Replication and Diversity in Machine-Tape Coevolutionary Systems

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Abstract

The origin and evolution of genetic system is studied by metaphor of machine-tape coevolutionary system. Mutation is taken as a rewriting process which machines act on tapes. A tape consists of a bit string, encoding a machine function. Tapes can be replicated only being read by adequate machines. It is reported in our previous studies that complex but stable autocatalytic structures evolve under effects of external noise. Ensembles of such autocatalytic networks are studied in this paper. Each network, embedded in a cell structure, can exchange machines with other networks. Each cell is assumed to be duplicated when a cell has a sufficient amount of mutually catalyzing machines. A daughter cell has the same kinds and populations of machines and tapes as its parental cell. It is found that developed cells are classified into two different types. One cell type has unstable dynamics which generates cell differentiation. The other cell type has stable dynamics which generates unlimitedly identical cell types. The former differentiating cells form an ecology with essentially large degrees of freedom. On the other hand, the latter cell types are cancer-like cells, whose dynamics cannot be effected by the other existing cells. Hence those cancer cells are characterized as those with independent small degrees of freedom.

1 Introduction

Biological processes are essentially very unstable. They consist of huge complicated chemical reactions. Not only due to their nonlinearity of interactions but to their context dependent usages of chemicals, it is very difficult to control by themselves. For example, a chemical A interacts with a chemical B to generate a chemical C but sometimes a chemical D. We cannot determine the whole possible reactions in advance. This nondeterministic and context dependent nature is not originated in statistics but is the essential feature of biological systems.

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On the other hand, life's other characteristics is to control stable self-reproduction. Most living things control their number of copies to balance with other living things. However, the above uncontrollable nature of living states may make it a difficult task.

John von Neumann first proposed an automaton model for self-reproduction [1]. In his abstract modeling, a necessary condition for self-replication is to distinguish a machine from its description tape. A machine (i.e. an entity which should be copied) is too unstable to replicate by itself. It can only be replicating by reading stable objects called tapes. Indeed, Neumann constructed replicating configurations consisting of machines and tapes in two dimensional plane with 29 automaton states.

However, possible self-replicating structures are quite fragile. A one bit flip of replicating pattern will lead to non-replicating structures. Even without external disturbance, replication becomes difficult. If we have two machines with different syntax for reading tapes, one machine may read tapes to produce different machines.

In the previous studies [2, 3], we have examined such situations by introducing simple machines and tapes model. Machines with different transition table compete in reading tapes. Due to external noise, machines make errors. We have found that external noise destabilize local replication (i.e. a machine reads a tape to produce the same machine and tape). But if the noise excesses some threshold, a network gives up local replication and acquires global replication. Namely, both machines and tapes are replicated globally to form a replicating network. We call a structure with such dual global replication a double loop structure.

Such core structure is stably retained even after removing external noise. Stable replication requires stable core structures. But on the other hand, we notice that it is too stable for evolution. Once there appears a stable core network, evolution will no longer be possible. To maintain evolutionability and diversity, it is important to remain certain kinds of instability in networks. In other words, a network should be balanced between stability and instability, being to be susceptible to open environments.

In the present paper, we study the ensemble of networks to discuss more about replication and diversity. Each network of machines and tapes is put in a cell struc-

ture not to directly couple with other networks. Cells can exchange machines but not tapes among other cells. Each machine can replicate by reading adequate tapes. At the same time each cell can replicate when there appear many mutually catalyzing machines in a cell. Cells with temporally oscillatory core networks can have many machines at one time so that it can divide. A daughter cell has the same kinds and population of machines and tapes as its parental cell. Simulating dividing cell assembly, we find that there exist two different cell types. One cell type has unstable dynamics, which can duplicate but cannot leave identical cell types. The other cell type has stable dynamics, whose division turns out to be perfect replication. Those stable cells proliferate exponentially, which are very insensitive to inter-cellular interactions. Duplication of the unstable cells forms a differentiated cell assembly. It makes essentially large degrees of freedom. On the other hand, because of its context-free behavior and exponential growth nature, the latter cell types are to be called cancer cells. It consists in a product of small degrees of freedom. We also report that inter-cellular interaction can suppress the emergence of cancer cell.

Recently, Kaneko and Yomo [4] have studied an assembly of cells with metabolic networks. Based on their simulations, they propose a new theory for cell differentiation from the dynamical systems view point. Our model system compensates for their system in several aspects. First, we are not propose a model for cell development but a model for the origin of genetic systems. How different genetic systems come to evolve to cooperate is our main concerns. Second, our system consists of two objects, machines and tapes. With this notion of duality, we can take a cell replication as tape-rewriting process. A new view of mutation as a rewriting computational process will be proposed here. Third, our system changes the network topology itself. Stable core network is destabilized by the other core networks. Consumption of common chemicals brings about cell differentiation in Kaneko and Yomo's model. In our model, external machines to a cell destabilize its replication to produce diversity of genetic systems.

