CYBERNETICA, Vol. XXXV, N° 3-1992

A STOCHASTIC REACTION-DIFFUSION MODEL OF THE EPIGENETIC SYSTEM : STUDY OF LOCALIZED FLUCTUATIONS

SAHA A.K., TAPASWI P. K.

ABSTRACT

A stochastic reaction-diffusion model of the epigenetic system during embryonic development has been constructed following the method of mean field description of fluctuations. The analysis of the stochastic system is based on the study of localized fluctuation having a well defined range. It is observed that the internal fluctuation drives the system into a well ordered spatially dissipative stationary structure far from the thermodynamic equilibrium through nonoscillatory instability when the cross-diffusion coefficient is negative as in the analogous macroscopic system.

A.K. SAHA and P.K. TAPASWI, Embryology Unit, Indian Statistical Institute Calcutta, 700035, India

1. INTRODUCTION

Spontaneous appearance of ordered (dissipative) structures in biological systems far from the thermodynamic equilibrium has been proposed to be the key events leading to the formation of biological patterns and morphogenesis (Turing, 1952 : Lefever and Prigogine, 1968; Othmer and Scriven, 1971; Gierer and Meinhardt, 1972, 1974; Martinez, 1972; Glass and Kauffman, 1972; Glass and Perez 1974; Babloyantz and Hiernaux, 1975; Nicolis and Auchmuty, 1974; Auchmuty and Nicolis, 1975, 1976; Granero et al., 1977; Othmer, 1977; Nicolis and Prigogine, 1977; Murray, 1977,; Haken and Olbrich, 1978; Erneaux et al., 1978; Berding and Haken, 1982; Tapaswi and Saha, 1986 and many others). Extentive studies have been performed on a hypothetical model biochemical reaction called the Brusselator and the idea of structures arising out of local instabilities has been developed by a number of authors (Auchmuty and Nicolis, 1975; Boa and Cohen, 1976; Mahar and Matkawsky, 1977). An elegant discussion on self-organization and dissipative structures can be found in Nicolis and Prigogine (1977).

Inclusion of diffusion in a reaction scheme describing a homogeneous cellular system establishes a cell to cell information transport which enables a particular cell to learn its own position in the total ensemble of cells. Turing (1952) and Othmer and Scriven (1971) showed that the instabilities of the uniform state may arise from the interaction of reaction and transport (diffusion driven instabilities) and these instabilities may lead to non-uniform spatio-temporal concentration patterns.

Jorne (1977) has shown that the diffusive Lotka-Volterra mechanism can give rise to a stationary dissipative structure by the inclusion of a negative cross-diffusion coefficient. Tapaswi and Saha (1986) have shown that inclusion of a negative cross-diffusion coefficient in a reaction diffusion model of mRNA and protein synthesis during embryogenesis, using end product feedback inhibition (Godwin, 1963), drives the stable homogeneous system to instability and gives rise to a stable spatio- temporal heterogeneous structure.

In the present work a stochastic reaction diffusion model of mRNA and protein synthesis during embryonic development has been constructed. The analogous nonlinear macroscopic system driven far from equilibrium can be shown to undergo symmetry-breaking instabilities for some certain values of the parameters.

The purpose of the present study is to investigate the role of internal fluctuations around far-from-equilibrium states in the spontaneous emergence of patterns and dissipative structures which are precursors of differentiation and morphogenesis during embryogenesis. Our previous investigation in the deterministic level (Tapaswi and Saha, 1986) strongly advocates the presence of negative cross-diffusion i.e., active counter transport of a morphogen-type chemical compound in the epigenetic mechanism which is indispensable for the emergence of a dissipative structure far from the thermodynamic equilibrium. The idea of the stochastic analysis presented in the following sections is to further supplement our previous deterministic observations. In a non-equilibrium system, a local description of fluctuations is the correct means for differentiating between fluctuations of variable ranges and coherence lengths (Nicolis and Prigogine, 1977). To investigate the role of fluctuations on the critical behaviour of the macro-variables of the epigenetic system in the neighbourhood of the instabilities we have used the local fluctuation theory developed by Nicolis and Prigogine (1977) and Haken (1977).

