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ANALYSIS OF PATTERN FORMATION IN REACTION DIFFUSION MODELS WITH SPATIALLY INHOMOGENOUS DIFFUSION COEFFICIENTS

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Abstract—We consider a reaction diffusion system in one spatial dimension in which the diffusion coefficients are spatially varying. We present a non-standard linear analysis for a certain class of spatially varying diffusion coefficients and show that it accurately predicts the behaviour of the full nonlinear system near bifurcation. We show that the steady state solutions exhibit qualitatively different behaviour to that observed in the usual case with constant diffusion coefficients. Specifically, the modified system can generate patterns with spatially varying amplitude and wavelength. Application to chondrogenesis in the limb is discussed.

1. MODEL EQUATIONS

We consider a general reaction diffusion mechanism for pattern formation with spatially heterogeneous diffusion coefficients. Such a system could arise from a two step patterning process in which the spatial pattern in a control chemical regulates morphogen diffusivity in an overlying reaction diffusion system. Although several authors have considered reaction diffusion systems with spatially varying parameters [1–5], we are not aware of an analytic treatment for the case of spatially varying diffusion coefficients.

The model, in one space dimension, is described by three coupled partial differential equations;

$$u_t = \gamma f(u,v) + (D_u(c)u_x)_x, \tag{1.1a}$$

$$v_t = \gamma g(u,v) + (D_v(c)v_x)_x, \tag{1.1b}$$

$$c_t = \theta^2 c - \nu^2 c_{xx}, \tag{1.1c}$$

where $u(x,t)$ and $v(x,t)$ are the concentrations of chemicals (termed morphogens) at position x and time t, and f and g represent their chemical reaction kinetics. The system has been non-dimensionalised so that γ is a scale factor proportional to the length of the domain, and the diffusion coefficients of u and v are respectively $D_u(c)$ and $D_v(c)$. Here c is the concentration of the control chemical which is assumed to degrade at a rate θ^2 and have diffusion coefficient ν^2. Equations (1.1a–1.1c) are defined on the interval $[0,1]$ with zero flux boundary conditions in u and v. The boundary conditions in c are

$$c_x(0,t) = 0, \qquad c(1,t) = c_0. \tag{1.2}$$

If we now assume that equation (1.1c) reaches a stable equilibrium on a fast time scale in which no significant changes in morphogen concentration take place, then equation (1.1c) for c can be replaced by the equilibrium concentration of c, $c_0 \cosh \delta x / \cosh \delta$ where $\delta = \theta/\nu$. The system then reduces to the pair of reaction diffusion equations (1.1a) and (1.1b) with diffusion

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coefficients a function of x. We first consider a simple case in which we assume that the diffusion coefficients of u and v are respectively D^- and μD^- when c is less than a value ϕ, and D^+ and μD^+ otherwise. Here μ, D^- and D^+ are positive constants. Hence were are assuming that each diffusion coefficient can be approximated by a simple step function with discontinuity at the spatial position $x = \xi$, where $c = \phi$, that is, D_u and D_v are given by

$$D_u = \begin{cases} D^- & x < \xi, \\ D^+ & x \geq \xi, \end{cases} \qquad D_v = \begin{cases} \mu D^- & x < \xi, \\ \mu D^+ & x \geq \xi. \end{cases} \tag{1.3}$$

Without loss of generality, we consider only the case $D^- < D^+$.

2. LINEAR ANALYSIS

The system of equations (1.1a)–(1.1c) will produce diffusion driven spatial patterns [6] only if the uniform steady state (u_0, v_0) is stable to homogeneous perturbations and unstable to inhomogeneous perturbations. We linearise the model about (u_0, v_0) and look for solutions of the form $u - u_0 = \exp \lambda t X_u(x)$, $v - v_0 = \exp \lambda t X_v(x)$, with $\lambda > 0$. Substituting these expressions into the linearised model gives a pair of ordinary differential equations for X_u and X_v.

