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Pattern Formation in Reaction-Diffusion Model with Long-Range Interaction

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Abstract: To describe the re-differentiation phenomenon of cancer cells a mathematical model is proposed to study mechanisms of self-organization phenomena of a multicellular system. The model is written by a reaction-diffusion equation with a long-range interaction. Further, we investigate spatial and temporal pattern formation through the mathematical analysis of our model.

Keywords: Reaction-Diffusion Model, Long-Range Interaction, Cell-to-Cell interaction, Autonomous Decentralized System

1 Introduction

Recently, the increasing of complex systems in several technological fields, much as computer, distribution, traffic industries e.g., has required the construction of autonomous decentralized systems. The modeling of these autonomous decentralized systems has been conventionally guided by mechanisms of biological self-organization phenomena. One of the most significant self-organization phenomena in this field is morphogenesis, a part of embryology, which treats highly organized arrangements of differentiated cells. Morphogenesis involves many complex and dynamical processes as cell division, cell differentiation, cell movement, and more.

Reaction-diffusion models describing the concentration's pattern formation of chemical substances have achieved important results in theoretical studies of morphogenesis[1), 2), 3)]. Since, even though these models have simple mechanisms, they can generate a great variety of spatial and temporal patterns, simple gradients, spatially cyclic patterns, and temporally oscillation patterns, reaction-diffusion models have recently applied to traffic signal network[4), 5), 6)].

Conventional reaction-diffusion models assume the principle of local (short-range) interaction between constituent elements of a system. Such assumption can apply the ideal situation that ignores the effects of an environment around a system. Though the conventional models have succeeded in explaining various pattern formations of simple systems as the first approximation, environmental effects do not affect existent systems but also are considered to be dominant in some situations. However, systematic studies hardly have targeted role of environmental effects. Therefore, it is important to construct a realistic model, which includes environmental effects, especially non-local (long-range) interactions beyond the nearest neighbor via environments.

It has been recently known that long-range interactions via an environment play an important role for various pattern formations in developmental biology[7), 8)]. In particular, we have noticed and investigated long-range cell-to-cell communication via extracellular matrix (ECM) regarding the re-differentiation phenomenon of cancer cells[9)]. Re-differentiation is an interesting phenomenon that cancer cells develop back to normal cells under special situations.

In this paper, we propose a mathematical model, which

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describes the re-differentiation phenomenon of cancer cells, in order to study mechanisms of self-organization phenomena in multicellular systems and for examining technological applications of reaction-diffusion models with long-range interactions. Further, we investigate spatial and temporal pattern formation through the mathematical analysis of our model.

2 Biological Background

Cancer is a serious disease destroying all of the functions of our living body, but it is an important object for studying essential features of the cell, such as cell division, cell movement, cell differentiation, and more. Canceration of cells is deeply related to cell-to-cell communication from the macroscopic viewpoint, namely a cancer cell refuses communication with the surrounding cells. Since a normal cell efficiently communicates with other cells, the normal cell finally generate order in the living body and maintain the order through the process of cell division, cell differentiation, and others. Though many biological experiments over the past few decades have been accomplished in order to study the mechanism of cell-to-cell communication, this problem is yet to be solved.

On the contrary, in theoretical studies, the "morphogenetic field" as important but conceptual idea regarding the mechanism of cell-to-cell communication has been proposed by B. Goodwin[10), 11)]. A "morphogenetic field" is extracellular environment controlling communication between cells by transportation of chemical substances and propagation of mechanical and electromagnetic forces, to generate orders of the multicellur system and maintain order. His idea leads us to set forth a hypothesis about anormal behavior of the cancer cell as follows: An anormalization of morphogenetic field causes a cell to refuse communication with surrounding cells. Regarding this hypothesis, experimental results of B. Mintz et al. give us important suggestions[12), 13)].

