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An Autonomous Decentralized Model with Nonlocal Interaction: Roles of an Extracellular Matrix in Organization of a Multicellular System

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SUMMARY

The reaction-diffusion model is one of the theoretical approaches used to realize autonomous decentralized systems. The model conventionally assumes that all components of a system locally interact with each other under ideal conditions, ignoring any effect from the environment. However, it has recently become clear that nonlocal interactions mediated by the environment play an important role in the ontogenesis of multicellular organisms, a typical autonomous decentralized system. In this paper, we discuss the "redifferentiation" phenomenon of cancer cells in which such a nonlocal interaction is considered to play an essential role. Further, we propose a model to reproduce this phenomenon and mathematically analyze our model to construct autonomous decentralized systems with nonlocal interactions mediated by the environment in the future. © 2004 Wiley Periodicals, Inc. Electron Comm Jpn Pt 3, 87(7): 55–65, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/ecjc.10101

Key words: autonomous decentralized system; reaction-diffusion model; nonlocal interaction; environment; cancer cell.

1. Introduction

In a variety of technological fields such as computers, distribution, transportation, and many more, the recent trend toward huge systems has made it essential to construct controllable autonomous decentralized systems.

The self-organizing phenomena of multicellular organisms have always served as a major guideline for modeling autonomous decentralized systems. In particular, ontogenesis is one of the most significant phenomena. Basically, ontogenesis begins with a single fertile egg and repeats cell division, followed by cell differentiation and movement, as a complex process of shape formation.

Reaction-diffusion models of chemical substances have been successful as a theoretical approach to clarifying the mechanism of such shape formation. Starting with Turing's study [1], a large number of reaction-diffusion models [2, 3] have been proposed. They form a large variety of spatiotemporal patterns, including not only simple gradient patterns but also complicated spatial patterns and temporal oscillation patterns. Such a reaction-diffusion model has recently drawn attention as a theoretical model for realizing autonomous decentralized systems. It has currently been applied to control models for traffic signal networks [e.g., 4–6].

Most reaction-diffusion models conventionally have assumed that all components of a system locally interact with each other under ideal conditions, ignoring any environmental effect. However, it should be noted that any real technological system involves some structure as an environ-

ment behind the components of the system. In this situation, all of the components do not necessarily locally interact with each other. In fact, in recent years it has been shown in the field of developmental biology that even in the ontogenesis of multicellular organisms, nonlocal interactions mediated by physical structures as the environment play an important role [7, 8].

In this paper, we discuss the redifferentiation of cancer cells, in which such a nonlocal interaction is considered to play an essential role. Further, we propose a model to reproduce this phenomenon and mathematically analyze our model to construct autonomous decentralized systems with nonlocal interactions mediated by the environment in the future.

2. Relation between Order Formation of Cell Population and Extracellular Environment

Usually, an individual maintains the order of a system based on communication between cells through the processes of proliferation, differentiation, and repeated alternation.

Cancer is a phenomenon in which an individual produces an abnormal group of cells, so-called cancer cells, that contravene such an order. It is a serious disease that is deeply associated with the essential functions of cells such as cell proliferation, differentiation, and others. Cancer cells keep proliferating infinitely by cutting off all contact with surrounding cells. Then, they disorder a cell population and hinder the functions of various organs that maintain the life activity of the individual. Finally, the individual, including the cancer cells themselves, is destroyed. The question arising here is: What is the relation between carcinogenesis of cells and the extracellular environment?

A series of experiments conducted by Mintz and colleagues give an important clue to this question [9, 10]. In their experiment on chimeric mice with both normal and cancer cells, they obtained the interesting result that cancer cells return to normal and newly start cell redifferentiation in a special extracellular environment. First, they prepared two different types of mice on a genetic level: a female mouse with normal cells and another mouse with powerful cancer cells derived from teratocarcinoma. Next, they implanted an early embryo in the womb of the female mouse with the cancer cells of the other mouse. After the embryo grew in the womb, the female mouse finally gave birth to a chimeric mouse of normal characteristics. Since they were careful to select a female mouse that could be strictly distinguished from the other mouse on the genetic level, it was possible to clearly identify which part of the newly born chimeric mouse's body came from the cancer cells. Surprisingly, they could not find cancerous tissue anywhere in the body. In other words, even the parts derived from the cancer cells did not show signs of cancer.

This means that the cancer cells completely return to normal ones at the levels of both tissues and cells in the womb. Namely, when powerful cancer cells behaving selfishly are placed in an appropriate environment, they no longer can behave arbitrarily. Instead, they become members of the embryo having a neatly organized state and regain a strong capability of communication. Further study must be made before concluding that the same effect appears in all kinds of cells. However, the results of these experiments suggest that the carcinogenesis of normal cells and the redifferentiation of cancer cells are affected not only by the mutation of the original cancer genes and the cancer-suppressing genes in a cell, but also by changes in the extracellular environment controlling the interactions between cells [11, 12].

