Proportion Regulation in Globally Coupled Nonlinear Systems

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Abstract

As a model of proportion regulation in differentiation process of biological system, globally coupled activator-inhibitor systems are studied. Formation and destabilization of one and two cluster state are predicted analytically. Numerical simulations show that the proportion of units of clusters is chosen within a finite range and it is selected depend on the initial condition.

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The regulation of proportion among different cell types in a tissue is a general and important aspect of biological development. It is well known that the proportion between the two different cell types is roughly constant irrespective of the slug size of cellular slime mold *Dictyostelium discoideum* (Dd) amoebae [1–4]. Initially the same type of aggregative cells, when dissociated, randomly mixed, and reaggregated, differentiate into two types of cells (prespore and prestalk cells) without pattern formation. It is known now that cell differentiation starts independently on the cell position, and later cell sorting forms the two-zoned prestalk-prespore pattern in slug of Dd [3–5]. Similar regulation mechanism can be observed in caste populations of social insects such as ants and bees [6,7]. In the division of work, proportion is regulated irrespective of the size of society nor the artificial partial extinction by the experimenter.

No theoretical model exists to describe the proportion regulation. Any pattern formation model such as Turing type instability with diffusive coupling [8] is incompatible with the observation that the Dd cells start to differentiate independent to their positions. A large population of identical units interacting equally to the other units (globally coupled nonlinear system) is a good candidate to describe the phenomena. It is an idealized model of the cases, when the diffusion length of chemical factor, e.g. differentiation inducing factor (DIF) or pheromone, is large enough compared to the cell size, or when the individual units moves around to interact with others.

Recently, globally coupled chaotic map [9,10] and globally coupled oscillators [11–16] are studied and interesting phenomena including clustering and their destabilization are observed. However, analysis of cluster state is difficult for these systems because the unit itself is complex enough. It is also doubtful that chaos or oscillation is playing essential roles in proportion regulation of biological system such as Dd. In this respect, a minimum model of clustering is preferable.

Our model of globally coupled system is composed of *N* activator-inhibitor type units which have two variables *u* and *v*. The dynamics of each unit is modeled as
\[ \dot{u}_j = au_j - bv_j - u_j^3 + K_1(\bar{u} - u_j), \]
\[ \dot{v}_j = cu_j - dv_j + K_2(\bar{v} - v_j), \]
\[ \bar{u} \equiv \frac{1}{N} \sum_{i=1}^{N} u_i \quad \text{and} \quad \bar{v} \equiv \frac{1}{N} \sum_{i=1}^{N} v_i. \]  

(1)

Here, two component \( u_j \) and \( v_j \) of \( j \)-th unit are considered as activator and inhibitor by assuming that \( a, b, c, \) and \( d \) are positive. Each unit couples with all other units through the averaged field \( \bar{u} \) and \( \bar{v} \). We assumed that both \( K_1 \) and \( K_2 \) are non-negative. They can be regarded as the susceptibility of each component because this type of global coupling can be considered as the fast limit of diffusion velocity.

First, we investigate the properties of individual unit by setting \( K_1 = K_2 = 0 \). Steady stationary solutions \( (u_0, v_0) \) are easily solved by setting \( \dot{u} = \dot{v} = 0 \). Depend on the parameter \( s \equiv ad - bc \), the number and the stability of the fixed point changed. Linear stability of these fixed points can be analyzed by setting \( u = u_0 + \delta u, v = v_0 + \delta v, |\delta u|, |\delta v| \ll 1 \), and \( \delta u = \delta u_0 e^{\lambda t}, \delta v = \delta v_0 e^{\lambda t} \). Linearization of (1) leads the eigenvalue equation

\[ 0 = \lambda^2 - (a - d - 3u_0^2)\lambda - s + 3du_0^2. \]  

(2)

The fixed point \( (u_0, v_0) \) is stable if the conditions \( 0 > a - d - 3u_0^2 \) and \( 0 < -s + 3du_0^2 \) are satisfies. We assume that \( a < d \) and \( s < 0 \) from now. In this case, the trivial solution \( (0, 0) \) is the unique attractor of the dynamical system of one individual unit. [17].