The process of synthesis of mRNA and protein (enzyme), that is, transcriptions and translation during embryonic development investigated here is based on the following recognized reactions scheme :

$$\text{DNA} + \text{Nucleotide} \xrightarrow{\text{RNA polymerase}} \text{RNA} + \text{DNA [transcription]}$$

DNA + mRNA + Nucleotide → 2mRNA + DNA [transcription enhancement or positive feedback by mRNA, Scholer et al., 1984]

$$\text{mRNA} + \text{Aminoacids (carried by tRNA)} \xrightarrow{\text{on polysome template}} \text{Enzyme (Protein)} + \text{mRNA [translation]}$$

mRNA + Enzyme → Nucleotide + Enzyme [degradation]

Enzyme (Protein) + Proteolytic enzymes → Aminoacids.

We know that the number of DNA molecules is fixed (constant) in each cell and remains unchanged throughout the entire transcription and translation process. Furthermore, if we assume that all the transcriptional and translational components (such as tRNA, aminoacids, nucleotides, different activating and inhibiting enzymes namely, RNA polymerase, proteolytic enzymes etc.) other than mRNA and protein (enzyme) are maintained at a constant concentration in the cellular pool, the mRNA protein (enzyme) model investigated here can be represented by the following two equations :

$$\begin{aligned} \frac{dx}{dt} &= \mu + \alpha_1 x - \beta_1 xy \\ \frac{dy}{dt} &= \alpha_2 x - \beta_2 y \end{aligned} \tag{1.1}$$

where x and y denote the concentration of mRNA and protein (enzyme) respectively in each cell and μ, α_1, α_2 are the rate constants of the reactions.

In section 2 we shall investigate this model in the deterministic level after coupling it with diffusion terms accouting for the intercellular communications and in section 3 we shall study this coupled reaction-diffusion system in the stochastic level using local fluctuation theories.

2. THE DETERMINISTIC MODEL

Let us first consider a deterministic (macroscopic) reaction-diffusion system involving mRNA (x) and enzyme (protein) molecules (y). The enzyme molecules are assumed to be quickly converted in the system to small polypeptide molecules which still possess their same enzymatic properties as before conversion and are capable of diffusion through intercellular gap junctions. Now taking into account the self-diffusion and cross-diffusion of the small enzyme (polypeptide) molecules the system (1.1) can then be represented by the following reaction-diffusion equations with zero flux boundary conditions :

$$\begin{aligned} \frac{\delta x}{\delta t} &= \mu + \alpha_1 x - \beta_1 xy + D_1 \Delta^2 y \\ \frac{\delta y}{\delta t} &= \alpha_2 x - \beta_2 y + D_2 \Delta^2 y \end{aligned} \tag{2.1}$$

where Δ^2 is the laplacian (diffusion) operator and D_1 and D_2 are the constant coefficients of cross-diffusion and self-diffusion respectively. Since mRNA (x) is a macromolecule it cannot diffuse through the intercellular gap-junctions, but the y molecules are supposed to be small polypeptides formed from the protein or enzyme molecules and are usually capable of diffusing through the gap-junctions.

The boundary conditions imposed are

$$\frac{\delta x}{\delta r}\Big|_{r=0,L} = \frac{\delta y}{\delta r}\Big|_{r=0,L} = 0 \; (0 \le r \le L) \tag{2.2}$$

The equilibrium points (x_0, y_0) in the positive orthant of the system (2.1) are given by

$$x_0 = \frac{\beta_2 y_0}{\alpha_2} \; and \; y_0 = \frac{1}{2}\left\{\frac{\alpha_1}{\beta_1} + \left(\frac{\alpha_1^2}{\beta_1^2} + \frac{4\mu\alpha_2}{\beta_1\beta_2}\right)^{1/2}\right\}$$