In this paper, we focus on the extracellular matrix (ECM) as an extracellular environment able to suppress the abnormal behavior of cancer cells. The ECM is a gel-like medium composed of complex protein filaments forming a global network between cells. It is joined to the cytoskeleton in each cell by transmembrane matrix receptors such as integrin, penetrating the cell membrane. Previously, the ECM was regarded merely as a cementing material that retains water and fills the gap between cells. At best, its only role was believed to be the physical support of cells.

However, recent researches have shown that interactions between the ECM and cells through integrin cause the transmission of a variety of signals controlling cell proliferation, differentiation, and death inside the cells. Namely, the ECM is an extracellular environment that acts as a solid-phase cytostatic factor maintaining the constant transmission of signals through the integrin and other transmembrane matrix receptors. For example, fibronectin, which is one of the components of the ECM, joins with various cell proliferation factors such as protease, fibrocyte growth factor, and others. Fibronectin adjusts the speed of cell proliferation by increasing or decreasing the activity of cell proliferation factors.

Further, recent researches have shown that the ECM is an essential factor for two mechanisms of controlling cell proliferation.

The first is the trigger mechanism of cell proliferation. The genes of a cell are activated by two kinds of signal through the same transmission paths in the cell [13]. One is a signal transmitted from the ECM to the inside of the cells through integrin. The other signal is transmitted from the extracellular fluid to the inside of the cells through cell proliferation factor receptors. This fact also means that for cell proliferation, signals from both the ECM–integrin system and the cell proliferation factors–their receptors system must always work at the same time in a cell. Namely,

in the absence of a signal from the ECM, all cells fail to proliferate even if they are given cell proliferation factors. This phenomenon is generically called anchorage dependence of cells [14, 15].

The second is the contact inhibition mechanism between adjacent cells. This is well known as a phenomenon in which the ECM transmits signals that inhibit cell proliferation to cells when the cells contact each other. The effect of contact inhibition greatly contributes to the well-ordered formation of spatiotemporal patterns in a cell population [16, 17].

It has become biologically clear that the mutation of the original cancer genes and the cancer-suppressing genes destroys the functions of anchorage dependence and contact inhibition. In this sense, the mutation of genes is clearly one of the essential factors in cellular carcinogenesis.

The mechanisms described above are based on the local signaling properties of the ECM. However, it should be noted that the ECM constitutes a global system having some global properties of signal transmission that affect cell proliferation, for the following two reasons.

(a) The ECM is a global dynamic system having viscoelastic properties. It is well known that the ECM plays a direct role in formation of the particular shapes of multicellular organisms [16, 17]. Murray and colleagues have proposed models of shape formation in animals based on the dynamics of the ECM [18, 19]. In these models, they assume that the ECM constitutes a global system having viscoelastic properties.

(b) The ECM has a mechanism for mutual conversion between mechanical and chemical reactions. Biological researches have already shown that the cell–ECM system has a mechanochemical mechanism that interconverts between mechanical and chemical reactions [16–19].

Biologically, the findings above suggest that the ECM globally affects a variety of chemical reactions in a cell population [20, 21]. Specifically, the ECM having global structure probably acts as a go-between mediating nonlocal interactions between cells beyond adjacent regions. In this connection, recent experiments on *Drosophila* and mice have shown a very interesting phenomenon called the "cytoname" [7, 8]. In this phenomena, a cell itself, by expanding its cytoplasm as a pseudopod, goes beyond its neighboring cells to reach a remote source of signals, where it picks up signals itself. However, another phenomenon has also been discovered, which implies that the cytoname alone is not sufficient to explain various situations of shape formation [22]. Therefore, nonlocal interactions between cells mediated by the ECM are regarded as a strong candidate for an alternative mechanism.

It is already recognized that both the ECM and integrin are strongly connected with carcinogenesis of cells. Regarding this, the following are a few of the experimentally identified differences between normal and cancer cells [16, 17].

(a) The quantity of fibronectin decreases in the vicinity of cancer cells.

(b) The quantities of integrin and cadherin, which is an intercellular adhesion molecule, decreases in cancer cells.

Since these situations disrupt communication between cells, the cells start to proliferate abnormally.

From this discussion, it can be inferred that for order formation in multicellular organisms, the ECM plays an important role as extracellular environment in the presence of integrin. Also, we can estimate that changes in the properties of the ECM alter the behavior of cells. Further, these inferences lead us to the assumption that changes in the properties of the ECM cause redifferentiation of cancer cells. To examine this assumption, we attempt to model the dynamics of the cell–ECM system in Section 3.