$$(D_u X_u')' + (a - \lambda) X_u + b X_v = 0, \tag{2.4a}$$

$$(D_v X_u')' + c X_u + (d - \lambda) X_v = 0, \tag{2.4b}$$

where $'$ denotes differentiation with respect to x. On each of $[0, \xi)$ and $(\xi, 1]$, D_u and D_v are constant. We may therefore solve equations (2.4a) and (2.4b) separately on each of these intervals and match the solutions at $x = \xi$ according to the conditions

$$\lim_{x \to \xi^-} X_{u,v}(x) = \lim_{x \to \xi^+} X_{u,v}(x), \tag{2.5a}$$

$$\lim_{x \to \xi^-} D^- X_{u,v}'(x) = \lim_{x \to \xi^+} D^+ X_{u,v}'(x). \tag{2.5b}$$

Equation (2.5a) guarantees that the solution is continuous; equation (2.5b) ensures continuity of flux.

Consider first $[0, \xi)$. On this interval we add s/D^- times (2.4b) to (2.4a) to give

$$(X_u + s X_v)'' + \left[a - \lambda + \frac{cs}{\mu}\right] \left[X_u + \frac{[b + (d - \lambda)s/\mu]}{[a - \lambda + cs/\mu]} X_v\right] = 0. \tag{2.6}$$

We choose s such that

$$\frac{b + (d - \lambda)s/\mu}{a - \lambda + cs/\mu} = s, \tag{2.7}$$

which defines a quadratic in s, which is independent of D^-, with roots s_1 and s_2. For each $j = 1, 2$, equation (2.6) becomes an equation in the single variable $X_u + s_j^- X_v$, with general solution $A_j \cos(\alpha_j^- x) + B_j \sin(\alpha_j^- x)$. Here A_j and B_j are constants of integration and $\alpha_j^- = [a - \lambda + c s_j/\mu]^{1/2}$, so that α_1^- and α_2^- are inversely proportional to $\sqrt{(D^-)}$. This gives us two simultaneous equations in X_u and X_v, which we solve by introducing the parameters $\Gamma_u = X_u(\xi)$ and $\Gamma_v = X_v(\xi)$ and imposing zero flux boundary conditions at $x = 0$;

$$X_u(x) = \frac{1}{(s_2 - s_1)} \left[\frac{(\Gamma_u + s_1 \Gamma_v) s_2}{\cos(\xi \alpha_1^-)} \cos(\alpha_1^- x) - \frac{(\Gamma_u + s_2 \Gamma_v) s_1}{\cos(\xi \alpha_2^-)} \cos(\alpha_2^- x)\right], \tag{2.8a}$$

$$X_v(x) = \frac{1}{(s_2 - s_1)} \left[\frac{(\Gamma_u + s_2 \Gamma_v)}{\cos(\xi \alpha_2^-)} \cos(\alpha_2^- x) - \frac{(\Gamma_u + s_1 \Gamma_v)}{\cos(\xi \alpha_1^-)} \cos(\alpha_1^- x)\right], \tag{2.8b}$$

for $x \in [0, \xi)$. Similarly for $x \in (\xi, 1]$

$$X_u(x) = \frac{1}{(s_2 - s_1)} \left[\frac{(\Gamma_u + s_1 \Gamma_v) s_2}{\cos((1 - \xi)\alpha_1^+)} \cos(\alpha_1^+ (1 - x)) - \frac{(\Gamma_u + s_2 \Gamma_v) s_1}{\cos((1 - \xi)\alpha_2^+)} \cos(\alpha_2^+ (1 - x))\right], \tag{2.8c}$$

$$X_v(x) = \frac{1}{(s_2 - s_1)} \left[\frac{(\Gamma_u + s_2 \Gamma_v)}{\cos((1 - \xi)\alpha_2^+)} \cos(\alpha_2^+ (1 - x)) - \frac{(\Gamma_u + s_1 \Gamma_v)}{\cos((1 - \xi)\alpha_1^+)} \cos(\alpha_1^+ (1 - x))\right]. \tag{2.8d}$$

