a single type of active Y molecule remains after a sufficiently long time. We call this “surviving type”, i_r ($1 \leq i_r \leq k$). Contrastingly, at least m types of X^0 species, that can be catalyzed by the remaining Y^{0i_r} molecule species remain. Accordingly, for a cell that survived after a sufficiently long time, a single type of Y^{0i_r} molecule catalyzes the synthesis of (at least) m kinds of X molecule species, while the multiple

types of X molecules catalyze this single type of Y^{0i} molecules. Thus, the original symmetry regarding the catalytic specificity is broken as a result of the difference between the synthesis speeds.

Due to autocatalytic reactions, there is a tendency for further increase of the molecules that are in the majority. This leads to competition for replication between molecule types of the same species. Since the total number of Y molecules is small, this competition leads to all-or-none behavior for the survival of molecules. As a result, only a single type of species Y remains, while for species X , the numbers of molecules of different types are statistically distributed as guaranteed by the uniform replication error rate.

Although X and Y molecules catalyze each other, a change in the type of the remaining active Y molecule has a much stronger influence on X than a change in the types of the active X molecules on Y , since the number of Y molecules is much smaller.

With the results so far, we can conclude that the Y molecules, i.e., the minority species, control the behavior of the system, and are preserved well over many generations. We therefore call this state the minority-controlled (MC) state.

4.3.4 Evolvability

An important characteristic of the MC state is evolvability. Consider a variety of active molecules $0i$, with different catalytic activities. Then the synthesis rates γ_x and γ_y depend on the activities of the catalyzing molecules. Thus, γ_x can be written in terms of the molecule's inherent growth rate, g_x , and the activity, $e_y(i)$, of the corresponding catalyzing molecule Y^{0i} :

$$\gamma_x = g_x \times e_y(i); \gamma_y = g_y \times e_x(i).$$

Since such a biochemical reaction is entirely facilitated by catalytic activity, a change of e_y or e_x , for example by the structural change of polymers, is more important. Given the occurrence of such a change to molecules, those with greater catalytic activities will be selected through competition evolution, leading to the selection of larger e_y and e_x . As an example to demonstrate this point, we have extended the model to include k kinds of active molecules with different catalytic activities. Then, molecules with greater catalytic activities are selected through competition.

Since only a few molecules of the Y species exist in the MC state, a structural change to them strongly influences the catalytic activity of the protocell. On the other hand, a change to X molecules has a weaker influence, on the average, since the deviation of the average catalytic activity caused by such a change is smaller, as can be deduced from the law of large numbers. Hence the MC state is important for a protocell to realize evolvability.

4.4 Experiment

Recently, there have been some experiments to construct minimal replicating systems in vitro. As an experiment corresponding to this problem, we describe an in-vitro replication system, constructed by Yomo's group[18].

In general, proteins are synthesized from the information on DNA through RNA, while DNA are synthesized through the action of proteins. As a set of chemicals, they autonomously replicate themselves. Now simplifying this replication process, Matsuura et al.[18] constructed a replication system consisting of DNA and DNA polymerase i.e., an enzyme for the synthesis of DNA, and so forth. This DNA polymerase is synthesized by the corresponding gene in the DNA, while it works as the catalyst for the corresponding DNA. Through this mutual catalytic process the chemicals replicate themselves.

As for the amplification of DNA, PCR is widely used, and is a standard tool for molecular biology. In this case, however, enzymes that are necessary for the replication of DNA must be supplied externally. In this sense, it is not a self-contained autonomous replication system. In the experiment by Yomo's group, while they use PCR as one step of experimental procedures,

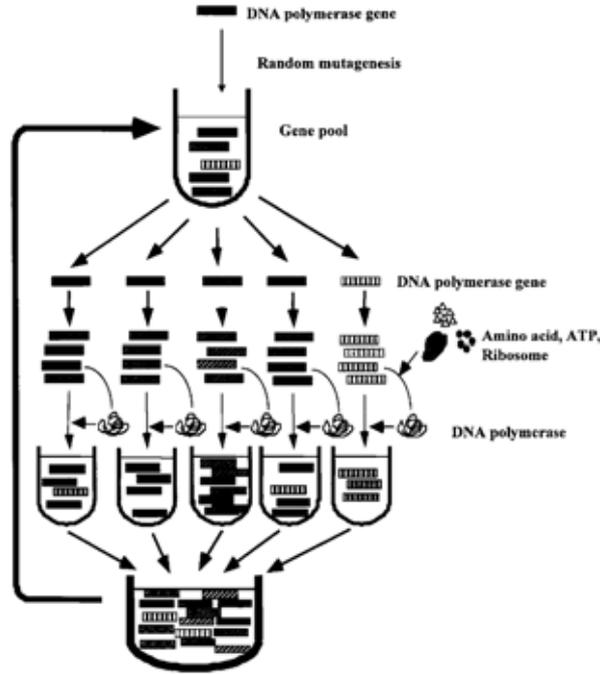


Figure 6: Illustration of in-vitro autonomous replication system consisting of DNA and DNA polymerase. See text and [18] for details. Provided with the courtesy of Yomo, Matsuura et al.

the enzyme (DNA polymerase) for DNA synthesis is also replicated in vitro within the system. Of course, some (raw) material, such as amino acid or ATP, have to be supplied, but otherwise the chemicals are replicated by themselves. (see Fig. 6 for the experimental procedure).

In this experiment, there is mutual synthetic process between gene and enzymes. Roughly speaking, the polymerase in the experiment corresponds to X in our model, while the polymerase gene corresponds to Y .

Now, at each step of replication, about $2^{30} \sim 2^{40}$ DNA molecules are replicated. Here, of course there are some errors. These errors can occur in the synthesis of enzyme, and also in the synthesis of DNA. With these errors, there appear DNA molecules with different sequences. Now a pool of DNA molecules with a variety of sequences is obtained as a first generation.

From this pool, the DNA and enzymes are split into several tubes. Then, materials with ATP and amino acids are supplied, and the replication process is repeated (see Fig. 6). In other words, the 'test tube' here plays the role of "cell compartmentalization". Instead of autonomous cell division, split into several tubes are operated externally.

In this experiment, instead of changing the synthesis speed γ_y or N in the model, one can control the number of genes, by changing the condition how the pool is split into several test tubes.

Indeed, they studied the two distinct cases, i.e., split to tubes containing a single DNA in each and split to tubes containing 100 DNA molecules. Recall that in the theory, the evolvability by minority control is predicted. Hence, the behavior between the two cases may be drastically different.

First, we describe the case with a single DNA in each tube. Here, the pool of chemicals is split into 10 tubes each of which has a single DNA molecule, and replication process described already progresses in each tube. Here, the sequence of DNA molecules could be different by

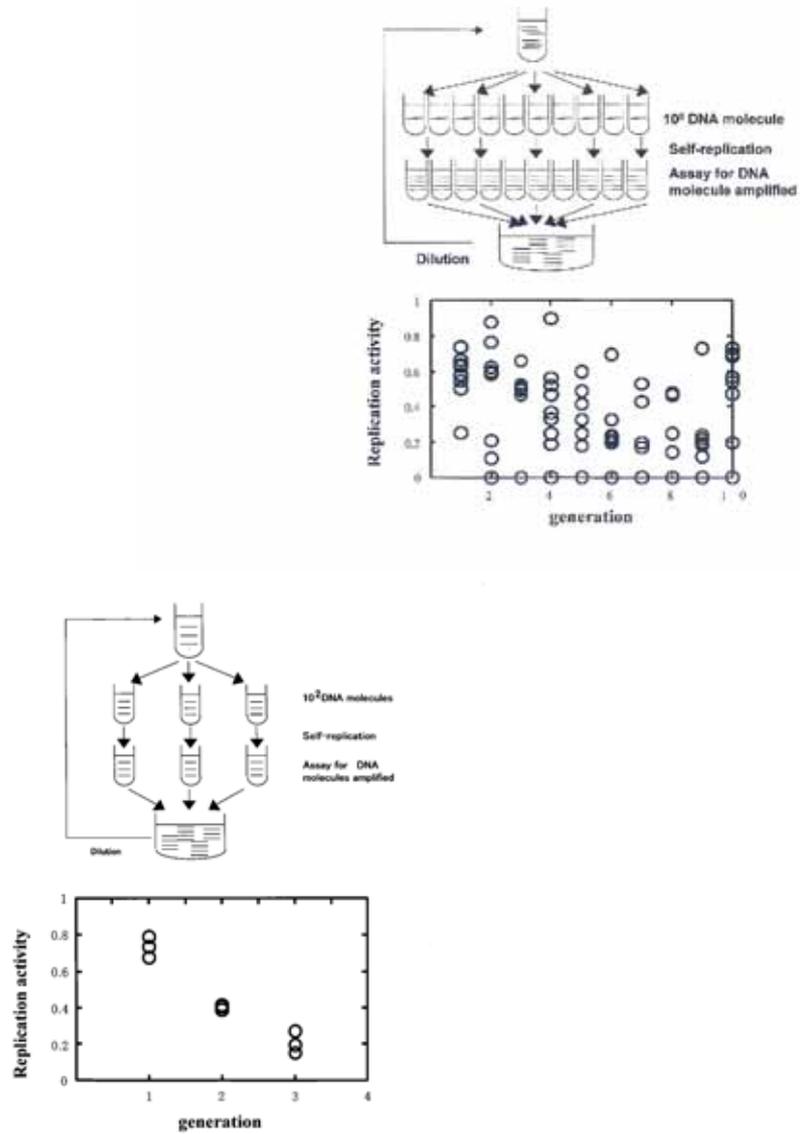


Figure 7: Self-replication activities for each generation, measured as described in the text. The activities for 10 tubes are shown. : Upper: result from a single DNA, where the next generation is produced mostly from the top DNA. Although activities vary by each tube, higher ones are selected, so that the activities are maintained. Lower: result from 100 DNA molecules. Adapted from [18] with the authors' courtesy.

tube, since there is replication error. Then the activity of DNA polymerase by each tube is also different, and the number of DNA molecules synthesized in each tube is different. In other words, some DNA molecules can produce more offspring, but others cannot. The variation of self-replication activity by tubes is shown in the upper column of Fig. 7. Then the contents of each tube are mixed. This soup of chemicals is used for the next generation. Then in this soup, the DNA molecules that have higher replication rate as well as their mutants generated from them are included with a larger fraction. Now a single DNA is selected from the soup in each of 10 tubes, and the same procedures are repeated. Hence, there is a larger probability that a DNA molecule with a higher reproduction activity is selected for the next generation. In other words, Darwinian selection acts at this stage. The self-replication activity from this soup is plotted in the third generation. Successive plots of the self-replication activity are given in the upper column of Fig. 7. As shown, the self-replication activity is not lost (or can evolve in some case), although it varies by each tube in each generation.

