Morphogenetic-cycle Model:
clarifying several stages of embryo, brain, lung, and heart

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Abstract: Development processes of multi-cellular systems have attracted attention for a long time. The macroscopic model having six categories of molecules shows that the antagonism between the negative controllers and the positive replication factors induces bifurcations in stem and pluripotent cells at rhythmic intervals comprising about 6-7 cell divisions. Our theoretical model for the morphogenetic process shows that this cycle of 6-7 cell divisions, i.e., branching time between periodic bifurcation events, corresponds to the emergence timings of early developing stage, the nervous system, the respiratory system, and the circulatory system.

Keywords: Morphogenesis, Organs, Cell division

I. INTRODUCTION

Development processes of multi-cellular systems have attracted attention for a long time. [1,4,8,9]

Development processes of multi-cellular systems can be examined separately from two viewpoints of space and time. In this report, we especially examine the temporal aspects.

The deterministic differential equation model of six variables [2], which is extended from the minimum hypercycle model describing the smallest self-reproduction system [3], shows the oscillations of molecular densities due to the negative enzyme system and the gene group in the minimum hyper-cycle, which has the cycle of about six or seven-fold beats of fundamental clock.

Next, we examined in detail about the timing when organs of human beings and mouse are formed. An important point is that the six or seven-beat cycle calculated by the model corresponds to the actual emergence timing of several stages of embryo and organs.

II. MORPHOGENETIC CYCLE [2,3]

1. Minimum hyper-cycle [3]

All of the molecules are classified into some categories, based on their representative physical characteristics.

At least two types of molecular categories (enzyme systems), which are for replicating gene groups and enzyme systems, are necessary for achieving a closed reaction cycle. Examples of the former and latter are DNA-replicase and ribosome protein, respectively. This leads to the conclusion that two types of gene groups are also inevitable and serve to code the two enzyme systems. The core cycle for self-replication can be modeled by these four molecular categories, two gene groups and two enzyme systems (Categories D1: Gene group 1 that codes enzyme system R1 for DNA production, D2: Gene group 2 that codes enzyme system R2 for enzyme production, R1: Enzyme system 1 for DNA production, and R2: Enzyme system 2 for enzyme production). [3]

Here, Di and Ri for i = 1 and 2 also denote the density of each molecular category. We assume that the production rate of a category due to the reaction of categories Dj and Rj is restricted by the smaller one of Dj and Rj.

Then, Eq. 1 can describe the densities of four categories averaged over all the cells at generation *N*.

$$D_i^{N+1} - D_i^N = \alpha_{ij} D_i^N \otimes R_j^N , i = 1,2 , j = 1,2 \qquad (1)$$

where $D_i \otimes R_j$ and α_{ij} denote min(*Di,Rj*) and a constant, respectively.

This system of D1, D2, R1, and R2, the 4-cylinder engine for life, can replicate each other.

2. Six-variable differential equation [2]

The negative enzyme system and its gene group (D3: Gene group 3 that codes protein system R3 for suppressing D2 gene expressions, and R3: Protein system 3 for suppressing D2 gene expressions) are then

incorporated into the minimum hyper-cycle, because the morphogenetic process of multi-cellar systems in mammals must include negative controllers such as Oct-4 and SOX2 for producing tissues and organs. [4, 5, 6]

Only the protein system generated in Category R3, a negative controller, attaches to the positive gene group D2. Thus, the production rate of R2 can be re-written in the form of min (D2-R3, R2).

Then, the densities of six categories averaged over all the cells at generation N are described by the following equations.

$$D_i^{N+1} - D_i^N = \alpha_{i1} D_i^N \otimes R_1^N , i = 1,2,3 \qquad (2)$$
$$R_1^{N+1} - R_1^N = \alpha_{12} D_1^N \otimes R_2^N$$
$$R_2^{N+1} - R_2^N = \alpha_{22} \delta(D_2^N - R_3^N) \otimes R_2^N \qquad (3)$$
$$R_3^{N+1} - R_3^N = \alpha_{32} D_3^N \otimes R_2^N$$

where $D_i \otimes R_j$ denotes $\min(Di,Rj)$ for i=1-3 and j=1-3, and also where $\delta(x)$ denotes the larger one of x or 0, i.e., max $(x, 0)$. (Here, the constant α_{i1} includes the influences of many types of molecules in the category and the molecule movements on reaction probability. There is an important constraint, i.e., the densities of D1, D2, and D3 are identical, because the three gene groups 1, 2, and 3 are in one set of DNA in each generation. Thus, α_{i1} for D1, D2, and D3 is a set having the identical value of 1.0. Initial densities of D1, D2, D3, R1, R2, and R3 are set to be 1.0, respectively.)

