



Kinetic Origin of Heredity in a Replicating System with a Catalytic Network

K. KANEKO

*Department of Pure and Applied Sciences, College of Arts and Sciences, University of Tokyo,
Komaba, Meguro-ku, Tokyo 153, Japan*

Abstract. The origin of heredity is studied as a recursive state in a replicating protocell consisting of many molecule species in mutually catalyzing reaction networks. Protocells divide when the number of molecules, increasing due to replication, exceeds a certain threshold. We study how the chemicals in a catalytic network can form recursive production states in the presence of errors in the replication process. Depending on the balance between the total number of molecules in a cell and the number of molecule species, we have found three phases; a phase without a recursive production state, a phase with itinerancy over a few recursive states, and a phase with fixed recursive production states. Heredity is realized in the latter two phases where molecule species that are population-wise in the minority are preserved and control the phenotype of the cell. It is shown that evolvability is realized in the itinerancy phase, where a change in the number of minority molecules controls a change of the chemical state.

Key words: catalytic network, evolvability, heredity, minority control, origin of life

1. Introduction

In recent studies on isologous diversification [1–3], we have shown that cell differentiation and developmental processes are general characteristics of systems of interacting and replicating cells that contain mutually catalytic molecules. In such systems, a cell consists of several chemicals that catalyze each other. When the chemicals in a cell exceed a given threshold, the cell divides. Even though detailed mechanisms are not programmed in advance, differentiation of cell types, irreversible processes from multipotent stem cells to commitment, and robust development can be found.

Then one may ask what the role of genes is. As a possible answer to this question, we conjectured that genes come into action to fixate the the differentiation provided by the interaction of units with autocatalytic reaction networks. The idea is that some of the chemicals of the network provide a hereditary starting point that plays a role in controlling the phenotype of the cell. Indeed, a related idea was already proposed in the context of evolution, by Waddington [4] and Newman [5].

Since a gene is a part of the larger structure that is DNA, its action should be represented merely by a component of the catalytic reactions in the chemical network. How is it possible then that some chemicals are able to control cell differentiation?

To answer this question, we have recently proposed a minority-control theory [6]. In a system of mutually catalyzing molecules, a state is selected through reproduction where a minor molecule species starts to control the chemical state of the cell. This state is preserved over many generations of cells. In this chemical state termed the 'minority controlled state', a separation of roles between two sets of molecule species appears. One set has large numbers of molecules, maintaining the diversity of the species, while the other has small numbers of molecules but a larger catalytic activity. The latter set has the following two properties:

Preservation property: The molecule species are preserved well over generations.

The number of molecules per species exhibits smaller fluctuations compared to other molecule species, and their chemical structure (such as polymer sequence) is preserved over a long time span, even under potential changes caused by thermodynamic fluctuations during the synthesis of these molecules.

Control property: A structural change in the molecule species or a change in the number of the molecules has a stronger effect on the behavior of a cell, for example on the growth rate of the cell.

These two properties form the basis for heredity, causing statistical correlations between the phenotypes of ancestor and offspring. Due to the control property, the minority molecules govern the phenotype, and due to the preservation property, they can transfer the information relevant for determining the phenotype to future generations. Indeed, once this minority controlled state is established, a new evolutionary incentive emerges for embedding the representation of heredity into the minority molecule. Thus the emergence of genetic information from the minority-controlled state is expected.

In this earlier study, we considered only two molecule species with different synthesis speeds, one being much higher than the other. Or, equivalently, the catalytic activity of the latter is much higher than the former due to the mutual catalyzation for the synthesis. The minority controlled state is a consequence of this difference in the synthesis speeds. Then, the question remains whether it is a generic property of chemical reaction networks to select states with large differences in synthesis speeds resulting in recursive production controlled by a few minority molecule species. Furthermore, it is necessary to clarify how specific chemical compositions are stabilized as recursive states through control by minority molecules. Here it is interesting to note that cell differentiation in a model with interacting cells [1] was initiated by difference in the concentration of minority molecules by cells.