They transplanted a part of the skin cancer cells of a mouse A in the womb of a normal female mouse B. As the result, a child mouse C born from the mother mouse B had no cancer cells. Namely, the cancer cells derived from the mouse A in the child mouse C changed to normal cells in the womb of the mouse B. This surprising phenomenon is called "re-differentiation" of the cancer cell. This means that the cancer cells recover the function of communication with other cells in the womb, and finally go back to their normal states. Therefore, their experimental results suggest that our hypothesis is right. From this, it can be considered that the womb is a typical morphogenetic field.

What is the mechanism of the re-differentiation of cancer cells? To study this phenomenon, we suppose that ECM is the main constituent of morphogenetic field because ECM is an extracellur environment, and as such, deeply concerned with the canceration of the cell. ECM is a network-like macromolecule structure based on Glucose, and is connected with almost all cells in the multicellur system via Integrin, which is the family of transmembrane matrix receptor embedded in cellmembrane. Traditionally, ECM has been believed a cement material filling in space between cells. However, from recent experimental reports it has been recognized that interactions between ECM and cells via integrin play an important role for controlling cell division. Namely, ECM is " extracellular cell increase factor" having local control mechanism of cell division as follows:

(A1) CGF (Cell Growth Factor) Activity: ECM activates cell division of the cell when ECM is coupled with cell growth factors.

(A2) Contact Inhibition: ECM inhibits cell division of the cells when the cells contact each other.

Further, we should note the following facts[14), 15)]:

(B1) ECM has a global macromolecule structure that generates mechanical forces, which propagates over longer range than diffusion transportation of chemical substances.

(B2) The cell has a translating mechanism between mechanical forces and intercellular chemical reactions.

From these facts, it is reasonable to assume that a cell communicates other cells far from the nearest neighbor by long-range interaction via ECM. Thus, we set forth the following assumption: Globally controlling mechanism of cell division, that is, cell-to-cell communication far from nearest neighbor by long-range interaction via the ECM globally controls cell division.

It is well known that the ECM is deeply concerned with

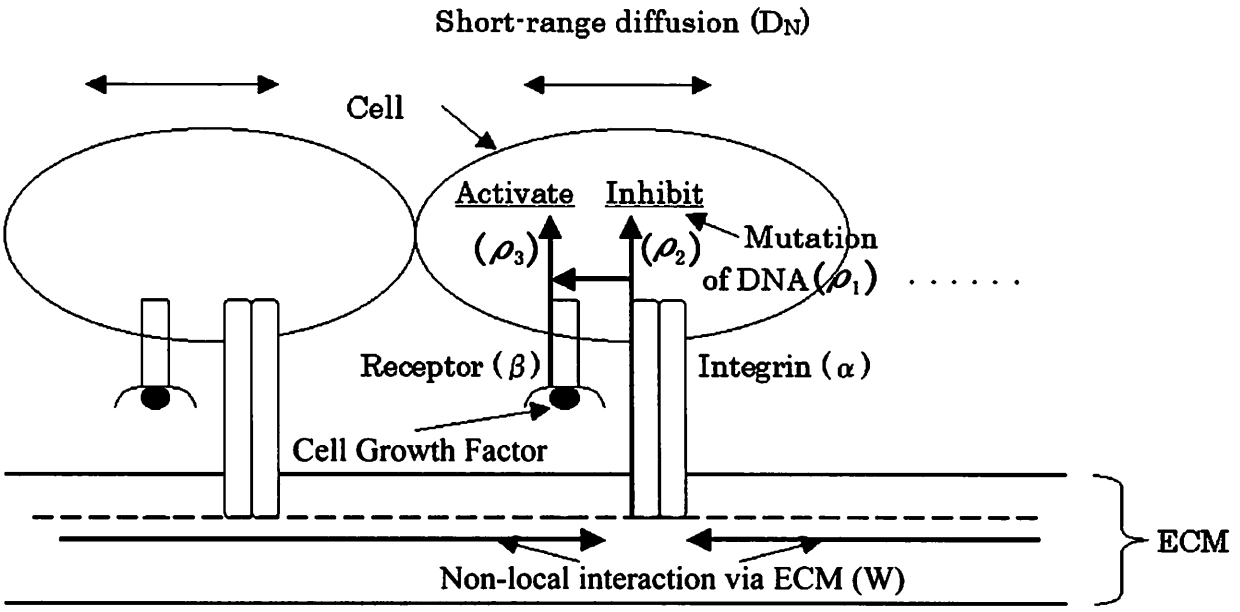

Fig. 1 Schematic picture of our model

the canceration of the cell[14), 15)]:

(C1) Fibronectin, which is one of constituents of the ECM, decreases in surroundings of the cancer cell.

