Morphogenetic Evolution of 3D Sheets Exploiting a Spatial Constraint

Shuhei Miyashita and Peter Eggenberger Hotz

Abstract— **In this paper we show how geometric constraints enable developmental processes to generate the morphology of three-dimensional folding sheets more easily. These sheets consist of artificial cells, which are connected and are able to exert forces on each other. To keep track of the complex pattern of connectivity, we introduce a cell connection map, which represents the internal states of the cells and is used to visualize these states. The performed simulations show that the system can easily produce some complicated morphogenetic forms and we show that the forms can be quantified as entropy by evaluating the cell connection map. This entropy was also used as a fitness function in order to evolve shapes. We would like to point out that once an adequate geometric constraint is given, the forms are generated by simple internal states and cell-cell interactions.**

I. Introduction

How an organism grows is still one of the big challenges of modern science. Multi-cellular organisms consist of large numbers of cells, which are able to form an organism by an intricate web of cell-cell interactions, a process called morphogenesis. As each cell contains the same genome, morphogenesis relies on autonomous and distributed processes with no centralized control. Although the elucidation of the molecular details of morphogenesis has made a lot of progress in biology, an overall picture is still lacking.

What is the essential morphology of multi-cellular organisms? There are several ways to categorize morphology. One is by focusing on the external appearance and say that the essential morphology is a cylinder or a cone [1]. However, when we focus on the internal organization, especially on the gastrointestinal tract of mammals, we would notice that the form is essentially a "tube" or a folded "sheet" as can be seen by the morphogenesis of the gastrointestinal tract [2]. Recently, Honda advocated that the form of a multi-cellular system is realized by folding sheets in complicated ways rather than by growing solid bodies [3].

Numerous attempts have been made to explain morphogenesis of multi-cellular organisms, focusing on the internal mechanisms of cells assuming special chemical substances. One significant mechanism that could work in the morphogenetic process is proposed by Turing [4] in his seminal paper. He described reaction-diffusion as a possible mechanism to explain some aspects of morphogenesis. In essence, reaction-diffusion mechanisms are means to break the symmetry among homogeneous cells in an autonomous and distributed way. This concept led to many related studies [5-7]. Although most research focused on the relation between chemical substances and pattern formation in animal markings, these mechanisms are not sufficient to explain all the mechanisms involved in morphogenesis.

Another important concept is positional information that enables the cells to know where they are [8-10]. Once again, these studies are mainly focusing on the internal mechanisms of cells without paying attention to the characteristics of the topology of the cell networks.

In other words, so far, little attention has been given to the topology of cell networks. That is, few researchers pointed out the possibilities of how the topology of a cell network plays a role in the morphogenetic processes. (Although the notion of topology of cell network is lacking, one exception is the research done by Odell et al [11]. They took a strictly mechanical approach, where physical interactions between the cells were programmed to simulate morphological processes). In fact, this can be said not only to the cell networks but also to the whole network (graph) theory. Traditionally, networks of complex topology have been described using the random graph theory of Erdös and Renyi [12]. For quite some time, the topology of the networks, which can be found in the real world, was thought to be random. But recently Barabasi and Albert showed that existing network models fail to incorporate some features of real networks [13]. They demonstrated that independently of the nature of the system and the identity of its constituents, the probability that a vertex in the network is connected to other vertices decays according to a power law. This new statistical notion (called "scale free network" since the characteristics do not depend on the scale) had a big impact on the theory of networks. Watts and Strogatz have introduced a new model that is called "small-world network" [14], which exhibits small-world properties, while it remains highly clustered. Since these new points of view have universal aspects, they have influenced a vast research area.

In the field of nano-technology, it was discovered that carbon atoms can create special forms such as fullerene or carbon nanohorn [15], which forms a projection. These forms are realized mainly because each carbon atom has four hands to connect to others. And by exploiting its geometric constraints, carbon atoms grow into specific forms easily. In other words, such forms are "easily" obtained by the geometric constraints of carbon atoms. This gives us a suggestion that when an adequate geometric constraint is given to the constituents of the system, the global forms are realized even without complicated internal states nor

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informational interactions.

Accordingly, as a working hypothesis, we assumed that morphogenesis depends on the following three conditions:

1) Morphogenesis is an autonomous, distributed process without any centralized control for all cells
2) Morphogenesis of living things is often using expanding and folding sheets in order to build three dimensional forms
3) The physical cell-cell interactions are constrained by the geometric topology of the cells

We used these three conditions as guidelines to screen the existing literature of morphogenetic models.

As for the rest, a lot of interesting research about morphogenesis can be found, especially in the field of artificial life. The numerous approaches for morphogenesis can be divided into several types: Linguistic grammars [16], cellular automata [17], [18], recurrent diagram networks expressing the bodies of simulated creatures [19], [20]. One of the first evolvable morphogenetic systems was Biomorphs, which was developed by Dawkins [21]. This system generates forms by random mutation followed by a non-random selection showing that this process can generate interesting and complex forms. Recently there was a renewal of interest in the relations between gene regulatory networks and morphology [22-27]. Tomita et al. extended the grid space into a graph model, maintaining the concept of internal states derived from Neumann's work [28]. In this model, all cells have three edges to connect to the neighbors. Furusawa and Kaneko found the phenomena of dynamical cell differentiation by creating their own model [29]. Our concern is to consider how network topology plays a role in the process of morphogenesis of a sheet form.

