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Rui Dilao
University of Lisbon
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EMERGENCE OF A COLLECTIVE STEADY STATE AND SYMMETRY BREAKING IN SYSTEMS OF TWO IDENTICAL CELLS

RUI DILÃO

Nonlinear Dynamics Group, Instituto Superior Técnico
Av. Rovisco Pais, 1049-001 Lisbon, Portugal
E-mail: rui@sd.ist.utl.pt; ruidilao@gmail.com

We consider a system of two coupled identical cells. The dynamics of the chemical substances in the individual cells are the same, and the coupling is proportional to the differences in the concentrations of its chemical constituents. Without coupling, the cells have a unique and identical stable steady state — the quiescent state. We show that the coupled system of cells can have a new collective stable steady state, not present if the cells were uncoupled. We obtain the conditions for the emergence of this collective steady state. When the collective stable steady state exists, the concentrations of the (two) morphogens assume different values inside the cells, introducing a symmetry breaking in the chemical characterization of the cells. This is a hypothetical mechanism of developmental differentiation in systems with a small number of identical cells.

1. Introduction

In order to describe the emergence of collective effects in aggregates of identical subunits or cells, Turing[1] studied the effect of coupling in finite arrays of identical systems arranged in a periodic geometry. The cells are characterized by its chemical constituents or morphogens, and the coupling between adjacent cells is proportional to the differences in the concentrations of the chemical substances. The mathematical analysis of the dynamics of the coupled (extended) system leads to the conclusion that, depending of the coupling parameters, a stable steady state of the uncoupled identical subsystems can become unstable. According to Turing, this instability, when complemented with the non-linear characteristics of the local dynamics, can eventually be in the origin of stable stationary patterns and of travelling wave type phenomena in spatially extended systems.

In the analysis of Turing, the local systems have identical dynamics and have a stable steady state. In a finite array of cells linearly coupled

by diffusion, and near the stable steady state, the time evolution of the concentrations of the morphogens is the sobreposition of time evolving eigenmodes associated with the linearized dynamical system. If the real part of the dominant eigenvalue is positive, an instability in the extended system appears. As the dominant eigenvalue can be real or complex, different types of patterns can eventually emerge in the extended system. If the dominant eigenvalue is real, Turing presented numerical evidence that asymptotically stable pattern can develop. If the dominant eigenvalue is complex, the asymptotic state has a wave type behaviour. In the Turing original approach, these effects are eventually dependent of the type of nonlinearity of the local dynamics. If the dominant eigenvalue of the extended dynamical system is real, the extended system is said to have a Turing instability.

The Turing instability has been analyzed by several authors. For example, in systems of reaction-diffusion partial differential equations, Othmer and Scriben[2] have done the linear analysis of the Turing instability for several topologies of the extended system. Their approach essentially, confirms the results of Turing and relates the Turing instability with the spectrum of the Laplacian (diffusion term). If the local dynamics of the system of reaction-diffusion equations has a limit cycle in phase space, Kopell and Howard[3], analyzed the possibility of travelling wave phenomena. In Dilão[4] a necessary and sufficient conditions for the appearance of the Turing instability in two-component systems of reaction-diffusion equations has been obtained.

In general, in reaction-diffusion systems, the asymptotic states can be strongly dependent on the initial conditions of the extended system[5], and it is not known if there is any relation between the attractors of the uncoupled and coupled systems. For the finite dimensional case, Smale[6], analyzed the interaction between two cells and found that, if we have at most four morphogens, a two cells system will oscillate for a choice of the coupling diffusion parameters. In this case, the oscillatory characteristics of the coupled system are already present in the uncoupled one-cell systems, being difficult to speak about emergent phenomena.

Our goal here is to investigate on the possibility of having a steady state of the coupled system that is not an attractor for the dynamics of the individual systems. If this is possible, then it makes sense to speak about emergent phenomena as a result of the aggregation and interaction of identical subsystems.

