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DIFFUSION-DRIVEN INSTABILITY IN THE GIERER-MEINHARDT MODEL OF MORPHOGENESIS

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ABSTRACT. In this paper, we consider the Gierer-Meinhardt model of morphogenesis. It is shown that the homogeneous equilibrium solution and the homogeneous periodic solution become diffusively unstable if the diffusion coefficients of the two substances are chosen suitably.

1. Introduction. In developmental biology, a fundamental problem is to understand morphogenesis, the generation of form and pattern starting from a comparatively featureless initial state. There are several steps of complexity in the course of biological development. At the lowest level one can find the genetic codes which constitutes the biochemical basis for all further steps. Next is the cell, the small biological unit, which varies in function and size. The organization, differentiation and localization of cells are the main subjects of morphogenesis. The morphogenesis field is a kind of pre-pattern given by concentration gradients of morphogens which trigger cell differentiation and localization. In his fundamental paper (Turing [1952]), Turing showed that a system of coupled reaction-diffusion equations can be used to describe differentiation and spatial patterns in biological systems. Turing's theory says that diffusion could destabilize an otherwise stable equilibrium of the reaction-diffusion system and lead to nonuniform spatial patterns, which could then generate biological patterns by gene activation. This kind of instability is usually called *Turing instability* (Levin and Segal [1985] and Murray [1989]), *diffusion-driven instability* (Okubo [1980]), or *homogeneity breaking instability* (Maginu [1979]).

Gierer and Meinhardt [1972] developed a detailed model of two coupled reaction-diffusion equations for the production and diffusion

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of two different kinds of substances, called the *activator* and *inhibitor*. Let $a(t,x)$ and $h(t,x)$ denote the concentration of the activator and inhibitor at time t and location x, respectively. The so-called Gierer-Meinhardt model of morphogenesis is:

$$\begin{aligned}\frac{\partial a}{\partial t} &= D_a \frac{\partial^2 a}{\partial x^2} + \rho\rho_0 + c\rho\frac{a^2}{h} - \mu a \\ \frac{\partial h}{\partial t} &= D_h \frac{\partial^2 h}{\partial x^2} + c'\rho' a^2 - \nu h,\end{aligned} \tag{1.1}$$

where D_a and D_h are the diffusion constants of the activator and inhibitor, respectively; $\rho\rho_0$ is the source concentration for the activator and ρ' is the one for the inhibitor; μ and ν are, respectively, the degradation coefficients of the activator and inhibitor; c and c' are connected with the activator and inhibitor production. System (1.1) can be interpreted in this way: two molecules of activator are necessary to activate and one to inhibit the source. Gierer and Meinhardt solved their equations numerically and produced a number of patterns relevant to the formation of biological structures. Analytical work has confirmed and extended the conclusions of the simulations of Gierer and Meinhardt. We refer to Berding and Haken [1982], Granero, Porati and Zanacca [1977], Haken and Olbrich [1978], Hunding and Engelhardt [1995], Keener [1978], Mimura and Nishiura [1979], Murray [1989], Segel [1984] and the references cited therein.

Granero-Porati and Porati [1984] considered the ODE version of the Gierer-Meinhardt model (1.1). Their analysis indicates that the ODE Gierer-Meinhardt model undergoes a Hopf bifurcation and a stable limit cycle exists under certain assumptions. The purpose of this paper is to discuss the stability of the equilibrium and the limit cycle as spatial homogeneous solutions of the reaction-diffusion Gierer-Meinhardt model (1.1). It is found that both the homogeneous equilibrium solution and the homogeneous periodic solution become unstable if the diffusion coefficients are chosen suitably, that is, diffusion-driven instability occurs.

This paper is organized as follows. The ODE Gierer-Meinhardt model is analyzed in Section 2. In Section 3 we consider the diffusion-driven instability of the equilibrium solution. The instability of the homogeneous periodic solution is studied in Section 4. Finally, a brief discussion is carried out in Section 5.