After the model is presented in section II, simulation results are given in section III. Following that is a general discussion of this model in section IV. And finally the conclusions are given in section V.

II. Model

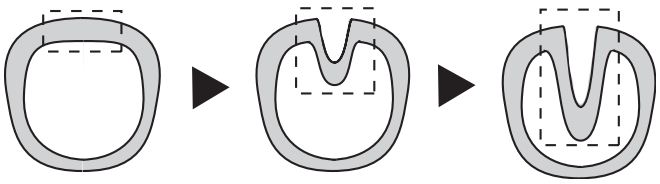

Fig. 1. Gastrulation. the internal wall of an embryo grows into a gastrointestinal tract.

During gastrulation, the internal wall of a mammalian embryo grows into a gastrointestinal tract [30]. Figure 1 represents the cross-sectional view of our model, which represents the growth of the gastrointestinal tract. In our model, we choose the cell as the level of abstraction. The system consists of cells connecting to each other. Note that although some settings are not plausible in biology, we would like to investigate how the spatial constraint affects the whole morphogenetic process.

In the following subsections, first the characteristics of the cells that we modeled are shown. Then we explain the physics, which is working in the system and in the last subsection the evolutionary mechanism used to evolve the models are introduced.

A. Cell behaviors

1) Cell behavior rules: cell division, forced cell division, and cell death: In our model, cells divide or die depending on the number of their neighbors. This is according to the fact that one of the possible biological mechanisms assumed to code the behavior of morphogenesis would be the concentration of chemical substances that diffuse into neighboring cells through certain channels. In other words, this concentration could reflect the number of neighbors, an effect which is called "community effect" in biology. This effect is a mechanism whereby a population of cells must be present to change the collective cell fate. This special form of cell differentiation (cell induction) involves autocrine signaling, where the cells secretes signals to their own receptors [2]. Once the cell division rule takes place, the cell divides into four cells. This type of cell division will sustain the symmetry of the cell network and makes the system symmetrical, which facilitates the analysis of the network. For future work we plan to implement asymmetry and compare them to the already obtained results. We also implemented a so called "forced" cell division rule as a third rule, which forces each cell to divide at each time step.

In the case of the cell death rule, the cell is deleted by cutting all connections to its neighbors.

2) Cell behavior rules are applied synchronously: The cell behavior rules are applied synchronously in a specific order. After a certain time (40 steps - arbitrary decided from experience - so that the system obtains enough time to converge into an unique form), all cells count their neighbors and execute one of the three defined rules (This means that each cell contains a "global clock").

3) Cell connection maps: It is difficult to keep track of the cell-cell connections after cell division in a two-dimensional topology. Therefore, we introduced a cell connection map, which describes the relation of the cell connections and can be visualized. Figure 2 shows how the cell connection map prescribe the relations when a cell divides.

In the map of Figure 2, a part of the cell connections are displayed at the top, and the cell connection map is shown at the bottom. Each square corresponds to a cell. When a cell divides, the respective square in the cell connection map is divided into four small squares. And the new squares are connected to the nearest neighbors (Moore or Neumann neighborhood). When a cell is deleted, the square corresponding to the cell is also removed. Due to this setting, the system is capable to grow like an expanding

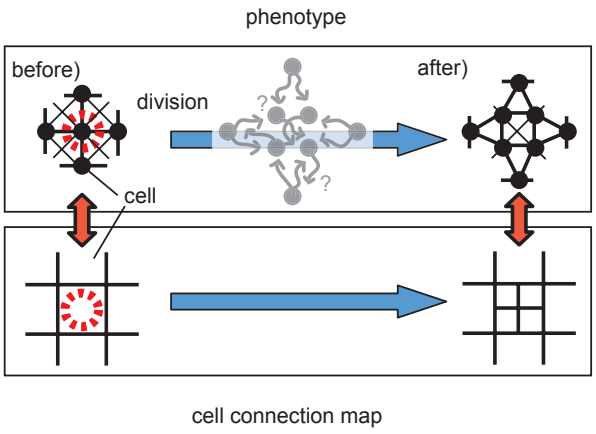

Fig. 2. Cell reconnection. A part of the cell connections are displayed at the top, and the cell connection map is shown at the bottom. The cells are represented as squares in the cell connection map. When a cell divides, its representation in the connection map is divided into four smaller ones, which corresponds to the birth of four new cells.

"sheet". We start the simulation with 4 or 16 cells, and the cell connection map is derived from 4 or 16 single squares. The important point to note here is that the map was introduced to implement a cell reconnection mechanism that sustains two-dimensional topologies in the system. The form is created through cell-cell mechanical interaction. It is also important to note that a cell connection map itself is also configured in an autonomous and distributed way through the morphogenetic process.