In order to pursue this program, we construct the simplest possible

collective system. This system is formed by two cells in contact. The interaction between the cells is made through a common wall where the flow of mass is made possible. Then, we analyze the dynamics of the system described by a generic vector field obtained from the mass conservation law, and we determine the conditions for the emergence of a collective steady state. This is done in section 2. To characterize chemically the cells, in section 3, we introduce an auto-catalytic kinetic model with two chemical substances, and we analyze the bifurcations of the dynamics of the two-cell system. We show that new stable steady states appear by a pitchfork bifurcation (emergent steady states). Finally, in section 4, we present the main conclusions of the paper, and we discuss the significance of this approach to developmental biology.

2. The dynamics of the two-cell system

We consider two identical cells in contact through a common wall. We suppose that the state of each cell is described by the concentrations of two chemical substances or morphogens X and Y. As the cells are considered equal, in each cell, the chemical processes involving the two morphogens are described by the same vector field. We also assume that the chemical variables in the system other than X and Y are constant inside the cells, and the concentration of the morphogens evolve in time to a stable steady state. We denote by (X^*, Y^*) the steady state value, and to simplify the notation, we can make the choice $(X^*, Y^*) = (0, 0)$. As X and Y evolve in time according to the mass action law[7], the rates of change of X and Y are proportional to sums of products of concentrations of chemical substances. Therefore, the vector field describing the time evolution of the two morphogens has the generic form,

$$\begin{aligned} \frac{dX}{dt} &= f(X,Y) = aX + bY + f^*(X,Y) \\ \frac{dY}{dt} &= g(X,Y) = cX + dY + g^*(X,Y) \end{aligned} \tag{1}$$

where a, b, c and d are constants, and the functions $f^*(X,Y)$ and $g^*(X,Y)$ are homogeneous polynomial of degree greater than one.

Denoting by A the Jacobian matrix of the vector field (1) evaluated at the fixed point $(0,0)$, if $DetA > 0$ and $TrA < 0$, then this fixed point is asymptotically stable.

The constants a, b, c and d in (1) are the marginal reaction rates, and the role of the morphogens in the chemical reactions is classified according

to the signs of these constants. For example, if b is positive, we say that Y activates the production of X, or, simply, Y is an activator. Similarly, if c is negative, X represses the production of Y, or X is a repressor. If the sign of a is positive X is a self-activator, and if the signs of a is negative X is a self-repressor. These definitions have only a local meaning. In a chemical reaction, it can happen that the signs of the marginal reaction rates are different near different fixed points in phase space. In this case, the chemical reaction behaves differently across the phase space.

We consider that the two cells are in contact through a common wall and the morphogens flow from one cell to the other cell through specialized channels on the wall. Assuming that the flow occurs from regions with larger concentrations to regions with lower concentrations, the concentration of morphogens in the two cells evolve in time according to the system of equations,

$$\begin{aligned} \frac{dX_1}{dt} &= f(X_1, Y_1) + \mu(X_2 - X_1) \\ \frac{dY_1}{dt} &= g(X_1, Y_1) + \nu(Y_2 - Y_1) \\ \frac{dX_2}{dt} &= f(X_2, Y_2) + \mu(X_1 - X_2) \\ \frac{dY_2}{dt} &= g(X_2, Y_2) + \nu(Y_1 - Y_2) \end{aligned} \tag{2}$$

where μ and ν are constant flow rates or diffusion coefficients, and the quantities X_i and Y_i refer to the concentration of morphogens inside cell number i.

As, X and Y are different chemical components, and the intercellular communication is done by specialized channels, it is natural to expect that the flow rates or diffusion coefficients are different, $\mu \neq \nu$.

The two-cell dynamical system, described by (2), has a fixed point at $(X_1, Y_1, X_2, Y_2) = (0, 0, 0, 0)$. Now, we want to investigate the change in the stability of the zero fixed point of the two-cell system, when we vary the coupling parameters μ and ν. By construction, if $\mu = \nu = 0$, the fixed point $(0, 0, 0, 0)$ is stable, provided $DetA > 0$ and $TrA < 0$.