One might say that the maintenance of replication is not surprising at all, since a gene for the DNA polymerase is included in the beginning. However, enzyme with such catalytic activity is rare. Indeed, with mutations some proteins that lost such catalytic activity but are synthesized in the present system could appear, which might take over the system. Then the self-replication activity would be lost. In fact, this is nothing but the error catastrophe by Eigen, discussed in §2.1. Then, why is the self-replication activity maintained in the present experiment?

The answer is clear according to the theory in §4.2-4.3. In the model of §4.1, mutants that lost the catalytic activity are much more common (i.e., F times larger in the model). Still, the number of such molecules is suppressed. This was possible first because the molecules are in a cell. In the experiment also they are in a test tube, i.e., in a compartment. Now the selection works for this compartment, not for each molecule. Hence the tube (cell) that includes a gene giving rise to lower enzyme activity produces less offspring. In this sense, compartmentalization is one essential factor for the maintenance of catalytic activity (see also [8, 30, 31]). Here, another important factor is that in each compartment (cell) there is a single (or very few) DNA molecule (as the Y molecule in the model of §4.1-3). In the theory, if the number of Y molecules is larger, inactive Y molecules surpass the active one in population.

To confirm the validity of our theory, Matsuura et al.[18] carried out a comparison experiment. Now, they split the chemicals in the soup so that each tube has 100 DNA molecules instead of a single one. Otherwise, they adopt the same procedure. In other words, this corresponds to a cell with 100 copies of genome. Change of self-replication activity in the experiment is plotted in the lower column of Fig.7. As shown, the self-replication activity is lost by each generation, and after the fourth generation, capability of autonomous replication is totally lost. This result shows that the number of molecules to carry genetic information should be small, which is consistent with the theory.

When there are many DNA molecules, there can be mutation to each DNA molecule. In each tube, the self-replication activity is given by the average of the enzyme activities from these 100 DNA molecules. Although catalytic activity of molecules varies by each, the variance of the average by tubes should be reduced drastically. Recall that the variance of the average of N variables with the variance μ is reduced to μ/N , according to the central limit theorem of probability theory. Hence the average catalytic activity does not differ much by tube. Here, the mutant with a higher catalytic activity is rare. Most changes in the gene lead to smaller or null catalytic activity. Hence, on the average, the catalytic activity after mutations to original gene gets smaller, and the variance by tubes around this mean is rather small (see Fig. 7).

By the selection, DNA from a tube with a higher catalytic activity could be selected, but the variation by tubes is so small that the selection does not work. Hence deleterious mutations remain in the soup, and the self-replication activity will be lost by generations. In other words, the selection works because the number of information carrier in a replication unit (cell) is very

small, and is free from the statistical law of large numbers.

Summing up: In the experiment, it was found that replication is maintained even under deleterious mutations (that correspond to structural changes from active to inactive molecules in the model), only when the population of DNA polymerase genes is small and competition of replicating systems is applied. When the number of genes (corresponding to Y) is small, the information containing in the DNA polymerase genes is preserved. This is made possible by the maintenance of rare fluctuations, as found in our theory. The system has evolvability only if the number of DNA in the system is small. Otherwise, the system gradually loses its activity to replicate itself. These experimental results are consistent with the minority control theory described.

4.5 Discussion

4.5.1 Heredity from a kinetic viewpoint

In this section, we have shown that in a mutually catalyzing system, molecules Y with the slower synthesis speed and minority in number, tend to act as the carrier of heredity. Through the selection under reproduction, a state, in which there is a few active Y and almost zero inactive Y molecules, is selected. This state is termed the “minority controlled state”. Between the two molecule species, there appears separation of roles, between that with a larger number, and that with a greater catalytic activity. The former has a variety of chemicals and reaction paths, while the latter works as a basis for the heredity, in the sense of the two properties mentioned in §1.1 and §4.3, ‘preservation’ and ‘control’. We now discuss these properties in more detail.

[Preservation property]: A state that can be reached only through very rare fluctuations is selected, and it is preserved over many generations, even though the realization of such a state is very rare when we consider the rate equation obtained in the continuum limit.

[Control property]: A change in the number of Y molecules has a stronger influence on the growth rate of a cell than a change in the number of X molecules. Also, a change in the catalytic activity of the Y molecules has a strong influence on the growth of the cell. The catalytic activity of the Y molecules acts as a control parameter of the system.

Once this minority controlled state is established, the following scenario for the evolution of genetic information is expected. First, a new selection pressure is now possible to emerge, to evolve a machinery to ensure that the minority molecule makes it into the offspring cells, since otherwise the reproduction of the cell is highly damaged. Hence a machinery to guarantee the faithful transmission of the minority molecule should evolve. Now, the origin of heredity is established. Here, for this heredity, any specific metabolic or genetic contents transmitted faithfully is not necessary. It can appear from the loose reproduction system that Dyson considered (as in §2.2). This heredity evolves just as a result of kinetic phenomenon and is a rather general phenomenon in a reproducing protocell consisting of mutually catalytic molecules.

This faithful transmission of minority molecule provides a basis for critical information for reproduction of the protocells. Since this minority molecule is protected to be transmitted, other chemicals that are synthesized in connection with it are probable to be transmitted, albeit not always faithfully. Hence there appears a further evolutionary incentive to package life-critical information into the minority molecule. Now more information (‘many bits’ of information) are encoded on the minority molecule. Then, the molecules work as a carrier of genetic information in the today’s sense. With this evolution having more molecules catalyzed by the minority molecule, it is then easier to further develop the machinery to better take care of minority molecules, since this minority molecule is essential to many reactions for the synthesis of many other molecules.

Hence the evolution of faithful transmission of minority molecules and of coding of more information reinforce each other. At this point one can expect a separation of metabolism and

genetic information.

To sum up, how a single molecule starts to reign the heredity is understood from a kinetic viewpoint. We first show the minority controlled state as a rather general consequence of kinetic process of mutually catalytic molecules. This provides a basis for heredity. Taking advantage of the evolvability of minority controlled state, then, preservation mechanism of the minority molecule evolves, which allows for more information encoded on it, leading to separation of genetic information and metabolism. In this sense, the minority molecule species with slower synthesis speed, leading to the preservation of rare states and control of the behavior of the system, acts as an information carrier. The important point of our theory is that heredity arises prior to any metabolic information that needs to be inherited.

4.5.2 some remarks

In §2, we described two standpoints on the origin of life, i.e., genetic information first or complex metabolism first. We pointed out some difficulty at each standpoint. In the former picture, there was a problem on the stability against parasites, while the latter cannot solve how genetic information took over the original loose reproduction system. The minority control gives a new look to these problems.

The first problem in §2.1 was the appearance of parasitic molecules to destroy the hypercycle, i.e. mutually catalytic reaction cycle. If only the replication process of molecules is concerned, it is not so easy to resolve the problem. Here we consider the dual level of replication, i.e., molecular and cellular replication.

In the present theory for the origin of information, existence of a cell unit that reproduces itself is required. Two levels of reproduction, both molecules and cells are assumed here. Hence a cell with parasitic molecules cannot grow, and is selected out. Relevance of this type of two-level reproduction to avoid molecular parasites has been discussed [8, 30, 31]. Here, relevance of cellular compartment to the *origin of genetic information* is more important.

This two-level selection works effectively, with the aid of minority control of specific molecules for a cell. Indeed, surviving cells satisfy the minority control. With the selection pressure for reproduction of cells, there appears a state that is not expected by the rate equation for reaction of molecules, where the number of inactive Y molecules that are parasitic to the catalytic reaction is suppressed. Furthermore, resistance against parasitic (inactive) Y molecules is established by this minority controlled state.

This minority control also resolves the question on the genetic take-over, the problem in the "metabolism first" standpoint (in §2.2). Among several molecules, specific molecule species that are minority in population controls the behavior of a cell and is well preserved. The possible scenario mentioned in the beginning of this section gives one plausible answer how genetic take-over progresses.

The differentiation of role between the molecules looks like "symmetry breaking". When initially two states are equally possible, and later only one of them is selected, it is said that the symmetry is broken. In the differentiation of roles of molecules studied here, however, the molecules have different characters as to the replication speed from the beginning. Here a difference in one character (i.e., the replication speed) is "transformed" into the difference in the control behavior, and in the role as a carrier of heredity. In other words, a characteristics with already broken symmetry is transformed into a different type of symmetry breaking. This kind of transformation of one character's difference to another is often seen in biology, as we have already discussed in the study of morphogenesis and sympatric speciation[16, 17].

5 Recursive Production in an Autocatalytic Network

Now we come to the second question raised in §1. In the model of the last section, we considered a system consisting of two kinds of molecules. In a cell, however, a variety of chemicals form a complex reaction network to synthesize themselves. Here we study a model with a large number of chemical species, to discuss how a cell with such large number of components and complex reaction network can sustain reproduction, keeping similar chemical compositions [32, 33](see also [34]).

5.1 Model

To unveil general features of a system with mutually catalyzing molecules, we study a system with a variety of chemicals (k molecule species), forming a mutually catalyzing network. The molecules replicate through catalytic reactions, so that their numbers within a cell increase. (see Fig.1 again for schematic representation of the model).

We envision a (proto)cell containing k molecular species with some of the species possibly having a zero population. A chemical species can catalyze the synthesis of some other chemical species as



with $i, j = 1, \dots, k$ according to a randomly chosen reaction network, where the reaction is set at far-from-equilibrium. In eq.(7), the molecule i works as a catalyst for the synthesis of the molecule j , while the reverse reaction is neglected, as discussed in the hypercycle model. For each chemical the rate for the path of catalytic reaction in eq.(7) is given by ρ , i.e., each species has about $k\rho$ possible reactions. The rate is kept fixed throughout each simulation. Considering catalytic reaction dynamics, the reverse reaction process is neglected, and reactions $i \leftrightarrow j$ are not included. (Here we investigated the case without direct mutual connections, i.e., $i \rightarrow j$ was excluded as a possibility when there was a path $j \rightarrow i$, although this condition is not essential for the results to be discussed). Furthermore, each molecular species i has a randomly chosen catalytic ability $c_i \in [0, 1]$ (i.e., the above reaction occurs with the rate c_i). Assuming an environment with an ample supply of chemicals available to the cell, the molecules then replicate leading to an increase in their numbers within a cell.

Again, when the total number of molecules exceeds a given threshold (here we used $2N$), the cell is assumed to divide into two, with each daughter cell inheriting half of the molecules of the mother cell, chosen randomly.