B. Mechanical cell-cell interactions

Important aspects of development are the inherent physical properties of the used materials. The forms in this work are defined in a simulated three-dimensional environment as a surface mesh structure consisting of masses and springs that represent cells and their mechanical connections, respectively. These springs are generally passive and exert a force on the two connected vertices proportional to the deviation from the spring's rest length. Although it takes time to converge to a form, the form of cell network topology is unique to each sequence. The important point here is that although the map changes in an autonomous and distributed way, also the form corresponding to this map converges to a unique form.

We show the parameters of the system in Table I. The numeric equation solving the motion of the cell i is expressed in eq.1 with the parameters listed in table I.

$$m\ddot{\mathbf{q}}_\mathbf{i} + c\sum_j(\dot{\mathbf{q}}_\mathbf{i} - \dot{\mathbf{q}}_\mathbf{j}) + k\sum_j\left(1 - \frac{l}{|\mathbf{q}_\mathbf{i} - \mathbf{q}_\mathbf{j}|}\right)(\mathbf{q}_\mathbf{i} - \mathbf{q}_\mathbf{j}) + a\frac{\mathbf{q}_\mathbf{i} - \sum_j \mathbf{q}_\mathbf{j}}{|\sum_j \mathbf{q}_\mathbf{j}|} + g\mathbf{q}_\mathbf{i} = 0 \quad (1)$$

The indices i, j are the identification numbers of the cell. The position of a cell q_i is defined as a vector. The cell which exists in the neighborhood of cell i is denoted as j. Gravity is also added to the system. All mass points are subjected to a force from the center of the mass, which acts as a kind of internal pressure, keeping the structure from folding in itself (c.f. Table I). The differential equation is integrated by the Euler method ($\delta t = 0.01$, 1step=$30\delta t$).

TABLE I
SETS OF PARAMETERS.

Symbol	Definition	Value
m	mass	10
c	damper coefficient	30
k	spring coefficient	50
l	spring natural length	50
a	internal pressure	1000
g	gravity	25

C. Genetic Algorithms

Genetic Algorithms (GA) were originally designed as a search technique, inspired by evolution using natural selection to 'breed' good solutions [31-33]. These algorithms often find quickly a good solution in high-dimensional parameter space.

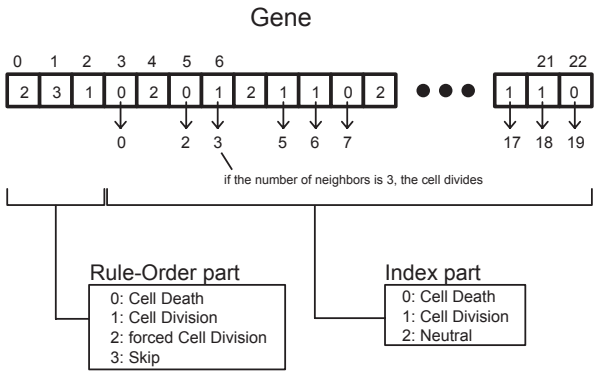

Fig. 3. Structure of a gene. The gene consists of 23 digits. The first three digits represent in which order the cell behavior rules are applied. Each of the next 20 digits represents a member out of a set of possible cell behavior rules(from 0 to 19 in the box 4 to 23, respectively).

1) Gene Coding: The structure of a gene was hand-coded. The gene consists of 23 digits (Figure 3). The first part of the gene (Rule-Order part) encodes the specific order in which the cell behavior rules are applied. Each type of behavior, Death, Division, Forced-Division, or Skip is specific by a unique value, 0, 1, 2, and 3, respectively. For example, if the numbers in the box 0, 1, 2 are 2, 0, 1, the forced cell division rule, cell death rule, and division rule are applied in this order starting with the forced cell division rule. And by implementing the Skip rule here, the system can avoid applying those rules three times each time in every case. In the next part of the gene (Index part), the position of gene indicates "number of neighbors" and thus the rule, such as Death, Division, or Neutral, that is indicated within a position

of the gene applies to any cell with number of neighbor = index. For example, if the number in box 6 is 1, each cell divides if the cell is surrounded by 3 cells. The index is limited up to 19, because that it has been known through the experiment that frequently used indices are under 10 in most case. Random numbers are used for the genes in the initial population. We used the Mersenne Twister algorithm for all random numbers [34].

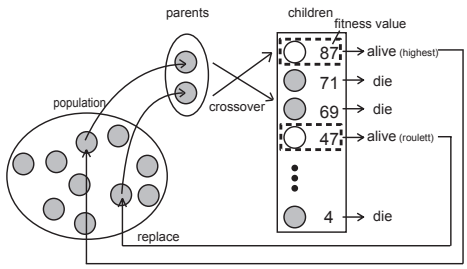

Fig. 4. Minimal generation gap. 40 individuals are prepared as a population. Two individuals are chosen as parents. By applying double crossover to those genes, new types of genes are generated as children. 40 children are created out of a parent set and roulette selection was applied.

2) Minimal Generation Gap algorithm is used for natural selection: The population consisted of 40 individuals. We chose the Minimal generation gap algorithm (Figure 4) as changing generation process [35]. Two individuals are chosen as parents. By applying double crossover to those genes, new types of gene are generated as children. 40 children are created by one parents set. The one which has most highest fitness and the other chosen by roulette selection are preserved and replaced as new parents instead of the old one.