To answer this question, we consider a protocell system consisting of a large number of molecule species that catalyze each other. By carrying out stochastic simulations of such catalytic reaction networks, we will show in this paper that a biochemical state with minority molecules can establish recursive production. In

other words, we will show that the dynamic change of the chemical composition is stabilized by minority molecules that catalyze majority molecules, and that the minority molecule species carries this information through reproduction. Furthermore, we will also show that this minority controlled state has evolvability, since by only a slight change in the number of the minority molecules, the total chemical composition is drastically altered.

2. Model

To study the general features of a system with mutually catalyzing molecules [11], we consider the following simple model. First, we envision a (proto)cell containing k molecule species. (Not all of these species are necessarily present. Some of the molecule species may have zero population). With a supply of chemicals available to the cell, the molecules replicate through catalytic reactions, so that their numbers within a cell increase. When the total number of molecules exceeds a given threshold (here we used $2N$), the cell divides into two, with each daughter cell inheriting half of the molecules of the mother cell, chosen randomly. Each chemical species catalyzes the synthesis of some other randomly chosen chemical as



with $i, j = 1, \dots, k$. The connection rate of the catalytic path is given by p (which will be taken to be 0.2 or 0.1 for most simulations here), and the connection is chosen randomly. (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). Each molecule species i has a given catalytic ability $c(i)$ and its own synthesis speed $g(i)$. Accordingly, the above reaction occurs with the rate $g(i)c(j)$.

During the replication process structural changes may occur that alter the activity of the molecules. Therefore the replicated molecule species can differ from that of the mother. The rate of such structural changes is given by μ , which may not be very 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 a replication 'error'. Here, for the simplest case, we take this 'error' to affect all molecule species equally, (i.e., with the rate $\mu/(k - 1)$), and could thus regard it as a background fluctuation. Generally in reality of course, even after a structural change, the replicated molecule would keep some similarity with the original molecule, and the replicated species with the 'error' would be within a limited class of molecule species. Later we will discuss this case also, but the basic conclusion will not be altered. Hence we use the simplest case for most simulations.

We simulated this model according to the following procedure. In the beginning, we choose connection matrix randomly. Unless otherwise mentioned, the parameters $c(i)$ and $g(i)$ are given from a random number over $[0, 0.5]$, and they

are fixed through each simulation. At each step, a pair of molecules, whose species is assumed to be i and j , is chosen randomly. If there is a connection between the species i and j , then according to the reaction (1), one molecule of the species i is added with the probability $g(i)c(j)$ if j catalyzes the synthesis of i , or j is added with the probability $g(j)c(i)$ if i catalyzes the synthesis of j . The replications are subjected to errors with the rate μ given above. The error rate μ is fixed at 0.01 through the simulations here, but this specific choice is not so important as long as it is not too large. Since our model deals with rather small numbers of molecules, a stochastic approach was chosen for the simulations rather than the usual ordinary differential equations for chemical concentrations which cannot describe some novel effects [7].

When the number of molecules within a cell is larger than $2N$, it is divided into two, and a new cell is created. The total number of cells, M_{tot} , is kept constant so that one protocell, randomly chosen, is removed whenever a (different) protocell divides into two. Often we use $M_{tot} = 1$ here, where only one of the daughter cells remains. In this case, our model is quite similar to a stochastic simulation of the population dynamics of k molecule species, but in addition large fluctuations arise at each division event. Hence a recursive state that continues production has to be selected, resulting in a choice of special initial conditions for the chemical composition. This selection of initial conditions through repetition of divisions is important, especially when N is not large (or k is large). This selection of initial conditions distinguishes our model from standard population dynamics of molecules. With this model we address the question how recursive production is achieved, and how evolutionary change of the recursive state is possible.