2 Modeling

In the previous study, we have simulated the evolution of machines and tapes in one cell. We have shown that external noise brings about autocatalytic structures, called core networks. Once these core networks are formed, they are stably replicated even without external noise. In other words, we cannot expect the further evolution of network once a core network appears. The notion of core network includes a hyper-cycle structure proposed by Eigen and Schuster [5, 6, 7] as a special case. If all tapes are replicated locally, a notion of core network coincides with that of hypercycle. In general, tapes in core networks are globally replicated.

In order to study the further evolution of core networks, we introduce a cell assembly in the present paper. That is, machines and tapes are contained in a cell structure. Each cell can have different sets of machines and tapes. Hence its dynamics consists of two parts. One is intra-cellular dynamics which represents the population dynamics of machines and tapes in each cellular structure. The other one is inter-cellular dynamics which represents the global dynamics of cell assembly.

We assume two different levels of replication. One is replication of machines and tapes. The other one is replication of cells, which contain an ensemble of machines and tapes. Hence these replications are not mutually independent. A cell division at the same time means transfer of the ensemble of machines and tapes included in a cell. In below, we first introduce fundamental processes of machine-tape reactions. Then we introduce intra- and inter-cellular dynamics. Finally, we introduce division conditions and definition of cell mutations.

Fundamental Processes

A tape has a bit string of a circular form. A machine consists of 3 different parts, a head, a tail and a transition table. Each head and tail is expressed by a 4 bit string, whose pattern will be compared with binary patterns of tapes. A transition table consists of 4 mappings; $(\sigma^m, \sigma^t) \rightarrow (\sigma'^m, \sigma'^t)$, where σ^m and σ^t represents a current binary state of machine and tape. Tape and machine state change to (σ'^m, σ'^t), respectively depending on a current state of machine and tape.

(1) Interaction of machines and tapes

Machine $\mathbf{M_i}$ reads tape $\mathbf{T_j}$ iff tape $\mathbf{T_j}$ has a same pattern of head $\mathbf{h_i}$ and tail $\mathbf{t_i}$ of a machine $\mathbf{M_i}$ in a different site of the tape. The sites from a first bit of $\mathbf{h_i}$ to that of $\mathbf{t_i}$ is called the reading frame.

Then machine $\mathbf{M_i}$ reads a tape $\mathbf{T_j}$ and rewrites the reading frame according to its own transition table. A half population of machine starts to read a tape with the internal state 1 and the other half does with the state 0. We assume that there exist a sufficient amount of resource so that a pair of machine and tape generates a new tape $\mathbf{T_l}$ and a new machine $\mathbf{M_k}$ translated from the tape many times.

$$\mathrm{M_i} + \mathrm{T_j} \Rightarrow \mathrm{M_k} + \mathrm{T_l} + \mathrm{M_i} + \mathrm{T_j} \qquad (1)$$

(2) Translation of tapes:

Not only bits of a reading frame, but every bit of tape is repeatedly picked up to construct a new machine from a first site of the reading frame. If a length of a tape is not long enough, the same bit is used for coding several different part of a machine. In the present model, we use a fixed length of 7-bit tapes and 16-bit machines. A first 8 bits are mapped onto head and tail parts in order. The next 8 bits are mapped onto a transition table. In order to cover 16 bits by 7 bits, several bits are used twice or three times.

Each tape has a source where an attached machine starts to search for the head and tail pattern. Starting from the site, patterns are searched for in the clockwise direction of a circular tape. When a head pattern is found, a tail pattern starts to be searched in the clockwise direction. The site of source can be updated ran-

domly when the tape is newly generated after its extinction. An identical tape with different source can make different machines by being read by the same machine. Note that every translational invariant tape in a same cell has the same source site.

Intra-cellular Dynamics

We assume a finite capacity N for both tapes and machines. By iterating the following procedures, we simulate the machine/tape reactions:

1. Compute concentration of tapes (f^T) and machines (f^M) by dividing the population number by the capacity size N.

$$f_i^M = \frac{m_i}{N}, f_j^T = \frac{t_j}{N}, \tag{2}$$

where m_i and t_j are the population of the $i-th$ machine and the $j-th$ tape, respectively.