(C2) Integrin decreases in the cancer cell.

Therefore, it is considered reasonable and proper that these functions of ECM-integrin system play an important role for re-differentiation phenomenon of the cancer cell.

3 Our Model

To study mechanisms of the re-differentiation phenomenon of cancer cells, we propose a schematic picture of our model as shown in Fig. 1. Fig.1 represents the schematic model of cell's dynamics on the ECM-Integrin system. Our reaction-diffusion model, based on this picture, is described as follows:

$$\partial N(x, t)/\partial t = D_N \nabla^2 N + \rho_1(N)N^2 + \rho^2(N)N^2 - \int_\Omega \int_{t_0}^{t} W(x, x'; t, t')F(N(x', t'))dx'dt', \quad (1)$$

where $N(x, t)$ is an cell density and Ω is the spatial domain in which the integral kernel W is defined. Eq. (1) is a partial functional differential equation that a change rate of the cell density at position x and time t depends on the cell density at all other positions x' and all past times t'. The first term of the right hand in eq. (1) represents the cell movement of short-range diffusion having a diffusion velocity $D_N > 0$. The second term represents the effect of the contact inhibition having the increasing ratio:

$$\rho_1(N) = -\rho_1 \alpha N + \rho_2, \quad (2)$$

where $\alpha > 0$ is a parameter of Integrin, and ρ_1 and ρ_2 are positive constants. The third term represents the effect of CGF activation having the increasing ratio:

$$\rho_2(N) = \rho_3 \alpha \beta, \quad (3)$$

where $\beta > 0$ is a parameter of Fibronectin, and ρ_3 is positive constant. The forth term represents the effect of the long-range interaction between cells far from the nearest neighbor via ECM, having a filter function:

$$F(N) = \alpha \beta \rho_4 N, \quad (4)$$

where ρ_4 is positive constant. The integral kernel $W(x, x'; t, t')$ is the weight function characterizing the essential feature of ECM. However, the details of W have never been understood yet. Therefore, we assume the integral kernel W on the basis of mathematical property as follows.

(D1) W depends on only $y = |x - x'| > 0$ and $s = |t - t'| > 0$,

$$W(x, x'; t, t') = W(y, s). \quad (5)$$

(D2) W is a positive function in the entire region of y and s,

$$W(y, s) \geqq 0 \quad \text{for} \quad \forall y > 0, \ \forall s > 0. \quad (6)$$

(D3) W is a monotone decreasing function of y and s,

$$W(y, s) \to 0 \quad \text{at} \quad y \to 0, \ s \to 0. \quad (7)$$

(D4) W satisfies the following normalization condition:

$\int^{\infty}_{-\infty}\int^{\infty}_{0} W(y, s)dsdy=1.$ (8)

Here, (D1) means that ECM is uniformly distributed throughout the womb. (D2) means that the regulation of the ECM is inhibitory in the entire region of womb. (D3) represents that the intensity of the inhibition decreases as y and s become larger. (D4) represents that the long-range effect of ECM is the average value of F(M), which is $\langle F(M)\rangle = \int^{\infty}_{-\infty}\int^{\infty}_{0} W(y, s)F(M(x-y, t-s))dsdy$. Thus, assumptions (A1) to (A4) can be biologically interpreted that ECM globally inhibits the function of cell division in the entire region of womb.

