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Edited by
William F. Lucas, Claremont Graduate School
Maynard Thompson, Indiana University

Thomas L. Vincent Alistair I. Mees
Leslie S. Jennings
Editors

Dynamics of Complex Interconnected Biological Systems

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Thomas L. Vincent
Department of Aerospace and
Mechanical Engineering
University of Arizona
Tucson, AZ 85721
USA

Alistair I. Mees
Mathematics Department
University of Western Australia
Nedlands 6009
Western Australia
Australia

Leslie S. Jennings
Mathematics Department
University of Western Australia
Nedlands 6009
Western Australia
Australia

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PREFACE

This volume contains the proceedings of the U.S. Australia workshop on Complex Interconnected Biological Systems held in Albany, Western Australia January 1-5, 1989. The workshop was jointly sponsored by the Department of Industry, Trade and Commerce (Australia), and the National Science Foundation (USA) under the US–Australia agreement.

Biological systems are typically hard to study mathematically. This is particularly so in the case of systems with strong interconnections, such as ecosystems or networks of neurons. In the past few years there have been substantial improvements in the mathematical tools available for studying complexity. Theoretical advances include substantially improved understanding of the features of nonlinear systems that lead to important behaviour patterns such as chaos. Practical advances include improved modelling techniques, and deeper understanding of complexity indicators such as fractal dimension.

Game theory is now playing an increasingly important role in understanding and describing evolutionary processes in interconnected systems. The strategies of individuals which affect each other's fitness may be incorporated into models as parameters. Strategies which have the property of evolutionary stabilty result from particular parameter values which may be determined using game theoretic methods. Since the main feature of living systems is that they evolve, it seems appropriate that any model used to describe such systems should have this feature as well. Evolutionary game theory should lead the way in the development of such methods.

The workshop brought together researchers in Australia and the USA who had worked on these problems or on methodologies which would be suitable for solving them. The participants included applied mathematicians, control theorists, mathematical biologists, and biologists. Each participant was invited to give an informal presentation in his or her field of expertise as related to the overall theme. The formal papers (contained in this volume) were written after the workshop so that the authors could take into account the workshop discussions, and relate their work to that of other participants. To further encourage this exchange, each paper contained in this volume was reviewed by two other participants who then wrote formal comments. These comments, with the author's reply in some cases, are appended to each paper. We feel that these comments and replies form a very valuable part of this volume in that they give the reader a share

Workshop in Albany by devoting a section of his paper (section 6) to re-examining an aspect of his model using a different mathematical approach.

Nick Caputi

Quite complicated biological situations can be modelled by relatively simple mathematical formulations and this paper is an excellent example of such an approach. The subtle competitive interaction between plant strains, involving the added complication of time lags in seed survival and persistence, has been modelled by Pakes as a system of difference equations. This model is easy to understand and describes the competition in terms of seed production and survival in a seed population which persists in the soil from year to year.

The model succeeds in fitting field data, from different locations, quite well and can also be used to make predictions. This is obviously valuable for future development of clover strains in any pasture breeding programme. Relatively simple descriptions give a strong insight into the way probable biological mechanisms interact and provide a comprehensible theoretical framework to test hypotheses and the sensitivity and importance of various measurable field parameters.

Unfortunately, it takes a fair number of years to evaluate the predictive capabilities of such models because they describe a microcosm of Evolution and are thus often, of their very nature, long term descriptors and predictors. Nevertheless, the class of models analysed by Pakes is pretty convincing as to the probable competitive mechanisms at work. The de Wit replacement principle is neatly linked into the dynamics and the fit with extant data and intuition persuades one that the models capture important aspects of the real world situation.

Phil Diamond

Two Dimensional Pattern Formation In a Chemotactic System

M.R. MYERSCOUGH, P.K. MAINI, J.D. MURRAY,

K.H. WINTERS

Abstract

Chemotaxis is known to be important in cell aggregation in a variety of contexts. We propose a simple partial differential equation model for a chemotactic system of two species, a population of cells and a chemoattractant to which cells respond. Linear analysis shows that there exists the possibility of spatially inhomogeneous solutions to the model equations for suitable choices of parameters.