2. Make a total cN numbers of new machines and tapes from reaction of machines and tapes. Here the coefficient c gives a rate of new machines in a total capacity N. One generation is defined as the period needed to make cN new machines. The rate of reaction f_{ij} is given by,

$$f_{ij} = \frac{f_i^M f_j^T}{\sum_{k,l} f_k^M f_l^T}. \tag{3}$$

3. Remove d^M % of old machines and d^T % of old tapes.

4. Put the new machines and tapes back in a cell. Hence the population of tape j and machine i of the next generation becomes,

$$t_j' = (1-d^T)t_j + \sum_{k+i\to j} cf_{ki}N. \tag{4}$$

$$m_i' = (1-d^M)m_i + \sum_{k+j\to i} cf_{kj}N, \tag{5}$$

If no reactions occur, the second terms in the above equations vanish. It should be noted here that each machine has its unique description tape but the inverse is not true. Generally a tape encodes several machines depending on which machine reads the tape.

5. Taking an integer part of the above population, we obtain the actual population of the next generation. Hence the machine or tape whose concentration (f_i^M,f_j^T) is lower than N^{-1} is removed from the system.

Inter-cellular Dynamics

1) Interaction among cells

Only machines can be exchanged between cells. We assume that machines are corresponding to active chemicals, which can go across a cell membrane to interact with tapes in other cells. On the other hand, tapes are inactive chemicals which cannot cross the membrane. Introducing this diffusion processes of machines, time evolution of machine population in the above equation will become,

$$m_i^{'a} = (1-d^M)m_i^a(1-\epsilon) + \sum_{k+j\to i} cf_{kj}N, \tag{6}$$

$$m_i^{"a} = m_i^{'a} + \epsilon\frac{\sum_b m_i^{'b}m^a}{\sum_c m'^c}, \tag{7}$$

where $m'^a = \sum_j m_j^{'a}$ and $m^a = \sum_j m_j^a$. Population dynamics of tapes is same as before (i.e. eq.(4)). It should be remarked that tapes as well as machines have a cell index. In Eq.(6), m_i^a denotes a population of machine type i in a cell a. Combining equations 4),6) and 7), we complete population dynamics $\{m_i^a, t_j^a\} \to \{m_i^{"a}, t_j^{"a}\}$ for one generation.

The strength of interactions between cells is given by the parameter ϵ. A large ϵ value gives a large amount of machine flow between cells.

2) Cell division dynamics

We assume that a cell can divide when it possesses an enough amount of machines and tapes. The degree of this fertility of a cell is measured by the number of non-parasitic machines in a cell. If the cell fertility excesses a given division threshold T_D, the cell divides. Once a cell divides, it cannot be divided after G_{nd} generations. We also assume that if a cell fertility goes below the removal threshold T_R, the cell will be removed from a system. Hence the division/removal thresholds and non-replicating periods are main system parameters in the present simulation.

When division occurs, a population of every machine and tape is halved and transfered to descendant cells. Hence a division event always makes two cells with identical network structures.

Active Cell Mutation Rates

Average active mutation rates are computed for each cell. In the present study, no external noise is taken into account. *Mutation* is only caused deterministically. We call it active mutation since it does not replicate a tape but actively rewrites it. A rewritten tape can be taken as a miss-copy of the original tape. The rate of this mutation is measured by the rewriting rate for an interacting pair of machine and tape. If a machine i rewrites a tape j by w bits, a mutation rate of this reaction is given by,

$$\mu_{ij} = \frac{w}{L_{ij}}, \tag{8}$$

where L_{ij} denotes a length a machine i reads a tape j. Cell mutation rate is given by averaging over the all possible reactions in a cell. Namely, a mutation rate of a cell type a is computed as,

$$\mu^a = \frac{\sum_{(ij)} \mu_{ij} m_i^a t_j^a}{\sum_{(ij)} m_i^a t_j^a}. \quad (9)$$

We use this mutation rate for characterizing each cell type. Since different cell mutation rate indicates different network topologies or different composition of machines and tapes.

3 Results of Simulation: differentiation vs. replication

As an initial soup, we prepare roughly 20 randomly selected cells. Each cell contains 10 randomly selected machines and a few tapes. A machine without the description tape is unstable and smoothly removed from a cell. Hence a cell which contains machines with no description tapes will die out smoothly. On the other hand, a cell which evolves a core network will be stably sustained in a system.

Here we give a definition of a core network. A core network is an auto-catalytic network, where constituting machines are generating and being generated by the other machines within the auto-catalytic network. Necessary tapes to encode these machines are self-maintained in a core network. Different from a fixed state core, an oscillatory core changes its topology in the course of time. Not only populations of machines and tapes but a network topology itself varies in time. In Fig.1, we draw examples of temporal changes of topologies of core network. It changes from Fig.1-a) to Fig.1-g) and back to the same topology Fig.1-a) after approximately 23 generations in this example. This periodicity is dependent on a core structure.