In this paper, we consider one-dimensional space for the sake of simplicity. Further, according to (D1) to (D4), we can formally take the range of the spatial integral range to $\{\Omega \mid -\infty \leqq x' \leqq \infty\}$ and the lower limit of the time integral to $t_0 = -\infty$. Furthermore, since we choose the parameters as follows: $D_N = 1$, $\rho_1 = 1$, $\rho_2 = 1$, $\rho_3 = \alpha$, $\rho_4 = \beta > 0$, Eq. (1) is finally described as follows:

$$\partial N(x, t)/\partial t = \partial^2 N/\partial x^2 - \alpha N^3 + (1+\alpha^2\beta)N^2 - \alpha\beta\int^{\infty}_{-\infty}\int^{\infty}_{0} W(y, s)N(x-y, t-s)dsdy. \quad (9)$$

Although Eq. (9) is not the exact model based on experimental facts, the conceptual framework of our model is quite clear as illustrated in Fig. 1.

4 Numerical Simulations

In this section, we analyze the behavior of the multicellular system described as Eq. (1). As discussed, cell groups placed on normal ECM form normal tissue in the presence of Integrin. This corresponds to Turing pattern formation of Eq. (1) from the mathematical viewpoint. Thus, in mathematical analysis, the parameter α, which indicates the function of Integrin, should be divided into $\alpha = 0$ and $\alpha \neq 0$.

(Case. 1) $\alpha = 0$:

This case is corresponding to the situation without the effects of ECM. Then, Eq. (9) is

$$\partial N(x, t)/\partial t = \partial^2 N/\partial x^2 + N^2. \quad (10)$$

Fig. 2 show the numerical result under the following condition: Initial condition is N(x, 0) = 1.0 + random, the boundary condition is Derichlet type. As shown in Fig. 3, cell density rapidly diverge in the region around the position x = 17 at the time t = 70.

(Case. 2) $\alpha \neq 0$:

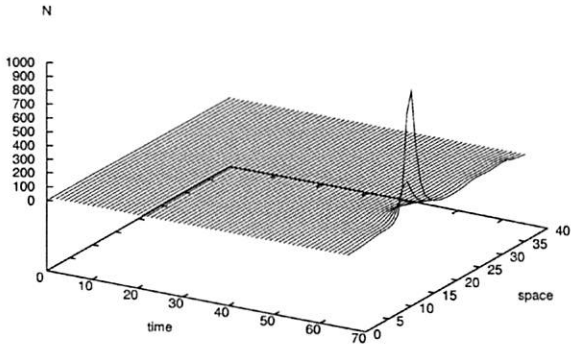

Fig. 2 Behavior of solution of Eq. (10)

(Case. 2-1) $W(y, s) = \delta(y)\,\delta(s)$:

This case is corresponding to the situation that ECM has the spatially local effect without time delay.

After performing a linear stability analysis under the assumption that the linearized equation of (9) has the solution of the form $\exp(\lambda t + ikx)$, we obtain the following characteristic equation of λ:

$$\lambda = -k^2 - 1/\alpha + \alpha\beta, \quad (11)$$

where where k is a wave number and λ is a frequency number. If $\mathrm{Re}\,\lambda < 0$, the solution of the linearized equation is stable. Here, we employ the parameter β as a bifurcation parameter. When the bifurcation parameter β is getting larger from a small value, if $\mathrm{Re}\,\lambda$ becomes $\mathrm{Re}\,\lambda > 0$, then the solution becomes unstable. Therefore, $\mathrm{Re}\,\lambda = 0$ is the bifurcation point of the linear stability. This bifurcation point corresponds to the following function:

$$\beta = k^2/\alpha + 1/\alpha^2. \quad (12)$$

In this case, the critical wave number $k_C = 0$ becomes unstable at this point $\beta = \beta_T = 1/\alpha^2$. However, a new steady state formed near the bifurcation point β_T is spatial homogeneous.