3. Our Model

Figure 1 shows a schematic diagram of our model. Most reaction-diffusion models describing the dynamics of cell populations have assumed that all cells of a system interact locally with each other [23]. However, as mentioned in Section 2, the ECM mediates not only local interactions between adjacent cells but also nonlocal interactions between cells beyond adjacent regions. Therefore, a mathematical model satisfying this requirement can be formulated as

$$\frac{\partial N(\mathbf{x},t)}{\partial t} = D_N\vec{\nabla}^2 N + G_1(N) + G_2(N) - \int_\Omega \int_{t_0}^{t} W(\mathbf{x},\mathbf{x}';t,t')F(N(\mathbf{x}',t'))dt'd\mathbf{x}' \quad (1)$$

where $N \equiv N(x, t) \geq 0$ is the density of a cell population, and Ω is the spatial domain in which the integral kernel W is well-defined. In Eq. (1), the first term on the right-hand side shows the short-range diffusion motion of cells, the second the contact inhibition of the cells, the third the anchorage dependence of the cells, and the fourth a nonlocal interaction between cells beyond adjacent regions mediated by the ECM.

For simplicity, in this paper we assume that the space is one-dimensional. Under this supposition, we further assume that the lower limit of time integration and the range of space integration in the fourth term on the right-hand side of Eq. (1) are $t_0 = -\infty$ and $\{\Omega | -\infty \leq x' \leq \infty\}$, respectively. However, these assumptions do not cause any loss of generality in the following analysis.

Based on Fig. 1, the details of these terms are modeled in the following way. First, the second term on the right-hand side is written as $G_1(N) = \rho_1(N)N^2$. Here $\rho_1(N)$, which represents the intensity of the contact inhibition, is given by

$$\rho_1(N) = -\rho_1 \alpha N + \rho_2 \tag{2}$$

where α is a parameter expressing the properties of the integrin. In Eq. (2), the first term on the right-hand side expresses the inhibition effect, observed only when there is an integrin-mediated bond between a cell and the ECM, that is, when the cells are in normal states. It suggests that the greater the density of the cell population, the greater the inhibition effect. The second term on the right-hand side of Eq. (2) expresses the degree of abnormality regarding the inhibition effect resulting from the carcinogenesis of cells.

The third term on the right-hand side of Eq. (1) is written as $G_2(N) = \rho_2(N)N^2$. Here $\rho_2(N)$, which represents the intensity of the anchorage dependence of cells, is given by

$$\rho_2(N) = \rho_3 \alpha \beta \tag{3}$$

where β is a parameter expressions the properties of the cell proliferation factor receptors. Equation (3) suggests that cell proliferation occurs only when both the integrin and fibronectin exist at the same time. The functions $\rho_1(N)$ and $\rho_2(N)$ are graphed in Fig. 2, where we assume ideal conditions ignoring the explicit spatial dependence of these functions.

Next, the integrand F in the fourth term on the right-hand side of Eq. (1) is actually a filter function that expresses the cascade reaction of signaling inside and outside a cell. As shown in Fig. 1, this cascade reaction works via the integrin. This means that the integrand F is described as

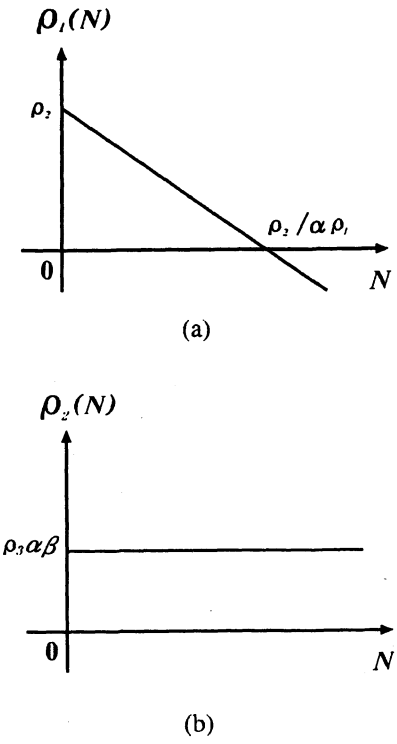


Fig. 2. Coupling of local interactions between cells. (a) Contact inhibition; (b) ECM–dependency.

$$F(N) = \rho_4 \alpha N \tag{4}$$

The integral kernel $W(\mathbf{x}, \mathbf{x}', t, t')$ in the fourth term on the right-hand side of Eq. (1) is actually a weight function that expresses the spatiotemporal properties of the nonlocal interaction between cells mediated by the ECM. Here, we

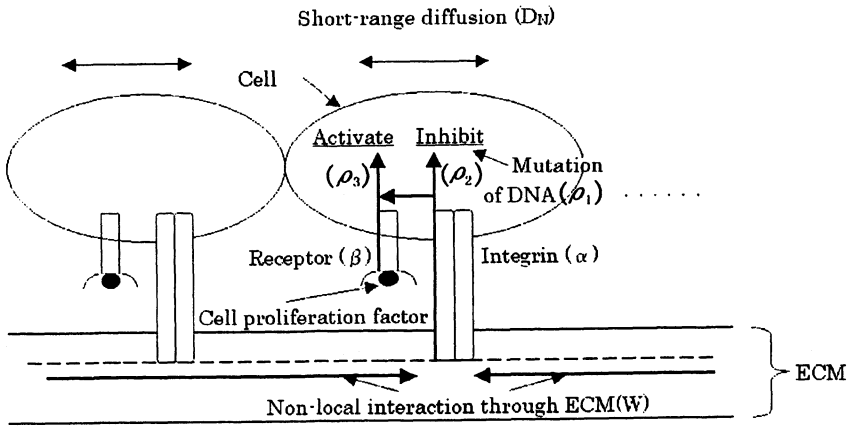


Fig. 1. Schematic model of a cell's dynamics on the ECM.

assume that the integral kernel W satisfies four mathematical conditions.