It may be noted that in deriving the solution (2.8) we have assumed that each of $s_1 - s_2$, and $\cos(\xi\alpha_j^-)$ and $\cos((1-\xi)\alpha_j^-)$ for $j = 1$ or 2, are non-zero. Similar analysis may be carried out in these special cases, but the solutions for u and v cannot, in general, satisfy continuity of flux at $x = \xi$ (2.4b). The solution (2.8) trivially satisfies the continuity condition (2.8a), and satisfies the continuity of flux provided

$$P(\lambda)\Gamma_u + Q(\lambda)\Gamma_v = 0,$$
$$R(\lambda)\Gamma_u + S(\lambda)\Gamma_v = 0,$$

where

$$P(\lambda) = \frac{(s_1T_2^- - s_2T_1^-)(s_1T_2^+ - s_2T_1^+)}{s_2 - s_1},$$
$$Q(\lambda) = s_1s_2\frac{(T_2^- - T_1^-) + (T_2^+ - T_1^+)}{(s_2 - s_1)} = s_1s_2R(\lambda),$$
$$S(\lambda) = \frac{(s_1^-T_1^- - s_2^-T_2^-) + (s_1T_1^+ - s_2T_2^+)}{(s_2 - s_1)},$$

and $T_j^- = D^-\alpha_j^- \tan(\xi\alpha_j^-)$, $T_j^+ = D^+\alpha_j^+ \tan((1-\xi)\alpha_j^+)$, for $j = 1, 2$. Thus nontrivial solutions for X_u and X_v exist for values for λ that satisfy the dispersion relation

$$F(\lambda) = P(\lambda)S(\lambda) - Q(\lambda)R(\lambda) = (T_1^- + T_1^+)(T_2^- + T_2^+) = 0. \tag{2.9}$$

In contrast to the case of homogeneous diffusion coefficients, this dispersion relation cannot be solved analytically. We can show, however, that the roots of (2.9) are real and bounded above; and this enables us to find their values by simple numerical solution. In Figure 1 we plot a modified form of the dispersion relation as a function of λ. This modified form is qualitatively similar to the actual dispersion relation but grows more slowly, so we can see more clearly the behaviour of the dispersion relation near the roots and the infinities. The infinities correspond to values of λ for which $F(\lambda)$ is undefined because, either $\alpha_i^{\pm} = (2n+1)\pi$ for some integer n and $i = 1, 2$ or $s_1^{\pm} = s_2^{\pm}$, contradicting the assumptions under which the dispersion relation is derived. The infinities are therefore artifacts of our analysis which may be ignored.

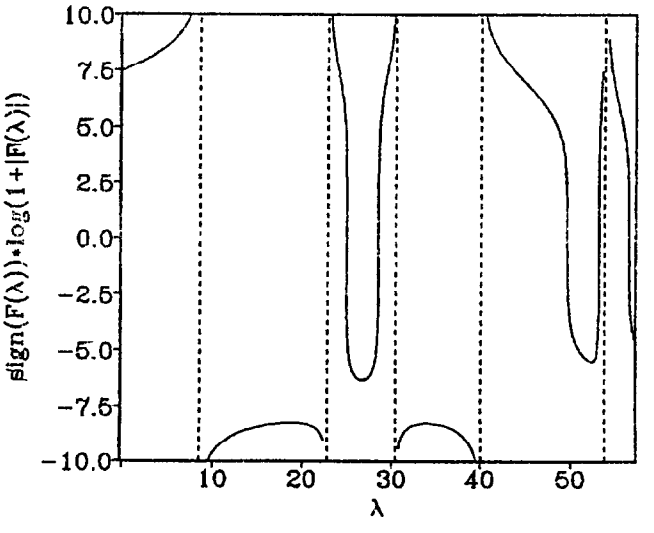

Figure 1. Typical form of the dispersion relation for system (1.1) for Schnackenberg kinetics, $f = a - u + u^2v, g = b - u^2v$ [7]. Parameter values are $a = 0.1$, $b = 0.9$, $\gamma = 1000$, $D^- = 0.1$, $D^+ = 1.0$ and $\mu = 10$.

