Appl. Math. Lett. Vol. 5, No. 5, pp. 19–22, 1992
Printed in Great Britain.

0893-9659/92 $5.00 + 0.00

MORPHOGENETIC PREPATTERN DURING EMBRYONIC DEVELOPMENT—A NONLINEAR ANALYSIS

J. CHATTOPADHYAY AND P. K. TAPASWI
Embryology Research Unit, Indian Statistical Institute
203, B. T. Road, Calcutta—700 035, India

(Received November 1991 and in revised form March 1992)

Abstract—By considering a nonlinear reaction-diffusion negative feedback epigenetic control system, involving synthesis of the mitotic-inducing and inhibiting proteins simultaneously with intercellular self-diffusion and negative cross-diffusion of the latter only, Tapaswi and Saha [1] have showed the system generates a Turing structure during embryonic development. In this paper, we have observed, by using Lyapunov's direct method, that the pattern, thus generated, is globally asymptotically stable.

1. INTRODUCTION

The problem of spontaneous pattern formation in biology, and the autoregulation of highly ordered patterns, is one of the major challenges for theoretical biology. Turing [2] demonstrated that auto catalytic biochemical reactions coupled with internal diffusion, but without external control, could break up from the original homogeneous state and form stable well defined inhomogeneous concentration gradients and patterns. Spontaneously created prepatterns in reaction diffusion systems may act as ideal, robust and well controlled platforms for spatial organisation in the early embryo. Genes may respond well to the 'positional informations' and thus may be activated in regions where prepattern concentration is high, thus generating a reliable system for globally controlled cell differentiation [3]. Tapaswi and Saha [1] have showed the mechanism of the formation of the primary layers of differentiation, namely, endoderm, mesoderm and ectoderm, during the embryonic development with the help of a reaction diffusion model involving negative cross diffusion of the inhibitor of mRNA synthesis.

In this paper, we have derived conditions under which a stable prepattern may be generated by the model of Tapaswi and Saha [1], with the help of a suitable Lyapunov's function.

2. THE MATHEMATICAL MODEL

Let $x(t)$, $y(t)$ and $z(t)$ denote the concentration of mRNA, activator and inhibitor, respectively, at any time t. The controlled biochemical system then can be represented by the following equations:

$$\begin{aligned} \frac{\partial x}{\partial t} &= \frac{1}{1+y} - \gamma_1 x, \\ \frac{\partial y}{\partial t} &= x - \gamma_2 y + D_{23} \frac{\partial^2 z}{\partial r^2}, \\ \frac{\partial z}{\partial t} &= y - \gamma_3 z + D_{33} \frac{\partial^2 z}{\partial r^2}, \end{aligned} \tag{2.1}$$

where D_{23} and D_{33} are the cross-diffusion and self-diffusion coefficient of z, respectively.

The authors are grateful to the anonymous referee for his valuable comments and suggestions in improving the standard of this paper.

The model equation (2.1) has to be analysed with the following zero flux boundary conditions

$$\left.\frac{\partial x}{\partial r}\right|_{r=0,R} = \left.\frac{\partial y}{\partial r}\right|_{r=o,R} = \left.\frac{\partial z}{\partial r}\right|_{r=o,R} = 0. \tag{2.2}$$

3. GLOBAL STABILITY

We shall show that the steady state pattern which has been generated [1] by the system (2.1) is globally asymptotically stable, under certain parametric conditions.

THEOREM 1. *The system (2.1) with boundary conditions (2.2), and initial conditions* $x(r,0) = \phi_1(r)$, $y(r,0) = \phi_2(r)$ *and* $z(r,0) = \phi_3(r)$, *where* ϕ_1, ϕ_2 *and* ϕ_3 *are non-negative continuous functions, which are not identically zero on a subinterval* $[0,R]$ *and have vanishing derivative at* $r = 0, R$, *is globally asymptotically stable, if the following conditions*

$$\begin{aligned} &(i) && \gamma_i \quad (i = 1,2,3) > 0, \\ &(ii) && D_{22} > d_{23} \quad (d_{23} = -D_{23} > 0), \\ &(iii) && \gamma_1\gamma_2 > \frac{1}{4} > \gamma_2\{\gamma_3 + \pi^2(D_{22} - d_{23})\}, \quad \text{and} \\ &(iv) && \frac{\partial y}{\partial r} \le \frac{\partial z}{\partial r} \end{aligned} \tag{3.1}$$

are satisfied.