3. Recursive States and Itinerancy

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 path rate p , besides the total cell number M_{tot} , the catalytic activity $c(i)$ and growth rate $g(i)$. By investigating many sets of parameters and also by choosing various random networks, we have found that there are roughly three types of behaviors:

- (1) Fast switching states without recursiveness
- (2) Itinerancy over several recursive states
- (3) Achievement of fixed recursive states

In the first phase, there is no clear recursive production and the dominant molecule species changes frequently. At one time step, some chemicals may be dominant but only a few generations later, this information is lost, and the number of the molecules in this species goes to zero. Due to the autocatalytic nature, the population of one species can be amplified, only to be replaced by another population catalyzed by it. No stable set of catalytic networks is formed that excludes other 'parasitic' molecules. (See for example the dynamics of chemicals around the last

stage of Figure 1a). In phase (1), this type of dynamics continues forever, without showing any quiescent state as around the middle of Figure 1a)).

In the second phase, alternately, recursive states which last over many generations (typically a thousand generations) and fast switching states appear (See Figure 1a).*

In the third phase, on the other hand, a recursive state is established, and the chemical composition is stabilized such that it is not altered by the division process. Once reached, this state is permanent and the system remains in it as long the simulation lasts (see Figure 1b).

To be precise, the recursive state observed in phases (2) and (3) is not necessarily a fixed point with regards to the population dynamics of the chemical concentrations. In some cases (as shown in Figure 1b), the chemical concentrations oscillate in time, but the nature of the oscillation is not altered by the process of cell division. In dynamical systems terms, the recursive state here is an attractor, and this attractor can be a limit cycle (or could be chaos or some other low-dimensional attractors), even though often it actually is a fixed point attractor. (In all of these cases there are fluctuations due to the small number of molecules, of course). Generally, all the observed recursive states consist of 5–10 species, except for those species which exist only as a result of replication errors with the number just one or two.

Which of the states (1), (2), (3) appears depends, of course, on the parameters and the specific choice of the network. First, we discuss how the phase changes when varying N and k , when $c(i)$ and $g(i)$ are distributed homogeneously over $[0, 0.5]$. We choose $M_{tot} = 1$, and $p = .2$, while we have not yet elucidated any clear dependence on p and M_{tot} so far.

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 (2), and then to (3) with the increase of N , or with the decrease of k . This is schematically drawn in Figure 2.

We now study what role the catalytic activity plays in maintaining the recursive states. In Figure 3, we have plotted the population of each molecule species as a function of the catalytic activity. For phase (1), no clear structure is discernible, although a slight tendency for the average population to decrease with an increase in the catalytic activity exists as is shown in Figure 3a). The maximum of each population, however, depends only minimally on the catalytic activity, implying that almost all species can be the dominant species at some time.

For phase (2), a clear structure can be observed and the maximum populations decrease for increasing catalytic activity. Indeed, this negative correlation between catalytic activity and population is not surprising. If the catalytic activity is higher it can help the synthesis of other molecules. Since the total number of molecules is limited, the fraction of that molecule population itself should be less.

* Such switching between several recursive states is also studied as chaotic itinerancy [8, 9].