We solve the full nonlinear steady state equations numerically on a two dimensional rectangular domain. By using mode selection from the linear analysis we produce simple pattern elements such as stripes and regular spots. More complex patterns evolve from these simple solutions as parameter values or domain shape change continuously. An example bifurcation diagram is calculated using the chemotactic response of the cells as the bifurcation parameter. These numerical solutions suggest that a chemotactic mechanism can produce a rich variety of complex patterns.

1. Introduction

There are numerous biological phenomena which involve organisation or pattern formation in one, two or three spatial dimensions. Examples of these include spatial distribution of species in ecology, the spatial spread of an epidemic and pattern formation (morphogenesis) during development.

Mathematical models describing these phenomena will necessarily have a spatial component.

Spatial models for developing systems should produce one of two types of behaviour. The model may either be robust or produce a variety of spatial patterns for comparatively small changes in initial conditions or model parameters (sensitive). Robust models are required to describe the morphogenesis of systems such as the skeletal system where essentially the same pattern is always produced in every individual. Models which produce a variety of pattern are suitable, for example, for describing pigmentation pattern. There can be a wide variation of pigment markings between individuals in the same species or closely related species but the patterns are all generated by the same mechanism. We investigate in this paper a simple mechanism which can produce a variety of complex patterns in a population of motile cells.

Migration, localisation and aggregation of cells leading to spatial pattern play an important role in many developing systems. Examples of such systems include skeletal structures in the vertebrate limb (Hinchliffe and Johnson 1980), slime mould aggregration (Loomis 1975) and the neural system and pigmentation cells (Le Douarin 1982). We consider here a simple model for motile cells whose aggregation is driven by chemotaxis and investigate what type of patterns such a system can produce in two dimensions.

Chemotaxis is the process whereby motile cells migrate in response to a gradient of some chemical substance. The cells may either migrate towards high concentrations of this particular substance (chemoattraction) or away from high concentrations (chemorepulsion). Chemotaxis is known to operate in the aggregation of slime mould amoebae and in the localisation of leukocytes in tissue where bacterial inflammation is occurring (Alt and Lauffenburger 1987). We consider here a population of motile cells responding to a chemoattractant. This chemoattractant is produced by the cells themselves and so promotes aggregation and localisation of cells in clusters of high cell density.

2. Mathematical Model

We propose a simple model based on the models for slime mould aggregation which were first proposed by Keller and Segel (1970). The model comprises a population of motile cells of density $\bar{n}$ and a chemoattractant of concentration $\bar{c}$. The cells undergo both random and chemotactic motion and are able to divide and, where cell density is high, to differentiate, die or

be removed from the population in some other way. The chemoattractant is produced by the cells themselves, diffuses through the cells' environment and decays linearly. These factors may be captured in a mathematical formulation as follows:

Equation for cell density

$$\underbrace{\frac{\partial \bar{n}}{\partial \bar{t}}}_{} = \underbrace{D_n \bar{\nabla}^2 \bar{n}}_{\substack{\text{random} \\ \text{motion}}} - \underbrace{\bar{\alpha} \bar{\nabla} \cdot (\bar{n} \bar{\nabla} \bar{c})}_{\substack{\text{chemotactic} \\ \text{motion}}} + \underbrace{\bar{r} \bar{n} (\bar{N} - \bar{n})}_{\substack{\text{replication} \\ \text{and removal}}} \tag{1a}$$

Equation for chemoattractant concentration

$$\underbrace{\frac{\partial \bar{c}}{\partial \bar{t}}}_{} = \underbrace{D_c \bar{\nabla}^2 \bar{c}}_{\substack{\text{diffusion}}} + \underbrace{\frac{\bar{S} \bar{n}}{\bar{\beta} + \bar{n}}}_{\substack{\text{production} \\ \text{by cells}}} - \underbrace{\gamma \bar{c}}_{\substack{\text{linear} \\ \text{decay}}} \tag{1b}$$