During the replication process, structural changes, e.g., the alternation of a sequence in a polymer, may occur that alter the catalytic activities of the molecules. Therefore, the activities of the replicated molecule species can differ from those of the mother species. The rate of such structural changes is given by the replication 'error rate' μ . As a simplest case, we assume that this 'error' leads to all other molecule species with equal probability (i.e., with the rate $\mu/(k-1)$), and could thus regard it as a background fluctuation. In reality, of course, even after a structural change, the replicated molecule will keep some similarity with the original molecule, and a replicated species with the 'error' would be within a limited class of molecule species. Hence, this equal rate of transition to other molecule species is a drastic simplification. Some simulations where the errors in replication only lead to a limited range of molecule species, however, show that the simplification does not affect the basic conclusions presented here. Hence we use the simplest case for most simulations.

In statistical physics, people study mostly the case the total number of molecules N is very large, at least much much larger than a number of molecule species k . In this case, the continuum description is relevant. When N/k is rather small, some molecules species can often fluctuate

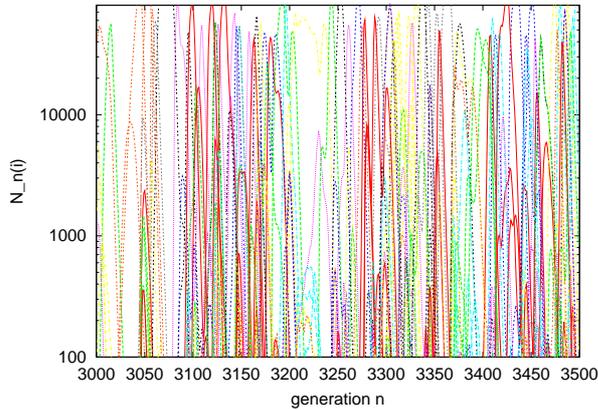


Figure 8: The number of molecules $N_n(i)$ for the species i is plotted as a function of generation n of cells, i.e., at each successive division event n . A random network with $k = 500$ and $\rho = .2$. Dominant species change successively in generation.

around 0, where the discreteness $0,1,2,\dots$ will be important, as already discussed. In order to take the importance of the discreteness in the molecule numbers into account, we adopted a stochastic rather than the usual differential equations approach, by taking a variety of possible chemicals, where N and k are of a comparable order.

The model is simulated as follows: At each step, a pair of molecules, say, i and j , is chosen randomly. If there is a reaction path between species i and j , and i (j) catalyzes j (i), one molecule of the species j (i) is added with probability c_i (c_j), respectively. The molecule is then changed to another randomly chosen species with the probability of the replication error rate μ . When the total number of molecules exceeds a given threshold (denoted as N), the cell divides into two such that each daughter cell inherits half ($N/2$) of the molecules of the mother cell, chosen randomly[2].

Again, to include competition, we assume that there is a constant total number M_{tot} of protocells, so that one protocell, randomly chosen, is removed whenever a (different) protocell divides into two. However, the result here does not depend on M_{tot} so much. We choose mostly $M_{tot} = 1$, in the results below but the simulation with $M_{tot} = 100$ gives essentially the same behavior.

5.2 Result

5.2.1 Phases

Our main concern here is the dynamics of these molecule numbers N_i of the species i in relationship with the condition of the recursive growth of the (proto)cell. In our model there are four basic parameters; the total number of molecules N , the total number of molecule species k , the mutation rate μ , and the reaction path rate ρ . By carrying out simulations of this model, choosing a variety of parameter values N, k, μ, ρ , also by taking various random networks, we have found that the behaviors are classified into the following three phases[32, 33]:

- (1) Fast switching states without recursiveness
- (2) Achievement of recursive production with similar chemical compositions
- (3) Switch over several quasi-recursive states

In the phase (1), there is no clear recursive production and the dominant molecule species changes by generation frequently. Even though each generation has some dominating species as with regards to the molecule numbers, the dominating species change every few generations. At one generation, some chemical species are dominant but only a few generations later. Information

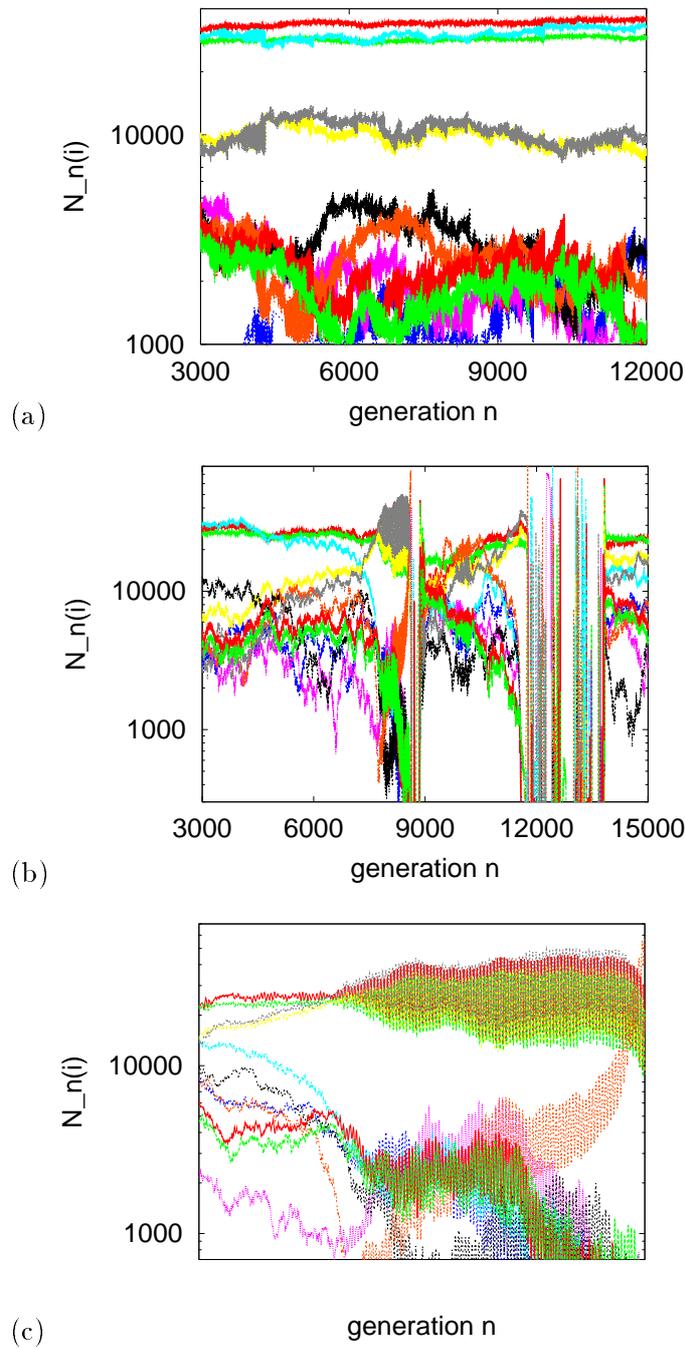


Figure 9: The number of molecules $N_n(i)$ for the species i is plotted as a function of generation n of cells, i.e., at each successive division event n . results from a random network with $k = 200$ and $\rho = .1$ was adopted, with $N = 64000$ and $\mu = 0.01$ (a), and $\mu = 0.1$ (b). Only some species (whose population get large at some generation) are plotted. in (a), a recursive production state is established, while in (b), a few quasi-recursive states are visited successively. (c): Expansion of Fig (b) around the time step 100000.

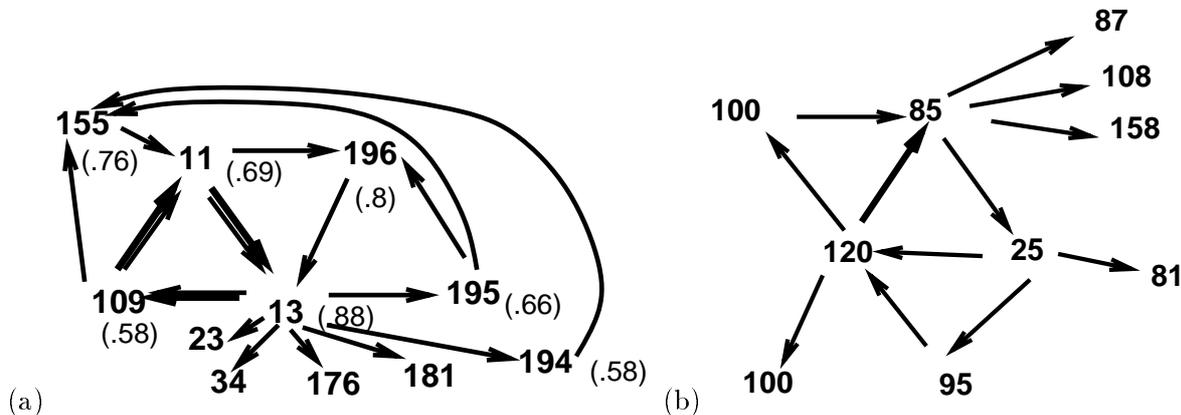


Figure 10: The catalytic network of the dominant species that constitute the recursive state. The catalytic reaction is plotted by an arrow $i \rightarrow j$, as the replication of the species j with the catalytic species i . The numbers in () denote c_i of the species. Only the species that continue to exist with the population larger than 10 is plotted. (Note many other species can exist at each generation, through the replication error). (a): corresponding to the recursive state of Fig.9 a, where the three species connected by thick arrows are the top 3 species in Fig.9 a. The network (b) is another example observed in a different set of simulations with $k = 200$ and $\rho = .1$, but with a different reaction network from Fig.9.

regarding the previously dominating species is totally lost often to the point that its population drops to zero (see Fig.8). Here no stable mutual catalytic relationships are formed among molecules. Hence, the time required for reproduction of a cell is quite large, and much larger than the case (2).

In the phase (2), a recursive state is established, and the chemical composition is stabilized such that it is not altered much by the division process (see Fig.9). Generally, all the observed recursive states consist of 5-12 species, except for those species with one or two molecule numbers, which exist only as a result of replication errors. These 5-12 chemicals mutually catalyze, by forming a catalytic network as in Fig.10, which will be discussed later. The member of these 5-12 species do not change by generations, and the chemical compositions are transferred to the offspring cells. Once reached, this state is preserved throughout whole simulations, lasting over more than 10000 generations.

The recursive state observed here is not necessarily a fixed point with regards to the population dynamics of the chemical concentrations. In some case, the chemical concentrations oscillate in time, but the nature of the oscillation is not altered by the process of cell division.

For example, in the recursive state depicted in Fig.9a), 11 species remain in existence throughout the simulation. As shown, three species have much higher populations than others, which form a hypercycle as $109 \rightarrow 11 \rightarrow 13 \rightarrow 109$. (The numbers 11,13,.. are indices of chemical species, initially assigned arbitrarily). The hypercycle sustains the replication of the molecules, and is called 'core hypercycle'. The catalytic activities of the species satisfy $c_{13} > c_{109} > c_{11}$, and accordingly the respective populations satisfy $N_{11} > N_{109} > N_{13}$.