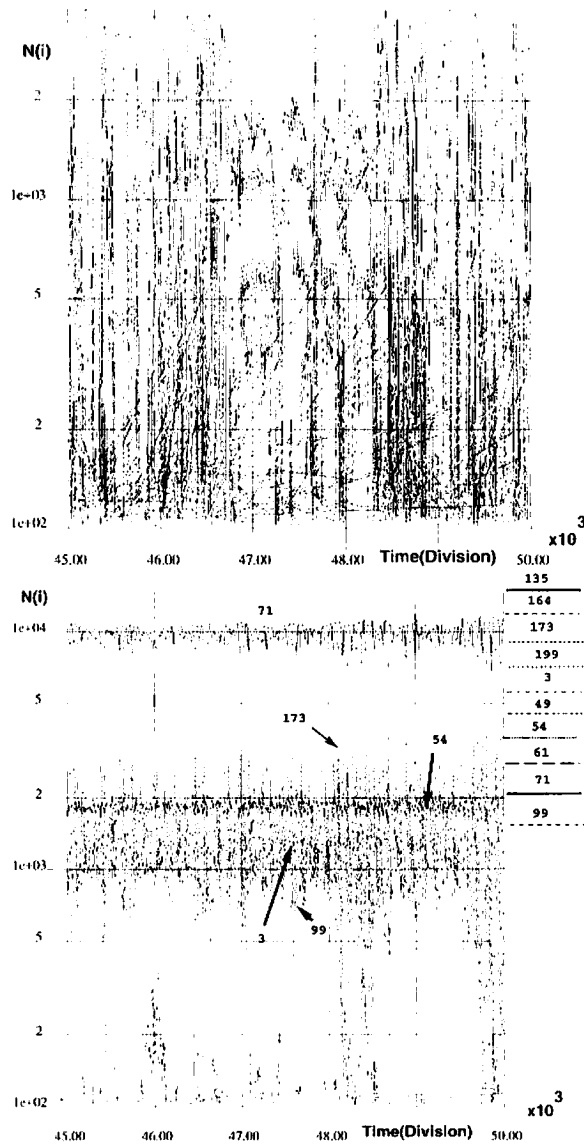


Figure 1. The number of molecules $N(i)$ for the species i is plotted at each successive division event. In both (a) and (b), the same random network with $k = 200$ and $p = .2$ was used while $N = 2000$ in (a), and $N = 6000$ in (b). Only the species with $N(i) > 10$ are plotted at each time. The straight lines are artifacts of the drawing occurring when $N(i)$ dips below 10 and then at a later time increases to above 10 again. The parameters $c(i)$ and $g(i)$ are randomly distributed over $[0, 0.5]$ and are fixed through the simulation. In (a), there appears a recursive state around 45.8×10^3 -th generation, and another recursive state appears around 47×10^3 -th generation and repeats collapse and reappearance up to 48×10^3 -th generation. In (b), a single recursive state lasts through the whole simulation, where 5 species (71, 173, 3, 54, 99 in the order of population size) continue to exist.

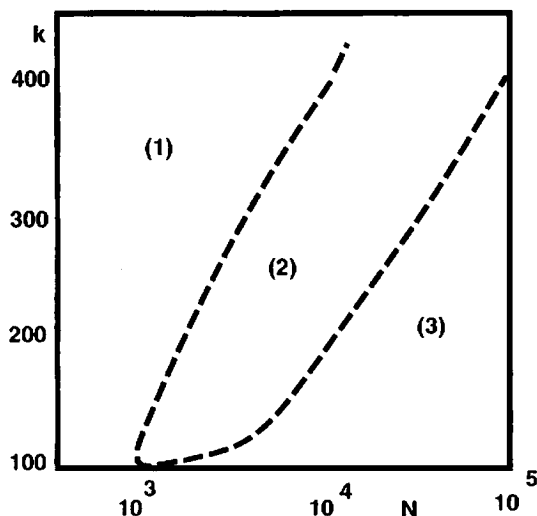


Figure 2. Schematic phase diagram, plotted as a function of the total number of molecules N , and the total possible number of molecule species k .

This negative correlation is amplified and fixed in phase (3), (as shown in Figure 3b). Here, only a few molecule species with small populations and high catalytic activity survive. Although these molecules are in the minority population-wise, their existence is essential for maintaining this recursive structure. The major species have lower catalytic activities, and accordingly they cannot catalyze efficiently other major molecule species. Indeed, the species with the majority of the population are catalyzed by the minority species. The latter is catalyzed by species with larger populations but with smaller catalytic activities. The surviving molecule species form a mutually catalyzing reaction network validating the assumptions made in the minority control theory.

For example, in the recursive state in Figure 1b, there are 5 species whose population remains in existence for all the time. The network structure of these molecule species is shown in Figure 4, with other molecules that exist not over all the time but over relatively long time span. The catalytic activities of the key species are $c(99) = .48 > c(54) = .39 > c(71) = .063$, while the respective populations are $N(71) \gg N(54) \gg N(99)$. The recursive state here is achieved by catalysis of the species 99 whose population is a minority in the network. When the total population is much smaller, the species 99 may decrease due to fluctuations and competition with other molecules catalyzed by the species 71. For example, in the collapse of the recursive state in Figure 2a, the population of the species 3 increases due to catalyzation by 71, and a state dominated by 71, 54, and 3 is formed. Since the catalytic activity of these molecules is not so high, the state is dynamically unstable and allows for an increase in the populations of other molecules. For example, the increase of the