The following is one example of cell evolution from an initial soup, which contains two cells with oscillatory core states and 8 cells with fixed state cores. Out of 8 fixed state cores, only one core has a non-trivial property, maintaining many machines and tapes. For given control parameters, only an oscillatory core can divide. Fig.2 is a cell phylogeny from a cell number 5 of an oscillatory core state. The other oscillatory state is destabilized to become a fixed state.

When a cell divides, it leaves an identical set of machines and tapes with the identical populations. Hence the duplicated cells show identical oscillations at least for a short period of time.

Same tapes will be created from the duplicated two identical cells. However sources of new tapes which do not present at the division time will be updated randomly. A source is a site from which machine starts to search for its head pattern. Therefore an identical tape with different source can make different machines being read by the same machine.

It seems that an assembly, which is consisted of a unique type of core structure, will not produce diversity of core networks. A cell division event always makes identical core structures. Even an oscillatory core cannot be destabilized by the own internal machines. But it can be perturbed by the external machines from other core networks under the inter-cellular interactions.

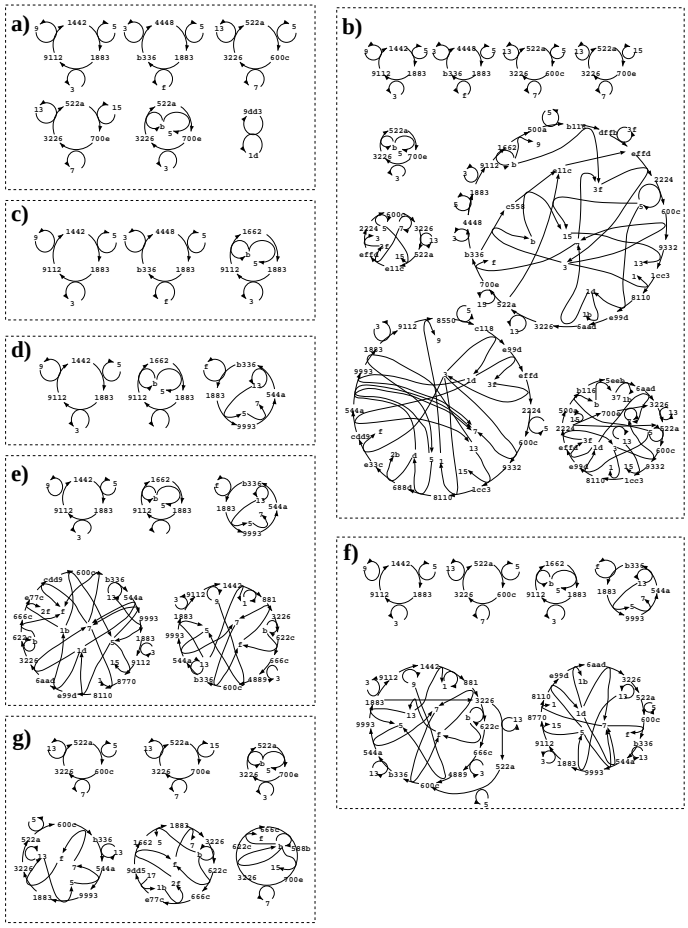

Figure 1: Oscillatory core networks at several generations within a period of time are selected and depicted by drawing their embedded autocatalytic loops separately. Within a loop, each machine and tape is denoted by its hexadecimal number converted from its binary representation. A symbol 9112 $\rightarrow^9$ 1443 indicates that a machine 9112 reads a tape 9 to generate a tape 9 and a machine 1443. All machines in core networks are mutually catalyzing. The topology of this core network changes from a) to g) and back to a) during each period of time.

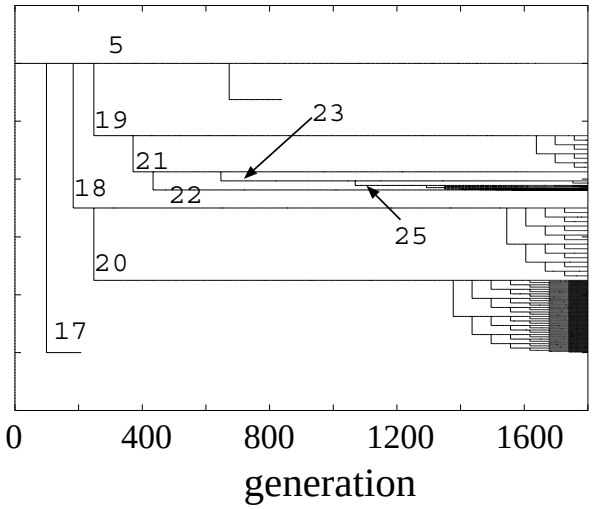

Figure 2: A cell phylogeny from an initial cell of an oscillatory core. The horizontal axis shows the generations. The lines connect cells with their direct descendants by a cell division. Division and removal thresholds T_D and T_R are given by 67 and 1, respectively with a non-dividing time G_{nd} by 50.