2. Analysis of the ODE model. Suppose that the concentrations of the activator and inhibitor are only time dependent. The Gierer-Meinhardt model (1.1) becomes a system of ordinary differential equations:

$$\begin{aligned} \frac{\partial a}{\partial t} &= \rho\rho_0 + c\rho\frac{a^2}{h} - \mu a \\ \frac{\partial h}{\partial t} &= c'\rho' a^2 - \nu h. \end{aligned} \tag{2.1}$$

There is a unique interior equilibrium $E^* = (a^*, h^*)$, where

$$a^* = \frac{c'\rho'\rho\rho_0 + c\rho\nu}{c'\rho'\mu}, \qquad h^* = \frac{c'\rho'}{\nu}(a^*)^2. \tag{2.2}$$

The Jacobian matrix of the linearized system of (2.1) at E^* is

$$J = \begin{bmatrix} \frac{2c\mu\nu}{c\nu + c'\rho'\rho_0} - \mu & -\frac{c}{\rho}\left(\frac{\mu\nu}{c\nu + c'\rho'\rho_0}\right)^2 \\ \frac{2\rho(c\nu + c'\rho'\rho_0)}{\mu} & -\nu \end{bmatrix} \triangleq \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}. \tag{2.3}$$

The characteristic equation is

$$\lambda^2 - \lambda \operatorname{tr} J + \det J = 0, \tag{2.4}$$

where

$$\operatorname{tr} J = \frac{2c\mu\nu}{c\nu + c'\rho'\rho_0} - \mu - \nu, \qquad \det J = \mu\nu > 0.$$

The characteristic roots can be expressed as

$$\lambda_{1,2} = \alpha(\mu) \pm i\omega(\mu),$$

where

$$\alpha(\mu) = \frac{1}{2}\operatorname{tr} J, \qquad \omega(\mu) = \frac{1}{2}\sqrt{4\det J - \alpha^2}.$$

Assume

$$\nu > \frac{c'\rho'\rho_0}{c}. \tag{2.5}$$

It is easy to see that $\lambda_{1,2}$ have negative real parts if

$$\mu < \frac{\nu(c\nu + c'\rho'\rho_0)}{c\nu - c'\rho'\rho_0} \triangleq \mu_0, \quad \mu_0 > 0. \tag{2.6}$$

When $\mu = \mu_0$, $\alpha(\mu_0) = 0$, $\omega_0 \triangleq \omega(\mu_0) = \sqrt{\det J}$. Thus, $\lambda_{1,2} = \pm i\omega_0$. Since the transversality condition

$$\frac{d}{d\mu}\alpha(\mu)\bigg|_{\mu=\mu_0} = \frac{c\nu - c'\rho\rho_0}{2(c\nu + c'\rho\rho_0)} > 0$$

holds, the Hopf bifurcation theorem implies that a family of periodic solutions bifurcates from the equilibrium E^* when μ passes through μ_0. By using a formula in Marsden and McCracken [1976] (see Granero-Porati and Porati [1984]), the bifurcating periodic solutions are stable if (2.5) holds and $\mu > \mu_0$.

The above analysis can be summarized as follows:

THEOREM 2.1. *Suppose* (2.5) *holds.*

(1) *If* (2.6) *is satisfied, then* E^* *is asymptotically stable.*

(2) *A Hopf bifurcation occurs at* E^* *when* $\mu = \mu_0$.

(3) *The bifurcation periodic solutions exist for* $\mu > \mu_0$ *and is orbitally stable.*

REMARK 2.2. Since $\mu_0 > \nu$, the condition $\mu > \mu_0$ implies $\mu > \nu$, which is the condition of pattern observed by Gierer and Meinhardt [1974].

3. Instability of the equilibrium solution. Notice that the equilibrium E^* given by (2.2) is a spatially homogeneous solution of the reaction-diffusion Gierer-Meinhardt model (1.1). In this section we will derive conditions for the instability of the equilibrium solution by using Turing's technique (see Turing [1952] or Murray [1989]).