3) Fitness Function: The form of living things plays an important role in their environment. However, their evaluation is quite difficult and tends to be arbitrary. In this research, we hypothesize that the more complicate organ the individual has, the better - that means the individual gets highly functional gastrointestinal tract for digestion and acquires a high probability to survive. Here, we decided to evaluate the form by analyzing the proposed cell connection map, it can be easily estimated by defining "entropy", which represents the complexity. As a fitness value we used this entropy - which is described by the following equation (2), where S_i denotes the area of each cell in the cell connection map with subscript i as an identification number for each cell.

$$F = -\frac{1}{N}\sum_{i} log\frac{S_i}{S_T} \tag{2}$$

The characteristics of this fitness value are as follows:

1) The larger the entropy of the area size gets, the higher the value of the fitness becomes, if the sum of the areas is the same.
2) The larger the number of cells is, the bigger the value becomes, if the sum of the areas is the same.
3) If cell distribution is the same, it doesn't depend on the scale.

We set the area of the whole map to 1.0. S_T represents the sum of all areas of the cells. We normalized the value by dividing a number of cells, N.

III. Simulations and Results

By applying those settings using several parameter sets, such as initial number of cells, neighbor conditions, and seeds of Mersenne Twister Algorithm, some fundamental morphogenetic processes are observed.

A. Fitness Transition and diversity of the phenotype

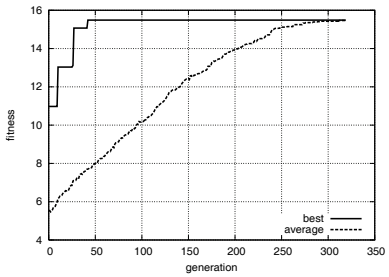

Fig. 5. Fitness Transition. Between generation 50 to the generation 150, diversity of the phenotype is observed. All the interesting forms of Figure 6 are obtained in this window.

Figure 5 shows the fitness transition graph. We show 10 examples of evolved phenotypes in Figure 6. Top views are shown on the left, and side views are shown on the right in each example. All these phenotypes are using the Moore neighborhood to count the number of the neighbors. The initial numbers of cells are listed in the brackets. The conditions of the cell death and cell division are listed in each example. The alphabets in those blankets represent the order of cell behavior rules, DE: cell death, DI: cell division, and FD: forced cell division, respectively. The numbers after N and F represent the number of cells that comprise each individual and the fitness value, respectively. Those phenotypes were always generated in the early stage of the evolution (approximately between the generation 50 and 150). Note that the number of cells is in the order of thousand.

B. Two examples of exponential growth in detail

Figure 7 and Figure 8 illustrates two examples sequences of the implemented morphogenetic process. In both sequences, the number of cells increases exponentially.

1) Exponential growth sequence A: In Figure 7 the morphogenesis of the exponential growth called sequence A is illustrated. As the figure shows, once the shape part (A) is created, it does not change any more. At the same time, same kinds of clusters are generated in other part (B, C and so on). This shows that the system keeps generating many "clusters" whose sizes remain the same in different parts of the body.