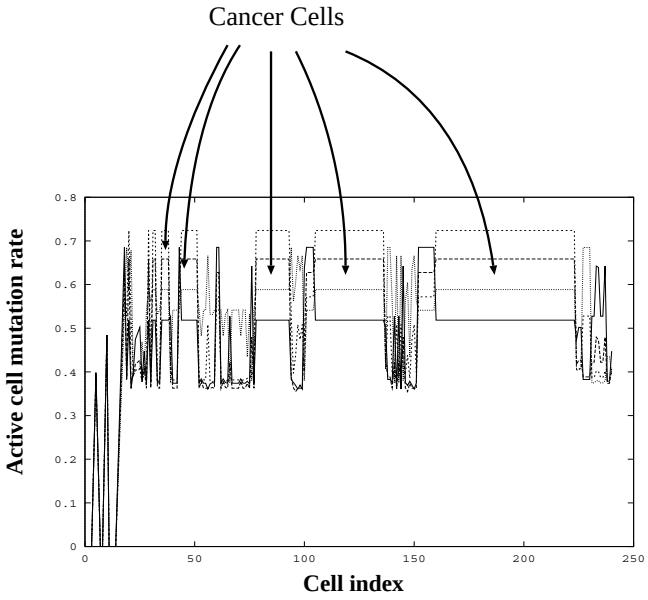

Figure 3: Active cell mutation rates at successive generations are overlaid against each cell index. The same level of cell mutation rates implies the same core network. Those corresponding to cancer cells are indicated in the figure. Division and removal thresholds T_D and T_R are given by 67 and 1, respectively with a non-dividing time G_{nd} by 50.

Tapes which do not constitute a core network are called peripheral tapes. A core topology is insensitive to how peripheral tapes code machines. But such peripheral tapes can become a big disturbance to a core structure when being read by external machines. Peripheral tapes often update their source since they are temporally extinguished and regenerated by definition.

Hence whether a cell can divide to leave identical cell types or not depends on how peripheral tapes are utilized by the external machines. In Fig.2, we see that an example of cell phylogeny in the course of time. Three different cell types, 18, 19 and 20, appear at the generation around 300. Until the generation around 1500, only the descendants of cell 21 can make the descendants. It is remarkable that this cell 21 fails to make exact copies. It differentiates, and leaving a variety of core networks. During this stage, other cells do not show any divisions.

After 1500 generations, all other cells begin to duplicate. As is seen in Fig.2, those divisions besides cell 21 look like bifurcations. That is, daughter cells always duplicate when their parents duplicates. It seems that such bifurcation can only increase identical core networks, and showing no differentiation. This is more clearly observed in Fig.3, where cell mutation rates at several generations are overlaid for each cell. We see that the descendants of cell 21 are becoming alike from each other. On the other hand, the descendants from other cells are exactly identical. Henceforth we call those cells which show complete replication cancer cells.

In Fig.4, we show the temporal evolution of cell mutation rates for the several descendants of cell 21. At the generation marked by 1, cells 76 and 56 begin to differentiate. At the next generation marked by 2, the new differentiation occurs. As the result, we have more than seven different cell types at the end 1800 generations for this cell lines. We note that different cell descendants sometimes can have the same cell mutation rates. In Fig.4, a cell type B appears at the different portion of the cell line of cell 56. Both cells 56 and 58 are descendants of cell 21, but their evolutionary pathway become quite different. It seems that the initial instability in cell 21 is inherited to the cell 58's cell line.

After 1500 generations, the descendants from all the other cells besides cell 21 will dominate the assembly. At the same time, the average cell mutation rates is elevated. Distribution of cell mutation rates averaged over generations 1800-1850 are depicted in Fig.5. We see that cells with rather high mutation rates are dominating the assembly. Distributed mutation rates($0.4 \sim 0.54$) with low population number are the descendants of cell 21. We will look into these mechanisms by the experiments in the following section.