(1) W is a function of $y \equiv |\mathbf{x} - \mathbf{x}'|$ and $s \equiv t - t'$:

$$W(\mathbf{x}, \mathbf{x}', t, t') = W(y, s) \qquad \text{where } t - t_0 \geq s \geq 0 \quad (5)$$

(2) W is positive in the entire region of both y and s:

$$W(y, s) \geq 0, \forall y, \forall s \quad (6)$$

(3) $W(y, s)$ is a monotonically decreasing function of both y and s:

$$W(y, s) \to 0 \text{ for } y \to 0, s \to 0 \quad (6')$$

(4) $W(y, s)$ is normalized as follows:

$$\int_{-\infty}^{\infty} \int_{0}^{\infty} W(y, s) ds dy = 1 \quad (7)$$

Thus, the dynamics of the cell–ECM system is finally written as

$$\begin{aligned} &\frac{\partial N(x,t)}{\partial t} \\ &= D_N \frac{\partial^2 N}{\partial x^2} - \rho_1 \alpha N^3 + (\rho_2 + \rho_3 \alpha \beta) N^2 \\ &\quad -\rho_4 \alpha \int_{-\infty}^{\infty} \int_{0}^{\infty} W(y, s) \\ &\quad \times N(x - y, t - s) ds dy \end{aligned} \quad (8)$$

Of course, although this model is not strict, the picture shown in Fig. 1 is easy to understand. It can reasonably serve as the starting point for proposing more realistic models in future research. For simplicity, applying the set of parameters $D_N = 1$, $\rho_1 = 1$, $\rho_2 = 1$, $\rho_3 = \alpha > 0$, $\rho_4 = \beta > 0$ with appropriate units, Eq. (8) is rewritten as

$$\begin{aligned} &\frac{\partial N(x,t)}{\partial t} \\ &= \frac{\partial^2 N}{\partial x^2} - \alpha N^3 + (1 + \alpha^2 \beta) N^2 \\ &\quad -\alpha \beta \int_{-\infty}^{\infty} \int_{0}^{\infty} W(y, s) \\ &\quad \times N(x - y, t - s) ds dy \end{aligned} \quad (9)$$

4. Mathematical Analysis

The changes in the properties of the integrin and the ECM actually correspond to the changes in the parameter α and the integral kernel W in Eq. (9). As understood from observations of the ontogenesis of various multicellular organisms, cell populations placed in a normal extracellular environment finally form normal shapes in the presence of transmembrane matrix receptors. Mathematically speaking, this corresponds to the formation of a spatially inhomogeneous steady-state pattern, that is, a Turing pattern, and a temporal oscillation pattern.

Therefore, we are interested in whether Eq. (9) has asymptotic solutions such as a Turing pattern and a temporal oscillation pattern from an appropriate initial condition, that is, a spatially homogeneous steady state, for appropriate values of the parameter α of the integrin and the integral kernel W of the ECM [24].

First, in the following mathematical analysis, we separate the situation $\alpha = 0$ from the situation $\alpha \neq 0$. As discussed in Section 2, the ECM influences cell proliferation only if the integrin exists. This means that $\alpha = 0$ corresponds to a situation in which the ECM does not affect cell proliferation and $\alpha \neq 0$ a situation in which the ECM affects cell proliferation. For $\alpha \neq 0$, we consider two typical types of integral kernel W satisfying the mathematical conditions described above.

4.1. Case of $\alpha = 0$

In this case, Eq. (9) solves one of the conventional reaction-diffusion models of one variable as follows:

$$\frac{\partial N(x,t)}{\partial t} = \frac{\partial^2 N}{\partial x^2} + N^2 \quad (10)$$

which represents the dynamics of a cell population with no influences of the ECM. The behavior of a solution of Eq. (10) is graphed in Fig. 3. Starting at a point of time exceeding $t = 70$, the values in the neighborhood of $x = 17$ were seen to increase rapidly, resulting in divergence. This suggests that the solution will explode during a finite time.

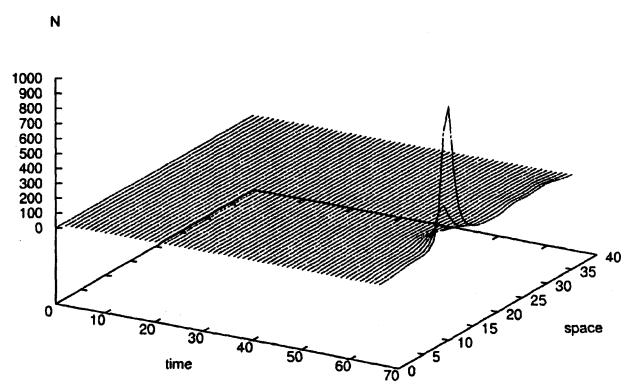


Fig. 3. Behavior of Eq. (10). Initial condition: $N(x, 0) = 1.0 + random$. Boundary condition: Dirichlet type.