It is evident that

$$y_0 > \frac{\alpha_1}{\beta_1} \; i.e., \beta_1 y_0 > \alpha_1 \tag{2.3}$$

The characteristic equation of the linearized system of (2.1) is given by

$$\lambda^2 + \lambda(\beta_2 + \mu/x_0 + m^2\pi^2 D_2) + \alpha_2\beta_1 x_0 + \beta_2\mu/x_0 + m^2\pi^2(\alpha_2 D_1 + \mu D_2/x_0) = 0 \tag{2.4}$$

Now three cases may arise :

1) When $D_1 = D_2 = 0$ (i.e., in the absence of diffusion) :
In this case the system is always locally stable because from (2.3) $\beta_1 y_0 > \alpha_1$.

2) When $D_1 > 0$, $D_2 > 0$ (i.e., with both positive diffusions) : Here the system is again always stable and the stability is attained earlier than in case (1).

3) If $D_1 < 0$ ($D_1 = -d_1$, $d_1 > 0$) i.e., the cross-diffusion is negative (remembering that D_2, the self-diffusion coefficient is always positive), the instability is attained at

$$d_1 \ge \frac{\mu D_2}{\alpha_2 x_0} + \frac{\alpha_2\beta_1 x_0^2 + \beta_2\mu}{m^2\pi^2\alpha_2 x_0} \tag{2.5}$$

Bifurcation occurs when equality holds in (2.5), that is

$$d_1 = \frac{\mu D_2}{\alpha_2 x_0} + \frac{\alpha_2\beta_1 x_0^2 + \beta_2\mu}{m^2\pi^2\alpha_2 x_0} \tag{2.6}$$

At the bifurcation point (2.6), the dominant eigenvalue is $\lambda_1 = 0$ and a stationary dissipative structure evolves provided the cross-diffusion coefficient is negative.

Next we shall investigate, by stochastic analysis of the same reaction diffusion process, the validity of the above deterministic observations i.e., whether the negativity of the cross-diffusion coefficient is an essential requirement for the diffusion driven instability leading to the spontaneous emergence of a dissipative structure and or a spatio - temporal prepattern for morphogenesis.

3. THE STOCHASTIC MODEL

In this section we shall follow simplified procedure, as developed by Haken (1977) and Nicolis and Prigogine, (1977) by considering the whole system as consisting of two interacting subsystems of volumes Δ V and V - ΔVwhere ΔVis a small volume and V - Δ V is the volume of the rest of the system.

Assuming the whole system is filled with such small volume Δ V we shall investigate the fluctuations in one of these volumes by averaging over the rest of the whole system. That is to say, we shall study the localized fluctuations (having a well-defined range) instead of a global analysis.

Let P (x, y, t) be the probability distribution within Δ V. Treating the reaction-diffusion system under investigations as a Markov process, one can then write the master equation as a closed-form equation (Prigogine et al. 1975; Nicolis and Prigogine 1977; Haken 1977) given by

$$\begin{aligned}\frac{d}{dt}p(x,y,t) &= \mu p(x-1,y,t) + \beta_1 y(x+1)p(x+1,y,t)\\ &+ \alpha_1(x-1)p(x-1,y,t) + \alpha_2 x p(x,y-1,t)\\ &+ \beta_2(y+1)p(x,y+1,t) - p(x,y,t)(\mu+\beta_1 xy+\alpha_1 x+\alpha_2 x+\beta_2 y)\\ &+ D_1[<x>\left\{(y+1)p(x-1,y+1,t)-yp(x,y,t)\right\}\\ &+ <y>\left\{(x+1)p(x+1,y-1,t)-xp(x,y,t)\right\}]\\ &+ D_2[<y>\left\{p(x,y-1,t)-p(x,y,t)\right\}\\ &+ (y+1)p(x,y+1,t)-yp(x,y,t)]\end{aligned} \tag{3.1}$$

Where the coefficients D_1 and D_2 are the effective diffusion frequencies of transport of repressor molecules accross $\Delta\Sigma$ and are given by

$$D_i \simeq \frac{D_i}{\ell \ell_r} \simeq \frac{\Delta\Sigma}{\Delta V}\cdot\frac{D_i}{\ell_r} \quad (i = 1,2) \tag{3.2}$$

where ℓ is the dimension of Δ V or coherence length of fluctuations. ℓ_r is the width of the layer surrounding the surface $\Delta\Sigma$ i.e. of the order of mean free path of the species and D_i are the macroscopic diffusion coefficients as referred to in section 2.