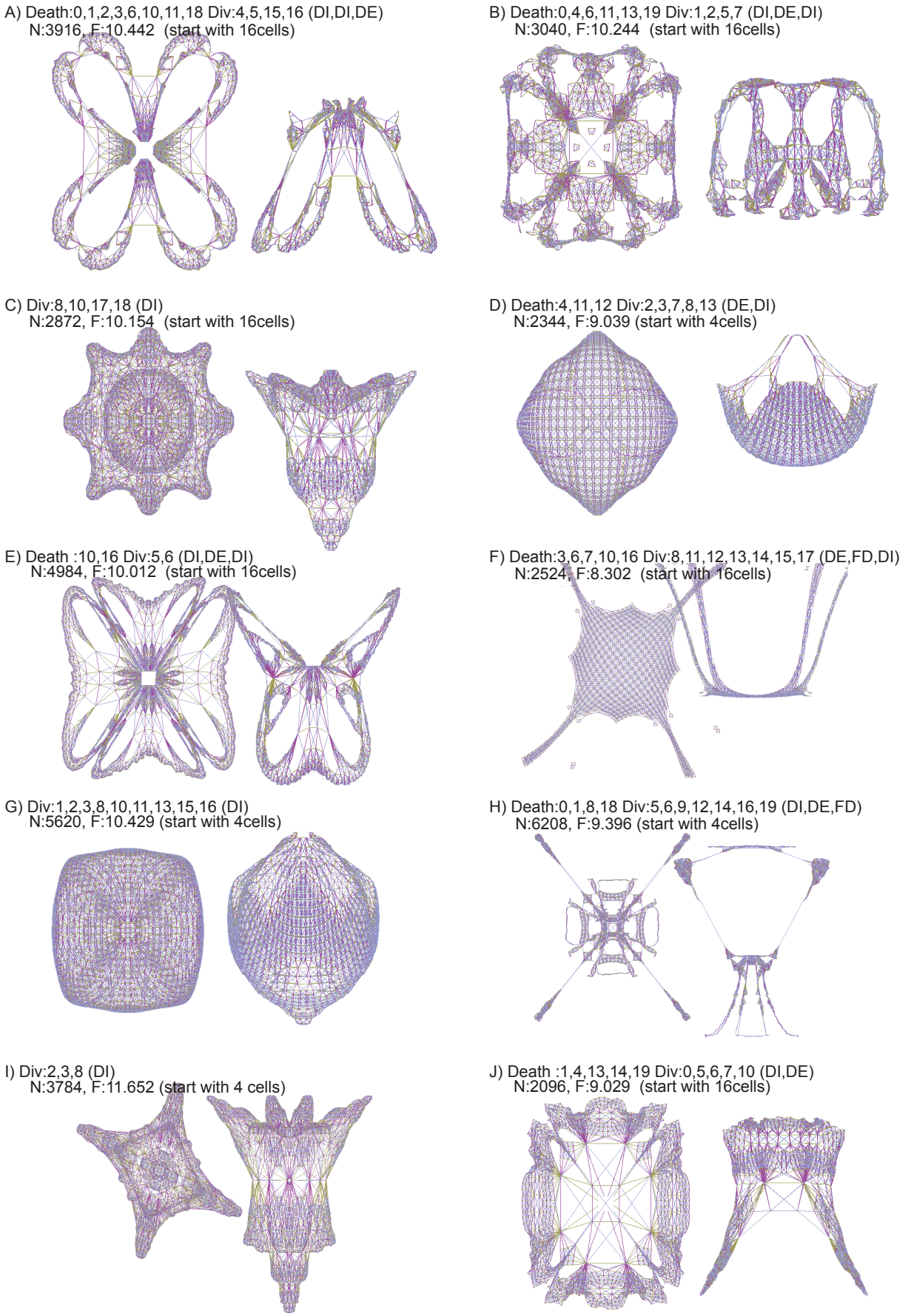

Fig. 6. Examples of phenotypes. Top views are shown on the left, and side views are shown on the right in each example. The conditions of the cell death and cell division are listed. The alphabets in those blankets represent the order of cell behavior rules, DE: cell death, DI: cell division, and FD: forced cell division, respectively. The numbers after the N: represent the number of cells that comprise each individual. And the numbers after the F: represent fitness value of each individual. The initial numbers of cells are listed in the brackets. Note that the number of cells is in the order of thousand.

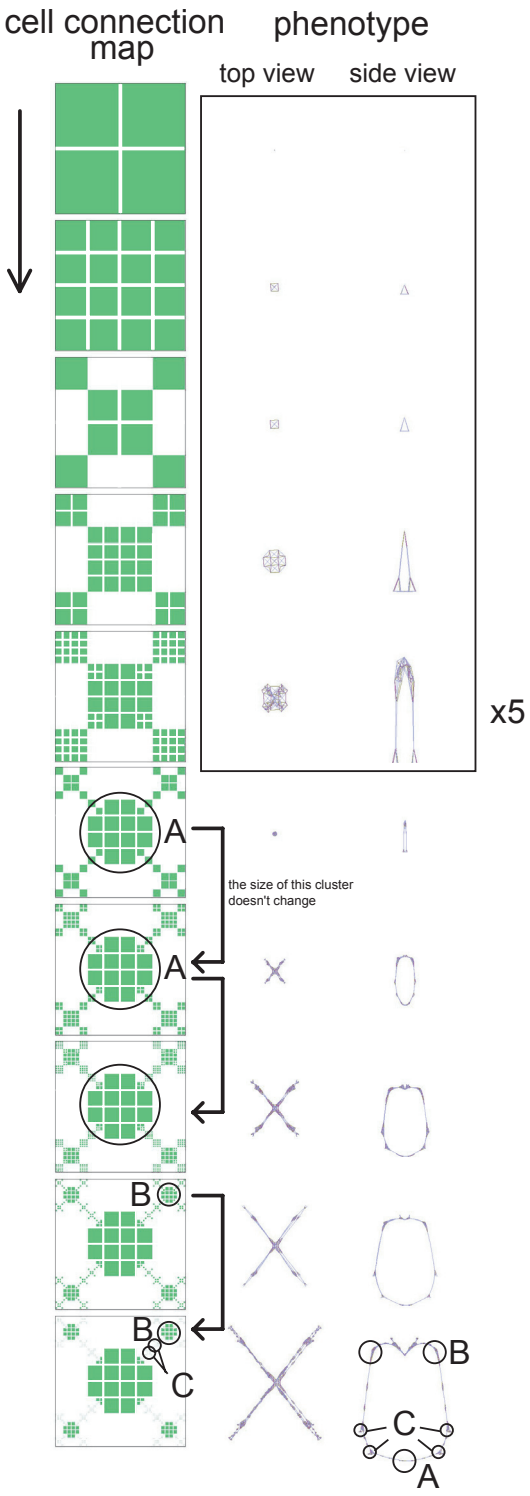

Fig. 7. Detail of exponential growth sequence A. Cell divides if the number of neighbor cells is 0,2,6, or 8 (using the Neumann neighbor). Cell is deleted if it is 1,3,5,7, or 9. The order of applied cell behavior rules is as follows: cell division, cell death, cell division. These three rules are kept applying repeatedly. This system keeps generating many ”clusters” whose sizes remain the same in different parts of the body.