In general both $T_1^- + T_1^+$ and $T_2^- + T_2^+$ cannot be zero. Without loss of generality, we may therefore assume that $T_1^- + T_1^+ = 0$ and $T_2^- + T_2^+ \neq 0$. This implies that $\Gamma_u + s_2\Gamma_v = 0$ and that the solutions for X_u and X_v take the form

$$X_u(x) = \frac{\Gamma_u \cos(\alpha_1^- x)}{\cos(\alpha_1^- \xi)}, \qquad X_v(x) = \frac{\Gamma_v \cos(\alpha_1^- x)}{\cos(\alpha_1^- \xi)}, \qquad x \in [0, \xi),$$

$$X_u(x) = \frac{\Gamma_u \cos(\alpha_1^+ (1-x))}{\cos(\alpha_1^+)(1-\xi))}, \qquad X_v(x) = \frac{\Gamma_v \cos(\alpha_1^+ (1-x))}{\cos(\alpha_1^+ (1-\xi))}, \qquad x \in [0, \xi).$$

Our linear analysis therefore predicts that the amplitude and wavelength of solutions will be constant on each of $[0, \xi)$ and $(\xi, 1]$, but that these constants will have different values on the two intervals. In particular, for $D^- < D^+$, the analysis predicts that pattern wavelength will be smaller on $[0, \xi)$ than it is on $(\xi, 1]$. This is in contrast to the homogeneous environment in which both the amplitude and wavelength of patterns are constant throughout the domain. For a wide range of parameter values the spatial patterns of the full model are qualitatively similar to the predictions made by the linear analysis. A typical profile is shown in Figure 2.

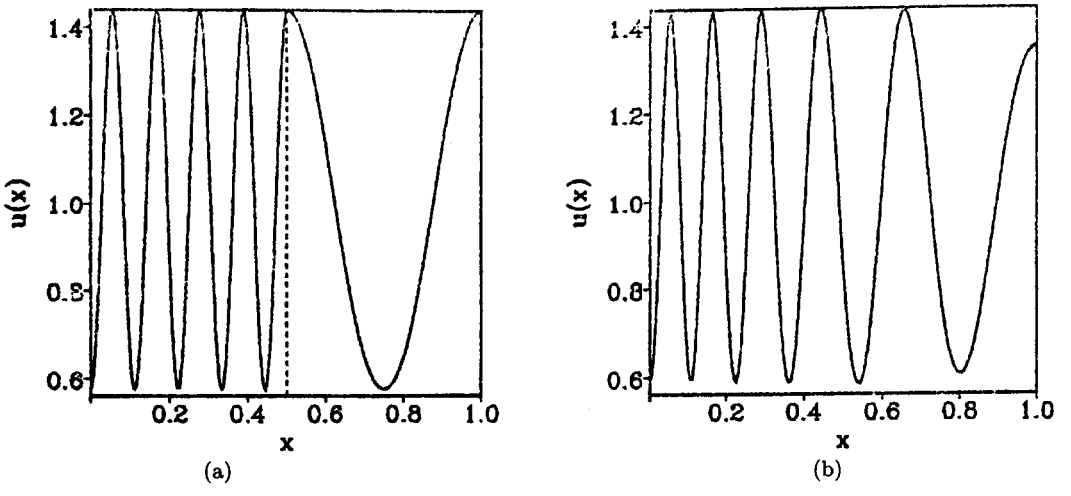

Figure 2. Typical solution profile of u for (1.1) with Schackenberg kinetics when the diffusion coefficients of both u and v vary (a) stepwise, (b) continuously. Note that in (a) the wavelength of the final pattern varies discontinuously across the domain, but in (b) this variation is continuous. The v solution profile is out of phase with that of u. In (a) the parameter values are the same as those in Figure 1, except here $D^+ = 2.0$. We have choosen $\xi = 1/2$. In (b) $D^+ = \mu D^- = \mu c(x)$, where $\mu = 10$ and $c(x)$ is the solution of (1.1c) and (1.2) for $c_0 = 2.0$, and $\cosh \delta = 20.0$. The solutions shown here, and all subsequent solutions, were computed using NAG library routine D03PGF which discretises the space derivatives using finite differences, and integrates in time using Gear's method.