To analyze the stability of the zero fixed point of the two-cell system, we linearize (2) around $(0, 0, 0, 0)$. By (1), we obtain the linear system,

$$\frac{d}{dt}\begin{pmatrix} X_1 \\ Y_1 \\ X_2 \\ Y_2 \end{pmatrix} = \begin{pmatrix} a-\mu & b & \mu & 0 \\ c & d-\nu & 0 & \nu \\ \mu & 0 & a-\mu & b \\ 0 & \nu & c & d-\nu \end{pmatrix} \begin{pmatrix} X_1 \\ Y_1 \\ X_2 \\ Y_2 \end{pmatrix} := M \begin{pmatrix} X_1 \\ Y_1 \\ X_2 \\ Y_2 \end{pmatrix} \tag{3}$$

where a, b, c and d are the marginal reaction rates of the local kinetics near the fixed point $(0, 0)$. To determine the eigenvalues of the matrix M, we write,

$$M - \lambda I_4 = \begin{pmatrix} A - B - \lambda I_2 & B \\ B & A - B - \lambda I_2 \end{pmatrix} \tag{4}$$

where,

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}, \quad B = \begin{pmatrix} \mu & 0 \\ 0 & \nu \end{pmatrix} \tag{5}$$

and I_n is the $n \times n$ identity matrix. The matrix A is the matrix of the marginal reaction rates near the zero fixed point of system (1). As we show in the Appendix A,

$$Det(M - \lambda I_4) = Det\,(A - \lambda I_2)\,.Det\,(A - 2B - \lambda I_2))\,. \tag{6}$$

Therefore, the characteristic polynomial of the matrix M is the product of two polynomials of degree two, and one of the polynomials is the characteristic polynomial of the matrix A. By (6), the eigenvalues of the matrix M are readily obtained, and we have,

$$\begin{aligned} \lambda_1 &= \tfrac{1}{2} TrA - \tfrac{1}{2}\sqrt{(TrA)^2 - 4DetA} \\ \lambda_2 &= \tfrac{1}{2} TrA + \tfrac{1}{2}\sqrt{(TrA)^2 - 4DetA} \\ \lambda_3 &= \tfrac{1}{2} Tr(A - 2B) - \tfrac{1}{2}\sqrt{(Tr(A - 2B))^2 - 4Det(A - 2B)} \\ \lambda_4 &= \tfrac{1}{2} Tr(A - 2B) + \tfrac{1}{2}\sqrt{(Tr(A - 2B))^2 - 4Det(A - 2B)}\,. \end{aligned} \tag{7}$$

As we are assuming that $DetA > 0$ and $TrA < 0$, by (7), $Real(\lambda_1) < 0$, $Real(\lambda_2) < 0$ and $Real(\lambda_3) < 0$. So, if λ_4 is real and positive, the zero fixed point of the two-cell system is unstable. Hence, by (7), if,

$$Det(A - 2B) = DetA - 2d\mu - 2a\nu + 4\mu\nu < 0 \tag{8}$$

then λ_4 is real and positive.

As $\mu > 0$, $\nu > 0$, $TrA = a + d < 0$, and $DetA = ad - bc > 0$, the condition (8) is verified only if, a and d have opposite signs. On the other hand, as $DetA = ad - bc > 0$, this implies that b and c must have opposite signs.

Therefore, the zero fixed point of the system of equations (2) can be destabilized by diffusion if one of the variables is a repressor and the other variable is an activator, one variable is a self-repressor, and the other variable is a self-activator. In Figure 1, we show the four possible configurations for the signs of the marginal reaction rates near the zero fixed point.

$$\begin{pmatrix} -(sR) & -(R) \\ +(A) & +(sA) \end{pmatrix} \begin{pmatrix} -(sR) & +(A) \\ -(R) & +(sA) \end{pmatrix} \nu > \mu$$

$$\begin{pmatrix} +(sA) & -(R) \\ +(A) & -(sR) \end{pmatrix} \begin{pmatrix} +(sA) & +(A) \\ -(R) & -(sR) \end{pmatrix} \mu > \nu$$

Figure 1. Signs of the marginal reaction rates enabling the destabilization by diffusion of the zero steady state of the two cells system. In the four cases shown, for the zero fixed point of the coupled system to be unstable, the diffusion coefficient of the self activator must be larger than the diffusion coefficient of the self inhibitor.