2) Exponential growth sequence B: Figure 8 represents a section of the cell connection map of sequence B (from left to right in each row). Magnifications of each part of the cell connection map are displayed in temporal order. Although most of the conditions are the same between sequence A and sequence B, the morphogenetic processes are different. After some steps, an arrayed square grid appears (A1, B1, C1 and so on). The square area of 16 cells becomes rounded after some steps (A3). Once this form is created, all these internal cells surrounded by 8 cells hold four-neighbors and thus keep dividing. The external eight cells surrounding these internal cells already have more than 10 neighboring cells. Therefore these cells cannot divide any more, which is a kind of ”expanding bag”. This bag can also be seen at other parts of the body (C3, D3 that are not appeared here yet). This shows that the system is growing, creating many expanding bags throughout the body.

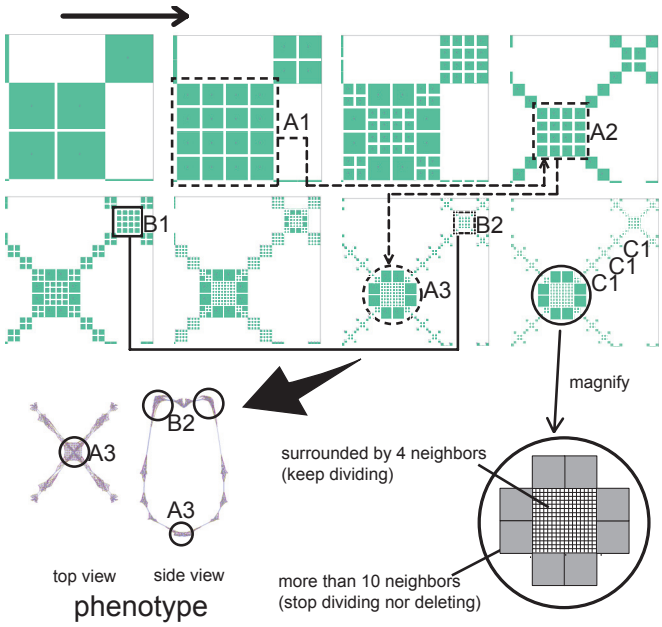

Fig. 8. Detail of exponential growth sequence B (from left to right in each row). Cell divides if the number of neighbors is 0,2,4,6, or 8 (using the Neumann neighbor). Cell is deleted if it is 1,3,5,7, or 9. The order of applied cell behavior rules is the same as that of sequence A: cell division, cell death, cell division. These three rules are kept applying repeatedly. This process is a kind of ”expanding bag”.

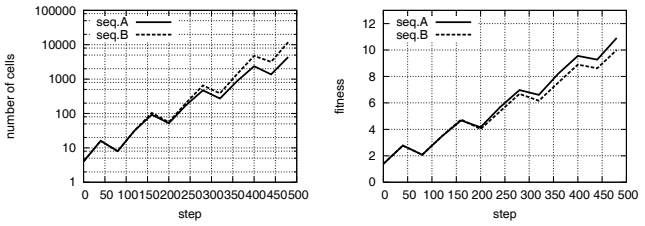

Fig. 9. Left: Fitness value transition graph. Right: Number of cells transition graph. Both X-axis represent time steps. Although the number of cells in sequence B is always larger than that of sequence A, the fitness in sequence B is smaller than that in sequence A.

3) Comparison of sequence A and sequence B: We quantified the characteristics of morphogenesis of these sequences using the fitness function in Figure 9. The number of cells transition graph and fitness value transition graph are shown on the left and the right, respectively. Both X-axis represent time steps. Although the number of cells in sequence B is always larger than that of sequence A, the fitness in sequence B is smaller than that in sequence A. This means that the uniformity of the whole system in sequence A per cell is larger than that in sequence B. It implies that many kinds of cell behavior rules are not needed for getting complicated forms.

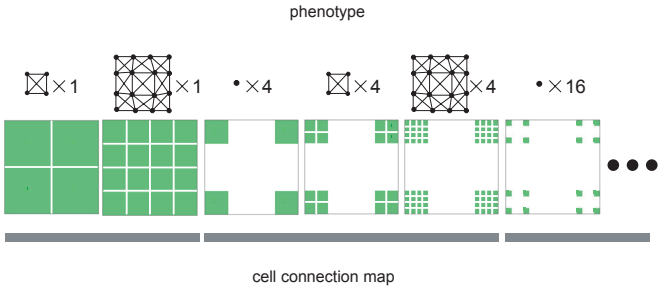

Fig. 10. Self-replication. If the number of neighbor cells is 0,2,5,7, or 9 (in Neumann neighborhood condition), the cell divides. If the number of neighbors is 1,3,4,6, or 8, the cell is deleted. Each group keeps changing the number of cells that comprise the network generating new groups.

4) Self-replication: Figure 10 shows one of the examples of self-replication process. Each group keeps changing the number of cells that comprise the network generating new groups. Notice that the sizes of each individual that has the same cell connections are identical.