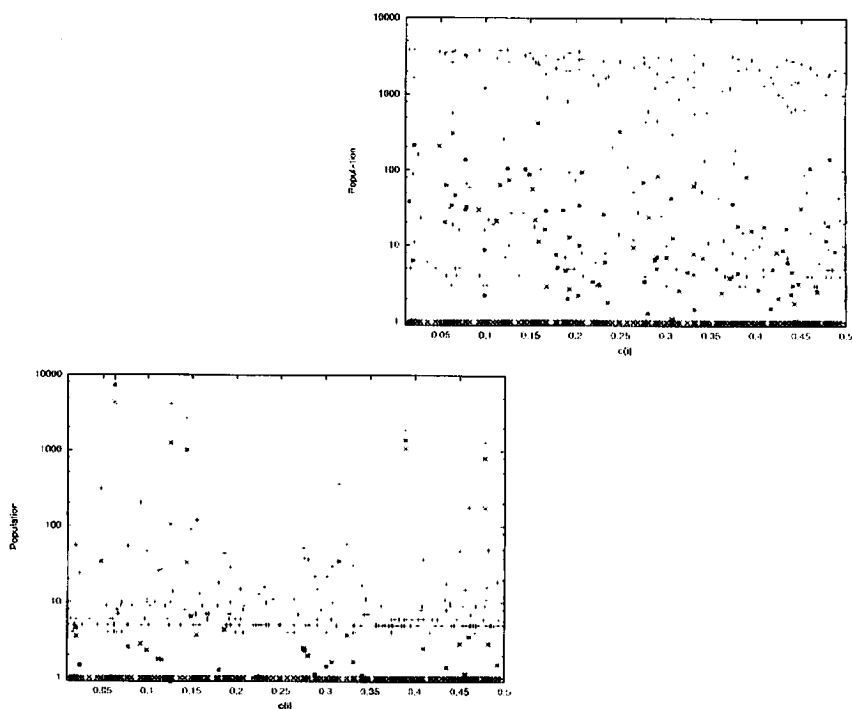


Figure 3. Average (*), maximal (+) and minimal (\times) populations of the species i , plotted as a function of their catalytic activity $c(i)$. The average, maximum and minimum are taken over the 500000–1000000th division. In (b), the five dominant species are discernible, which are species 71, 173, 3, 54, 99 in order of population size (i.e., in the reverse order of $c(i)$).

species 61 leads to the increase of species 18 and 137 ..., successively, and the recursive state is replaced by the fast switching state.

By examining several reaction networks, we came to understand itinerancy and the stability of recursive states as follows. As for the recursive state, one might won-

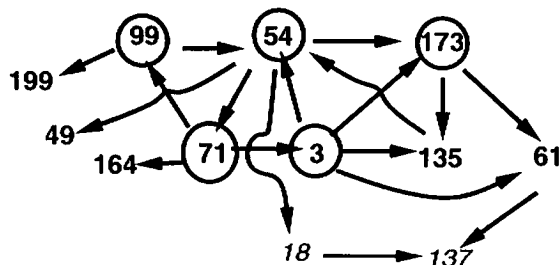


Figure 4. The core network for the recursive state (with numbers in bold), and a part of the parasitic molecules (with numbers in italic).

der why the species with higher catalytic activities are not taken over by parasitic molecule species that have lower catalytic activities and are catalyzed by molecules with higher catalytic activities. To sustain a recursive state, the emergence of such parasitic molecule species should be suppressed. In our model, molecules with higher catalytic activities are catalyzed by a molecule species with lower activities but larger populations. Hence, the parasitic molecule species cannot easily invade to disrupt the mutually catalytic core network. Since the minority molecule (say the species 99 in the above example) and majority molecule (71 in the above example) form a mutual catalytic network (with the aid of another molecule (54)), a large fluctuation is required to destroy this mutually supporting network.

For recursive stability, it is important that there are two levels of replication, i.e., molecular replication and cellular replication [10]. As parasitic molecules with lower catalytic activity appear, recursiveness is lost, and the state starts to change, while the total growth speed of the cell generally decreases. With cellular replication, the selection of initial conditions maintaining the recursive state is thus favored. In the minority controlled state, minority and majority molecules catalyze and reinforce each other, and the recursive state is stabilized.