Let us denote the number of cell divisions after the mother cell generation as N. Generation N is less than 50, because an adult human body can be generated by about 50 cell divisions from a fertilized egg. Accordingly, the number of cells at generation N is defined as P(N). There are many types of cells among P(N) such as somatic and stem cells. A cell must have one set of DNA. Thus, the number of cells, P(N), is equal to D_i^N.

Broadly speaking, computational results obtained by Eqs. (2) and (3) show nearly exponential or hyperbolic increases of Di and Ri. Then, the antagonism between the negative controller R3 and the positive factors R1 and R2 induces bifurcation events at rhythmic intervals constituting about 6-7 divisions although the intervals are slightly chaotic and the vibrational amplitude is attenuated. It is stressed that this cycle of 6-7 divisions, i.e., branching time between periodic bifurcation events, corresponds to the emergence timings of blastocysts,

germ layers, tissues, and organs, which can be observed for about every 6-7 cell divisions. (Figs. 1 and 2)
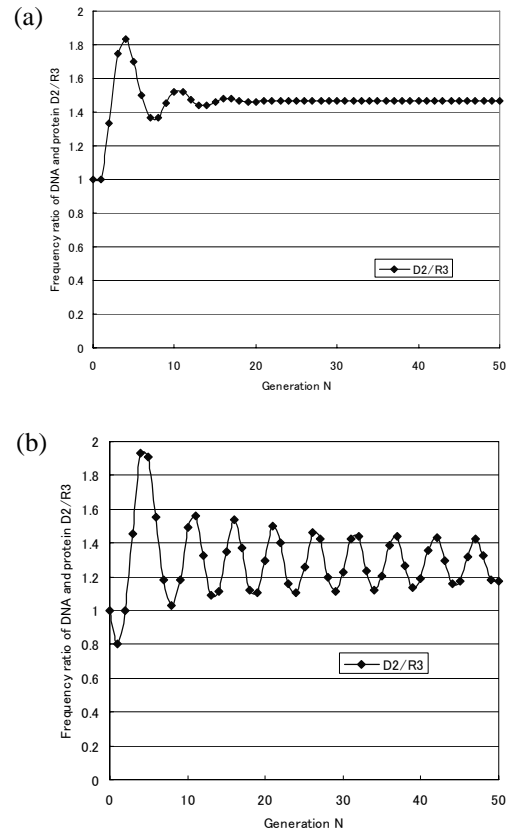

Fig.1. Time histories of D2/R3 during 50 generations of the morphogenetic process. (a) $\alpha_{i2} = 1.0$ and (b) $\alpha_{i2} = 1.5$

The flexible shapes of transcription factors may give the parameters of α_{i2} various values. However, it is stressed that three system parameters, α_{i2}, have less influence on the time cycle of bifurcations. The cycle of about 6-7 divisions is stable. (Fig. 1b) [2]

The condition of D2/R3 > 1.0 means that a part of D2 is not covered by R3. This implies that several types of proteins in D2 emerge and also several types of somatic cells are produced to make organs and tissues. The condition of D2/R3 < 1.0 means that D2 is completely blocked by redundant R3, which implies stem or iPS cells. This oscillation of D2/R3, which implies the amount of D2 uncovered by protein group R3, will lead to the changes in the gene combination for expressions. This corresponds to the fact that iPS cells can be reprogrammed by the presence of much Oct-4.

III. MORPHOGENETIC PROCESS

1. Human beings

The morphogenetic process of human beings began with the fertilization. We examine the date when each of the organs is formed. (Fig.2)

At first, we examine the early stage of the morphogenetic process, from a fertilized egg to germ layers. (Fig.3) A fertilized egg becomes blastocysts with 4 or 5 days, diploblastics with 8 or 9 days, germ layers with 15 or 16 days. Cell cycle of human beings is about 16–24 hours. Thus we can consider that embryos undergo cell division about once a day. However, the first cleavage needs about 24 hours, and the following each division before moluras needs about 12 hours. Thus, it takes 6 or 7 times of cell divisions between a fertilized egg and blastocysts, 4 or 5 times of cell divisions between blastocysts and diploblastics, and 7 or 8 times of cell divisions between diploblastics and germ layers. According to these results, we can see that important structures are formed by around 6-7 times cell divisions in the early stage of the morphogenetic process.
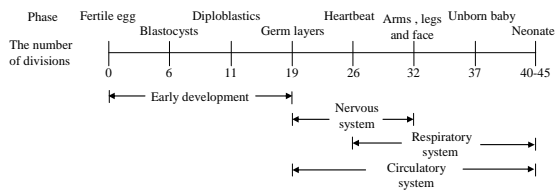

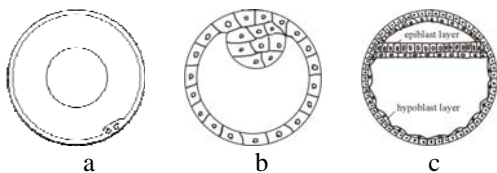Fig.2. Simple overview of the morphogenetic process of human beings.