where the operator $\bar{\nabla}^2$ represents $\frac{\partial^2}{\partial \bar{x}^2} + \frac{\partial^2}{\partial \bar{y}^2}$, D_n and D_c are diffusion coefficients for the cells and the chemoattractant respectively, $\bar{\alpha}$ is the chemotactic coefficient, $\bar{r}$ is the mitotic rate of the cells, $\bar{N}$ the carrying capacity of the cells' environment, $\bar{S}$ and β determine the rate of synthesis of the chemoattractant and γ its rate of decay. We can write these equations in non-dimensional form by setting

$$\begin{aligned} n &= \frac{\bar{n}}{\bar{\beta}}; \quad c = \frac{\gamma \bar{c}}{\bar{S}}; \quad t = \gamma \bar{t}; \quad \mathbf{x} = \bar{\mathbf{x}} \sqrt{\frac{\gamma}{D_c}}; \\ D &= \frac{D_n}{D_c}; \quad \alpha = \frac{\bar{S} \bar{\alpha}}{D_c \gamma}; \quad r = \frac{\bar{r} \bar{\beta}}{\gamma}; \quad N = \frac{\bar{N}}{\bar{\beta}} \end{aligned} \tag{2}$$

which gives

$$\begin{aligned} \frac{\partial n}{\partial t} &= D \nabla^2 n - \alpha \nabla \cdot (n \nabla c) + r n (N - n) \\ \frac{\partial c}{\partial t} &= \nabla^2 c + \left\{ \frac{n}{1+n} - c \right\}. \end{aligned} \tag{3}$$

We consider a finite domain where neither cells nor chemoattractant can cross the boundary of the domain. Hence Neumann boundary conditions apply, namely

$$\mathbf{s}(\mathbf{x}) \cdot \nabla c(\mathbf{x}, t) = \mathbf{s}(\mathbf{x}) \cdot \nabla n(\mathbf{x}, t) = 0, \quad \mathbf{x} \in \partial \mathcal{D} \tag{4}$$

where $\mathbf{s}(\mathbf{x})$ is the outward unit normal to the boundary $\partial \mathcal{D}$.

Equations (3) have one homogeneous steady state,

$$n = n_0 = N \text{ and } c = c_0 = N/(1+N). \tag{5}$$

Setting $n = n_0 + u$, $c = c_0 + v$ with $|u|$, $|v| << 1$ in equations (3) we get the linearised system,

$$\begin{aligned} \frac{\partial u}{\partial t} &= D\nabla^2 u - \alpha N \nabla^2 v - rNu \\ \frac{\partial v}{\partial t} &= \nabla^2 u + \left\{ \frac{u}{(1+N)^2} - v \right\}. \end{aligned} \tag{6}$$

We set $(u, v) \propto e^{i\mathbf{k}\cdot\mathbf{x}+\sigma t}$ in (6) and obtain the dispersion relation as the appropriate solution of

$$\sigma^2 + ((D+1)k^2 + rN + 1)\sigma + Dk^4 + \left\{ rN + D - \frac{N\alpha}{(1+N)^2} \right\} k^2 + rN = 0. \tag{7}$$

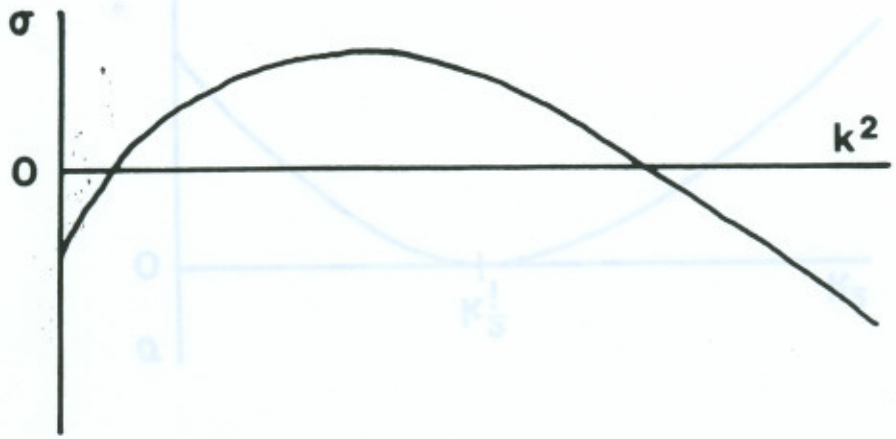

Figure 1. Dispersion curve $\sigma(k^2)$.