This also allows us to explain how the itinerancy over (partially) recursive states appears in phase (2). When the number of molecules is not so large, the numbers of some molecule species that are not in the original core network start to increase. Since the total number of molecules in a cell is limited, the minority molecules may then decrease in number, and, if the total number of molecules is small enough, even become extinct. If that happens, the molecule species with a large population loses the main source that catalyzes it. Hence several molecules mostly of lower catalytic activity start to compete for growth. Consequently, the diversity of molecule species increases, and a stable recursive production cycle of cells is not established. There, the dominant species change frequently. After the system has been in a fast switching state for a while, another (or possibly the same) core network structure is formed where the existence of a minority molecule species with a higher catalytic activity stabilizes the recursive state.

With the above considerations it is quite reasonable to expect the transition from phase (2) to (3) for increasing N . After all, for larger N , the number of molecules in the minority species also increases thus protecting them from the extinction. However, the transition from (2) to (3) also strongly depends on the network structure. For some reaction networks, a simple core structure is easily formed and the recursive state is maintained even for small N . For some other networks, the itinerancy at the phase (2) is observed for large N . Although it is not so easy to distinguish these two cases by just examining the network structure, some differences seem to exist in the dynamics of the recursive state. If the state falls on a fixed point, recursiveness is stabilized for smaller N . On the other hand, when the population shows oscillatory behavior, dynamic instability is generated, and fluctuations in the species with small molecule numbers are continuously amplified. Hence the state is subjected to larger overall perturbations and stabilized only at larger N .

Acknowledgement

The authors would like to thank Walter Fontana, Tetsuya Yomo, Shin'ichi Sasa and Takashi Ikegami for useful discussions and Frederick Willeboordse for critical reading of the manuscript. This research was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (11CE2006).

References

1. Kaneko, K. and Yomo, T.: Isologous Diversification: A Theory of Cell Differentiation, *Bull. Math. Biol.* **59** (1997), 139–196.
2. Kaneko, K. and Yomo, T.: Isologous Diversification for Robust Development of Cell Society, *J. Theor. Biol.* **199** (1999), 243–256.
3. Furusawa, C. and Kaneko, K.: Emergence of Rules in Cell Society: Differentiation, Hierarchy, and Stability, *Bull. Math. Biol.* **60** (1998), 659–687.
4. Waddington, C.H.: *The Strategy of the Genes*, George Allen and Unwin LTD., Bristol, 1957.
5. Newman, S.A. and Muller, G.B.: Epigenetic Mechanisms of Character Origination, *J. Exp. Zool.* **288** (2000), 304.
6. Kaneko, K. and Yomo, T.: On a Kinetic Origin of Heredity: Minority Control in Replicating Molecules, *J. Theor. Biol.*, accepted.
7. Togashi, Y. and Kaneko, K.: Transitions Induced by the Discreteness of Molecules in a Small Autocatalytic System, *Phys. Rev. Lett.* **86** (2001), 2459.
8. Kaneko, K.: Clustering, Coding, Switching, Hierarchical Ordering, and Control in Network of Chaotic Elements, *Physica* **41D** (1990), 137–172.
9. Tsuda, I.: Dynamic Link of Memory-Chaotic Memory Map in Nonequilibrium Neural Networks, *Neural Networks* **5** (1992), 313.
10. Szathmary, E. and Maynard Smith, J.: From Replicators to Reproducers: the First Major Transitions Leading to Life, *J. Theor. Biol.* **187** (1997), 555–571.
11. Eigen, M. and Schuster, P.: *The Hypercycle*, Springer, 1979.
12. Ikegami, T. and Hashimoto, K.: Poster presentation in the present conference.
13. Segre, D., Ben-Eli, D. and Lancet, D.: Compositional Genomes: Prebiotic Information Transfer in Mutually Catalytic Noncovalent Assemblies, *Proc. Natl. Acad. Sci. USA* **97** (2000), 4112–4117.