Let us consider a one cluster state which is defined as a state that every unit has the same value \( (u(1), v(1)) \), i.e.

\[ (u_j, v_j) = (u(1), v(1)) \quad \text{for} \quad j = 1, ..., N. \]

It is generally difficult to analyze the stability of cluster state in the globally coupled system because we must solve eigenvalue problem of \( 2N \) dimensional matrix. Following analyzing method, however, we obtain sufficient condition for destabilization of a cluster state easily. First, \( N \) units are assumed to form \( M \) clusters state \( \{(u(i), v(i))\}, i = 1, ..., M \). Next, we consider one additive unit (test unit) \( (u(t), v(t)) \) in that \( M \) clusters state and make an
approximation that the effect to the test unit from $N$ units is simply external force. This approximation is justified in the limit of $N \to \infty$. By investigating the stability of this test unit, we argued the stability condition of original $M$ clusters state as follows. Noting that the test unit has at least $M$ “entrained” solutions to each cluster, i.e., $(u(t), v(t)) = (u(i), v(i))$, the linear stability of these entrained solutions can be analyzed. If one of the entrained solutions is unstable, we conclude that the original cluster state is unstable. We named this stability analysis method of the cluster state Test Unit Analysis (TUA) [18].

Now, we carry out TUA for the one cluster state $\{(0, 0)\}$ given in the previous paragraph, i.e., we consider a stability of test unit $(u(t), v(t))$ in the external force created by the $N$ units in one cluster state. In this case both of the average fields $\overline{u}$ and $\overline{v}$ vanish and equations for the test unit are written in the form:

$$\dot{u} = (a - K_1)u - bv - u^3,$$
$$\dot{v} = cu - (d + K_2)v.$$  \hspace{1cm} (3)

Fixed point of test unit can be obtained by setting $\dot{u} = \dot{v} = 0$. Using $v = cu/(d + K_2)$ given from (3), $u$ satisfies

$$0 = h_1(u) \equiv (d + K_2)u^3 + ((d + K_2)(K_1 - a) + bc)u.$$  \hspace{1cm} (4)

Note that $h_1(0) = 0$ because the test unit has the entrained solution $(u, v) = (0, 0)$. To investigate the stability of one cluster state, we analyze the test unit linear stability around entrained solution $(0, 0)$. By setting $u = \delta u$ and $v = \delta v$, linear stability analysis of (3) leads the eigenvalue equation:

$$0 = \lambda^2 - (a - d - K_1 - K_2)\lambda - (a - K_1)(d + K_2) + bc.$$  \hspace{1cm} (4)

The stability conditions of the entrained solution of the test unit to the one cluster state are now given as:

$$0 > a - d - K_1 - K_2$$ \hspace{1cm} (5)
$$0 < -s - aK_2 + K_1(d + K_2).$$  \hspace{1cm} (6)
From the condition for existence and stability of one cluster solution in the non-coupling case, (5) is automatically satisfied. Therefore the critical condition for the stability is given by R.H.S of (6) equals to 0 where a pitch-fork bifurcation occurs. Although this stability condition is for the entrained solution of the test unit, it is obvious that the original one cluster solution is unstable if (6) is broken. From the fact mentioned above, one cluster state is linearly unstable when \( K_2 > K_{2c} \). Fig. 1 shows a result of numerical simulation for \( K_2 < K_{2c} \). Parameters are \( N = 100, a = 0.4, b = 1, c = 0.5, d = 1, K_1 = 0, \) and \( K_2 = 0.2 \). Simple Euler method with \( dt = 0.01 \) are adopted. One cluster state (Fig. 1(c)) is realized from a uniform random initial condition (Fig. 1(b)). When \( K_2 > K_{2c} \), the one cluster state becomes unstable and each unit separates into two subpopulations, i.e.,

\[
(u_i, v_i) = \begin{cases} 
(u(1)_i, v(1)_i) & \text{for } i = 1, \ldots, N(1) \\
(u(2)_i, v(2)_i) & \text{for } i = N(1) + 1, \ldots, N 
\end{cases}
\]

Here, \( N(1) \) is a number of units which belongs to the first cluster. This state is defined as two clusters state and we focus on it in the next paragraph.