The dispersion curve is illustrated in Figure 1. When $\sigma(k^2) > 0$ the homogeneous solution is unstable to small perturbations provided the solution domain allows disturbances of wave number $k = |\mathbf{k}|$. The homogeneous solution is stable for k^2 very small or very large. For k^2 small the perturbation from the homogeneous steady state has a long wavelength. The gradient of chemoattractant is so low in this case that cell death and reproduction smooths out any deviation from the homogeneous steady state before chemotactic cell migration can take effect. For very large k^2 the perturbations have a small wavelength and on such a small length scale random cell motion quickly disrupts cell pattern and hence eliminates any chemotactic effect. When $\sigma = 0$, k^2 satisfies

$$Dk^4 + \left\{ rN + D - \frac{N\alpha}{(1+N)^2} \right\} k^2 + rN = 0. \tag{8}$$

For unstable modes to exist at least one root of (8) must be real and non-negative. This implies that

$$\begin{aligned} rN + D &< \frac{N\alpha}{(1+N)^2}, \qquad \text{and} \\ \left\{ rN + D - \frac{N\alpha}{(1+N)^2} \right\}^2 &> 4rND. \end{aligned} \tag{9}$$

On a finite domain a number of discrete modes given by k^2 will be unstable. By a suitable parameter choice we can cause only one mode to be linearly unstable (see Figure 2). Patterns of this wave number will then dominate the subsequent evolution of the system. To isolate the mode k_i^2 we choose our parameters so that the maximum value of $\sigma(k^2)$ occurs at k_i^2 and is zero, i.e equation (8) holds and has equal roots in k^2. Therefore we require

$$rN + D - \frac{N\alpha}{(1+N)^2} = -2\sqrt{(rND)}. \tag{10}$$

We take the negative square root in agreement with (9) so that k_i^2 is non-negative. Substituting (10) into (8) we have

$$k_i^2 = \sqrt{(rN/D)}. \tag{11}$$

On a rectangular domain of dimensions $L_x \times L_y$ we can use (10) and (11) to select a pattern with ℓ half wavelengths in the x direction and m half wavelengths in the y direction by choosing the parameters such that (10) is satisfied and

$$\pi^2 \left\{ \frac{\ell^2}{L_x^2} + \frac{m^2}{L_y^2} \right\} = \sqrt{(rN/D)}. \tag{12}$$

We refer to this pattern as the (ℓ, m) mode.

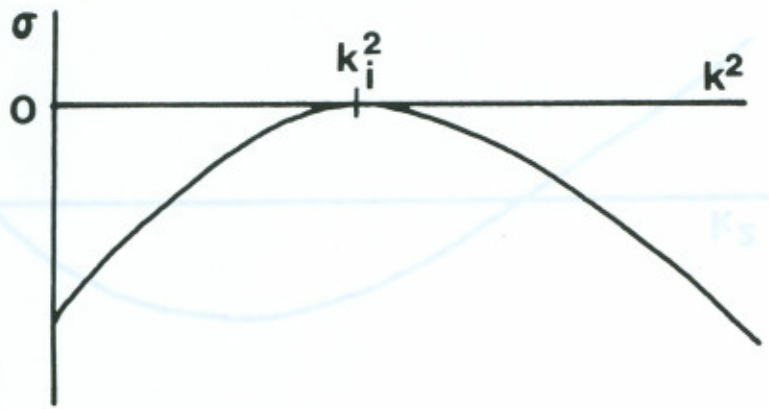

Figure 2. Mode isolation. Dispersion curve showing isolated mode k_i^2.