(Case. 2-2) $W(y, s) = a/2 \cdot e^{-a|y|} \cdot be^{-bs}$ for $a > 0$, $b > 0$:

This case is corresponding to the situation with long-range interaction via ECM. Here, the parameter a is a scale parameter charactering a spatial property of ECM's dynamics, and the parameter b is a scale parameter characterizing temporal one. In this paper, we give only the results of a linear stability analysis. Fig. 3 shows the phase diagram at the first bifurcation point in parameter space (a^2, b), where T is the region generating Turing pattern and H is the region generating the temporal

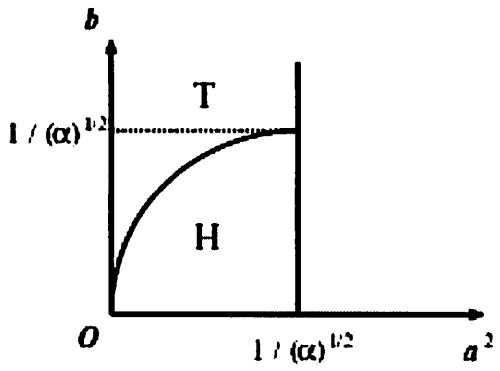

Fig. 3 Phase diagram in parameter space (a^2, b)

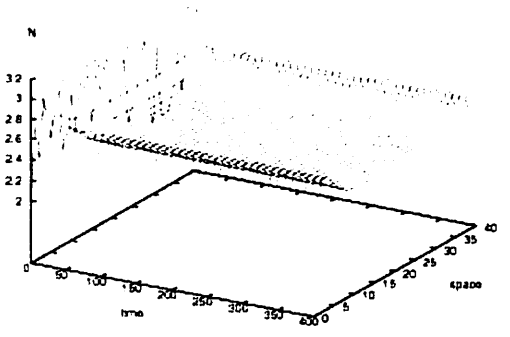

Fig. 4 Spatial inhomogeneous pattern

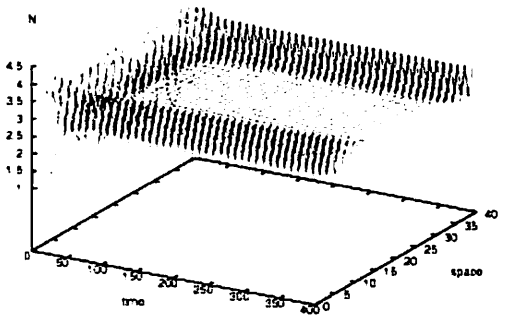

Fig.5 Spatial inhomogeneous- temporal ocsillationary

oscillating pattern formed by Hopf bifurcation.

Fig. 4 shows the numerical result under the following condition: Initial condition is N(x, 0) = 1.0 + random, Boundary condition is Derichlet type, α = 0.5, β = 3.96, a = 1.2, and b = 2.0. As shown in Fig. 3, cell density form Turing pattern, that is, spatial inhomogeneous steady pattern.

Fig. 5 shows the numerical result under the following condition: Initial condition is N(x, 0) = 1.0 + random, Boundary condition is Derichlet type, α = 0.5, β = 3.0, a = 0.5, and b = 0.7. As shown in Fig. 4, cell density form spatial inhomogeneous and temporal cyclic pattern.

5 Conclusion and Discussion

In this paper, we proposed a reaction-diffusion model with long-range interaction as a model that describes the re-differentiation phenomenon of cancer cells. From the results of the numerical simulations, we find that the behaviors of an asymptotic solution in the case of $\alpha \neq 0$ is different from the case of $\alpha = 0$. In the former case, the asymptotic solution diverges in finite time. On the contrary, the latter generate (a) spatial homogeneous steady pattern (case. 2-1), (b) spatial inhomogeneous steady pattern and spatial inhomogeneous-temporal oscillationary pattern (case. 2-2). If the bifurcation parameter β becomes larger beyond the first bifurcation point, more complex patterns can be generated, according to bifurcation theory.

In biological viewpoint, the numerical simulations mean that in the case of $\alpha = 0$ (the situation with no effects of ECM) cells starting from an initial condition (stationary state + fluctuation) anormally increase in finite time. On the contrary, In the case of $\alpha \neq 0$ (the situation with effects of long-range interaction via ECM) cells starting from same condition become stationary state by inhibiting anormal increase of cells.