For simplicity we assumed that \( K_1 = 0 \). Let a two clusters state \((u(1)_i, v(1)_i), (u(2)_i, v(2)_i)\) having its proportion \( p : 1 - p \), here \( p \) is defined as \( p \equiv N(1)/N \) and \( 0 < p < 1 \) are satisfied. Because the averaged fields \( \bar{u} \) and \( \bar{v} \) become \( pu(1)_i + (1 - p)u(2)_i \) and \( pv(1)_i + (1 - p)v(2)_i \), respectively, \( u(1)_i, v(1)_i, u(2)_i, v(2)_i \) satisfy the following equations:

\[
\begin{align*}
0 &= au_{(1)} - bv_{(1)} - u_{(1)}^3 \\
0 &= cu_{(1)} - dv_{(1)} + K_2(1 - p)(v_{(2)} - v_{(1)}) \\
0 &= au_{(2)} - bv_{(2)} - u_{(2)}^3 \\
0 &= cu_{(2)} - dv_{(2)} + K_2 p (v_{(1)} - v_{(2)})
\end{align*}
\]

Eliminating \( v_{(1)} \) and \( v_{(2)} \), transforming from \((u_{(1)}, u_{(2)})\) to \((u_{(1)}, \phi)\) where \( \phi \) is a new variable defined by \( \phi \equiv u_{(2)}/u_{(1)} \), one can get two equations which are easily analyzed:

\[
u_{(1)}^2 = \frac{s + aK_2(1 - p) - aK_2(1 - p)\phi}{d + K_2(1 - p) - K_2(1 - p)\phi^3} = \frac{(s + aK_2 p)\phi - aK_2 p}{(d + K_2 p)\phi^3 - K_2 p}.
\]
\( \phi \) obeys

\[
(\phi - 1)(bcK_2(1 - p)\phi^3 - s(d + K_2)\phi^2 - s(d + K_2)\phi + bcK_2p) = 0.
\]

Note that \( \phi = 1 \) expresses \( u(1) = u(2) \), i.e., one cluster state. The solution must satisfies the inequality \( u_{(1)}^2 > 0 \). Therefore the condition for existence of two clusters solution is:

\[
K_2 > K_{2c} \equiv -s/a. \quad (7)
\]

Under the condition (7), we use TUA again to analyze the stability of the two clusters state, i.e., we consider a stability of test unit entrained solution in the external force created by the \( N \) units in the two clusters state. The test unit equations are:

\[
\begin{align*}
\dot{u} &= au - bv - u^3 \\
\dot{v} &= cu - dv + K_2(pv(1) + (1 - p)v(2) - v).
\end{align*}
\]

By setting \( \dot{u} = \dot{v} = 0 \), we obtain fixed points of the test unit. Note that there exist two entrained solutions to the cluster \((u(1), v(1))\) and \((u(2), v(2))\). To investigate the stability of two cluster state, we analyze the test unit linear stability around entrained solution \((u(1), v(1))\). By setting \( u = u(1) + \delta u, v = v(1) + \delta v \), linearization around \((u(1), v(1))\) leads the eigenvalue equation:

\[
0 = \lambda^2 - (a - d - K_2 - 3u_{(1)}^2)\lambda - (a - 3u_{(1)}^2)(d + K_2) + bc. \quad (8)
\]

The entrained solution becomes unstable if the constant term in (8) becomes 0. The stability condition is

\[
0 > \{(aK_2 + s)((2ad - 3bc)K_2 + 2ds)^2(d + K_2p)\}
\times\{-9bcK_2p + 2(ad + 3bc)K_2 + 2ds\}. \quad (9)
\]

From the fact that first braces of R.H.S. of (9) are positive definite, the last braces determine the stability. Bifurcation line is given by solving about \( p \), i.e.,

\[
p = p_c(K_2) = \frac{1}{9bc} \left( \frac{2ds}{K_2} + 2(ad + 3bc) \right). \quad (10)
\]
where a transcritical bifurcation occurs. For example, $p_c = 7.6/9 - 0.2/4.5K_2$ for the case $a = 0.4, b = 1, c = 0.5, d = 1$. Typical phase diagram is shown in Fig. 2. In the case of $K_2 < K_{2c}$, there does not exist two clusters solution. In the case of $K_2 > K_{2c}$, on the other hand, one of the two clusters solution with a proportion lain in the region B is realized. The two clusters state in the region C is linearly unstable and is not realized. Note that the bifurcation diagram is symmetric to $p = 0.5$ because the proportion of the other cluster is $1 - p$. Therefore possible proportion has a minimum $p_{\text{min}} = 1 - p_c(K_2)$ and maximum $p_{\text{max}} = p_c(K_2)$ value for given $K_2$. To investigate the dynamical process we perform numerical simulations. Fig. 3 shows the formation of two clusters state from a uniform random initial condition with $K_2 = 0.3 > K_{2c}$. Other parameters are the same as in Fig. 1. At $T = 500$, two clusters state is selected with a proportion $p : 1 - p = 49 : 51$. In Fig. 4, the proportion regulation under artificial partial extinction is shown. We start with the relaxed state of previous simulation (shown in Fig. 3(c)) with removing the 49 units which belongs to the cluster with negative $u$ value (hatched in Fig. 4(a)). The remained 51 units make a two clusters state with proportion $p : 1 - p = 23 : 28$ in the region B again. Three or more clusters state have not been observed.