4 Turning off cellular interactions

At one generation, some cells begin to replicate unlimitedly. But it doesn't seem that such cells have particular topologies. To reveal the mechanism of the unlimited growth of cells, we turn off the inter-cellular interactions at certain generations (Fig.6). Shortly after turning off the interaction, most cells start to replicate exponentially. This exponential growth is as same as what we observe in Fig.3 where inter-cellular interactions are allowed.

This experiment tells us that inter-cellular interaction

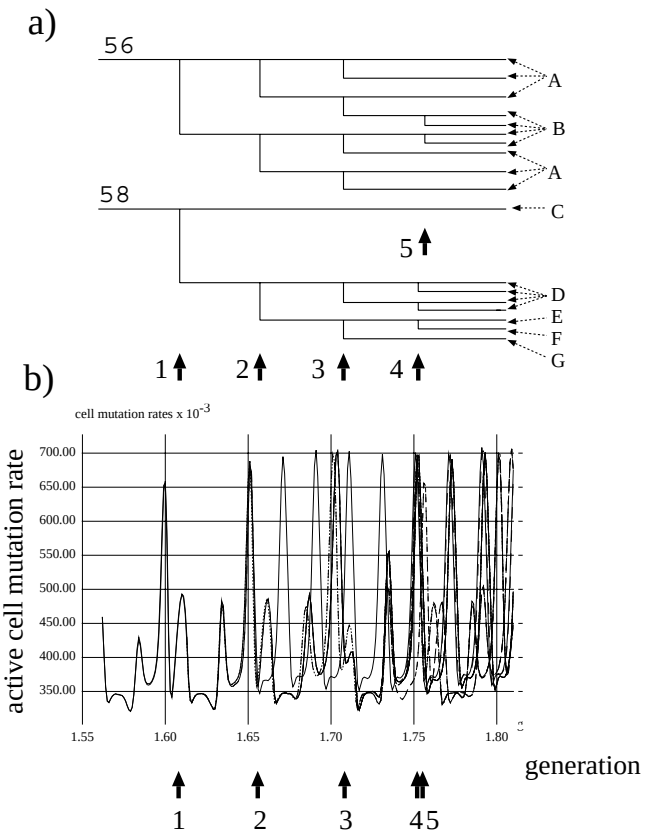

Figure 4: a) A partial phylogeny of descendants of cell 21. As in Fig.2, cells are connected with their direct descendants by lines. Alphabets attached to each end of cell lines are corresponding to groups having same active mutation rates. 7 different cell types (marked by A to G) can be specified with respect to their active mutation rates. b) Temporal evolution of active cell mutation rates. Those of descendants in the above phylogeny a) are overlaid. Marks (1,2,3,4 and 5) indicate division events. Division and removal thresholds T_D and T_R are given by 67 and 1, respectively with a non-dividing time G_{nd} by 50.

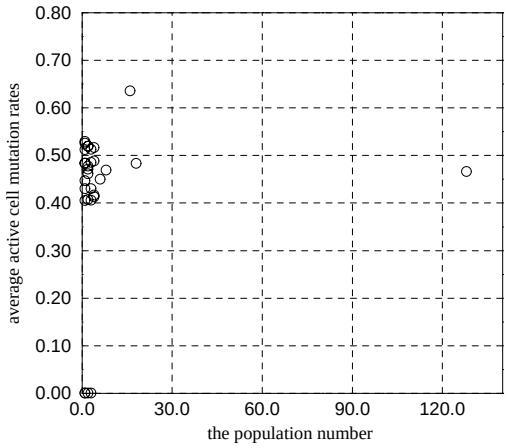

Figure 5: Active cell mutation rates, which are averaged over 50 generations, are plotted against the number of the cells having the mutation rates. Active mutation rates with a large cell number imply cancer cells. Those with the low cell number are corresponding to those of differentiable cell types. Division and removal thresholds T_D and T_R are given by 67 and 1, respectively with a non-dividing time G_{nd} by 50.

suppresses cells to become cancer cells. In other words, inter-cellular interactions keep cells in unstable states to prevent from exact replication.

Oscillating core networks can only become unstable cell states. It is known from our previous studies [8] that oscillating core structures have roughly 4 types. These are,1)periodic oscillation with its machine number ranging from 50 to 110; 2)Same number of machines with quasi-periodic oscillations; 3) Amplitude of machine number is bounded between 80 and 110 with quasi-periodic oscillations; 4) Quasi periodic oscillation with a small amplitude, where the average machine number is roughly 100.

If the core type 3) appears at a certain stage, it definitely shows strong replication. But we note that the core networks in both cancer and differentiable cells have rather common structures, which belong to the core type 2). Hence stability of core networks may be strongly dependent on their context, i.e. what kinds of cell structures exist in a cell assembly.