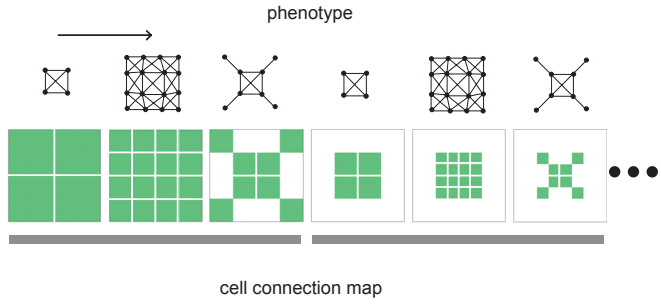

Fig. 11. Oscillation. By applying forced cell division rule once and cell death rule that activates if the number is 1 or 5 (in Moore neighborhood condition) two times consecutively, the system shows oscillation process.

5) Oscillation: Figure 11 shows one of the examples of oscillation process. By applying forced cell division rule once and cell death rule that activates if the number is 1 or 5 two times consecutively, the system shows oscillation process.

6) Stop growth, annihilation: Several models in other parameters showed annihilation and growth saturation behaviors. The simplest model of annihilation behavior can be observed by setting the number of neighbors 0 for cell division and 2 for cell death applying division rule and death rule one after another. The growth saturation model can be observed by setting 0 for the cell division rule and any numbers except for 2 for the cell death rule, respectively.

IV. Discussions

A. Types of formation

As we have seen several types of phenotypes, we noticed that there are several types of morphogenetic process in this system. They are (1) Net (A,B,E,J in Figure 6) that have widely spread distribution, (2) Balloon (D,G) that contain at least one expanding big surface. (3) Nods (C,I) that some parts are keep growing compared to the others, (4) Rope (H) that consists of narrow string like forms, (5) Separate (in Figure 10) that divides into several (or many) groups, and (6) Others.

B. Types of cell number growth

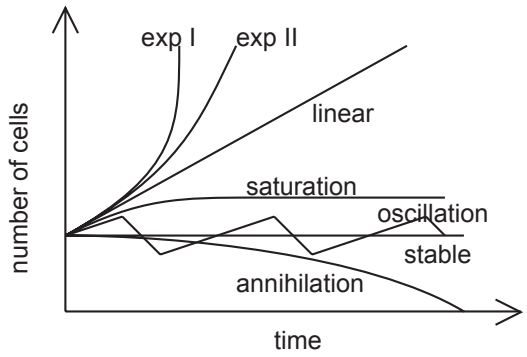

Fig. 12. Types of Cell number growth. (1) Exponential growth that most cell keeps dividing, (2) Exponential growth that some part stop dividing after some steps while others keeps dividing, (3) Linear growth that the number of cell division in each time is stable, (4) Saturation that the whole cells stop dividing at the end, (5) Oscillation that keeps the size changing the constituent elements, (6) Stable that does not change at all, (7) Annihilation that all cells vanish by cell death.

By observing the increase in the number of cells in each sequence, the types of cell growth can be intuitively classified (Figure 12). (1) Exponential growth in which most cell keeps dividing, (2) Exponential growth in which some cells stop dividing after certain time passes while others keeps dividing, (3) Linear growth that the number of cell division in each time is stable, (4) Saturation that the all cells stop dividing at the end, (5) Oscillation that keeps the size changing some constituent element, (6) Remain that does not change at all, (7) Annihilation that all cells vanish by cell death.

C. The essential meanings of Cell Connection Map

As we mentioned above, the cell connection map was basically introduced to keep track of the cell connections and sustain two-dimensional topologies. But for some people, it may sound that the system depends too much on this map. Let us examine what kind of information that the cell

connection map which we showed in Figure 13 codes. The information that the map codes are follows:

1) How many cell divisions are taken place. (the size of the square in the cell connection map)
2) In which direction (left, right, top or bottom) neighbor cells position.
3) The position order of the neighbor cells.

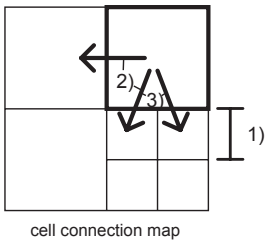

Fig. 13. Information that the cell connection map codes.

As the table above shows, we could replace the cell connection map by an approach using only internal states of the cells and still get the same results. It is important to realize that the characteristics of the cell connection map are not essential in order to easily evolve complicated forms.

V. Conclusion

These results lead to the following conclusion.

1) By exploiting cell-cell network topology as conditions of cell behavior, several types of morphogenetic behaviors of three-dimensional sheets could be easily realized in an autonomous and distributed way. Although these morphogenetic processes are sensitive to the topology of cell connections, we showed representational power of the cell network topology.
2) The sheet forms could be easily quantified by evaluating the cell connection maps by measuring the entropy.

Acknowledgment

Many thanks to Nathan Labhart, and Maic Hadron for helpful suggestions. This research is supported by the Swiss National Science Foundation, project #200021-105634/1.