Our method of analysis is also applicable when only one diffusion coefficient is regulated in a threshold way. Here we consider the simplest case wherein the diffusion coefficient of u is independent of the concentration of c but that of v changes in a simple step function manner, such that

$$D_v = \begin{cases} D^- & x < \xi, \\ D^+ & x \geq \xi. \end{cases} \tag{2.10}$$

As before the solutions of the linearised model capture the key qualitative behaviour of the patterns generated by the full model. In this case, however, the solutions may be isolated in one part of the domain, or are oscillatory with spatially varying amplitude of oscillation (Figure 3). The behaviour is therefore more complicated than for the previous case and our linear analysis may be used to delimit regions of the parameter space in which the different types of spatial pattern occur. (For full details of the analysis see [8].)

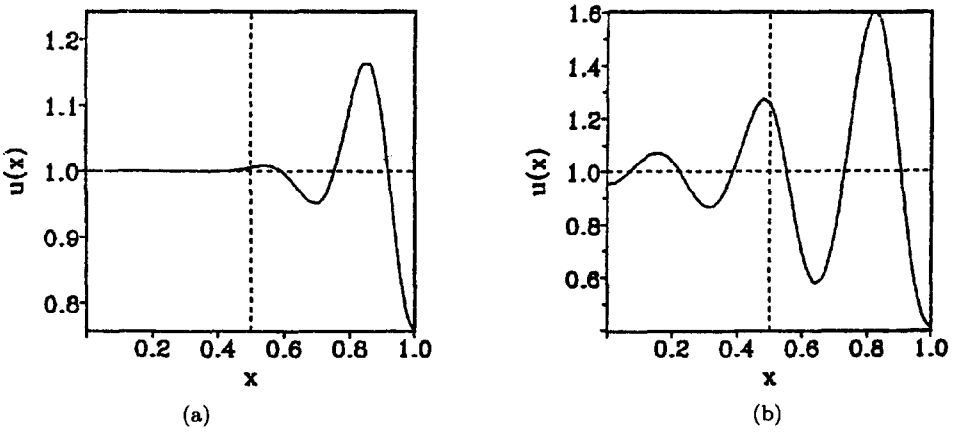

Figure 3. Typical solution of u for (1.1) and (1.2) with Schnackenberg kinetics when only the diffusion coefficient of v is spatially varying. Here $D_u \equiv 1$ and $D_v = c(x)$. Parameter values are $c_0 = 15.0$, $\gamma = 1000$ and (a) $\cosh(\delta) = 15.0$, (b) $\cosh(\delta) = 15.0/7.0$. Again the solution profile of v is out of phase with that of u.