4. THE MOMENT EQUATIONS AND THEIR PROPERTIES

Multiplying both sides of the master equation (3.1) by x,y,x^2,xy and y^2 respectively and then summing over all values of x and y, we have the first and second order moment equations as given by

$$\frac{d<x>}{dt} = \mu + \alpha_1 <x> - \beta_1 <xy> \tag{4.1}$$

$$\frac{d\langle y\rangle}{dt} = \alpha_2\langle x\rangle - \beta_2\langle y\rangle \tag{4.2}$$

$$\frac{d\langle x^2\rangle}{dt} = \mu + (\alpha_1 + 2\mu)\langle x\rangle + 2\alpha_1\langle x^2\rangle + \beta_1\langle xy\rangle - 2\beta_1\langle x^2y\rangle$$

$$+ 2D_1[\langle x\rangle\langle xy\rangle + \langle x\rangle\langle y\rangle - \langle x^2\rangle\langle y\rangle] \tag{4.3}$$

$$\frac{d}{dt}\langle xy\rangle = \mu\langle y\rangle + (\alpha_1 - \beta_2)\langle xy\rangle + \alpha_2\langle x^2\rangle - \beta_1\langle xy^2\rangle$$

$$+ D_1[\langle x\rangle\langle y^2\rangle - \langle x\rangle\langle xy\rangle - \langle y\rangle\langle xy\rangle$$

$$- 2\langle x\rangle\langle y\rangle + \langle y\rangle\langle x^2\rangle]$$

$$+ D_2[\langle x\rangle\langle y\rangle - \langle xy\rangle] \tag{4.4}$$

$$\frac{d\langle y^2\rangle}{dt} = \alpha_2\langle x\rangle + \beta_2\langle y\rangle + 2\alpha_2\langle xy\rangle - 2\beta_2\langle y^2\rangle$$

$$+ 2D_1[\langle x\rangle\langle y\rangle + \langle y\rangle\langle xy\rangle - \langle x\rangle\langle y^2\rangle]$$

$$+ 2D_2[\langle y\rangle^2 - \langle y^2\rangle + \langle y\rangle] \tag{4.5}$$

Now putting $x = \langle x\rangle + \delta x$ and $y = \langle y\rangle + \delta y$ in equations (4.1) to (4.5) gives

$$\frac{d\langle x\rangle}{dt} = \mu + \alpha_1\langle x\rangle - \beta_1(\langle x\rangle\langle y\rangle + \langle \delta x.\delta y\rangle) \tag{4.6}$$

$$\frac{d\langle y\rangle}{dt} = \alpha_2\langle x\rangle - \beta_2\langle y\rangle \tag{4.7}$$

$$\frac{d}{dt}\langle \delta x^2\rangle = \mu + \alpha_1\langle x\rangle + \beta_1\langle x\rangle\langle y\rangle + 2(\alpha_1 - \beta_1\langle y\rangle)\langle \delta x^2\rangle$$

$$+ (\beta_1 - 2\beta_1\langle x\rangle)\langle \delta x\,\delta y\rangle - 2\beta_1\langle \delta x^2\delta y\rangle$$

$$+ 2D_1[\langle x\rangle\langle y\rangle + \langle x\rangle\langle \delta x\,\delta y\rangle - \langle y\rangle\langle \delta x^2\rangle] \tag{4.8}$$