Inequality (8) gives a simple condition for instability of the zero fixed point of the coupled two-cell system. From (8), it follows that, if $a > 0$, $d < 0$, $DetA > 0$, $0 < \mu < a/2$, and,

$$\nu > \frac{DetA - 2d\mu}{2a - 4\mu} \tag{9}$$

the fixed point $(X_1, Y_1, X_2, Y_2) = (0, 0, 0, 0)$ is unstable. Similarly, if $d > 0$, $a < 0$, $DetA > 0$, $0 < \nu < d/2$, and,

$$\mu > \frac{DetA - 2a\nu}{2d - 4\nu} \tag{10}$$

the $(0, 0, 0, 0)$ fixed point is unstable.

In Figure 2, we show the regions of stability of the $(0, 0, 0, 0)$ fixed point as a function of the diffusion coefficients μ and ν, calculated from (9) and (10).

The main result of this section is summarized in the following theorem:

Theorem 2.1. *We consider systems (1) and (2), with $TrA < 0$ and $DetA > 0$. For the choice, $\mu = \nu = 0$, the zero steady state of system (2) is stable. If the signs of the elements of the diagonal and anti-diagonal entries of the matrix A have opposite signs, $\mu > 0$, $\nu > 0$, and,*

$$DetA - 2d\mu - 2a\nu + 4\mu\nu < 0$$

then, the zero steady state of system (2) is unstable.

If the zero fixed point of the system of equations (2) is unstable, the local structure of the flow in phase space near the zero fixed point splits into a direct sum of a stable and an unstable manifold[8]. By (7), the stable manifold has dimension three and the unstable manifold is one-dimensional.

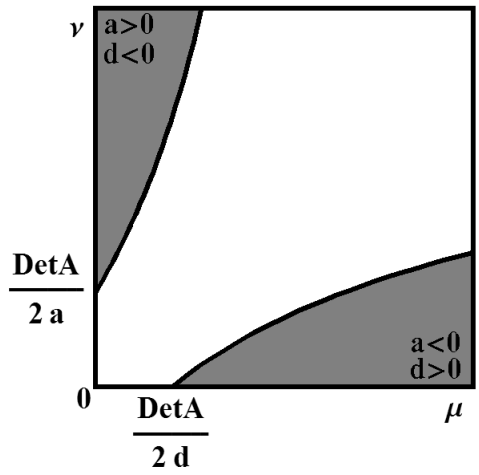

Figure 2. Bifurcation diagram of the zero fixed point of system (2), as a function of μ and ν. For μ and ν in the gray regions, the zero fixed point of system (2) is unstable.

Therefore the unstable fixed point is of saddle-node or saddle-focus type. This suggests that, in the coupled system, by variation of μ and ν a new fixed point appears. To analyze the bifurcations that appear by changing the coupling parameters, we study a specific example.

3. The emergent steady states and symmetry breaking

In order to test the results of the previous section, we consider the Brusselator model[9] of chemical kinetics. This model consists on the kinetic mechanisms,

$$\begin{aligned} A &\longrightarrow^{k_1} U \\ B+U &\longrightarrow^{k_2} V+D \\ 2U+V &\longrightarrow^{k_3} 3U \\ U &\longrightarrow^{k_4} E \end{aligned}$$

where k_1, k_2, k_3 and k_4 are positive rate constants, and A, B, U and V represent different chemical substances, and U is autocatalytic. By the mass action law[7], and assuming that A and B are constants (open system),

we obtain the system of equations,

$$\begin{aligned}\frac{dU}{dt} &= Ak_1 - k_4U - Bk_2U + k_3VU^2\\ \frac{dV}{dt} &= Bk_2U - k_3VU^2\,.\end{aligned} \tag{11}$$