In the phase (3), after one recursive state lasts over many generations (typically a thousand generations), a fast switching state appears until a new (quasi-)recursive state appears. As shown in Fig.9 b, for example, each (quasi-)recursive state is similar to that in the phase (2), but in this case, its lifetime is finite, and it is replaced by the fast switching state as in the phase (1). Then the same or different (quasi-)recursive state is reached again, which lasts until the next switching occurs. In the example of Fig.9b (see also Fig.9c) for its expansion), around the 12000th generation, the core network is taken over by parasites to enter the phase (1) like

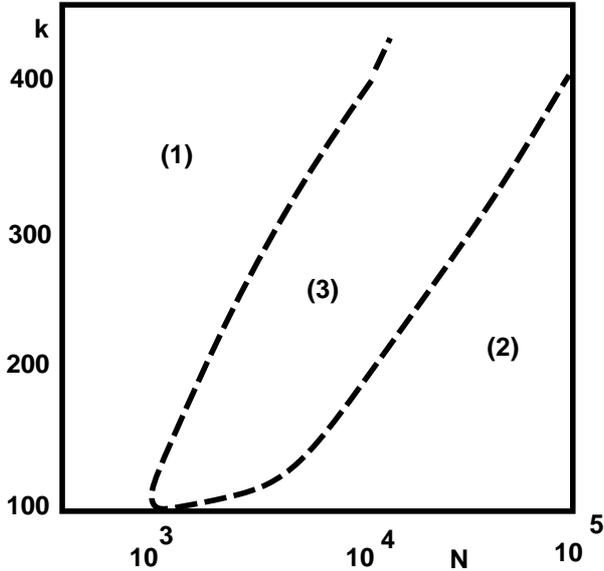


Figure 11: Schematic representation of the phase diagram of the three phases, plotted as a function of the total number of molecules N , and the total possible number of molecule species k .

fast switching state which in turn gives way for a new quasi-recursive state around the 14000th generation.

In the example of Fig. 9b, there is another type of switching, as shown around 85000th generation, as shown in Fig.9c with magnification. Here, the quasi-recursive state is still stable, but the core hypercycle consisting of dominant species changes. As in Fig.9c, a switch occurs from an initial core hypercycle (109,11,13), to the next core hypercycle (11, 13, 195, 155) around the 8500th generation.

This latter switching is the competition among core networks, while the former drastic switch is due to the invasion of parasitic molecules, which is most commonly observed. The mechanism of this switching is discussed again in §5.2.4.

5.2.2 Dependence of Phases on the Basic Parameters

Although the behavior of the system depends on the choice of the network, there is a general trend with regards to the phase change, from (1), to (3), and then to (2) with the increase of N , or with the decrease of k , as schematically shown in Fig.11. By choosing a variety of networks, however, we find a clear dependence of the fraction of the networks on the parameters, leading to a rough sketch of the phase diagram. Generally, the fraction of (2) increases and the fraction of (1) decreases also with the decrease of ρ or μ . For example, the fraction of (1) (or (3)) gets larger as k is decreased from $k \lesssim 300$ for $N = 50000$ (with $\rho = .1$ and $\mu = .01$), while dependence on ρ will be discussed below.

For a quantitative investigation, it is useful to classify the phases by the similarity of the chemical compositions between two cell division events[34]. To check the similarity, we first define a k -dimensional vector $\vec{V}_n = (p_n(1), \dots, p_n(k))$ with $p_n(i) = N_n(i)/N$. Then, we measure the similarity between ℓ successive generations with the help of the inner product as

$$H_\ell = \vec{V}_n \cdot \vec{V}_{n+\ell} / (|\vec{V}_n| |\vec{V}_{n+\ell}|) \quad (8)$$

In Fig.12, the average similarity $\overline{H_{20}}$ and the average division time are plotted for 50 randomly chosen reaction networks as a function of the path probability ρ . Roughly speaking the

networks with $\overline{H_{20}} > .9$ belong to (2), and those with $\overline{H_{20}} < .4$ to (1), empirically. Hence, for $\rho > 0.2$, the phase (1) is observed for nearly all the networks (e.g. 48/50), while for lower path rates, the fraction of (2) or (3) increases. The value $\rho \sim .2$ gives the phase boundary in this case.

Generally speaking, a positive correlation between the growth speed of a cell and the similarity H exists. In Fig.12, the division time is also plotted, where to each point with a high similarity H , a lower division time corresponds. The network with higher similarity (i.e., in the phase (2)) gives a higher growth speed. Indeed, the recursive states maintain higher growth speeds since they effectively suppress parasitic molecules. In Fig. 12, by decreasing path rates, the variations in the division speeds of the networks become larger, and some networks that reach recursive states have higher division speeds than networks with larger ρ . On the other hand, when the path rate is too low, the protocells generally cannot grow since the probability to have mutually catalytic connections in the network is nearly zero. Indeed there exists an optimal path rate seems (e.g., around .05 for $k = 200$, $N = 12800$ as in Fig.12) for having a network with high growth speeds. Consequently, under competition for growth, protocells having such optimal networks will be evolved as will be discussed in §5.3.

Besides the correlation between the growth speed and similarity, the correlation with the diversity of the molecules also exists. Protocells with higher growth speed and similarity in the phase (2) have higher chemical diversity also. In the phase (1), one (or a very few) molecule species is dominant in the population, while about 10 species have higher population in the phase (2) with higher growth speed, where the chemical diversity is maintained.

5.2.3 Maintenance of Recursive Production

How is the recursive production sustained in the phase (2)? We have discussed already the danger of parasitic molecules that have lower catalytic activities and are catalyzed by molecules with higher catalytic activities. As discussed in §2.1, such parasitic molecules can invade the hypercycle. Indeed, under the structural changes and fluctuations, the recursive production state could be destabilized. To answer the question on the itinerancy and stability of recursive states, we have examined several reaction networks. The unveiled logic for the maintenance of recursive state is summarized as follows.

(a) Stabilization by intermingled hypercycle network:

The 5-12 species in the recursive state form a mutually catalytic network, for example, as in Fig. 10. This network has a *core hypercycle network*, as shown in thick arrows in Fig.10a. As shown in Fig.13, such core hypercycle has a mutually catalytic relationship, as “ A catalyzes B , B catalyzes C , and C catalyzes A ”. However, they are connected with other hypercycle networks such as $G \rightarrow D \rightarrow B \rightarrow G$, and $D \rightarrow C \rightarrow E \rightarrow D$, and so forth. The hypercycles are intermingled to form a network. Coexistence of core hypercycle and other attached hypercycles are common to the recursive states we have found in our model.

This intermingled hypercycle network (IHN) leads to stability against parasites and fluctuations. Assume that there appears a parasitic molecule to one species in the member of IHN (say X as a parasite to C in Fig.13). The species X may decrease the number of the species C . If there were only a single hypercycle $A \rightarrow B \rightarrow C \rightarrow A$, the population of all the members A, B, C would be easily decreased by this invasion of parasitic molecules, resulting in the collapse of the hypercycle. In the present case, however, other parts of the network (say, that consisting of A, B, G, D in Fig.13), compensate the decrease of the population of C by the parasite, so that the population of A and B are not so much decreased. Then, through the catalysis of the species B , the replication of the molecule C progresses, so that the population of C is recovered. Hence the complexity in the hypercycle network leads to stability against the attack of parasite molecules.

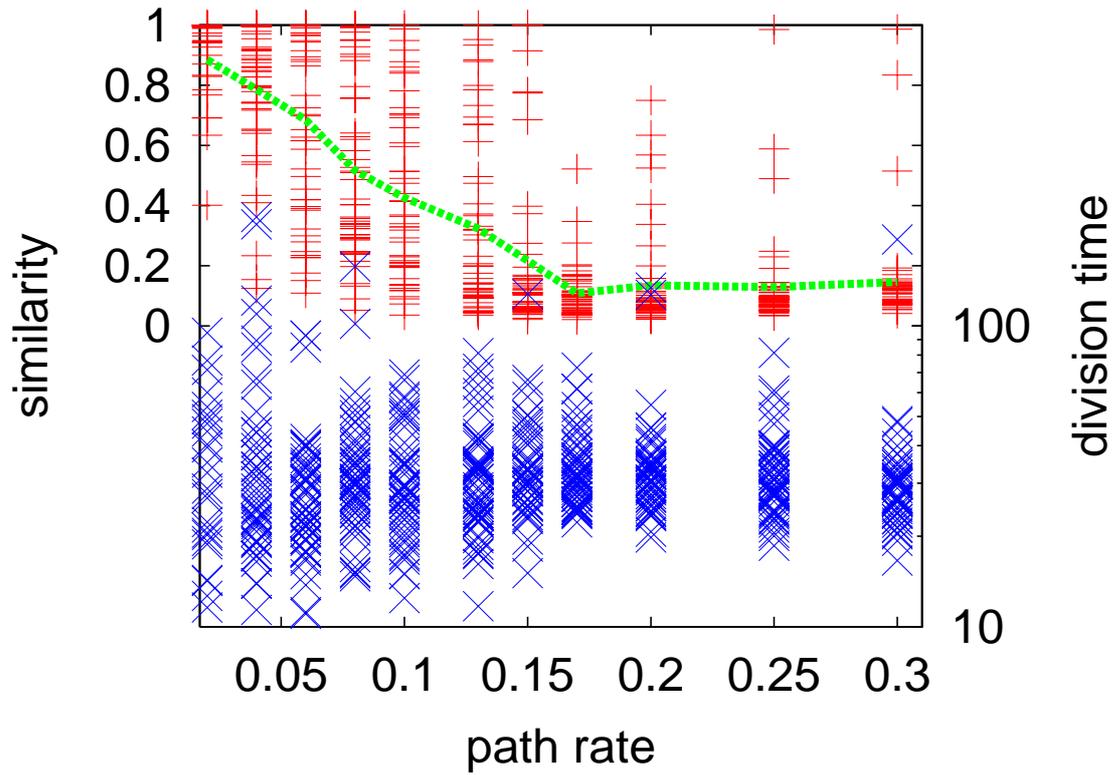


Figure 12: The average similarity $\overline{H_{20}}$ (+), and the average division time (\times) are plotted as a function of the path rate ρ . For each ρ , data from 50 randomly chosen networks are plotted. The average is taken over 600 division events. The dotted line indicates the average of $\overline{H_{20}}$ over the 50 networks for each ρ . For $\rho > .2$, networks over 98 % have $H < .4$, and they show fast switching, while for $\rho = .08$, about 95% belong to the phase (2) or (3) At $\rho = 0.02$, 25 out of 50 networks cannot support cell growth, 4 cannot at $\rho = 0.04$. (Adapted from [33]).