Generally, whether solutions of Eq. (10) show divergence or convergence depends on the initial conditions. This can be qualitatively demonstrated by renormalization group analysis [25, 26].

4.2. Case of $\alpha \neq 0$

In this case, the steady-state solutions N of Eq. (9) satisfy

$$\frac{\partial^2 N}{\partial x^2} - \alpha N^3 + (1 + \alpha^2\beta)N^2 - \alpha\beta N = 0 \quad (11)$$

It is clear that the spatially homogeneous steady-state solutions $N_0 = 0$, $1/\alpha$ and $\alpha\beta$, satisfy Eq. (11). In this paper, we restrict the parameters α and β to satisfy the condition $0 < 1/\alpha < \alpha\beta$, that is, $\alpha^2\beta > 1$, and select the initial condition as follows:

$$N_0(x,t) = 1/\alpha, \quad \forall t < 0, \quad \forall x \in R \quad (12)$$

This is one of the spatially homogeneous steady-state solutions N_0 described above. To examine how fluctuations develop with time in the neighborhood of this initial condition N_{int}, we substitute an infinitesimal quantity n expressed $n \equiv N - 1/\alpha$ into Eq. (9). As a result of using Eq. (11), we get a linear equation in n:

$$\frac{\partial n(x,t)}{\partial t} = \frac{\partial^2 n}{\partial x^2} + (2\alpha\beta - 1/\alpha)n - \alpha\beta \int_{-\infty}^{\infty}\int_{0}^{\infty} W(y,s)n(x-y,t-s)dsdy \quad (13)$$

Next, we assume $n(x, t) \sim \exp(\lambda t + ikx)$ as a special solution of Eq. (13). In this case, the necessary and sufficient condition for n to be a nontrivial solution is that the eigenevalue λ satisfies the characteristic equation

$$\lambda + k^2 + 1/\alpha n - 2\alpha\beta + \alpha\beta\overline{W}(\lambda, k^2) = 0 \quad (14)$$

where the function $\overline{W}$ is defined as

$$\overline{W}(\lambda, k^2) \equiv \int_{-\infty}^{\infty}\int_{0}^{\infty} W(y,s)e^{-iky}e^{-\lambda s}dsdy \quad (15)$$

4.2.1. Case with W as delta function

We assume

$$W(y,s) = \delta(y)\delta(s) \quad (16)$$

Substituting Eq. (16) into Eq. (15) gives

$$\overline{W}(\lambda, k^2) = 1 \quad (17)$$

Further, substituting Eq. (17) into Eq. (14), we obtain the characteristic equation

$$\lambda = -k^2 - \frac{1}{\alpha} + \alpha\beta \quad (18)$$

For the initial state N_{int} to be stable, the condition Re $\lambda < 0$ must be satisfied. Gradually increasing the bifurcation parameter β starting from a small value makes the initial state N_{int} unstable under the condition Re $\lambda > 0$. Therefore, the condition Re $\lambda = 0$ represents the bifurcation point of stability. This bifurcation point appears in the curve described as

$$\beta = k^2/2\alpha + 1/2\alpha^2 \equiv f(k^2) \quad (19)$$

The graph $y = f(x)$, where $x \equiv k^2 > 0$, is shown in Fig. 4. In Fig. 4, the unstable region satisfying the condition Re $\lambda > 0$ is seen in the upper part of the graph. Here β_T in the graph is given by

$$\beta_T = 1/2\alpha^2 > 0 \quad (20)$$

Figure 4 also suggests that the mode of the wave number satisfying $k_C = 0$ becomes unstable when β is reached at the bifurcation point β_T. Any new steady state appearing in the neighborhood of the bifurcation point β_T is found to be spatially homogeneous.

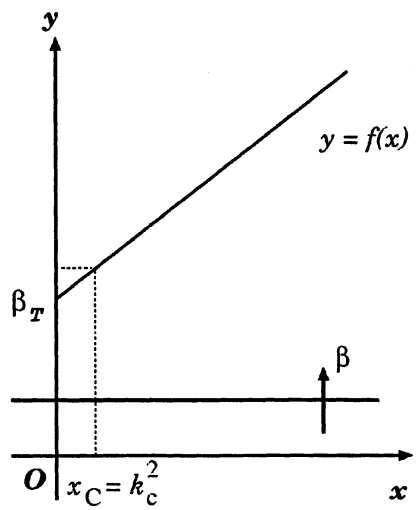


Fig. 4. Graph of $y = f(x)$.