This system of equations has a fixed point with coordinates,

$$(U_0, V_0) = (Ak_1/k_4, Bk_2k_4/(Ak_1k_3))\,.$$

With the new coordinates, $X = U - U_0$ and $Y = V - V_0$, the system of equations (11) assumes the form,

$$\begin{aligned}\frac{dX}{dt} &= (Bk_2 - k_4)X + \frac{A^2k_1^2k_3}{k_4^2}Y + \frac{Bk_2k_4}{Ak_1}X^2 + \frac{2Ak_1k_3}{k_4}XY + k_3X^2Y\\ \frac{dV}{dt} &= -Bk_2X - \frac{A^2k_1^2k_3}{k_4^2}Y - \frac{Bk_2k_4}{Ak_1}X^2 - \frac{2Ak_1k_3}{k_4}XY - k_3X^2Y\,.\end{aligned} \tag{12}$$

The system of equations (12) describes the dynamics in each cell in the system of two coupled cells. Assuming that all the constants k_1, k_2, k_3, k_4, A and B are positive, if $B < k_4/k_2 + A^2k_1^2k_3/(k_2k_4^2)$, the system of equations (12) has a stable fixed point for $(X, Y) = (0, 0)$, a stable focus, provided $(A^2k_1^2k_3/k_4^2 - bk_2 + k_4)^2 < 4A^2k_1^2k_3/k_4$. If $B > k_4/k_2 + A^2k_1^2k_3/(k_2k_4^2)$, this fixed point is unstable and system (12) has a stable limit cycle in phase space. The system of equation (12) has a supercritical Hopf bifurcation for $B = k_4/k_2 + A^2k_1^2k_3/(k_2k_4^2)$ and has no other attractors in phase space.

By (5), the matrix of marginal reaction rates of the system of equations (12) is,

$$A = \begin{pmatrix} (Bk_2 - k_4) & \frac{A^2k_1^2k_3}{k_4^2} \\ -Bk_2 & -\frac{A^2k_1^2k_3}{k_4^2} \end{pmatrix}\,. \tag{13}$$

If $(Bk_2 - k_4) > 0$, we are in the conditions of Theorem 2.1 (Figure 1), and the zero fixed point of the two-cell system is unstable if,

$$\begin{aligned}0 < \mu &< \frac{Bk_2 - k_4}{2}\\ \nu &> \frac{A^2k_1^2k_3}{k_4^2}\frac{k_4 + 2\mu}{2(Bk_2 - k_4) - 4\mu}\,.\end{aligned} \tag{14}$$

In this case, the chemical substance X (or U) is a repressor and Y (or V) is an activator. Also, X is a self-activator and Y is a self-repressor.

For the choice of parameters, $A = 2$, $k_1 = k_2 = k_3 = k_4 = 1$, the local system (12) has a supercritical Hopf bifurcations for $B = 5$, and the instability conditions (14) become,

$$\begin{aligned} 0 < \mu < \frac{B-1}{2} \\ \nu > 4\frac{1+2\mu}{2(B-1)-4\mu}\,. \end{aligned} \tag{15}$$

Taking, B, μ and ν as free parameters, the two-cell coupled system (2) with the local vector field (12) becomes,

$$\begin{aligned} \frac{dX_1}{dt} &= (B-1)X_1 + 4Y_1 + \frac{B}{2}X_1^2 + 4X_1Y_1 + X_1^2Y_1 + \mu(X_2 - X_1) \\ \frac{dY_1}{dt} &= -BX_1 - 4Y_1 - \frac{B}{2}X_1^2 - 4X_1Y_1 - X_1^2Y_1 + \nu(Y_2 - Y_1) \\ \frac{dX_2}{dt} &= (B-1)X_2 + 4Y_2 + \frac{B}{2}X_2^2 + 4X_2Y_2 + X_2^2Y_2 + \mu(X_1 - X_2) \\ \frac{dY_2}{dt} &= -BX_2 - 4Y_2 - \frac{B}{2}X_2^2 - 4X_2Y_2 - X_2^2Y_2 + \nu(Y_1 - Y_2)\,. \end{aligned} \tag{16}$$

If conditions (15) are not verified, $(0, 0, 0, 0)$ is the only fixed point of the system of equations (16). Taking $B = 3$ (away from the supercritical Hopf bifurcation), and choosing $\mu = 1/2$, by (15), if $\nu > 4$, the zero fixed point of the system of equations (16) is unstable. For these parameter values, the numerical analysis of the fixed points of the system of equations (16) shows that (16) has a pitchfork bifurcation[8] for $\nu = 4$, and, for $\nu > 4$, two new stable steady states (stable nodes) appear. These stable fixed points are the new steady states of the two-cell system. In Figure 3, we show the X_1 coordinate of the new fixed points as a function of the bifurcation parameter ν.