The linearized system of (1.1) at E has the form (where $\bar{a} = a - a^*$,

$\bar{h} = h - h^*$).

$$\begin{aligned} \frac{\partial \bar{a}}{\partial t} &= D_a \frac{\partial^2 \bar{a}}{\partial x^2} + a_{11}\bar{a} + a_{12}\bar{h} \\ \frac{\partial \bar{h}}{\partial t} &= D_h \frac{\partial^2 \bar{h}}{\partial x^2} + a_{21}\bar{a} + a_{22}\bar{h}, \end{aligned} \tag{3.1}$$

where a_{ij}, $i, j = 1, 2$, are defined in (2.3). System (3.1) can be solved by separation of variables and expanding a and h in spatial Fourier series. Assume that

$$\begin{pmatrix} \bar{a} \\ \bar{h} \end{pmatrix} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} \cos kx e^{\sigma t}, \tag{3.2}$$

where σ and k are the frequency and wavenumber, respectively. The eigenvalue equation is

$$\begin{vmatrix} \lambda + D_a k^2 - a_{11} & -a_{12} \\ -a_{21} & \lambda + D_h k^2 - a_{22} \end{vmatrix} = 0. \tag{3.3}$$

Solving for λ, we obtain

$$\lambda_{1,2} = \frac{1}{2}[(\hat{a}_{11} + \hat{a}_{22}) \pm \sqrt{(\hat{a}_{12} + \hat{a}_{22})^2 - 4(\hat{a}_{11}\hat{a}_{22} - a_{12}a_{21})}], \tag{3.4}$$

where

$$\hat{a}_{11} = a_{11} - D_a k^2, \qquad \hat{a}_{22} = a_{22} - D_h k^2.$$

The case when $k = 0$ corresponds to the neglect of diffusion and by the assumption, E^* is stable. It is required that $\operatorname{tr} J < 0$ and $\det J > 0$. If $D_a = D_h = D$, we can see that the homogeneous solution E^* is stable. This means that diffusion-driven instability occurs only when $D_a \neq D_h$.

To have instability, at least one of the following conditions must be violated by the Routh-Hurwicz criterion

$$\hat{a}_{11} + \hat{a}_{22} < 0, \tag{3.5}$$

$$\hat{a}_{11}\hat{a}_{22} - a_{12}a_{21} > 0. \tag{3.6}$$

Clearly, the first condition (3.5) is not violated when $\operatorname{tr} J < 0$. Therefore, only the violation of the second condition (3.6) gives rise to diffusion-driven instability. Reversal of the inequality gives

$$H(k^2) = D_a D_h k^4 - (a_{11}D_h + a_{22}D_a)k^2 + \det J < 0. \tag{3.7}$$

Since $H'(k^2) = 2D_aD_hk^2 - (a_{11}D_h + a_{22}D_a)$, the minimum of $H(k^2)$ occurs at $k^2 = k_m^2$, where

$$k_m^2 = \frac{a_{11}D_h + a_{22}D_a}{2D_aD_h}.$$

Thus, a sufficient condition for instability is that (see Okubo [1980])

$$a_{11}D_h + a_{22}D_a > 2(a_{11}a_{22} - a_{12}a_{21})^{1/2}(D_aD_h)^{1/2}. \tag{3.8}$$

THEOREM 3.1. *Assume that* (2.5) *and* (2.6) *hold. The equilibrium solution* E^* *of the reaction-diffusion system* (1.1) *is diffusively unstable if* (3.8) *is satisfied.*