4.2.2. Case with W as exponential function

Next, we assume

$$W(y, s) = a/2 \cdot e^{-a|y|} \cdot be^{-bs} \text{ for } a > 0, b > 0 \quad (21)$$

where a and b are scale parameters representing the spatial and history properties of a nonlocal interaction between cells mediated by the ECM. Substituting Eq. (21) into Eq. (15) gives

$$\overline{W}(\lambda, k^2) = \frac{a^2}{(k^2 + a^2)} \cdot \frac{b}{(\lambda + b)} \quad (22)$$

Further, substituting Eq. (22) into Eq. (14), we obtain the characteristic equation

$$\lambda + k^2 + \frac{1}{\alpha} - 2\alpha\beta + \frac{\alpha\beta a^2 b}{(k^2 + a^2)(\lambda + b)} = 0 \quad (23)$$

that is,

$$\lambda^2 + c_k\lambda + d_k = 0 \quad (24)$$

where c_k and d_k are represented as

$$c_k = k^2 + 1/\alpha - 2\alpha\beta + b \quad (25)$$

$$d_k = b\left\{k^4 + 1/\alpha - 2\alpha\beta + \frac{\alpha\beta a^2}{(k^2 + a^2)}\right\} \quad (26)$$

Therefore, the eigenvalues are

$$\lambda_\pm = \{-c_k \pm (c_k{}^2 - 4d_k)^{1/2}\}/2 \quad (27)$$

For the initial state N_{int} to be stable, both of the conditions Re $\lambda_+ < 0$ and Re $\lambda_- < 0$ must be satisfied simultaneously. In other words, both of the conditions $c_k > 0$ and $d_k > 0$ must be satisfied simultaneously with respect to all values of the wave number k. Hence, when β is gradually increased from a small value, the initial state N_{int} becomes unusable if either of the conditions Re $\lambda_+ > 0$ and Re $\lambda_- > 0$ is satisfied. The former is equal to the condition $c_k < 0$, which corresponds to the Hopf bifurcation, and the latter the condition $d_k < 0$, which corresponds to the Turing bifurcation, with respect to a specific wave-number region. Therefore, the conditions $c_k = 0$ and $d_k = 0$ represent the bifurcation point of these bifurcations. These bifurcation points appear in the curves described as

$$\beta = k^2/2\alpha + b/2\alpha + 1/2\alpha^2 \equiv g(k^2) \quad (28)$$

$$\beta = \frac{\alpha k^4 + (\alpha a^2 + 1)k^2 + a^2}{\alpha^2(2k^2 + a^2)} \equiv f(k^2) \quad (29)$$

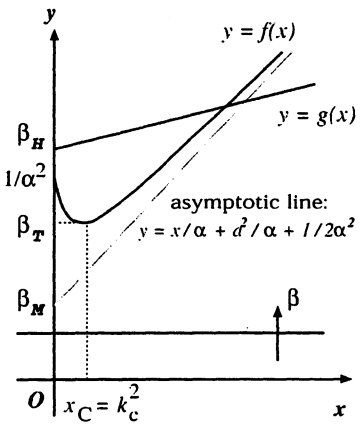
Plots of $y = f(x)$ and $y = g(x)$ where $x \equiv k^2 > 0$ are shown in Figs. 5(a) and 5(b). In Figs. 5(a) and 5(b), the unstable region satisfying the conditions $c_k < 0$ and $d_k < 0$ is seen in the upper part of the graph. β_H and β_T in the graph are represented as

$$\beta_H = 1/2\alpha^2 + b/2\alpha > 0 \quad (30)$$

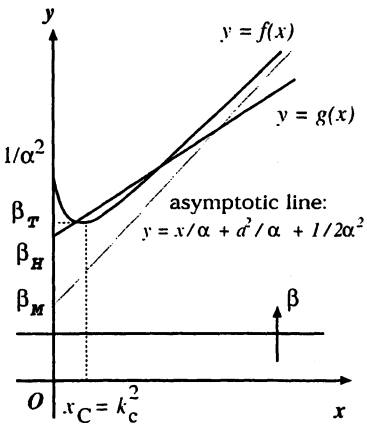
$$\beta_T = 1/2\alpha^2 + a(2\alpha - \alpha^2 a^2)^{1/2}/2\alpha > 0 \quad (31)$$

As shown in Fig. 5(a), a Turing bifurcation occurs at the bifurcation point β_T if the condition $\beta_H > \beta_T$, that is, $b > (2\alpha - \alpha^2 a^2)^{1/2}/\alpha$, is satisfied. In addition, we must consider another condition $0 < a < 1/\alpha^{1/2}$, so that the position x, which gives the larger value of the two extreme values in $y = f(x)$, is positive.

Thus, the condition for a Turing bifurcation is



(a)



(b)

Fig. 5. Graphs of $y = f(x)$ and $y = g(x)$. (a) $\beta_H > \beta_T$; (b) $\beta_H < \beta_T$.

$$b > a(2\alpha - \alpha^2 a^2)^{1/2}/\alpha, \quad 0 < a < 1/\alpha^{1/2}. \quad (32)$$

When β is gradually increased starting from a small value, the condition Re $\lambda_{\pm} < 0$ are satisfied for small β. When β is reached at the bifurcation point β_T, the condition $d_{k_C} = 0$ appears in the mode whose wave number is given by

$$k_C = \pm[\{-\alpha a^2 + a(2\alpha - \alpha^2 a^2)^{1/2}\}/\alpha]^{1/2} \quad (33)$$

and mode λ_+ becomes unstable while mode λ_- remains stable.