$$\frac{d}{dt}\langle \delta x\,\delta y\rangle = \alpha_2\langle \delta x^2\rangle + (\alpha_1 - \beta_2 - \beta_1\langle y\rangle)\langle \delta x\,\delta y\rangle$$

$$- \beta_1\langle x\rangle\langle \delta y^2\rangle - \beta_1\langle \delta x\delta y^2\rangle$$

$$+ D_1[\langle x\rangle\langle \delta y^2\rangle + \langle y\rangle\langle \delta x^2\rangle$$

$$- (<x> + <y>)<\delta x \delta y> - 2<x><y>]$$

$$- D_2 <\delta x \delta y> \tag{4.9}$$

$$\frac{d}{dt} <\delta y^2> = a_2 <x> + \beta_2 <y> + 2a_2 <\delta x \delta y> - 2\beta_2 <\delta y^2>$$

$$+ 2D_1[<x><y> + <y><\delta x \delta y> - <x><\delta y^2>]$$

$$+ 2D_2[<y> - <\delta y^2>] \tag{4.10}$$

Where $<\delta x^2>$ and $<\delta y^2>$ are the mean-square deviations of x and y respectively and $<\delta x \delta y>$ is the covariance of x and y. From the equation (4.10) we note that diffusion contributes explicitly to the evolution of fluctuations through the last term (of the right hand side) which expresses the deviation of the probability distribution function from the Poissonian regime. In the limit $D_2 \to \infty$, equation (4.10) is dominated by the diffusion term only and the system evolves to a steady state having a Poissonian distribution characterized by $<\delta y^2> = <y>$. This agrees qualitatively with the results of Nicolis and Prigogine (1977).

Again since $<y>_{eq.}$ is a linear function of $<x>_{eq.}$ the latter also assumes a Poissonian distribution at the steady state when $D_2 \to \infty$. Hence we have (Nicolis and Prigogine, 1977).

$$<dx_i dx_j>_{eq.} = <x_i>_{eq.} \delta_{ij}^{kr} = \bar{x}_{i.eq.} d_{ij}^{kr} \tag{4.11}$$

Where $x_{i.eq.}$ are the macroscopic equilibrium values and

$$\delta_{ij}^{kr} = 0 \text{ for } i = j \tag{4.12}$$

$$\neq 0 \text{ for } i \neq j$$

So that, when $D_2 \to \infty, <dxdy> = 0$ and hence from equations (4.1) and (4.2) we see that the system gives rise to statistical averages identical to the macroscopic (deterministic) values.

Moreover, if $D_1 = D_2$ so that D_1 also tends to infinity, we find from equations (4.8) that at the steady $<y>_{eq.} = 0$, implying $<x>_{eq.} = 0$ also. That is to say the system becomes extinct as $t \to \infty$. This is biologically unrealistic and hence the effective cross-diffusion coefficient must have a finite value and cannot be equal to the effective self-diffusion coefficient D_2 when the latter tends to infinity.

Also, if we assume that the system has initially a Poissonian distribution, it is clear from equation (4.10) that as t increases the system deviates further and further from the Poissonian regime.

The point is now to investigate whether the system reaches to a new stable steady state characterised by non-Poission distribution. The problem is investigated in the next section.

5. ONSET OF INSTABILITY

We set :

$$\mu = \hat{\mu} N^2$$

$$a_1 = \hat{a}_1 N$$

$$a_2 = \hat{a}_2 N \qquad (5.1)$$

$$\beta_2 = \hat{\beta}_2 N$$

$$\tau = Nt$$

where N is the number of mRNA molecules at equilibrium in ΔV. We have also assumed for the sake of simplicity, that the inhibition constant β_1 is equal to unity.