Next, IHN is also relevant to the stability against fluctuations. It is known that the population dynamics of a simple hypercycle often leads to heteroclinic cycle[35], where the population of one (or a few) member approaches 0, and then is recovered. For a continuum model, such heteroclinic cycle can continue forever, but in a stochastic model, due to fluctuations, the number of the corresponding molecule species is totally extinct sometimes. Once this molecule species goes extinct completely, and then its recovery by replication error would require a very long time. Hence, to achieve stability against fluctuations, a state with the heteroclinic cycle dynamics or any oscillation in which some of the population goes very low should be avoided. Indeed, by forming IHN, such oscillatory instability is often avoided or reduced. Due to coexistence of several hypercycle processes, instability in each hypercycle cancels out, leading to fixed-point dynamics or oscillation with a smaller amplitude. Thus the danger that the population of some molecules in the hypercycle goes to zero by fluctuations is reduced.

Stability of coexistence of many species is discussed as 'homeochaos' [36], while stable reproduction in reaction network is also seen in [37].

(b) Minority in the core hypercycle;

Now we study more closely the population dynamics in a core hypercycle. Here, the number of molecules N_j of molecule species j , is in the inverse order of their catalytic activity $c(j)$, i.e., $N_A > N_B > N_C$ for $c_A < c_B < c_C$. Because a molecule with higher catalytic activity helps the synthesis of others more, this inverse relationship is expected. Indeed, the population sizes of just three species A, B, C , with the catalytic relationship $A \rightarrow B \rightarrow C \rightarrow A$ are estimated by taking the continuum limit $N \rightarrow \infty$ and obtaining a fixed point solution of the rate equation for the concentrations of the chemicals as discussed in [7]. From a straightforward calculation we have: $N_A : N_B : N_C = c_A^{-1} : c_B^{-1} : c_C^{-1}$.

Here, the C molecule is catalyzed by a molecule species with higher activities but larger populations (A). Hence, the parasitic molecule species cannot easily invade to disrupt this mutually catalytic network. Since the minority molecule (C) is catalyzed by the majority molecule (A) (with the aid of another molecule (B)), a large fluctuation in molecule numbers is required to destroy this network.

The stability in the minority molecule is also accelerated by the complexity in IHN. If the catalytic activity of C is highest, the recursive state here is mainly achieved by catalysis of the molecule C . On the other hand, this also implies that C is the minority in the core network. (The population of the molecule C is usually larger than D, E , etc. in Fig.13, though.) Hence the attack to C molecule is most relevant to destroy this recursive state. In the IHN, this minority molecule species is involved in several hypercycles as in C in Fig.13. This, on the one hand, demonstrates the prediction in §4.5, that more species are catalyzed by the minority molecules, while on the other hand, leads to the suppression of the fluctuation in the number of minority molecules, as will be discussed in §5.4. With the decrease of the fluctuation, the probability that the minority molecules is extinct is reduced, so that the recursive state is hardly destroyed.

(c) Localization in a Random Network

The present system belongs to a class of system with reaction and diffusion, while the structural change by replication error leads to the diffusion within the network space. With random connection in the catalytic network, the present system is nothing but a reaction-diffusion in a random network. Generally, such problem is related with the Anderson localization, where concentrations are localized within some part of the network, depending on the degree of the connectivity in the network and the strength of the diffusion coupling. From this viewpoint, the formation of IHN, localized only within a limited species in the global network, may be understood as an example of such localization. It will be interesting to study the stability of the recursive production, in terms of the localization transition in the reaction network[38].

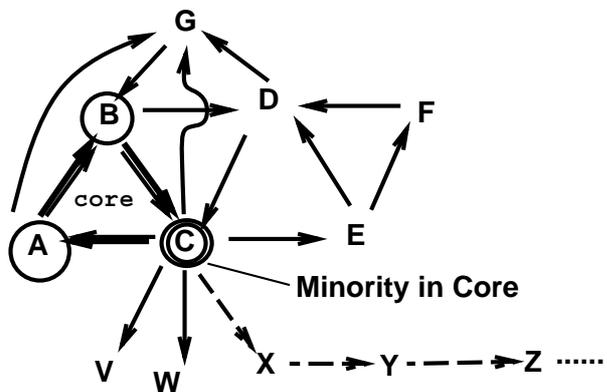


Figure 13: An example of mutually catalytic network in our model. The core network for the recursive state is shown by circles, while parasitic molecules (X, Y, \dots) connected by broken arrows, are suppressed at a (quasi-)recursive state.

5.2.4 Switching

Next, we discuss the mechanism of switching. In the phase (3), the recursive production state is destabilized, when the population of parasitic molecules increase. For example, the number of the molecule C may be decreased due to fluctuations, while the number of some parasitic molecules (X) that are not originally in the catalytic network but are catalyzed by C , may increase. Frequency of such fluctuation increases as the total population of molecules in a cell is smaller. If such fluctuation appears, the other molecule species in the original network loses the main source of molecules that catalyze their synthesis, successively. Then the new parasitic molecule X occupies a large portion of populations. However, the molecule's main catalyst (C) soon disappears, the synthesis of X is stopped, and this species X is taken over by some molecules Y that are catalyzed by X (see the broken arrows in Fig.13). Then, within a few generations, dominant species changes, and recursive production does not continue. Indeed, this is what occurred in the phase (1). Then the parasitic molecule X is taken over some other Y . This take-over by parasites continues successively, until a new (or same) recursive state with hypercycle network is formed. Hence the fluctuation in the minority molecule in the core network is relevant to the switching process.

5.3 Evolution

Model A

The next question we have to address is whether the recursive production state is achieved through evolution. To check this problem we have extended our model to further include a “mutational” change of network at each division event. (model A). To be specific, at each division event we add or delete randomly (with equal probability) a few reaction paths, whose connection $i \rightarrow j$ is again chosen randomly. Here to see the evolution of catalytic activity, the index of the species is ordered with the value of catalytic activity, i.e., the index j is ordered so that c_j monotonically increases with j . Since the mutational change is assumed to be random, a new path is added or deleted independent of the catalytic activity. In the simulation displayed here, there are 5 mutations of the network path at every generation. We have carried out numerical experiments of this model, to see if the path rate of the network stays around the state supporting the recursive production.

An example of the time series of path rates at each generation is shown in Fig.14, as well as the time series of the division time, and chemical diversity. Corresponding to this time series,

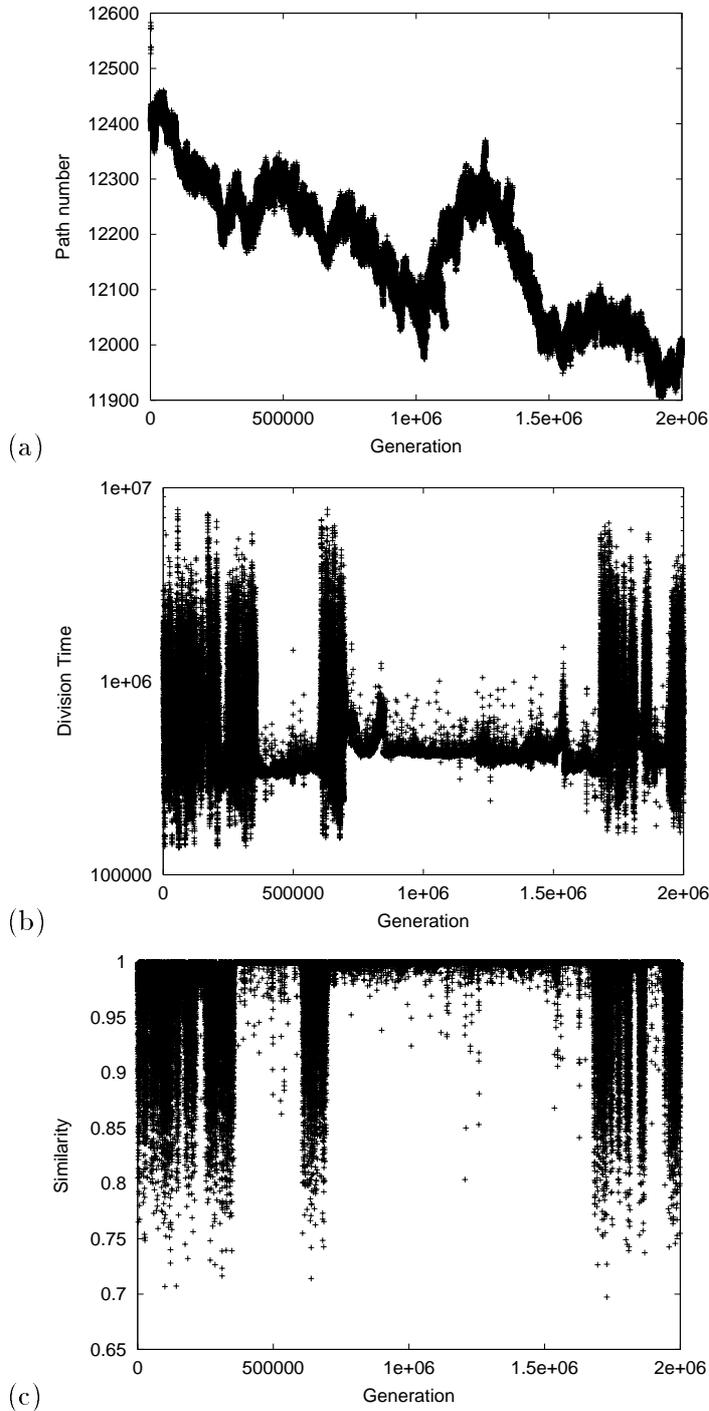


Figure 14: Evolution of path-rates, recursiveness, and division time, plotted versus generation. The total number of species k is 500, where c_i is chosen as $100^{-(k-i)/k}$, so that it ranges from 0.01 to 1.0 equally in logarithmic scale. The number of molecules N in a cell is set at 50,000, so that the cell divided when the total molecule number is 100,000. The initial path rate is set at $\rho = 0.1$, i.e., 125,000 paths totally. At every division 5 paths are "mutated", i.e., with equal probability 5 paths are added or eliminated randomly. Totally there are $M_{tot} = 100$, so that one of 100 cells are eliminated when one cell is divided into two. (a) the total path number. The path rate is obtained by dividing the number by k^2 . (b) the division time, i.e., the required steps for a cell divide (c) the similarity $H^1(i)$, defined in §5.2.