What kinds of core network can coexist with other core networks is more important for generating diversity in a cell assembly than an individual structures. The followings are the phenomenological evidences for the coevolution of different cell structures:

1) If there exists only one unique core structure from the beginning, the divisions will turn out to be perfect replication with exponential growth of the population number.

2) If there exist more than two different cells, division of cells can become unstable. A fixed state core cannot differentiate by itself. But cells with oscillatory core networks will be differentiated under the existence of fixed

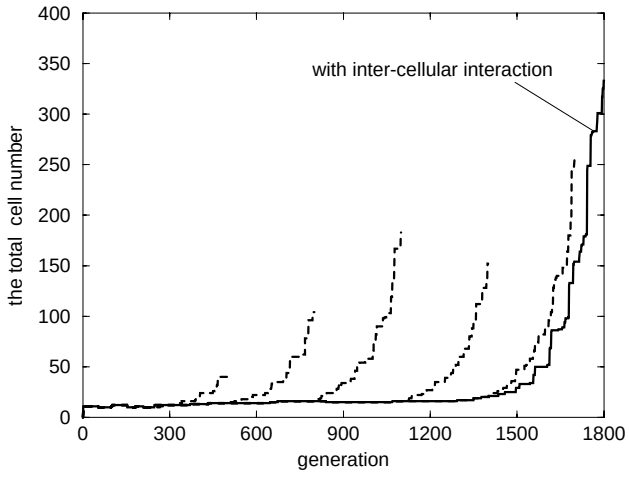

Figure 6: Inter-cellular interaction is turned off at several different generations (indicated by broken lines). Shortly after turning off the interaction, we see that a total number of cells exponentially grows. The right-most curve represents a growth curve of a system with inter-cellular interaction.

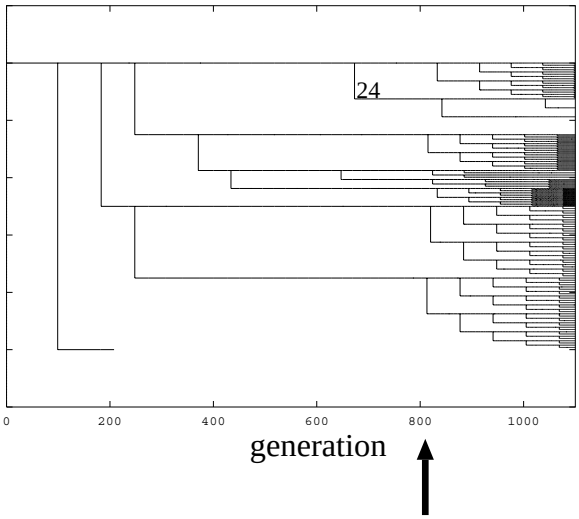

Figure 7: A cell phylogeny obtained by the interaction turning-off experiments. The interaction is turned off at generation 800, which is indicated by an arrow. We note that a cell 24 which has died at time step around 800 in Fig.2 will survive to replicate at later stages. Also a first parental cell 5 will begin to replicate.

state cores.

3) If we allow cells to interact but not to divide, oscillating cores are gradually extinguishing. Hence an assembly will be consisted of fixed state cores only.

4) Inter-cellular interactions can inhibit the emergence of cancer cells.

5) Morphology of phylogeny certainly changes after turning off the inter-cellular interactions. As is seen in Fig.7, most cells become cancer cells after the turning off event. Even a removed cell(i.e. cell 24) in Fig.2 can survive to divide. On the other hand, not every cell becomes a cancer cell with inter-cellular interactions. The environment for cancer cells are equivalent to those without inter-cellular interactions. However, the environment for the other cells are inflow machines from the cancer cells. Emergence of cancer cells accelerates the division of unstable cells without suppressing the differentiation.

5 Discussions

We have studied evolution of machine-tape networks in cell assembly.

Under the present conditions, cellular systems with only oscillatory core networks can divide. We found that there exist two different cell types. One cell type divides to leave different cell structures as its descendants. The others do perfect replications.

Whether a cell can perform perfect replication or not depends on the underlying dynamics of a core network. If a cell has a stable core network, it is not disturbed by the external machines from other cells. But if a core network is unstable, external machines will give a big disturbance to the core network. However such stability cannot be determined independently. It is strongly dependent on a structure of a cell assembly, which core networks are constituting of. Inter-cellular interactions prevents cells from becoming cancer cells. Namely, *who reads tapes* determines the stability of core networks. A small difference caused in the process of machines reading tapes will be enhanced to change the whole genetic code. Such instability may be related to the observation of description will be related to the "description instability" introduced by Tsuda [9]. BZ chaos absorbs external noise to generate stable periodicity. On the other hand, logistic chaos enhances external noise. If we simply take external noise as observation, stability of chaotic dynamics is dependent on how it is observed. Instability in networks with its description tapes may belong to this type of description instability.