4. Instability of the periodic solution. Suppose (2.5) and $\mu > \mu_0$ hold. By Theorem 2.1, the ODE Gierer-Meinhardt model (2.1) has a stable bifurcating periodic solution, denoted by $\phi(t) = (\phi_1(t), \phi_2(t))$, which has a minimum period, say T; i.e., we have

$$\frac{\partial}{\partial t}\phi(t) = F(\phi(t)), \qquad \phi(t) = \phi(t+T), \tag{4.1}$$

where

$$F(a,h) = \begin{pmatrix} F_1(a,h) \\ F_2(a,h) \end{pmatrix} = \begin{pmatrix} \rho\rho_0 + c\rho(a^2/h) - \mu a \\ c'\rho'a^2 - \nu h \end{pmatrix}.$$

Consider the following perturbed ordinary differential equation

$$(I + \varepsilon D)\frac{\partial w}{\partial t} = F(w), \tag{4.2}$$

where I is a 2×2 identity matrix, ε is a real parameter, $D = \operatorname{diag}(d_1, d_2)$ and $w = (a,h)^T$. By (4.1), we know that (4.2) has a periodic solution $w = \phi(t)$ in the case of $\varepsilon = 0$. Since this periodic solution is orbitally stable, $\varepsilon = 0$ is not a bifurcation point of the parameter ε. Thus, if $|\varepsilon|$ is sufficiently small, equation (4.2) has a periodic solution, denoted by $\psi(t,\varepsilon) = (\psi_1(t,\varepsilon), \psi_2(t,\varepsilon))$, with minimum period $L(\varepsilon)$. This periodic solution $\psi(t,\varepsilon)$ depends on ε smoothly and approaches $w = \phi(t)$ as

$\varepsilon \to 0$ and $L(0) = T$. In order to fix the phase of the periodic solution, we assume that

$$\frac{\partial}{\partial t}\psi_1(0,\varepsilon) = 0.$$

The function $\psi(t,\varepsilon)$ satisfies the following

$$(I + \varepsilon D)\frac{\partial}{\partial t}\psi(t,\varepsilon) = F(\psi(t,\varepsilon)),$$
$$\psi(t,\varepsilon) = \psi(t + L(\varepsilon),\varepsilon),$$
$$\psi(t,0) = \phi(t), \qquad L(0) = T.$$

Firstly, consider the linearized system of the ODE system (2.1) at $\phi(t)$. Let $w(t)$ be a solution of (2.1) and denote $\bar{z}(t) = w(t) - \phi(t)$. Then

$$\frac{\partial}{\partial t}\bar{z}(t) = \frac{\partial F(\phi(t))}{\partial w}\bar{z}(t), \tag{4.3}$$

where $(\partial F/\partial w)(\phi(t))$ is the 2×2 Jacobian matrix of $F(\cdot)$ at $\phi(t)$. Let $\Phi(t)$ denote the fundamental matrix solution of (4.3). Then a solution $\bar{z}(t)$ of (4.3) with initial value $\bar{z}(0)$ is $\bar{z}(t) = \Phi(t)\bar{z}(0)$. Let λ_i and $\bar{z}_i(0)$, $i = 1, 2$, denote the eigenvalues and eigenvectors of the matrix $\Phi(T)$ respectively, that is,

$$\lambda_i \bar{z}_i(0) = \Phi(T)\bar{z}_i(0) = \bar{z}_i(T), \quad i = 1, 2, \tag{4.4}$$

where λ_i are called the Floquet multipliers of the periodic solution $\phi(t)$. Since $(d\phi/dt)(0) = (d\phi/dt)(T)$, without loss of generality we assume that

$$\bar{z}_1(t) = \frac{d\phi}{dt}(t), \qquad \lambda_1 = 1. \tag{4.5}$$

Since $\phi(t)$ is assumed to be stable, we have $|\lambda_2| < 1$.