Fig.3. Morphogenetic process of early development. (a: fertile egg, b: blastocysts, c: diploblastics) [7, 8]

Secondly, we examine the nervous system. (Fig.4) Neural plate is formed on the 18th day. After that, neural plate develops into neural tube on the 22nd or 23rd day, into primary brain vesicle on the 27th or 28th day, and into secondary brain vesicle on the 31st–33rd day. Because of this, we can suppose that neural plate undergoes 4 or 5 times of cell divisions before forming neural tube, neural tube undergoes 5 or 6 of times cell divisions before forming primary brain vesicle, primary brain vesicle undergoes 4-6 times of cell divisions before forming secondary brain vesicle. According to these results, we can see that important structures are formed by about 6 times cell divisions in the nervous system. [9]
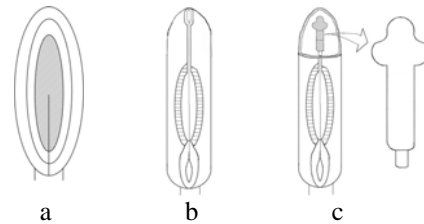

Fig.4. Morphogenetic process of the nervous system. (a: neural plate, b: neural tube, c: primary brain vesicle) [7, 8]

Next, we will see about the respiratory system. (Fig.5) At the beginning of the respiratory system, lung bud is differentiated from foregut on the 24th-26th day. After that, lung bud develops into trachea and primary bronchus on the 29th or 30th day, into secondary bronchus on the 34th or 35th day, and into tertiary bronchus on the 41st or 42nd day. Thus, we can conclude that lung bud undergoes 4-6 times of cell divisions before forming trachea and primary bronchus, primary bronchus undergoes 5 or 6 times of cell divisions before forming secondary bronchus, secondary bronchus undergoes 7 or 8 times of cell divisions before forming tertiary bronchus. Therefore, we can see that important structures are formed by around 6-7 times of cell divisions in the respiratory system.
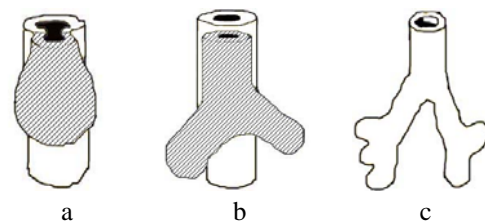

Fig.5. Morphogenetic process of the respiratory system. (a: lung bud, b: trachea and primary bronchus, c: secondary bronchus) [7, 8]

Finally, let us see the circulatory system. [7, 8] At the beginning of the circulatory system, cardiogenic cord is formed on the 17th-19th day, and cardiogenic

cord develops into cardiac tube on the 22nd or 23rd day. After that, common atrium is formed on the 26th or 27th day. Bilobed atrium is formed on the 30th or 31st day, while 3-chamberd heart is formd on the 34th or 35th day. The 4-chamberd heart is formed on the 48th or 49th day. Thus, we can suppose that cardiogenic cord undergoes 4-6 times of cell divisions before forming cardiac tube, cardiac tube undergoes 4 or 5 times of cell divisions before forming common atrium, common atrium undergoes 4 or 5 times of cell divisions before forming bilobed atrium, bilobed atrium undergoes 4 or 5 times of cell divisions before forming 3-chamberd heart, 3-chamberd heart undergoes 14 or 15 times of cell divisions before forming 4-chamberd heart. Therefore, we can see that some structures are formed by about 4-6 cell divisions between cardiogenic cord and 3-chamberd heart, although 3-chamberd heart and 4-chamberd heart are not formed by the cycle.

From the above investigations, we can show that most of the morphogenetic cycles of these four organs correspond to the result of section II, about 6-7 cell divisions.

2. Mouse

We also investigate about the morphogenetic process of mouse. At the morphogenetic process of mouse, blastocysts are formed on the 3rd or 4th day, germ layers and neural plate are formed on the 8th or 9th day, and neural tube is formed on the 11th or 12th day. (The emergence timings corresponding for human beings are the 4th or 5th day for blastocysts, the 15th and 16th day for germ layers, the 18th day for neural plate, and the 22nd or 23rd day for neural tube.) Then, the cell cycle of mouse is approximately half of human beings. Thus, the morphogenetic cycle, 6-7 cell divisions, will apply to the early stages of both human beings and mouse.

We should examine the later stages of the morphogenetic processes of both species further, in order to confirm the similarity.

IV. CONCLUSION

Equations 2 and 3 of the sixvariable differential equation shows the morphogenetic cycle of six-seven fold beats of cell divisions.

The experimental data on morphogenetic processes of human beings and mouse shows the possibility that important organs of mammals are formed by every 6-7 times of cell divisions.

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