Thus, our theoretical study of the re-differentiation phenomenon of cancer cells provides new insights into morphogenesis formation as follows: long-range cell-to-cell communication via ECM (extracellular environment) plays an important role for biological pattern formation.

From the standpoint of technological applications, our model provides more general frame including non-local interaction between the elements of a system, for the modeling autonomous decentralized system. Especially, non-local interaction model is useful in modeling of autonomous decentralized system under inhomogeneous environments.

Finally, it should be noted that the generated patterns of our model depend on the integral kernel W(y, s) characterizing spatial-temporal properties of the effect of ECM. In this paper, we analyze the typical cases, which is satisfied with

the assumptions (D1) to (D4), it is important to explore whether more general integral kernel W(y, s). Although an integral kernel W(y, s) must be determined by experimental facts, it is difficult to obtain quantitative data because ECM is very physically and chemically complex structure. Therefore, we need to at least theoretically explore various possibilities of an integral kernel W(y, s). These studies will be considered in a future paper.

References

1) A. Turing: The Chemical Basis of Morpogenesis, Phil. Trans. Roy. Soc. London B237, vol. 32, pp. 37-72 (1952).

2) A. Geirer and H. Meinherdt: A Theory of Biological Pattern Formation, Kybernetik, vol. 12, pp. 30-39 (1972).

3) A. J. Koch and H. Meinherdt: Biological Pattern Formation: From Basic Mechanisms to Complex Structure, Rev. Mod. Phys., vol. 66, pp. 1481-1507 (1994).

4) H. Yuasa and M. Ito: Reaction-Diffusion Equation on a Graph and Autonomous Decentralized System (in Japanese), Transaction of SICE, vol. 35, pp. 1447-1453 (1999).

5) M. Sugi, H. Yuasa, and T. Arai: Autonomous Decentralized Control based on Reaction-Diffusion Equation on a Graph (in Japanese), Transaction of SICE, vol. 39, pp. 51-58 (2003).

6) K. Sekiyama, J. Nakanishi, K. Takagawa, T. Azuma, and T. Fukuda: Self-Organization of Urban Traffic Signal Network (in Japanese), IEEE International Conference on Systems, Man, and Cybernetics, (SMC 2001) vol. 4, pp. 2481-2486 (2001).

7) F. A. Ramirez-Weber, and T. B. Kornberg: Cytonames: Cellular Processes that Project to the Principal Signaling Center in Drosophila Imaginal Discs, Cell, vol. 97, pp. 599-607 (1999).

8) F. A. Ramirez-Weber, and T. B. Kornberg: Signaling Reaches to New Dimension in Drosophila Imaginal Disks, Cell, vol. 103, pp. 189-198 (2000).

9) K. Ogawa and Y. Miyake: An Autonomous Decentralized Model with a Non-local Interaction (in Japanese), Transaction of IEICE, vol. J86-A, pp. 19-28 (2003).

10) B. C. Goodwin, S. Kauffman, and J. D. Murray: Is Morphogenesis an Intrinsically Robust Process?, J. Theor. Biol., Vol. 117, pp. 79-106 (1985).

11) B. C. Goodwin: How the leopard changes its spots: the evolution of complexity, Springer-Verlag (1994).

12) B. Mintz, and K. Illmensee: Normal Genetically Mice Produced from Malignant Teratocarcinoma Cells, Proc. Natl. Acod. Sci. U. S. A., vol. 72, pp. 3585-3589 (1975).

13) T. A. Stewart, and B. Mintz: Successive Generations of Mice Produced from an Established Culture Line of Euploid Tratocarcinoma Cells, Proc. Natl. Acod. Sci. U. S. A., vol. 73, pp. 549-553 (1976).

14) B. Alberts, D. Bary, J. Lewis, M. Raff, ke Roberts, and J. D. Watoson: Moleculer Biology of The Cell, 3th ed., Garland Publishing, Inc., New York (1994).

15) S. F. Gilbert: Developmental Biology, 5th ed., Sinauer Assosiates, Inc., Massachusetts (1997).