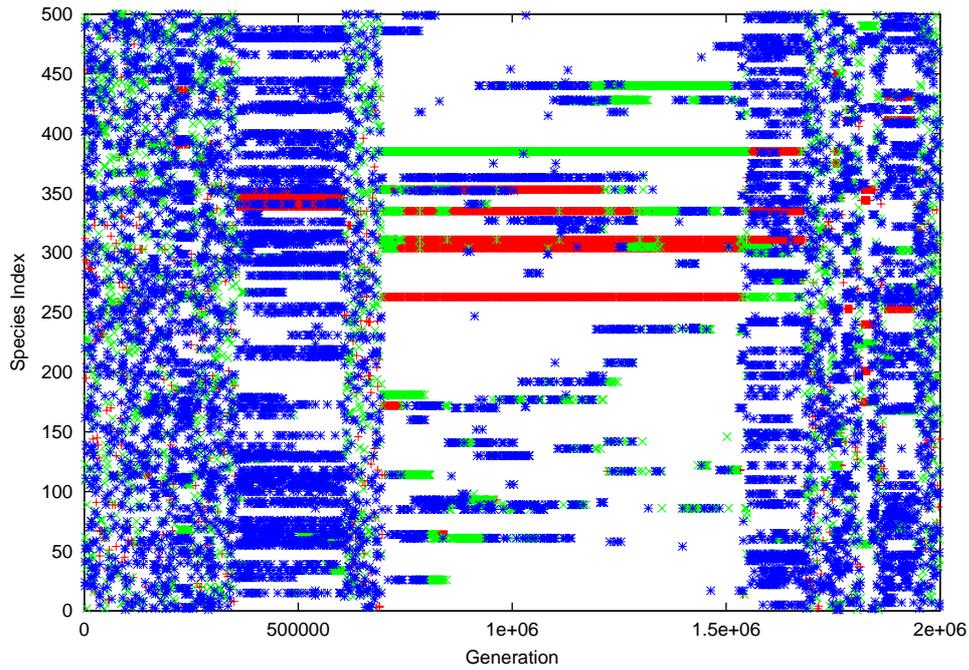


Figure 15: Evolution of cell: Those species i with $N(i) > 100$ are plotted with the vertical axis as the species index i , and the longitudinal axis as the generation. The data are from the result of the simulation for Fig.14.

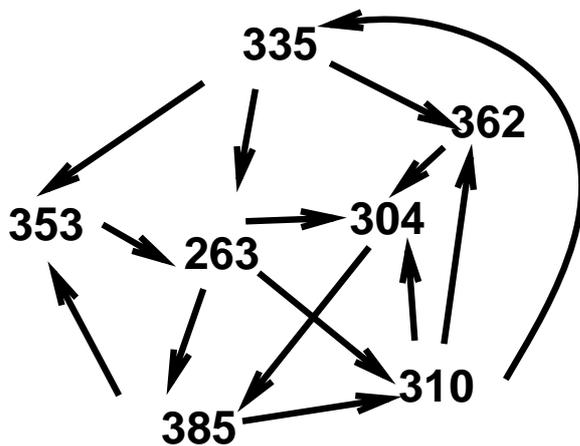


Figure 16: The catalytic network of the species that constitute the recursive state around 10^6 th generation of Fig.14 or 15.

the change of dominant species is plotted over generations in Fig.15.

As shown, the recursive state is achieved, and is maintained over many generations, until it switches to other states. At each reproduction, there are changes in the reaction paths here. In spite of such mutations, the recursive production state is sustained over many generations. In each recursive production state, the path rate remains rather low. Here, such network that supports the recursive production is selected and is maintained. Note that many molecules are catalyzed by the minority species in the core hypercycle network. In this sense, a prototype of the evolution to package the information into the minority molecule that is suggested in §4.5 is observed here.

An example of the network of dominant species is given in Fig. 16. Here intermingled hypercycle networks (IHN) are formed so that recursive production is formed. Again, there is a core hypercycle, and other hypercycles are connected with it. The surviving molecule species have a large connectivity in reaction paths, much larger than expected from a random network of the reaction path rate here. As in Fig 16. the IHN here forms a highly connected network, even though the average path rate remains small (As shown in Fig.14, the path per species is about 0.1 or lower). The paths forming the IHN are preserved over long generations, while a few paths are sometimes eliminated. Here, coexistence of several parallel paths among species is important to give the robustness of the recursive state against mutation that may delete one of the paths. As in the dynamics of the phase (3), the recursive production state is destabilized finally with the mutation of reaction paths, while after some generations, other recursive networks are formed through the mutation of the network.

To sum up, the phase (3) gives a basis for evolvability, since a novel, (quasi-)recursive state with different chemical compositions is visited successively.

Model B

So far, we have assumed that the structural change in the replication can occur equally to any other molecule species. Of course, this is a simplification, and the replication error occurs only to limited types of molecules species that have similarity to the original. To see this point, we have studied another model (model B) with some modifications from the original model of §5.1.

Here, the catalytic activity is set as $c_i = i/k$, i.e., the activity is monotonically increasing with the species index. Then, instead of global change to any molecule species by replication error, we modify the rule so that the change occurs only within a given range $i_0 (\ll k)$ i.e., when the molecule species j is synthesized, with the error rate μ , the molecule $j + j'$ with j' a random number over $[-i_0, i_0]$ is synthesized.

In this **model B**, we have not included any change of the network. The network is fixed in the beginning, and is not changed through the simulation. Instead, by local change of structural error, the range of species evolve by generations. Here we take species only with $i < i_{ini}$ in the initial condition, and examine if the evolution to a network with higher catalytic activities (i.e., with much larger i) progresses or not. In other words, we examine if the indices i in the network increase successively or not. An example is shown in Fig.17, where the catalytic activity increases through successively switching to one (quasi-)recursive state (consisting of species within the width of the order $2i_0$), to another.

Here the switching occurs as in the phase (3). With the pressure for selection of the protocells, cells with a new (quasi-)recursive state are selected that consist of molecules with higher catalytic activities (i.e., with larger indices of species). Again each recursive state consists of IHN, and the species with the highest catalytic activity in the core hypercycle is minority in population. Once the population of such species is decreased by fluctuations, there occurs a switch to a new state that has higher catalytic activities, and the species indices successively increase. Hence, evolution from a rather primitive cell consisting of low catalytic activities to that with higher activities is possible, by taking advantage of minority molecules.

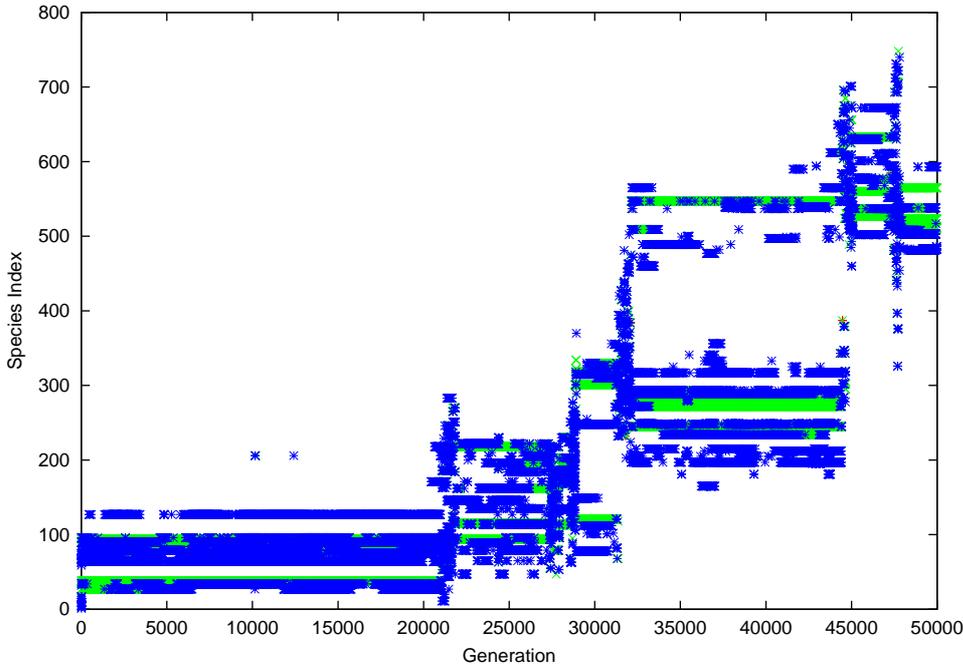


Figure 17: Evolution of species in a cell: Those species i with $N(i) > 100$ are plotted with the vertical axis as the species index i , and the longitudinal axis as the generation. The total number of species k is 5000, where c_i is chosen as $c_i = i/k$, so that it ranges from 0.0002 to 1.0 equally distributed. The number of molecules in a cell is set at 8,000, so that the cell divided when the total molecule number is 16,000. The path rate is set at $\rho = 0.1$. The replication error for the species occurs within the range of species $[i - 100, i + 100]$, instead of global selection from all species. Totally there are $M_{tot} = 10$ cells, so that one of 10 cells is eliminated when a cell is divided into two.

Note that this switching cannot occur if the total number of molecules N is small. When the number is too small, the mutation of paths to destroy the recursive state hardly occurs. On the other hand, if the total number of molecules is too large, it is harder to establish a recursive state, due to a larger possibility to change the network. Hence, there is optimal value of the number of molecules in a protocell to realize the recursive production as well as the evolution.

5.4 Statistical Law

To close the present section, we investigate the fluctuations of the molecule numbers of each of the species, by coming back to the original model studied in §5.2, without evolution of reaction paths. The characteristics of the fluctuations of the number of each molecule species over the generations can have a significant impact on the recursive production of a cell, since the number of each molecule species is not very large. In order to quantitatively characterize the sizes of these fluctuations, we have measured the distribution $P(N_i)$ for each molecule species i , by sampling over division events.

Our numerical results are summarized as follows:

- (I) For the fast switching states, the distribution $P(N_i)$ satisfies the power law

$$P(N_i) \approx N_i^{-\alpha}, \quad (9)$$

with $1 < \alpha \approx 2$, as shown in Fig. 18a. The exponent α depends on the parameters, and approaches 2 as alternation of dominant species is more frequent. For example, as shown in Fig.

18b, the exponent α increases from 1 to 2, with the increase of the error rate μ .

(II) For recursive states, the fluctuations in the core network (i.e., 13,11,109 in Fig.9a or 10a) are typically small, (and are roughly fit by Gaussian distribution). On the other hand, for species that are peripheral to but catalyzed by the core hypercycle, the number distribution is closer to log-normal distributions

$$P(N_i) \approx \exp\left(-\frac{(\log N_i - \overline{\log N_i})^2}{2\sigma}\right), \quad (10)$$

as shown in Fig.19.

Even though the distribution does not agree well with the log-normal distribution, at least, the distribution is roughly symmetric after taking the logarithm (i.e., as the 0-th approximation the distribution is not normal but log-normal). The origin of the log-normal distributions here can be understood by the following rough argument: for a replicating system, the growth of the molecule number N_m of the species m is given by

$$dN_m/dt = AN_m, \quad (11)$$

where A is the average effect of all the molecules that catalyze m . We can then obtain the estimate

$$d \log N_m/dt = \bar{a} + \eta(t), \quad (12)$$

by replacing A with its temporal average \bar{a} plus fluctuations $\eta(t)$ around it. If $\eta(t)$ is approximated by a Gaussian noise, the log-normal distribution for $P(N_m)$ is suggested. This argument is valid if $\bar{a} > 0$. As such this equation diverges with time, but here, the cell divides into two before the divergence becomes significant. Although the asymptotic distribution as $N \rightarrow \infty$ is not available then, the argument on the distribution form is valid as long as N is sufficiently large.