The two new stable fixed points that appear by the pitchfork bifurcation are the emerging collective steady states associated with the Brusselator model. As we have two distinct stable fixed points, inside the two cells, the steady state of each morphogen assume different values, implying that the emerged collective steady state induces a symmetry breaking in the two-cell system. It can be shown that this symmetry breaking is associated with an equivariant symmetry[8] obtained by changing the roles of the variables of the two-cell system.

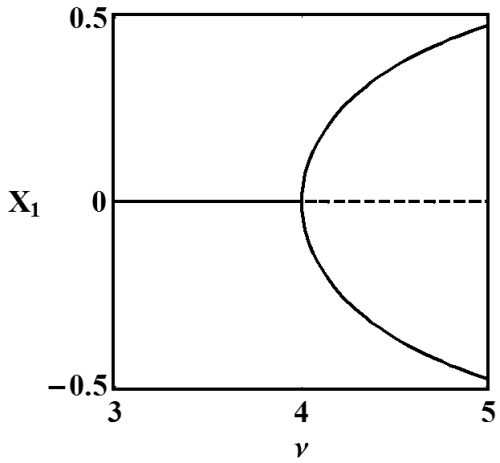

Figure 3. Bifurcation diagram of the zero fixed point of the system of equations (16), as a function of ν, and parameter values: $A = 2$, $B = 3$, $k_1 = k_2 = k_3 = k_4 = 1$ and $\mu = 1/2$. We show the X_1 coordinate of the fixed points. The zero fixed point has a pitchfork bifurcation for $\nu = 4$. For $\nu > 4$, two new stable fixed points are created by a pitchfork bifurcation, and the zero fixed point is unstable (dashed line).

4. Conclusions

We have shown that in a system of two coupled identical cells it is possible to generate a collective stable steady state that does not exists in the dynamical system associated with the individual cells. This collective steady state is a characteristics of the coupled system and suggests that the effect of coupling between identical cell can generate new states — collective states — that are not present in the dynamics of the individual cells.

One of the Roux classical experiments in embryology was to show that at the two-cell stage of the embryo, there is a symmetry breaking in the chemical characterizations of the cells. In this experiments with fertilized frog egg, the destruction of one of the cells results on the development of one-half of the embryo (Gilbert[10], pp. 593-594). On the other hand, similar experiments made by Driesch with sea urchin two-cell and four-cells embryos has shown that cell separation lead to the development of two and four complete larvae. Both experiments can be understood in the framework presented here. In the first experiments, we have a local mechanism that induces a symmetry breaking in the developmental pathway. In the second experiments, the two and four cells remained identical, leading to the development of several organisms.

Acknowledgments

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Appendix A

Here, we prove the determinant relation (6). The proofs will be based on the iterated application of the generalized Gauss reduction theorem for block matrices, (Gantmacher[11], pp. 45-46).

To prove (6), we consider the block matrix,

$$M' = \begin{pmatrix} A' - B & B \\ B & A' - B \end{pmatrix}$$

where A' and B are square matrices of dimension $n \times n$. Adding the second

row to the first one, we obtain,

$$M'' = \begin{pmatrix} A' & A' \\ B & A' - B \end{pmatrix}$$

By the Gauss reduction theorem for block matrices, $DetM' = DetM''$. Multiplying the first row by $-BA'^{-1}$ and adding to the second one, we obtain,

$$DetM'' = \begin{vmatrix} A' & A' \\ 0 & A - 2B \end{vmatrix} = DetA.Det(A - 2B)$$

As, $DetM' = DetM''$, and as $A' = A - \lambda I_2$, we obtain (6).