Since no boundary conditions are given to derive the wave number k_C, the wave number k_C does not depend on the size of the system. The instability of the mode whose finite wave number k_C is indicated by Eq. (33) implies that a Turing pattern appears. Conversely, if the condition $\beta_H < \beta_T$, that is, $b < (2\alpha - \alpha^2 a^2)^{1/2}/\alpha$, is satisfied, the condition $c_{k_{C=0}} = 0$ is satisfied at $\beta = \beta_H$ before a Turing bifurcation occurs at $\beta = \beta_T$, as shown in Fig. 5(b). In this situation, a pair of modes expressed by $\lambda_{\pm} = \pm\{b(1 - \alpha b)/2\alpha)^{1/2}\}i$ becomes unstable. While the condition $\beta > \beta_H$ is satisfied, a temporal oscillation associated with a Hopf bifurcation occurs. Figure 6 is a phase diagram represented by Eq. (33) in the parameter space (a^2, b). In Fig. 6, T denotes a Turing pattern and H a temporal oscillation pattern resulting from a Hopf bifurcation.

4.3. Numerical analysis

From the above analysis, it becomes clear that the initial state $N_{\text{int}} = 1/\alpha$ becomes unstable in the neighborhood of the bifurcation points β_T and β_H. To discuss a specific pattern formed after reaching instability regions, we also performed numerical simulations using several parameters. The results of these simulations are summarized in Figs. 7 and 8. In the simulations, we use the boundary condition of the Dirichlet type. From Fig. 7, which shows the result of calculation based on the parameter values $\alpha = 0.5$, $\beta = 3.96$, $a = 1.2$, and $b = 2.0$, we get a spatially inhomogeneous pattern as an asymptotic solution. From Fig. 8, which shows the result of calculation based on the parameter values $\alpha = 1.0$, $\beta = 3.0$, $a = 0.5$, and $b = 0.7$, we get a spatially inhomogeneous and temporally oscillating solution as an asymptotic solution.

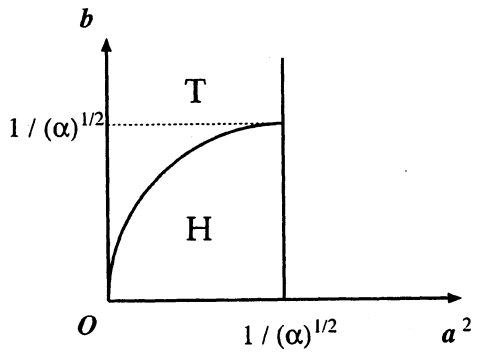


Fig. 6. Phase diagram in parameter space (a^2, b).

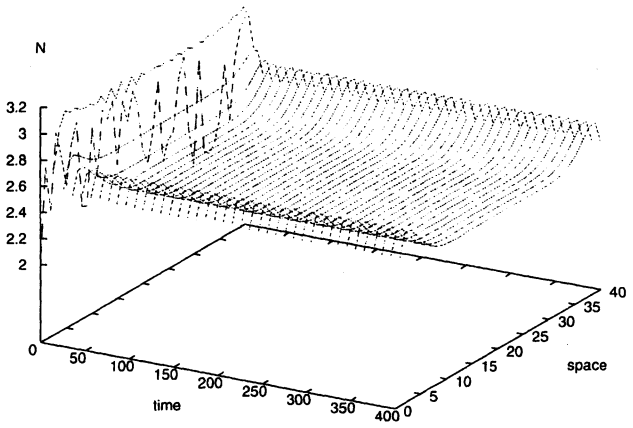


Fig. 7. Spatial inhomogeneous solution. Initial condition: $N(x, t) = 1.0 + random$. Boundary condition: Dirichlet type, $\alpha = 0.5$, $a = 1.2$, $b = 2.0$, $\beta = 3.96$.

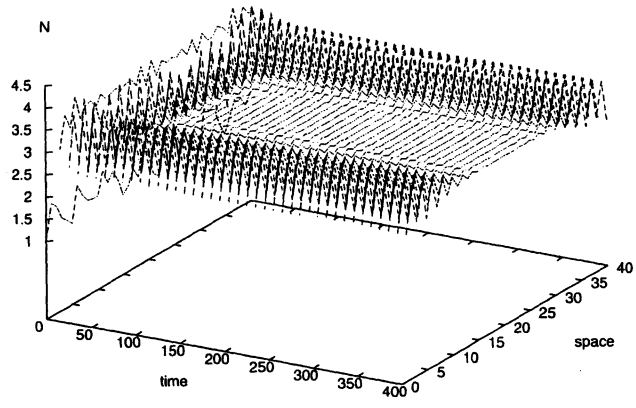


Fig. 8. Spatial inhomogeneous–temporal oscillationary solution. Initial condition: $N(x, t) = 1.0 + random$. Boundary condition: Dirichlet type, $\alpha = 1.0$, $a = 0.5$, $b = 0.7$, $\beta = 3.0$.