Obviously, $\hat{a}_1, \hat{a}_2$ and $\hat{\beta}_2 = 0$ (1), whereas $\hat{\mu} = 0(2)$. Now we introduce the moment vector $\underline{a} = (a_1, a_2)$ and the vector $\underline{b} = (b_{11}, b_{12}, b_{22})$ expressing the deviations from the Poissonian regime.

$$a_1 = \frac{<x>}{N}, b_{11} = \frac{1}{N}[<\delta x^2> - <x>]$$

$$a_2 = \frac{<y>}{N}, b_{12} = \frac{1}{N} <\delta x \delta y>$$

$$b_{22} = \frac{1}{N}[<\delta y^2> - <y>] \qquad (5.2)$$

Substituting (5.1) and (5.2) into equations (4.6) - (4.10) and then neglecting terms which are multipled by

$$\frac{1}{N}$$

(assuming N is very large), we obtain a closed set of nonlinear differential equations for the first two moments given by

$$\frac{da_1}{d\tau} = \hat{\mu} + \hat{a}_1 a_1 - a_1 a_2$$

$$\frac{da_2}{d\tau} = \hat{a}_2 a_1 - \hat{\beta}_2 a_2 \qquad (5.3)$$

and also a closed set of equations for b_{11}, b_{12} and b_{13} which in a coincise matrix form are given by :

$$\frac{d}{di}\begin{bmatrix} b_{11} \\ b_{12} \\ b_{22} \end{bmatrix} = \begin{bmatrix} 2\hat{\alpha}_1 a_1 \\ \hat{\alpha}_2 a_1 - a_1 a_2 \\ 0 \end{bmatrix}$$

$$+\begin{bmatrix} 2(\hat{\alpha}_1 - a_2 - a_2 D1) & 2a_1(D_1 - 1) & 0 \\ \hat{\alpha}_2 + D_1 a_2 & \hat{\alpha}_1 - \hat{\beta}_2 - a_2 - D_2 - D_1(a_1 + a_2) & a_1 (D_1 - 1) \\ 0 & 2(\hat{\alpha}_2 + D_1 a_2) & -2(\hat{\beta}_2 + D_1 a_1 + D_2) \end{bmatrix}\begin{bmatrix} b_{11} \\ b_{12} \\ b_{22} \end{bmatrix} \tag{5.4}$$

The characteristic equation of (5.4) with λ_n as the eigenvalues are given by

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 = 0 \tag{5.5}$$

where

$$p_2 = 3(B - A)$$

$$p_1 = 2A^2 + 2B^2 - 4C$$

$$p_0 = 4(A - B)(AB + C)$$

with

$$A = \hat{\alpha}_1 - a_2 - a_2 D_1 \tag{5.6}$$

$$B = \hat{\beta}_2 + a_1 D_1 + D_2$$

$$C = a_1(D_1 - 1)(\hat{\alpha}_2 + a_2 D_1)$$

6. ONSET OF A SPATIAL DISSIPATIVE STRUCTURE

Now we consider the microscopic system (3.1) characterized by two diffusion coefficients D_1 and D_2. Here we investigate the onset of spatial patterns through fluctuations, starting from an initial homogeneous system at the steady state.

The second moment equations admits nonoscillatory instability of the steady-state solutions if one of the eigenvalues vanishes. This happens when p_0 in (5.5) becomes zero. This situation arises when

$$C = 0$$

$$\text{and } A = 0 \tag{6.1}$$

in (5.6).
Condition (6.1) is simultaneously satisfied when

$$\beta_2 = \hat{\mu}/(\hat{a}_1 + \hat{a}_2)$$

$$and D_1 = -\hat{a}_2/a_2 \qquad (6.2)$$

Then at the bifurcation point

$$D_1 = -\hat{a}_2/a_2 (given \hat{\beta}_2 = \hat{\mu}/(\hat{a}_1 + \hat{a}_2))$$

the eigenvalues are given by

$$\lambda_1 = 0, \lambda_2 = -B and \lambda_3 = -2B$$

and the system emerges into a steady-state dissipative structure.

This observation is in agreement with our macroscopic observation made in section 2 where also, for the emergence of steady-state dissipative structure, the cross-diffusion coefficient (D_1) was required to be negative.