To clarify what selects the final state proportion, we perform numerical simulations of equations (1) with changing initial conditions. Parameters are the same as in Fig. 1 except $K_2 = 0.5$. We start from 500 initial conditions which are uniform random numbers between $-0.1$ and $0.1$ with different seeds. Fig. 5 shows a distribution of finally selected proportion value with a peak at $p = 0.5$. These results show that the initial condition determines the proportion between the two clusters.

Finally, we check a structural stability of these result by adding a small positive constant term $\epsilon$, i.e.,

$$\dot{u}_j = au_j - bw_j - u_j^3 + K_1(\pi - u_j),$$
$$\dot{v}_j = cu_j - dv_j + K_2(\nu - v_j) + \epsilon.$$

Numerical simulation shows that the distribution of proportion also has a finite width. The most probable proportion, however, moves from 0.5 because the added term $\epsilon$ breaks the
symmetry of (1). For example, the most probable value is about 0.25, $p_{\text{min}} \sim 0.1$, and $p_{\text{max}} \sim 0.4$, respectively, when $a = 0.6$, $b = 1$, $c = 2$, $d = 1$, $K_1 = 0$, $K_2 = 3$, and $\epsilon = 0.2$. From this result we conclude that the proportion regulation phenomena discussed in this letter is generic.

The DIF which regulate the proportion of two types cells are widely studied about the differentiation process of Dd, e.g., cyclic adenosine 3′-monophosphate (cAMP), ammonia, and concentration of cation are known as candidates. If we specify the inhibitor and if we control the susceptibility, the proportion between two kind of cells is expected to be controlled.

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[17] The dynamics of each unit varies depend on the parameters. Except \((u, v) = (0, 0)\) there exists a pair of fixed points if \(s \geq 0\). Hopf and pitch-fork bifurcation occur at \(a - d = 0\) and \(s = 0\), respectively. Around the co-dimension two bifurcation point, a global bifurcation occurs and coexistence of limit cycle and fixed points is observed. More detail structure, however, will be studied in the future.

[18] Note that the condition given by the TUA is only sufficient condition for the destabilization of the original cluster state and is not necessary condition. There is an example that the original cluster state is unstable even if TUA is stable. Consider a following globally coupled system:

\[
\dot{u}_j = u_j - u_j^3 + K(\bar{u} - u_j).
\]

Although the fixed point \(u_j = 0\) is unstable to the perturbation that every units move to the same direction, the entrained solution to 0 of the test unit is stable so as to \(K > 0\). The relation between the stabilities of the entrained test unit solution and the stability of the original cluster state remains as a further problem.

[19] The added term \(\epsilon\) also change the bifurcation type between one and two clusters state. Coexistence of one cluster solution and two clusters solution occurs in some range of \(K_2\).
FIGURES

FIG. 1. (a) Temporal evolution of the distribution of units with respect to $u$. Gray scale represents the number of units by changing from 0 to $N$ between white and black. Randomly distributed units aggregate into the origin and one cluster state is formed. (b) Initial distribution of units. Each unit has a uniform random number between $-0.1$ and $0.1$ for $u$ and $v$, respectively. (c) Snapshot of one clusters state at $T = 200$.

FIG. 2. Typical phase diagram of one and two clusters state. The upper line is given by (10) and the lower line denotes $1 - p_c$. The dotted line is $K_2 = K_{2c}$. In the region A, there is no two clusters solution. In B and C, there is a linearly stable and unstable two clusters solution, respectively.

FIG. 3. (a) Evolution of the distribution with respect to $u$. Units around the origin separate into two clusters state. (b) Initial distribution. Each unit has a uniform random number between $-0.01$ and $0.01$ for $u$ and $v$, respectively. (c) Snapshot of two clusters state at $T = 500$.

FIG. 4. (a) Evolution of the distribution. After a sudden decrease of $u$ of each unit to zero till $T \sim 10$, 51 units separate into two clusters again. (b) Initial distribution. 49 units in the hatched cluster are removed. (c) Snapshot at $T = 500$. Proportion $p : 1 - p = 23 : 28$ is selected.

FIG. 5. Probability distribution of selected proportion of two cluster state from 500 randomly chosen initial conditions.