References

[1] T. Motokawa: Living thing consists of cylinder shape, NHK publish (in Japanese) (1998)
[2] R. M. Twyman: Developmental Biology, BIOS Scientific Pulishers Ltd (2001)
[3] H. Honda: The mathematical and physical analysis of morphogenesis, Kyoritsu-shuppan (2000)
[4] A. M. Turing: A reaction-diffusion model for development, The chemical basis of morphogenesis, Phil Trans. Roy. Soc. of London, Series B; Biological Sciences, **237**, 5,PP.37-72 (1952)
[5] A. Giere, H. Meinhardt: A theory of biological pattern formation. Kybernetik, **12**, PP. 30-39 (1972)
[6] J. D. Murray: A pattern formation mechanism and its application to mammalian coat markings. In 'Vito Volterra' Symposium on Mathematical Models in Biology, **39**, PP. 360-399 (1979)
[7] J. D. Murray: On pattern formation mechanisms for Lepidopteran wing patterns and mammalian coat markings, Phil. Trans. Roy. Soc. of London B, **295**, PP. 473-496 (1981a)
[8] T. Boveri: Über die Polarität des Seeigeleiers. Eisverh. Phys. Med. Ges. Würzburg, 34, 145-175 (1901)
[9] C. M. Child: Patterns and Problems of Development. University of Chicago Press, Chicago (1941)
[10] L. Wolpert Positional Information and the Spatial Pattern of Cellular Differentiation, J. Theoret. Biol., **25**, PP.1-47 (1969)
[11] M. Odell, G. Oster, P. Alberch: The Mechanical Basis of Morphogenesis, Developmental Biology **85**, PP.446-462 (1981)
[12] P. Erdos, A. Renyi: Publ. Math. Inst. Hung. Acad. Sci. 5 (1960) 17.
[13] A. L. Barabasi, and R. Albert: Emergence of scaling in random networks, Science 286, 509-512 (1999).
[14] D. J. Watts and S. H. Strogatz: Collective Dynamics of Small-World Networks, Nature 393 (1998), 440-442.
[15] T. Kawai and Y. Miyamoto: The atomic structure of carbon nanohorn dahlia particle at the core: Numerical simulations for Y-junctions formation, International Conference on the Science and Application of Nanotubes (2004)
[16] A. Lindenmayer: Mathematical Models for Cellular Interaction in Development, Journal of theo-retical Biology, **18**, PP.280-300 (1968)
[17] C. G. Langton: Self-reproduction in cellular auto-mata, Physica D: Nonlinear Phenomena, **10**, Issues 1-2, PP.135-144 (1984)
[18] M. Gardner: Mathematical games - the fantastic combinations of john conway's new solitaire game, life. Scientific American, PP.120-123(1970)
[19] K. Sims: Interactive Evolution of Dynamical Systems, Proceedings of the Fisrt European Conferece on Artificial Life, Paris (1991)
[20] K. Sims: Evolving 3d morphology and behavior by competition. Artificial Life, **1**, Issue 4, PP.353-372 (1995)
[21] R. Dawkins: The Blind Watchmaker, Penguin Books (1986)
[22] K.Fleischer and A.H.Barr: A simulation testbed for the study of multicellular development : The multiple mechanisms of morphogenesis, Proceedings of the Workshop on Artificial Life, Santafe, NewMexico, PP.389-416 (1994)
[23] P. Eggenberger: Evolving morphologies of simulated 3d organisms based on differential gene expression, Fourth European Conference of Artificial Life, Cambiedge, MIT Press (1997).
[24] P. Eggenberger: Genome-pysics interaction as a new concept to reduce the number of genetic parameters in artificial evolution. Proceedings of the Congress of Evolutionary Computation, Canberra (2004)
[25] J. Bongard: Evolving modular genetic regulatory networks. Proceedings of The IEEE 2002 Congress on Evolutionary Computation PP.1872-1877 (2002)
[26] Sanjeev Kumar and Peter J. Bentley: On Growth, Form and Computers,Elsevier Academic Press (2003)
[27] Kenneth O. Stanley and Risto Miikkulainen: A Taxonomy for Artificial Embryogeny, Artificial Life, Vol. 9(2):pp.93-130,(2003)
[28] K. Tomita, H. Kurokawa, S. Murata: Graph Auto-mata: Natural Expression of Self-reproduction, Physica D: Nonlinear Phenomena, **171** No.4, PP.197-210 (2002)
[29] C. Furusawa and K. Kaneko: Emergence of Multicellular Organisms with Dynamic Differentiation and Spatial Pattern, Artificial Life 4 PP.79-93 (1998)
[30] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter: Molecular biology of the cell. 4th ed. Garland Science (2002): The Blind Watchmaker, Penguin Books (1986)
[31] J. H. Holland: Simulation of genetic systems by automatic digital computers. I. Introduction, II. Effects of linkage on rates of advance under selection, Australian Journal of Biological sciences, **10** pp.484-499 (1957)
[32] H. J. Bremermann: Optimization through evolution and recombination, Self-Organizing Systems, pp.93-106 (1962)
[33] J. H. Holland: Adaptation in natural and artificial system, Ann Arbor, The University of Michigan Press (1975)
[34] M. Matsumoto and T. Nishimura: Mersenne twister: A 623-dimensionally equidistributed uniform pseudorandom number generator, ACM Trans. on Modeling and Computer Simulations, 1998.
[35] H. Satoh, M. Yamamura, S. Kobayashi: Minimal Generation Gap Model for GAs Considering Both Exploration and Exploitation, Proceedings of IIZUKA '96, pp.494-497 (1996)