5. Discussion and Conclusions

The mathematical analysis in Section 4 shows that the asymptotic solutions for $\alpha = 0$ are different from those for $\alpha \neq 0$. Specifically, the former forms a Turing pattern or a temporal oscillation pattern depending on the parameters of the integral kernel W, while the latter diverges.

First, we discuss the biological implications of this finding associated with the redifferentiation of cancer cells. Our cell population starting from the initial conditions consisting of a steady state and a fluctuation proliferates abnormally (the solution diverges) if there is no influence from the ECM ($\alpha = 0$). However, if there is some influence from the ECM ($\alpha \neq 0$), the cell population does not proliferate abnormally but becomes normalized (the solution settles down to a Turing pattern) in the neighborhood of the first-order bifurcation point of β (namely, in the region where the density of the cell proliferation factor exceeds the threshold).

Thus, we obtain the new insight that the ECM as an extracellular environment plays an important role in the process of forming the order of a cell population. In particular, the inhibitory effect of nonlocal interactions between cells mediated by the ECM is probably significant.

This conclusion suggests a probable reason that hardly any examples of Turing patterns in the conventional reaction-diffusion models, which describe the dynamics of chemical substances, have been seen in real biological systems. In 1990, Castets and colleagues successfully reproduced the Turing pattern for chemical substances by using iodide as an activator, chlorite as an inhibitor, and malonic acid. Although at the laboratory level, it was the world's first experiment of that kind, the presence of starch was a major factor in the experiment because the starch formed a stable complex with the iodide and reduced the diffusion velocity of the iodide. As a result, the diffusion velocity of the activator became markedly lower than that of the inhibitor, so that the iodide formed a stable Turing pattern based on the principle of short range activation–long range inhibition [28].

The results of their experiment imply that in the real process of forming the shape of multicellular organisms, it is difficult to form a Turing pattern with only a reaction-diffusion system of chemical substances. As our analysis in this paper indicates, it is necessary to consider the properties of the ECM as extracellular environment underlying the system, in particular nonlocal interactions mediated by the ECM.

Equation (10), which describes the dynamics of a cell population with no influences of the ECM, is an example of conventional reaction-diffusion models of one variable. The mathematical analysis in Section 4 shows that the solution of Eq. (10) is qualitatively different from that of Eq. (9). Such a difference is also expected to appear when a comparison is made with conventional reaction-diffusion models of many variables. In connection with this, recent research shows that there is an interesting pattern, called the drift pattern, which is a peculiar solution exhibited by a model that is of the same mathematical class as our model [27]. We have undertaken a mathematical analysis of peculiar patterns formed by our model described by Eq. (9).

Reaction-diffusion models of the class proposed in this paper suggest that it is possible to expand the framework from an ordinary reaction-diffusion model, which is based on local interaction between the components of a system, to a generalized reaction-diffusion model introducing a nonlocal interaction. Applying our model to an autonomous decentralized system will expand the scope of application of any control model using conventional reaction-diffusion models from a uniform environment to a nonuniform environment.

Next, we discuss this possibility by using an example: the control model of road traffic flow. Recent traffic flow models based on a reaction-diffusion model control the traffic signal network as an autonomous decentralized system and focus on the offset between adjacent traffic signals. Here the "offset" is defined as the difference in timing of the green lights. With their assumptions limited to the real-time interaction between traffic signals, these models place traffic flow under control so that the system converges to an appropriate offset value. For such a control model, since there is no need to control the system so that it follows the optimum solution obtained in advance, it is possible to control the system on a real-time basis. Thus, it provides many benefits, so that even an unexpected vehicle accident makes it possible to take appropriate action, unlike the conventional control model for a traffic signal network with centralized control [4–6].

However, it should be noted that these reaction-diffusion models for a traffic signal network assume only local interaction between adjacent traffic signals. This assumption is effective if all traffic signals constituting the system are uniformly positioned within the environment, that is, a traffic signal network. In such a case, it can be assumed that a local environment is essentially identical to a global environment. In this sense, the conventional method of controlling traffic signals with a reaction-diffusion model is applicable to a control model in an ideal environment.

Often, however, the density of traffic signals in an actual traffic signal network is different from location to location. In this situation, it is not effective to approximate a local environment as a global one. One approach introducing the effect of a nonuniform environment into a model is to introduce nonlocal interaction between traffic signals. Any reaction-diffusion model of the class proposed by this paper appears to have naturally introduced nonlocal interaction based on biological findings. Therefore, it could be

expanded into a control model for an autonomous decentralized system considering the effects of environment. For example, it will be possible to explore a new possibility in engineering: GPS-based global control of traffic signals.

We are presently investigating the application of the reaction-diffusion model with nonlocal interactions mediated by the environment to the control model for a traffic signal network.

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