3. Steady State Pattern

We solved the steady state equations

$$D\nabla^2 n - \alpha\nabla\cdot(n\nabla c) + rn(N-n) = 0$$
$$\nabla^2 c + \left\{\frac{n}{1+n} - c\right\} = 0 \tag{13}$$

on a 1×4 rectangular domain $\mathcal{D}$. A norm $\|n\|$ was defined on the solutions to (13) by

$$\|n\| = \frac{\int_{\mathcal{D}} |N-n|\,dx\,dy}{\int_{\mathcal{D}} dx\,dy}. \tag{14}$$

Using this norm the trivial solution is the homogeneous steady state solution $n = N$, $c = N/(1+N)$. We solved equations (13) numerically using the finite element approximation with nine- noded rectangular elements in a standard Galerkin formulation. To investigate bifurcation behaviour and follow solutions we evaluated the Jacobian of (13) on the trivial branch using α as the bifurcation parameter. At points on the trivial axis where

bifurcation from the uniform steady state occurs the Jacobian is singular. Thus we could identify bifurcation points from the uniform steady state. We then computed the eigenvector corresponding to the zero eigenvalue of the Jacobian matrix at these bifurcation points and used it as a first guess for the solution on the non-trivial branch. Continuation proceeds along the branch. We are also able to step off a branch of solutions in the $\alpha - \|n\|$ plane and by continuation in another parameter such as S, r, N or domain size or shape to investigate how the solutions change with respect to this new bifurcation parameter. This is illustrated in Figure 3. Computations were performed using the ENTWIFE finite element package on the CRAY-1S at Harwell. Further details of the numerical methods are given in Riley and Winters (1987).

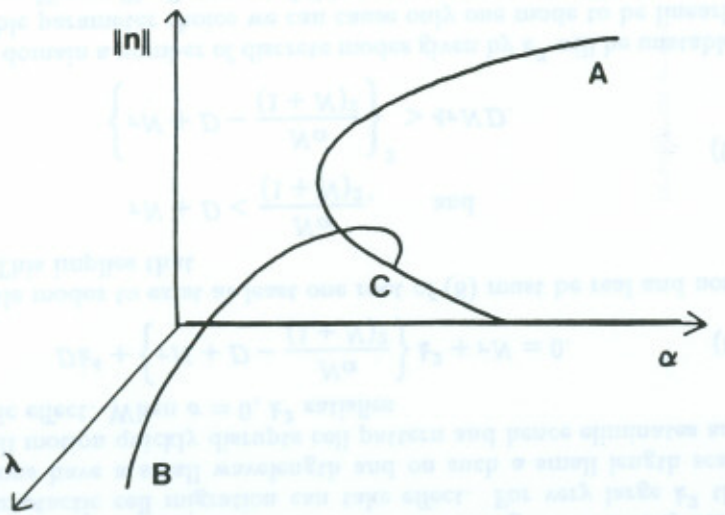

Figure 3. Bifurcation branches in three dimensions: A, bifurcation branch in the $\alpha - \|n\|$ plane; B, bifurcation branch in the $\lambda - \|n\|$ plane obtained by stepping off A at point C. Here λ represents any one of the parameter set.

To produce various patterns we selected each mode using (10) and (12) to give a good estimate of the appropriate parameter values. By allowing

α to vary we found numerically the exact point where bifurcation from the homogeneous steady state into each mode occurred. Using numerical continuation we stepped along the non-trivial branch until the solution was sufficiently far from the uniform steady state for the pattern to be well developed. Figures 4, 5 and 6 show some of the patterns we obtained in this way. The modes where $\ell = 0$, e.g. $(0,2)$ and $(0,3)$ all give lateral stripes (Figure 4). Longitudinal stripes are given by the modes with $m = 0$, e.g. $(2,0)$ (Figure 5).The modes $(0,4)$ and $(1,0)$ are degenerate as they have the same value of k^2 on a 1×4 domain. In order to select these modes we had to alter the domain size slightly so that the modes lost their degeneracy and could be separated. A variety of regular spots and blotches were produced in the modes where ℓ and m are both non-zero (Figure 6).