It is interesting to note that a stable cell can replicate perfectly but an unstable cell cannot. An assembly with unstable core networks holds much diversity than ones with stable core networks. Such diversity is well reflected in the distribution of active cell mutation rates. Different active mutation rate implies the underlying different core networks. Unstable cells are difficult to transfer its core structure to its descendants. As the result, unstable cells show cell differentiation but stable cells only show exact replication. The increasing population of stable cells gives positive feedbacks on the whole assembly, leading to exponentially growth of the cancer cells. At the same time, the differentiation of unstable cells are accelerated.

It is further noted that unstable cell community forms a system with an essentially large degrees of freedom.

On the other hand, a stable cell community is composed of a direct product of a small degrees of freedom.

This picture reminds us of "homeochaos" [10, 11], which is proposed as the possible mechanism for sustaining diversity in a large host-parasite network. In the model, chaotic instability is shared by almost all species by sustaining a high mutation rate, leading to weak high-dimensional chaos, termed "homeochaos". The cellular ensemble of network supports this view in the different context in the present model.

Fontana's Alchemy [12, 13] shares common features with our system. His level 0 system is corresponding to our simple fixed state core and a level 1 to stable core structures. Instead of meta-inhibition of self-copying in Fontana's model, we have introduced external noise to bring about core structures. A level 2 corresponds to the present model, inter-cellular interacting system. What he calls "glue" is to corresponding to machine exchanges between different core networks. Inter-cellular interactions are producing such glue machines. We found that machines produced in one cellular system is just for a self-maintenance [2, 3]. On the other hand, machines produced in a cell assembly are for cell communication.

Are there any biological implications? I propose the following points for the real experiments.

1) To study more about the relationship between symbiosis and genetic systems. For example, diversification in genetic systems of mitchondoria are strongly dependent on whether mitchondoria is in animal cells or in green plant cells [14]. We expect that this can be a good example of coevolutionary aspect of different core networks.

2) To study how mutation rate in one cell effects mutation rates in other cells.

3) To study the suppression of cancer cells in a cell assembly due to its inter-cellular interactions.

4) To study the context dependency of protein usages. One is for the cell replication and the other is for the cell communication. Multi-cellularity is an evolutionary event that generates from genetic systems for self-replication to those for cell communication. Such context dependent nature of chemicals are also reported experimentally [15].

Acknowledgment

The authors are grateful to K.Kaneko, T.Yomo, Y.P. Gunji and Y.Takagi for stimulating discussions. This work is supported by Grant-in-Aids (No.07243102) for Scientific Research on priority are "System Theory of Function Emergence" from the Japanese Ministry of Education, Science and Culture.

References

[1] J.von Neumann, *Theory of Self-reproducing Automata* (ed. A.W.Burks, Univ. Illinois Press, 1966)

[2] T.Ikegami and T.Hashimoto, *Coevolution of machines and tapes* in "Advances in Artificial Life" (eds. F. Moran et al. 1995, Springer).

[3] T.Ikegami and T.Hashimoto, *Active Mutation in Self-reproducing Networks of Machines and Tapes* (to appear Artificial Life journal).

[4] K.Kaneko and T.Yomo, "Isologous Diversification: A theory of Cell Differentiation" (preprint, 1995).

[5] M.Eigen and P.Schuster, *Hypercycle* (Springer-Verlag, 1979).

[6] M. Eigen, Sci. Am. (1993) July, 32.

[7] P.Schuster, Physica 22D(1986) 100.

[8] T.Hashimoto, *Evolution of Code and Communication in Dynamical Networks* (PhD. thesis, University of Tokyo, 1996).

[9] I.Tsuda, *Chaos-teki Noukan*(in Japanese, Science-sousho, 1990).

[10] K.Kaneko and T.Ikegami, Physica D 56 (1992) 406:;

[11] T.Ikegami and K.Kaneko, CHAOS 2 (1992) 397.

[12] W.Fontana and L.W.Buss, Proc.Natl.Acad.Sci. USA 91 (1994) 757-761.

[13] W.Fontana and L.W.Buss, Bull. Math. Biol. 56(1994) 1-64.

[14] S.Osawa, Micro.Biol.Rev. 56(1992)229-264.

[15] A.Vallesi et al. Nature 376(1995) 552–524.