Next, we consider the linearized system of the reaction diffusion system (1.1) at $\phi(t)$. Let $w(t,x)$ be a solution of (1.1) and denote $z(t,x) = w(t,x) - \phi(t)$. We have

$$\frac{\partial z}{\partial t} = D\frac{\partial^2 z}{\partial x^2} + \frac{\partial F(\phi(t))}{\partial w}z. \tag{4.6}$$

Suppose a solution of (4.6) has the form

$$z(t,x) = b(t)\, e^{ikx}, \tag{4.7}$$

where $k > 0$ is the spatial frequency. Then $b(t)$ satisfies the ordinary differential equation

$$\frac{\partial}{\partial t} b(t) = \left[-k^2 D + \frac{\partial F(\phi(t))}{\partial w} \right] b(t). \tag{4.8}$$

Let $\Psi(t,k^2)$ denote the 2×2 fundamental matrix solution of (4.8) and $\sigma_i(k^2)$ and $b_i(0,k^2)$ denote the eigenvalues and the eigenvectors of the matrix $\Psi(T,k^2)$ respectively, that is,

$$\sigma_i(k^2) b_i(0,k^2) = \Psi(T,k^2) b_i(0,k^2) = b_i(T,k^2), \quad i = 1,2. \tag{4.9}$$

Since $\Psi(t,0) = \Phi(t)$, without loss of generality we assume that

$$b_1(t,0) = \bar{z}_1(t) = \frac{d}{dt}\phi(t), \qquad \sigma_1(0) = \lambda_1 = 1. \tag{4.10}$$

Since $\Psi(T,k^2)$ depends smoothly on the parameter k^2 and $\lambda_1 = 1$ is a simple eigenvalue of $\Phi(T)$, we may assume that $\sigma_1(k^2)$ and $b_1(t,k^2)$ are continuously differentiable functions of k^2 if k is sufficiently small.

If there exists a number $k_0 \neq 0$ such that the second eigenvalue of $\Phi(T,k_0^2)$ satisfies $|\sigma_2(k_0^2)| > 1$, then $|b_2(nT,k_0^2)|$ becomes large as the integer n increases; thus $z(t,x)$ with the spatial frequency k_0 becomes large as the time increases. Therefore, by (4.10), $\phi(t)$ becomes unstable if $\sigma_1'(0) > 0$.

Notice that $b_1(t,k^2)$ also satisfies equation (4.8), that is,

$$\frac{\partial}{\partial t} b_1(t,k^2) = \left[-k^2 D + \frac{\partial F(\phi(t))}{\partial w} \right] b_1(t,k^2). \tag{4.11}$$

Since $b_1(t,k^2)$ is continuously differentiable in k^2 if k is sufficiently small, we can define $b_{1k^2}(t,k^2) = (\partial/\partial k^2) b_1(t,k^2)$ at $k^2 = 0$ for $t \in [0,T]$. From (4.11) and (4.10), we have

$$\frac{\partial}{\partial t} b_{1k^2}(t,0) = -D\frac{d\phi}{dt}(t) + \frac{\partial F(\phi(t))}{\partial w} b_{1k^2}(t,0) \tag{4.12}$$

and

$$b_{1k^2}(T,0) = b_{1k^2}(0,0) + \sigma_1'(0)\frac{d\phi}{dt}(0). \tag{4.13}$$

Finally, for the function $\psi(t,\varepsilon)$, similarly we can define $\psi_\varepsilon(t,\varepsilon) = (\partial/\partial\varepsilon)\psi(t,\varepsilon)$ at $\varepsilon = 0$ for $t \in [0,T]$. In fact, $\psi_\varepsilon(t,0)$ also satisfies equation (4.12) and

$$\psi_\varepsilon(T,0) = \psi_\varepsilon(0,0) - L'(0)\frac{d\phi}{dt}(0). \tag{4.14}$$