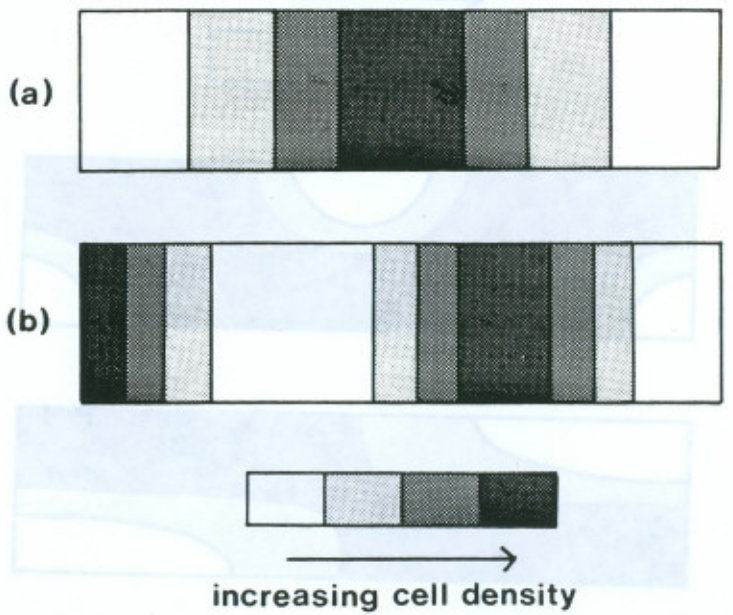

Figure 4. Lateral stripe patterns: (a) $(0,2)$ mode; (b) $(0,3)$ mode.

Because we are calculating the steady state solution we can say nothing about the stability of the patterns in Figures 4, 5,and 6. However the

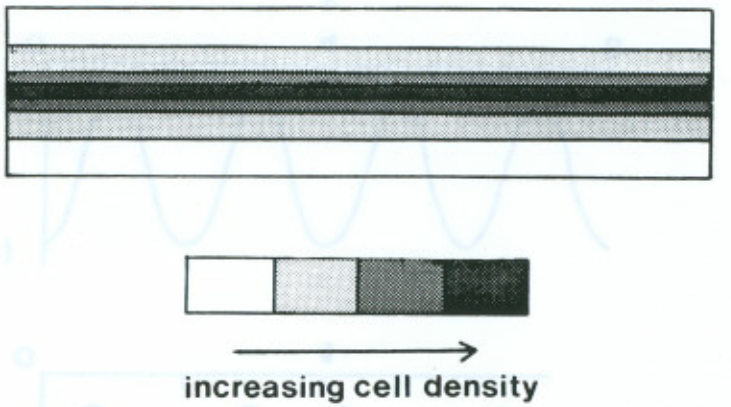

Figure 5. Longitudinal stripe patterns: $(2,0)$ mode.

results do suggest that a chemotactic model can produce basic pattern elements. These basic elements correspond to the patterns produced by the eigenfunctions of the linearised system. The model is also able to produce more complex patterns. For example if we start with the $(1,2)$ mode and continuously increase α, areas of high cell density form into spots and each spot divides to give a pair of spots. Changing the domain size and shape also produces interesting patterns. We elongated the domain in the y direction by stepping off the $(0,4)$ branch and continuing with L_y as the bifurcation parameter. Secondary peaks appeared in the interstices of the original peaks (Figure 7). These interstitial peaks grew until, when the domain length had doubled, they were the same height as the original peaks. Growth of the domain can also change the symmetry of the pattern and transform asymmetric spots into symmetric spots or bands. If we start with a pattern on the $(1,2)$ solution branch and step off that branch in the $\alpha - \|n\|$ plane using L_x as the continuation parameter the asymmetric spots move to the centre of the domain and the pattern becomes symmetric (Figure 8). These examples of changing domain shape illustrate the important effect of growth on pattern and suggest that if growth takes place while the pattern formation mechanism is still operative but on a timescale