Fluctuation drives the system into nonoscillatory instability when

$$D_1 < -\hat{a}_2/a_2.$$

7. DISCUSSION

A bimolecular reaction-diffusion system involving mRNA (x) and enzyme (y) during embryonic development has been investigated in this study. A deterministic (macrocopic) model involving reactions and transport mechanism is first considered. It is observed that the macroscopic system gives rise to a steady-state dissipative spatial structure if the cross-diffusion coefficient is negative.

The analogous stochastic model of the same reaction-diffusion system is then constructed following the method of mean-field description of Nicolis and Prigogine (1977) and Haken (1977). The analysis is based on the study of localized fluctuations having a well defined range (ℓ). It is noted that the stochastic system evolves to a spatial dissipative steady-state structure through non-oscillatory instability when the cross-diffusion coefficient is negative as in the analogous macroscopic system. Thus fluctuation drives the system into non-oscillatory instability leading to a stationary spatial dissipative structure.

Negative cross-diffusion implies active counter transport, that is, the diffusive substance moves towards a higher concentration of another substance whereas self-diffusion implies a passive transport and the diffusive substance moves from a higher to a lower concentration of the same substance. The self-diffusion coefficient is always positive whereas the cross-diffusion coefficient may be either positive or negative.

Although the existence of the negative cross-diffusion process in the epigenetic mechanism during embryonic development has not yet been experimentally established, the above study reveals that the existence of negative cross-diffusion in forming a stationary dissipative spatial structure as observed in the microscopic system is also a prerequisite condition if we consider the fluctuations of the diffusive system.

The results of this investigation are based on the truncation of the hierarchy of the moment equations to those for the second order variances. Regarding the

validity and limitations of the procedure we refer to the following observations (Nicolis and Prigogine, 1977) :

'Whenever the system has a unique asymptotically stable macroscopic steady-state, this truncation procedure is legitimate. But in the absence of an asymptotically stable macroscopic steady state, the higher order moments become increasingly important. Hence the results based on the truncation of the hierarchy of the moment equations can only be considered as short-time approximations of the systems behaviour starting from an initial distribution of the Poisson form. In fact, this procedure is sufficient to give a rudimentary idea of the behaviour of the system in the vicinity of the macroscopic steady-state.

For systems having marginal stability (e.g., the Lotka-Volterra model) or limit cycle, the solutions are expected to remain time-dependent. For bifurcating systems, on the other hand, after transient period of evolution we expect a new asymptotic solution to be established that is representative of the new regime beyond instability. One can really speak in this second case of 'order through fluctuations'.

REFERENCES

AUCHMUTY, J.F.G. and G. NICOLIS (1975), Bifurcation Analysis of Nonlinear Reaction-Diffusion Equations-I : Evolution Equations and the Steady-State Solutions. Bull. Math. Biol. 37, 323-365.

AUCHMUTY, J.F.G. and G. NICOLIS (1976), Bifurcation Analysis of Nonlinear Chemical Oscillations. Bull. Math. Biol., 35, 325-350.

BABLOYANTZ, A. and J. HIERNAUX (1975) : Models for Cell Differentiation and Generation of Polarity in Diffusion Governed Morphogenetic Field. Bull. Math. Biol., 37, 637-657.

BERDING, C. and H. HAKEN (1982) : Pattern Formation in Morphogenesis. J. Math. Biol., 14, 133-151.

BOA, J.A. and D.S. COHEN (1976) : Bifurcations of Localized Disturbances in a Model Biochemical Reaction. Siam J. Appl. Math., 30, 133-135.

ERNEUX, T., J. HIERNAUX and G. NICOLIS (1978) : Turing's Theory in Morphogenesis. Bull. Math. Biol., 40, 771-789.

GIERER, A. and H. MEINHARDT (1972) : A Theory of Biological Pattern Formation,. Kybernetik, 12, 30-39.

GIERER, A. and H. MEINHARDT (1974) : Applications of a theory of Biological Pattern Formation Based on Lateral Inhibition. J. Cell. Sci., 15, 321-376.