For the fast switching state, the growth of each molecule species is close to zero on the average. In this case the Langevin equation (12) can approach 0, and we need to consider the equation by seriously taking into account of the absorbing boundary condition at $N_m = 0$. By taking into account of the normalization of the probability, the stationary solution for the Fokker-Planck equation corresponding to eq.(12) for $\bar{a} \leq 0$ is given by

$$P(N) \propto N^{-(1+\nu)}, \quad (13)$$

with

$$\nu = |\bar{a}|/(\overline{a^2} - \bar{a}^2). \quad (14)$$

(see e.g., [40, 39]). Change of the exponent α against the error rate in Fig.18b will be understood as the change of the ratio of variance to the mean of a .

If several molecules mutually catalyze each other, however, one would expect that the fluctuations will not increase as in the Brownian motion as in eq. (12). For example, consider that the number of one species in the core cycle increase due to the fluctuation. Then it relatively decreases the number of molecules of the other species in the core network, resulting in the suppression of the catalytic reaction to replicate the increased species. Then the catalytic molecule of the original molecule species decreases. Hence the fluctuations in the core hypercycle is reduced.

Another reason for the reduction of fluctuation of the species in the core cycle is high connectivity in the IHN. The chemicals of core part has catalytic paths with a large number of molecule

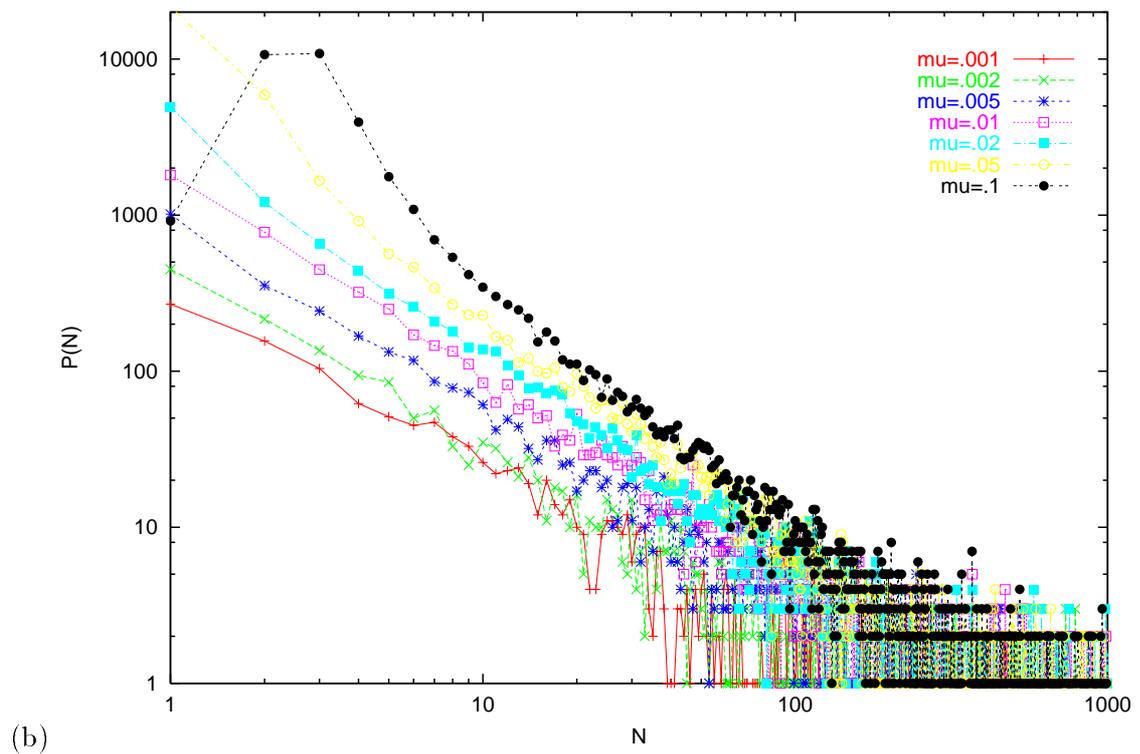
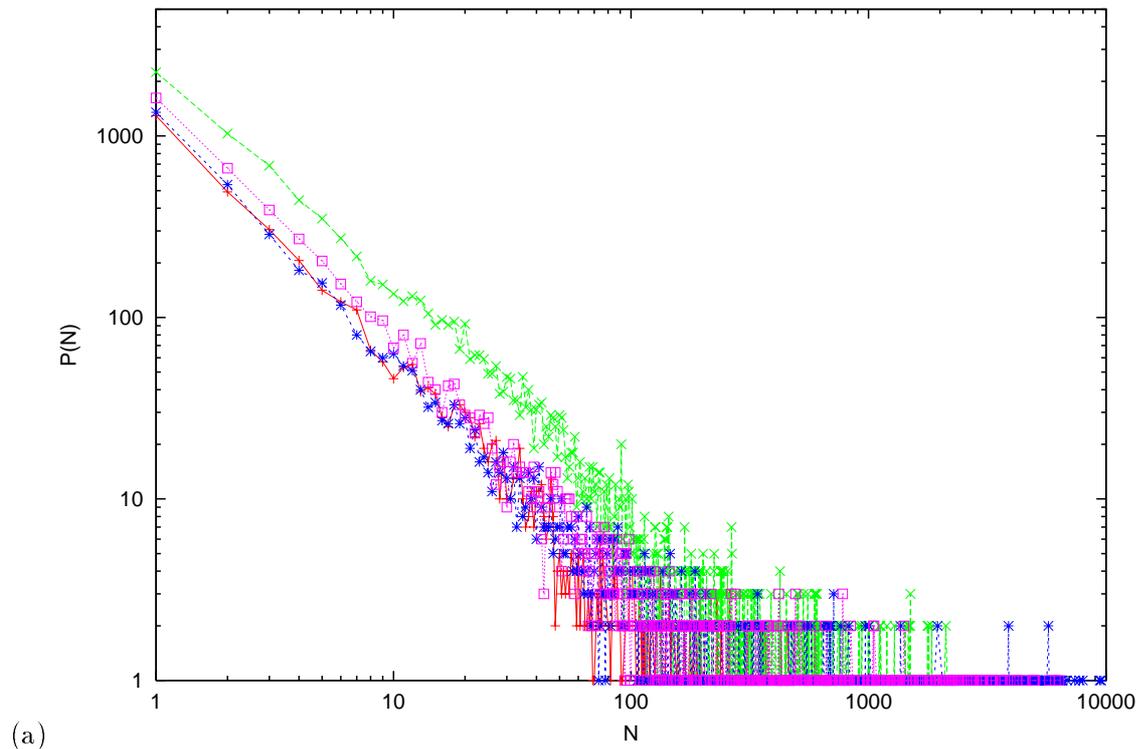


Figure 18: The number distribution of the molecules corresponding to the network in Fig.7 (fast switching states). (a); The distribution is sampled from 100000 division events. Plotted for 4 molecule species among 500. Log-Log plot. (b) Change of the distribution with the change of the error rate μ , for a specific molecule species.

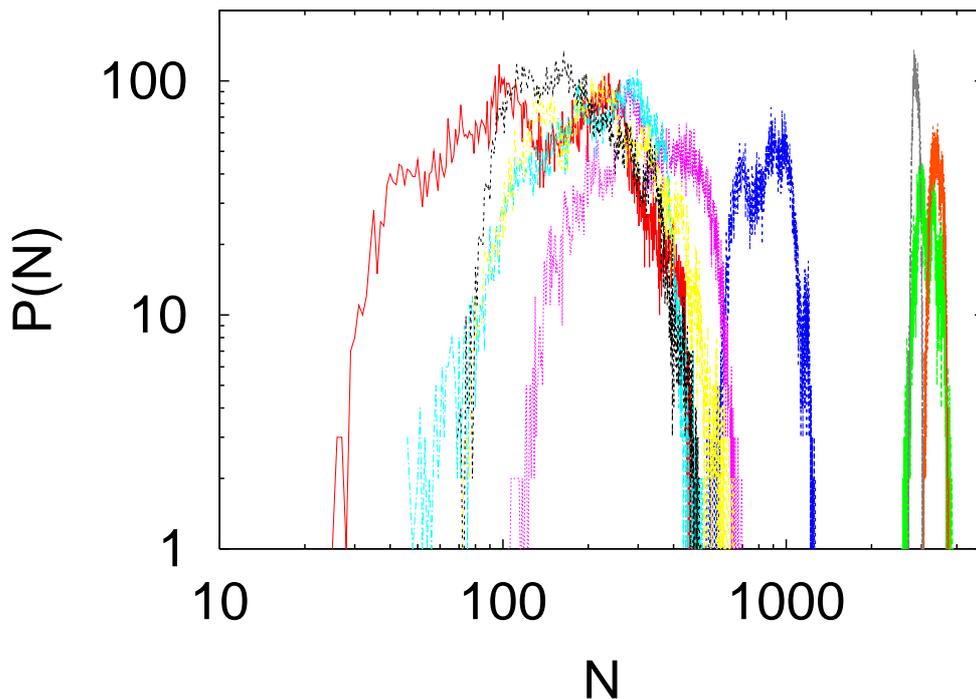


Figure 19: The number distribution of the molecules corresponding to the network in Fig.9a or 10a. The distribution is sampled from 1000 division events. From right to left, the plotted species are 11,109,13,155,176,181,195,196,23. Log-Log plot.

species. Hence many processes work in parallel to the synthesis of the core species. Then, fluctuations due to other chemical concentrations are added in parallel. Thus, the fluctuations can come close to Gaussian distribution (recall the central limit theorem).

Note also that for some networks, the distributions of the molecule numbers in the recursive sates may sometimes be intermediate between log-normal and Gaussian, and occasionally even have double peaks.

By studying a variety of networks, the observed distributions of the molecule numbers can be summarized as:

- (1) Distribution close to Gaussian form, with relatively small variances in the core (hypercycle) of the network.
- (2) Distribution close to log-normal, with larger fluctuations for a peripheral part of the network.
- (3) Power-law distributions for parasitic molecules that appear intermittently.

To quantitatively study the magnitude of variance in the IHN for the recursive production, we have also plotted the variance $\overline{(N_i - \bar{N}_i)^2}$ (\bar{N}_i is the average of the distribution $P(N_i)$). As can be seen in Fig.20, the variance in the core network are small, especially for the minority species (i.e., 13). For molecule species that do not belong to the core hypercycle, the variance scaled by the average increases as the average decreases. Suppression of the relative fluctuation in the core hypercycle comes from the direct feedback of the population change of the molecule species in the core, as well as multiple parallel reaction paths, as already mentioned.