This implies that $\psi_\varepsilon(t,0)$ is a particular solution of (4.12). Thus,

$$b_{1k^2}(t,0) = \psi_\varepsilon(t,0) + [\beta_1\bar{w}_1(t) + \beta_2(t)\bar{w}_2(t)], \tag{4.15}$$

where β_1 is a constant and β_2 is a constant as a function of t. Substituting (4.15) into (4.13) yields

$$\begin{aligned}\psi_\varepsilon(T,0) &+ [\beta_1\bar{w}_1(T) + \beta_2(T)\bar{w}_2(T)] \\ &= \psi_\varepsilon(0,0) + [\beta_1\bar{w}_1(0) + \beta_2(0)\bar{w}_2(0)] + \sigma_1'(0)\frac{d\phi}{dt}(0).\end{aligned}$$

By (4.4), (4.5) and (4.14), we have

$$[\sigma_1'(0) + L'(0)]\frac{d\phi}{dt}(0) = [\lambda_2\beta_2(T) - \beta_2(0)]\bar{w}_2(0).$$

Since $((d\phi/dt)(0), \bar{w}_2(0))$ are linearly independent eigenvectors of $\Phi(T)$, we obtain that

$$\sigma_1'(0) + L'(0) = 0. \tag{4.16}$$

Hence, $\sigma_1'(0) > 0$ only if $L'(0) < 0$.

Rewrite (2.1) as follows:

$$\begin{aligned}\theta_1\frac{\partial a}{\partial t} &= \theta_1\rho\rho_0 + \rho\frac{a^2}{h} - \theta_1\mu a \\ \theta_2\frac{\partial v}{\partial t} &= \rho' a^2 - \theta_2\nu h,\end{aligned} \tag{4.17}$$

where

$$\theta_1 = 1/c, \qquad \theta_2 = 1/c'.$$

By the Hopf bifurcation theorem (see Marsden and McKracken [1976]), the period of the periodic solution $\phi(t)$ is

$$L(\theta_1, \theta_2) \approx 2\pi/w_0, \tag{4.18}$$

where

$$w_0 = \sqrt{\mu_0 \nu} = \nu \sqrt{\frac{\theta_2 \nu + \theta_1 \rho' \rho_0}{\theta_2 \nu - \theta_1 \rho' \rho_0}}.$$

If the period $L(\theta_1, \theta_2)$ satisfies

$$\begin{aligned} \frac{d}{d\varepsilon} L(\theta_1 + \varepsilon D_a, \theta_2 + \varepsilon D_h)\Big|_{\varepsilon=0} \\ = D_a \frac{\partial}{\partial \theta_1} L(\theta_1, \theta_2) + D_h \frac{\partial}{\partial \theta_2} L(\theta_1, \theta_2) < 0, \end{aligned} \tag{4.19}$$

then $L'(0) < 0$. We thus have our main result in this section.

THEOREM 4.1. *Suppose that* (2.5) *and* $\mu > \mu_0$ $(> \nu)$ *hold so that the ODE Gierer-Meinhardt model* (2.1) *has an orbitally stable periodic solution* $\phi(t)$. *If* D_a *and* D_h *satisfy* (4.19), *then* $\phi(t)$ *is diffusively unstable as a homogeneous periodic solution of the reaction-diffusion Gierer-Meinhardt model* (1.1).

5. Discussion. For the ODE Gierer-Meinhardt model (2.1), it is known that under the condition (2.5), if $\mu < \mu_0$, where μ_0 is a (critical) value defined in (2.6), then the positive equilibrium E^* is asymptotically stable. When μ passes through the critical value μ_0, a Hopf bifurcation occurs and a periodic solution $\phi(t)$ exists for $\mu > \mu_0$ and is orbitally stable.

The positive equilibrium E^* and the periodic solution $\phi(t)$ are spatially homogeneous solutions of the reaction-diffusion Gierer-Meinhardt model (1.1). For the homogeneous equilibrium solution E^*, by using Turing's technique it was shown that diffusion-driven instability occurs. Thus, if an appropriate small perturbation is added to the equilibrium solution E^*, there will appear spatial inhomogeneity with certain periodic spatial structure in the solution of system (1.1). For the homogeneous periodic solution $\phi(t)$, we also found that diffusion-driven instability could occur if the diffusion constants are chosen suitably.

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