GLASS, L. and S.A. KAUFFMAN (1972) : Co-operative Components Spatial Localization and Oscillatory Cellular Dynamics. J. Theor. Biol., 34, 219-237.

GLASS, L. and R. PEREZ (1974) : Limit Cycle Oscillations in Compartmental Chemical Systems. J. Chem. Phys., 61, 5242-5239.

GOODWIN, B.C. (1963) : Temporal Organization in Cells. New-York : Academic Press.

GRANERO, M.I., A. PORATI and D. ZANACCA (1977) : Bifurcation Analysis of Pattern Formation in a Diffusion Governed Morphogenetic Field. J. Math. Biol., 4, 21-27.

HAKEN, H. (1977) : Synergetic, An Introduction to Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry and Biology. Springer-Verlag, Berlin.

HAKEN, H. and H. OLBRICH (1978) : Analytical Treatment of Pattern Formation in the Gierer-Meinhardt Model of Morphogenesis. J. Math. Biol., 6, 317-331.

JORNE, J. (1975) : Negative Ionic Cross-Diffusion Coefficient in Electrolytic Solution. J. Theor. Biol., 55, 529-532.

JORNE, J. (1977) : The Diffusive Lotka-Volterra Oscillating System. J. Theor. Biol., 65, 133-139.

LEFEVER, R. and I. PRIGOGINE (1988) : Symmetry-Breaking Instabilities in Dissipative System-II. J. Chem. Phys., 48, 1695-1700.

MAHAR, T.J. and B.J. MATKAWSKY (1977) : A Model Biochemical Reaction Exhibiting Secondary Bifurcation. Siam J. Appl. Math., 32, 394-404.

MARCHBANK, R.M. (1972) : Ion Transport and Metabolism in Brain. In Membrane and Ion Transport, Vol. 2, E. Bittar (Ed.). New-York : Wiley.

MARTINEZ, H.M. (1972) : Morphogenesis and Chemical Dissipative Structures : a Computer simulated Case Study. J. Theor. biol ., 36, 479-501.

MURRAY, J.D. (1977) : Lectures on Nonlinear-Differential Equation Models in Biology. Oxford : Oxford University Press.

NICOLIS, G. and J.F.G. AUCHMUTY (1974) : Dissipative Structures, Catastrophe and Pattern Formation : A Bifurcation Analysis, Proc. Natn. Acad. Sci., U.S.A., 71, 2748-2751.

NICOLIS, G. and I. PRIGOGINE (1977) : Self-Organization in Non-Equilibrium Systems. New-York : Wiley.

OTHMER, H.C. (1977) : Current Theories of Pattern Formation. In Lectures on Mathematics in Life Sciences, S. Levin (ed.), Vol. 9, pp. 55-86, American Mathematical Association.

OTHMER, H.C. and B. SCRIVEN (1971) : Instability and Dynamic Pattern in Cellular Network. J. Theor. Biol., 32, 507-537.

PRIGOGINE, I. and G. NICOLIS (1971) : Biological Order, Structure and Instabilities. Quart. Rev. Biophysics, 4, 107-148.

SCHOLER, H., A. HASLINGER, A. HEGUY, H. HOLTGREVE and M. KARIN (1986) : In Vivo Competition Between A Metallothionein Regulatory Element And SV 40 Enhancer. Science, 232, 76-80.

TAPASWI, P.K. and A.K. SAHA (1986) : Pattern Formation and Morphogenesis - A Reaction-Diffusion Model. Bull. Math. Biol., 48, 213-228.

TURING, A.M. (1952) : The Chemical Basis of Morphogenesis. Phil. Trans. R. Sc., B 237, 37-72.

TRIESMAN, R. and T. MANIATIS (1985) : Simian Virus 40 Enhancer Increases Num. of RNA polymerse II Molecules or Linked DNA, Nature, 315, 72-75.

USPENSKY, J.V. (1974) : Theory of Equation, New-York, Mc Graw-Hill.

VOLKENSHTEIN, M.V. (1985) : Biophysis : MIR Publishers.