Remark: Universal Statistics

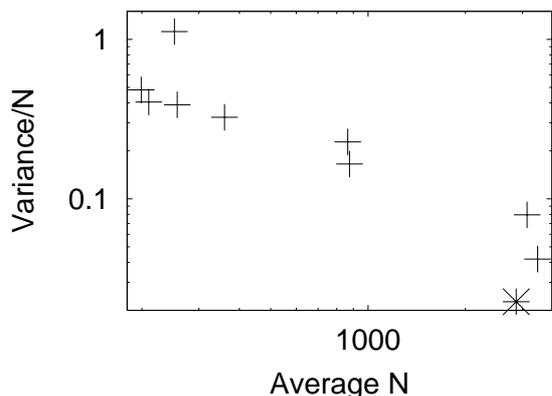


Figure 20: Scaled variance, i.e., the variance of the molecule number divided by its average is plotted against the average. From the largest to the smaller, the species 11 (the largest \overline{N}_i), 109 (the second largest), 13, 155, 194, 176, 195, 181, 196, 23, 34 (smallest \overline{N}_i) are plotted. Computed from the data in Fig.19. The asterisk denotes the species 13, that has largest catalytic activity here and the minority in the hypercycle core. Adapted from [33].

Quite recently Furusawa and the author[26, 42] have studied several models of minimal cell consisting of catalytic reaction networks, without assuming the replication process itself. In other words, the molecules are successively synthesized from nutrition chemicals transported from the membrane, where the level-(1) model of §3.2 is adopted. They have found universal statistical law of chemicals for a cell that grows recursively.

(i) The number of molecules of each chemical species over all cells generally obey the log-normal distribution. This distribution is universally observed for a state with recursive production. Existence of such log-normal distributions is also experimentally verified[26]. Ubiquity of log-normal distribution in the level-(2) model described in this section is thus supported in the level-(1) model.

(ii) A power law in the average abundances of chemicals. This is statistics against a huge number of molecule species. When the abundances of all chemical species are ordered according to the magnitude, the abundances of chemicals are inversely proportional to the rank of the magnitude. Such law was originally found in the linguistics by Zipf[41]. This Zipf's law on chemical abundances [26] is found to be universal when a cell optimizes the efficiency and faithfulness of self-reproduction. It is a universal statistics when the cell model shows a recursive growth under fluctuations in the molecule numbers. Furthermore, using data from gene expression databases on various organisms and tissues, the abundances of expressed genes exhibit this law. Thus, the universal statistics are also supported experimentally. It is shown that this power law of gene expression is maintained by a hierarchical organization of catalytic reactions. Major chemical species are synthesized, catalyzed by chemicals with a little less abundant chemicals. The latter chemicals are synthesized by chemicals with much less abundance, and this hierarchy of catalytic reactions continues until it reaches the minor chemical species.

Remark: Search for the deviation from universal statistics

So far we have observed ubiquity of log-normal distribution, in several models. The fluctuations in such distribution are generally very large. This is in contrast to our naive impression that a process in a cell system must be well controlled.

Then, is there some relevance of such large fluctuations to biology? Quite recently, we have extended the idea of fluctuation-dissipation theorem in statistical physics to evolution, and proposed linear relationship (or high correlation) between (genetic) evolution speed and (phenotypic) fluctuations. This proposition turns out to be supported by experimental data on

the evolution of E Coli to enhance the fluorescence in its proteins[43]. Hence the fluctuations are quite important biologically.

The log-normal distribution is also rather universal in the present cell, as demonstrated in the distribution of some proteins, measured by the degree of fluorescence[42]. Now, is this universality the final statement for "cell statistical mechanics"? We have to be cautious here, since too universal laws may not be so relevant to biological function. In fact, chemicals that obey the log-normal distribution may have too large fluctuations to control some function. Some other mechanism to suppress the fluctuation may work in a cell.

Indeed, the minority control suggests the possibility of such control to suppress the fluctuation, as discussed in §4.5. For a recursive production system, some mechanism to decrease the fluctuation in minority molecule may be evolved.

At least there can be two possibilities to decrease the fluctuation leading to deviation from log-normal distribution.

The first one is some negative feedback process. In general, the negative feedback can suppress the response as well as the fluctuation. Still, it is not a trivial question how chemical reaction can give rise to suppression of fluctuation, since to realize the negative feedback in chemical reaction, production of some molecules is necessary, which may further add fluctuations.

The second possible mechanism is the use of multiple parallel reaction paths. If several processes work sequentially, the fluctuations would generally be increased. When reaction processes work in parallel for some species, the population change of such molecule is influenced by several fluctuation terms added in parallel. If a synthesis (or decomposition) of some chemical species is a result of the average of these processes working in parallel, the fluctuation around this average can be decreased by the law of large numbers. Indeed, the minority in the core network that has higher reaction paths has relatively lower fluctuation as in Fig.20. Suppression of fluctuation by multiple parallel paths may be a strategy adopted in a cell. Note that this is also consistent with the scenario that more and more molecules are related with the minority species as discussed in §4.5. With the increase of the paths connected with the minority molecules, the fluctuation of minority molecules is reduced, which further reinforces the minority control mechanism. Hence the increase of the reaction paths connected with the minority molecule species through evolution, decrease of the fluctuation in the population of minority molecules, and enhancement of minority control reinforce each other. With this regards, search for molecules that deviate from log-normal distribution should be important, in future.

In physics, we are often interested in some quantities that deviate from Gaussian (normal) distribution, since the deviation is exceptional. Indeed, in physics, search for power-law distribution or log-normal distributions has been popular over a few decades. On the other hand, a biological unit can grow and reproduce, to increase the number. For such system, the components within have to be synthesized, so that amplification process is common. Then, the fluctuation is also amplified. In such system, the power-law or log-normal distributions are quite common, as already discussed here, and as is also shown in several models and experiments [26, 42]. In this case, the Gaussian (normal) distribution is not so common (normal). Then exceptional molecules that obey the normal distribution with regards to their concentration may be more important.

Also, the ubiquity of log-normal distribution we found is true for a state with recursive production. If a cell is not in a stationary growth state but in a transient process switching from one steady state to another, the universal statistics can be violated. Search for such violation will be important both experimentally and theoretically.

6 Summary

We have studied a problem of recursive production and evolution of a cell, by adopting a simple protocell system. This protocell consists of catalytic reaction network with replicating molecules. The basic concepts we have proposed through several simulations are as follows:

(i) **Minority control**

In a cell system with mutually catalytic molecules, replicating molecules with a smaller size in population are shown to control the behavior of the total cell system. This minority controlled state is achieved by preserving rare fluctuations with regards to the molecule number. The molecule species, minority in its number, works as a carrier of heredity, in the sense that it is preserved well with suppressed number fluctuations and that it controls the behavior of a cell relatively strongly. Since molecules that are replicated by this minority species are also preserved, more molecules will be synthesized with the help of it. In addition, reaction paths to stabilize the replication of this minority molecules is expected to evolve. Hence, the replication of more and more molecule species is packaged into the synthesis of this minority molecule, that also ensures the transmission of the minority molecule. The minority molecule species, thus, gives a basis for "genetic information". Hence evolution from loose reproduction system to a faithful replication system with genes is understood from a kinetic viewpoint of chemical reaction.

(2) **Recursiveness of production in an intermingled hypercycle network**

Next, a protocell model consisting of a variety of mutually catalyzing molecule species is investigated. When the numbers of molecules in a cell is not too small and the number of possible species is not too large in a cell, recursive production of a cell is achieved. This recursive production state consists of 5-12 dominant molecule species, which form intermingled hypercycle network(IHN). Within this IHN, there is a core hypercycle, while parallel multiple reaction paths in the IHN are important to ensure the stability of the state against invasion of parasitic molecules and against fluctuations in the molecule number.

(3) **Itinerant dynamics over recursive production states**

When the fluctuation in molecule number is not small enough, there appears switches over (quasi-)recursive production states. A given quasi-recursive state is destabilized by being taken over by some parasitic molecules. Then, the dominant molecule species change frequently by generations, where the growth speed of a cell is suppressed. After this transient, the fast change of chemical compositions is reduced so that a quasi-recursive production of a cell is sustained again. Each switching occurs with the loss of chemical diversity. Note that in high-dimensional dynamical systems, such switching over quasi-stable states through unstable transient dynamics is studied as chaotic itinerancy[44, 45, 46], where the loss of degrees of freedom is also observed in the process of switching.

Destabilization of a recursive state in the present model occurs through the decrease of the population of the minority molecules in the core hyper cycle. As this molecule species is taken over by parasitic molecules, the switching starts to occur. In this sense, the process in the switching is not random, but is restricted to specific routes within the phase space of chemical composition, as in the chaotic itinerancy. It is interesting to study the present switching over recursive state as a stochastic version of chaotic itinerancy.

(4) **Evolution through itinerant dynamics**

By considering change in the available reaction paths to the model, this hypercycle network evolves to recursive production states. Following the itinerant dynamics above, each recursive state is later destabilized, but later another recursive state is evolved. Through these successive visits of recursive states, a cell can evolve to have a chemical network supporting a higher growth speed. Since the minority species in the hypercycle network is relevant to this switch, minority molecules are shown to be important to evolution.

(5) Universal statistics and control of fluctuations

Statistics of the number fluctuations of each molecule species is studied. We have found that (i) power-law distribution of fast switching molecules (ii) suppression of fluctuation in the core hypercycle species and (iii) ubiquity of log-normal distribution for most other molecule species. The origin of log-normal distribution is generally due to multiplicative stochastic process in the catalytic reaction dynamics, as is confirmed in several other reaction network models. On the other hand, suppression of the number fluctuations of the core hypercycle is due to high connections in reaction paths with other molecules. In particular, reduced is the number fluctuations of the minority molecule species that has high catalytic connections with others. This suppression of fluctuation further reinforces the minority control for the reproduction of a cell. The deviation from ubiquitous log-normal distribution thus appears, which may be important in control of cell function.

In the present paper, we have not discussed cell-cell interaction, and restricted our study only to a production process of a single cell. Of course, cells start to interact with each other, as the cell density is increased through the cell division. Indeed, including the cell-cell interaction to the present cell model with reaction network, cell differentiation and morphogenesis of a cell aggregate are studied [15, 16]. Through instability of intra-cellular dynamics with cell-cell interaction, cell differentiation, irreversible loss of plasticity in cells, and robust pattern formation process appear as a general course of development with the increase of the cell number. Relevance of minority control and deviation from universal statistics to such multicellular developmental process will be an important issue to be studied in future.

acknowledgments

The author is grateful to T. Yomo, C. Furusawa, W. Fontana, Y. Togashi, A. Awazu, and K. Fujimoto for discussions. The work is partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, and Culture of Japan (11CE2006).

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