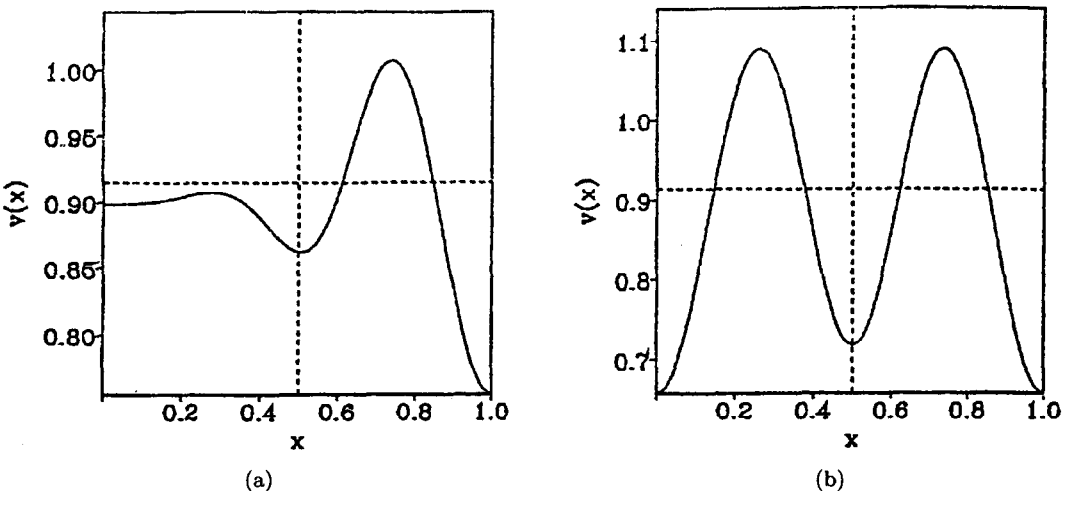

Figure 4. For model (1.1), imposing symmetric boundary conditions on c increases pattern complexity. (a) Solution for boundary conditions (1.2), (b) solution for symmetric boundary conditions (3.11). The solution profile shown is that for v for Schnackenberg kinetics with $D_u \equiv 1.0$ and $D_v = c(x)$. Here the parameter values are $c_0 = 15.0$, $\cosh\delta = 5.0$, $\gamma = 500$.

3. APPLICATION

Recently, Wolpert and Hornbruch [9] have shown that double anterior recombinant chick limbs produce two humeral elements. In these experiments the size of the limb is the same as that of a normal limb, which produces a single humerus. This result contradicts the usual reaction diffusion model for it is well-known that in this model the complexity of patterns depends on the size and geometry of the domain. However, if we now apply the model (1.1) assuming that the source of the control chemical is at the anterior margin of the limb we see that the experiment corresponds to imposing the symmetric boundary conditions on c;

$$c(0,t) = c_0 \qquad c(1,t) = c_0. \tag{3.11}$$

If we assume that the diffusion coefficient of v is proportional to the concentration of the control chemical c, then we have $D_v = \alpha c(x) = c_0 \cosh(\delta(x - 1/2))/\cosh(\delta/2)$ where α is the constant of proportionality. This represents a smoothly increasing diffusion coefficient for v which, biologically, could represent an increase in gap junction permeability of cells to v due to the presence of c [10]. The solution is a profile with two peaks in concentrations; the pattern in the right

hand side of the domain being a mirror image duplicate of that in the left, in agreement with the experimental results (see Figure 4). Here we have assumed that the diffusion coefficient is spatially-varying. However, as the dimensional diffusion coefficient occurs in the dimensionless system (1.1) in terms which also involve L, this can be thought of as a built-in scale factor which is transplanted with the tissue.

REFERENCES

1. A. Gierer and H. Meinhardt, A theory of biological pattern formation, *Kybernetik* **12**, 30–39 (1972).
2. J.F.G. Auchmuty and G. Nicolis, Bifurcation analysis of nonlinear reaction-diffusion equations—I. Evolution equations and the steady state solutions, *Bull. Math. Biol.* **37**, 323–365 (1975).
3. M. Herschkowitz-Kaufman, Bifurcation analysis of nonlinear reaction-diffusion equations: II. Steady state solutions and comparison with numerical simulations, *Bull. Math. Biol.* **37**, 589–636 (1975).
4. A. Hunding, Bifurcations in Turing systems of the second kind may explain blastula cleavage plane orientation, *J. Math. Biol.* **25**, 109–121 (1987).
5. T.C. Lacalli, Modelling the *Drosophila* pair-rule pattern by reaction-diffusion: Gap input and pattern control in a 4-morphogen system, *J. Theor. Biol.* **144**, 171–194 (1990).
6. A.M. Turing, The chemical basis of morphogenesis, *Phil. Trans. R. Soc. Lond.* **B237**, 37–72 (1952).
7. J. Schnackenberg, Simple chemical reaction systems with limit cycle behaviour, *J. Theor. Biol.* **81**, 389–400 (1979).
8. D.L. Benson, J.A. Sherratt and P.K. Maini, Diffusion driven instability in an inhomogeneous domain, *Bull. Math. Biol.* (1992).
9. L. Wolpert and A. Hornbruch, Double anterior chick limb buds and models for cartilage rudiment specification, *Development* **109**, 961–966 (1990).
10. H.G. Othmer and E. Pate, Scale-invariance in reaction-diffusion models of spatial pattern formation, *Proc. Natl. Acad. Sci. USA*, **77**, 4180–4184 (1980).