PROOF. Let the unique interior equilibrium point of the spatio-temporal system (2.1) (when $t \to \infty$) be denoted by $(\overset{*}{x}(r), \overset{*}{y}(r), \overset{*}{z}(r))$. We define a functional

$$V^t(x,y,z) = \frac{1}{2}\left[\int_0^R (x-\overset{*}{x})^2 + (y-\overset{*}{y})^2 + (z-\overset{*}{z})^2\right] dr. \tag{3.2}$$

It is easy to see that the integrand in (3.2) is non-negative for all positive x, y, z and it vanishes only for

$$x(r,t) \equiv \overset{*}{x}, \quad y(r,t) \equiv \overset{*}{y}, \quad z(r,t) \equiv \overset{*}{z}.$$

The rate of change of V^t along the solution of (2.1) is

$$\frac{dV^t}{dt} = \int_0^R \left\{(x-\overset{*}{x})\frac{\partial x}{\partial t} + (y-\overset{*}{y})\frac{\partial y}{\partial t} + (z-\overset{*}{z})\frac{\partial z}{\partial t}\right\} dr \tag{3.3}$$

$$\begin{aligned} &= \int_0^R \left\{(x-\overset{*}{x})\frac{\partial x}{\partial t} + \left(\frac{1}{1+y} - \gamma_1 x\right) + (y-\overset{*}{y})\left(x - \gamma_2 y + D_{23}\frac{\partial^2 z}{\partial r^2}\right)\right. \\ &\quad \left. + (z-\overset{*}{z})\left(y - \gamma_3 z + D_{22}\frac{\partial^2 z}{\partial r^2}\right)\right\} dr \\ &= \int_0^R \left[(x-\overset{*}{x})\left\{\left(\frac{\overset{*}{y}-y}{(1+y)(1+\overset{*}{y})}\right) - \gamma_1(x-\overset{*}{x})\right\} + (y-\overset{*}{y})\left\{(x-\overset{*}{x}) - \gamma_2(y-\overset{*}{y})\right\}\right. \\ &\quad \left. + (y-\overset{*}{y})D_{23}\frac{\partial^2 z}{\partial r^2} + (z-\overset{*}{z})\left\{(y-\overset{*}{y}) - \gamma_3(z-\overset{*}{z})\right\} + (z-\overset{*}{z})D_{22}\frac{\partial^2 z}{\partial r^2}\right] dr. \end{aligned} \tag{3.4}$$

By using the boundary conditions (2.2), equation (3.4) reduces to

$$\begin{aligned} \frac{dV^t}{dt} = &-\gamma_1\int_0^R (x-\overset{*}{x})^2\,dr + \int_0^R (x-\overset{*}{x})(y-\overset{*}{y})\,dr - \frac{1}{(1+\overset{*}{y})}\int_0^R \frac{(x-\overset{*}{x})(y-\overset{*}{y})}{(1+y)}\,dr \\ &- \gamma_2\int_0^R (y-\overset{*}{y})^2\,dr - D_{23}\int_0^R \frac{\partial y}{\partial r}\frac{\partial z}{\partial r}\,dr + \int_0^R (z-\overset{*}{z})(y-\overset{*}{y})\,dr \\ &- \gamma_3\int_0^R (z-\overset{*}{z})^2\,dr - D_{22}\int_0^R \left(\frac{\partial(z-\overset{*}{z})}{\partial r}\right)^2 dr. \end{aligned} \tag{3.5}$$

Without loss of generality, we can assume

$$\frac{\partial y}{\partial r} \leq \frac{\partial z}{\partial r}. \tag{3.6}$$

As the system generates a pattern if and only if the cross-diffusion coefficient is negative [1], we can take

$$D_{23} = -d_{23} \qquad (d_{23} > 0). \tag{3.7}$$

Now, using the hypotheses (3.6) and (3.7), and the Wirtinger inequality (see [4])

$$\int_0^1 \left(\frac{\partial z}{\partial r}\right)^2 dr \geq \pi^2 \int_0^1 (z)^2 \, dr; \tag{3.8}$$

in (3.5), we have

$$\begin{aligned} \frac{dV^t}{dt} \leq \int_0^R \Big[& -a_{11}(x-\overset{*}{x})^2 + a_{12}(x-\overset{*}{x})(y-\overset{*}{y}) - a_{13}(x-\overset{*}{x})(y-\overset{*}{y}) \\ & - a_{22}(y-\overset{*}{y})^2 + a_{23}(z-\overset{*}{z})(y-\overset{*}{y}) - a_{33}(z-\overset{*}{z})^2 \Big] \, dr, \end{aligned} \tag{3.9}$$

where

$$\begin{aligned} & a_{11} = \gamma_1, \quad a_{12} = a_{21} = -\frac{1}{2}\left\{1 - \frac{1}{(1+y)(1+\overset{*}{y})}\right\}, \quad a_{22} = \gamma_2, \\ & a_{13} = a_{31} = 0, \quad a_{23} = a_{32} = -\frac{1}{2}, \quad a_{33} = \gamma_3 + \pi^2 (D_{22} - d_{23}). \end{aligned} \tag{3.10}$$

The integrand in the r.h.s. of (3.9) can be written as

$$-\mathbf{X}^{\mathsf{T}} \mathbf{A} \mathbf{X},$$

where $\mathbf{X}^{\mathsf{T}}(x-\overset{*}{x}, y-\overset{*}{y}, z-\overset{*}{z})$ and

$$\mathbf{A} = \begin{bmatrix} \gamma_1 & -\frac{1}{2}\left\{1 - \frac{1}{(1+y)(1+\overset{*}{y})}\right\} & 0 \\ -\frac{1}{2}\left\{1 - \frac{1}{(1+y)(1+\overset{*}{y})}\right\} & \gamma_2 & -\frac{1}{2} \\ 0 & -\frac{1}{2} & \gamma_3 + \pi^2 (D_{22} - d_{23}) \end{bmatrix}. \tag{3.11}$$

From (3.9), it is obvious that $\frac{dV^t}{dt} < 0$ if the matrix $\mathbf{A}$ is positive definite, which is possible, if hypotheses (i)–(iii) are satisfied.

Thus, the diffusive system (2.1) evolves into a steady-state dissipative structure which is globally asymptotically stable under the parametric conditions (i)–(iv), as stated in the theorem. ∎

NOTE. Equation (3.5) is symmetric in $\frac{\partial y}{\partial r}$ and $\frac{\partial z}{\partial r}$. As there is no real loss of generality in equation (3.6), the theorem also goes through under changed parametric conditions if the inequality is reversed.

4. DISCUSSION AND CONCLUSION

The most important conclusion in this paper is that the system (2.1) generates a pattern which is a stable one in the following situations:

(1) The self-diffusion coefficient of the inhibitor must be larger than the absolute value of the cross-diffusion coefficient.

(2) The product of the degradation rates of mRNA and activator must exceed a threshold value.

(3) The product of the degradation rates of activator and inhibitor must remain below a certain threshold level.
(4) The spatial distribution of the activator is less than the spatial distribution of the inhibitor.
(5) In real biological situations, all the rate constants are positive ($\gamma_i > 0$). Negative cross-diffusion coefficient ($d_{23} = -d_{23}$ where $d_{23} > 0$) means active counter transport of the inhibitor against the concentration gradient of the activator. The existence and utility of active counter transport has been observed in many biological situations (see details in [1]). The other parametric conditions (ii)–(iv) are also biologically realistic, and thus the theorem may be tested in real biological terms by proper experimental set ups.

REFERENCES

1. P.K. Tapaswi and A.K. Saha, Pattern formation and morphogenesis: A reaction-diffusion model, *Bull. Math. Biol.* **48** (2), 213–228 (1986).
2. A.M. Turing, The chemical basis for morphogenesis, *Phil. Trans. R. Soc. London* **B 237** (1), 37–72 (1952).
3. L. Wolpert and W.D. Stein, Positional information and pattern formation, In *Pattern Formation*, (Edited by G.M. Malacinski and S.V. Bryant), Macmillan, London, (1984).
4. M.M. Denn, *Stability of Reaction and Transport Processes*, Prentice Hall, Englewood Cliffs, NJ, (1975).