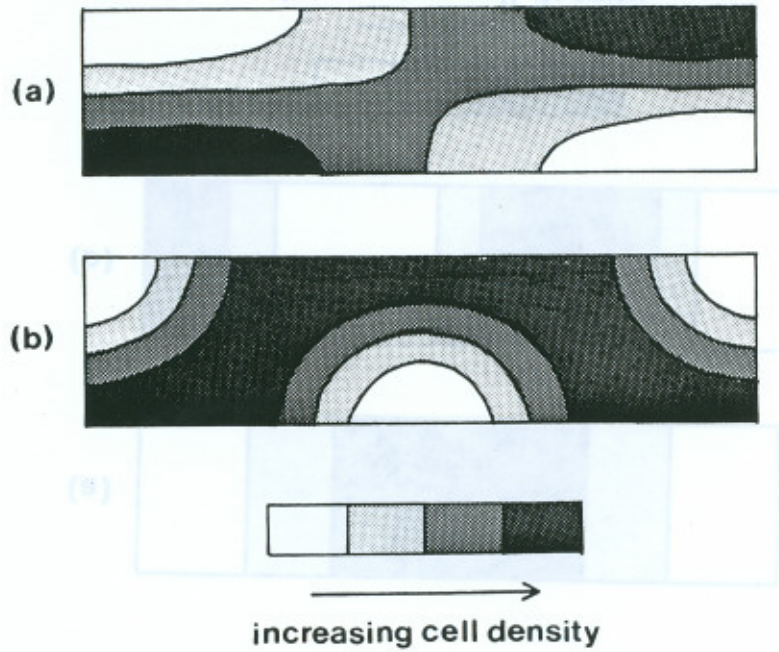

Figure 6. Spot patterns: (a) (1, 1) mode; (b) (1, 2) mode.

slower than cellular motile behaviour, such as chemotaxis, it will have an important bearing on final pattern.

In this section we have described some of the steady state patterns produced by the model. In the next section we investigate systematically the richness of possible pattern as just one parameter α is varied.

4. An Example of a Bifurcation Diagram

We found the first few primary bifurcation points as α increased for the parameter set given in Table 1. We continued along each of these branches.

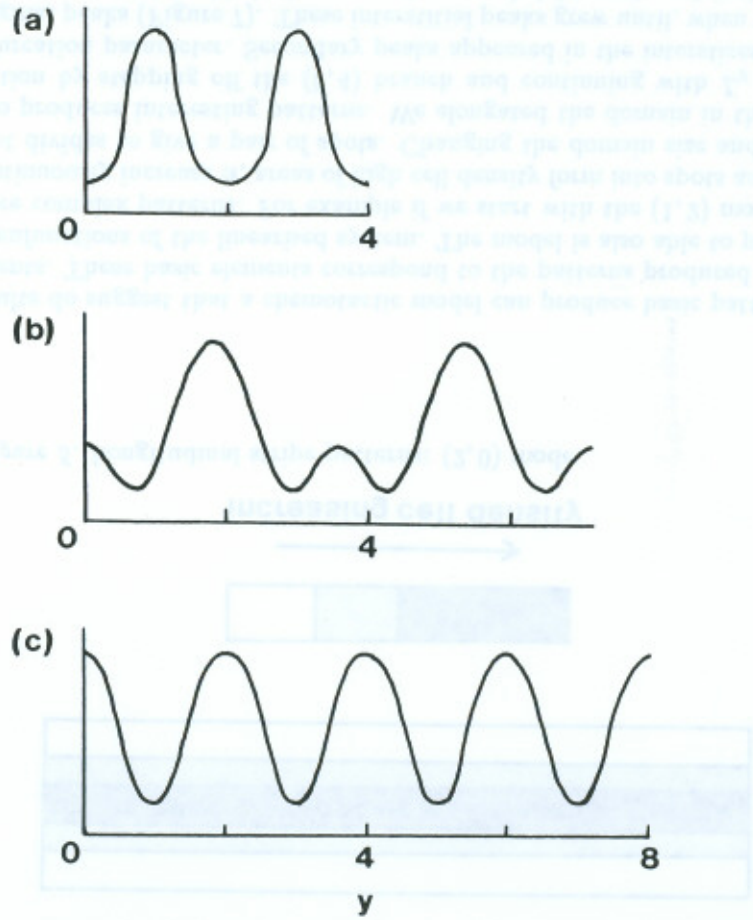

Figure 7. Schematic diagram of the cross-section in the y direction of cell density patterns as L_y increases: (a) $L_y = 4$; (b) $L_y = 7.6$; (c) $L_y = 8$.

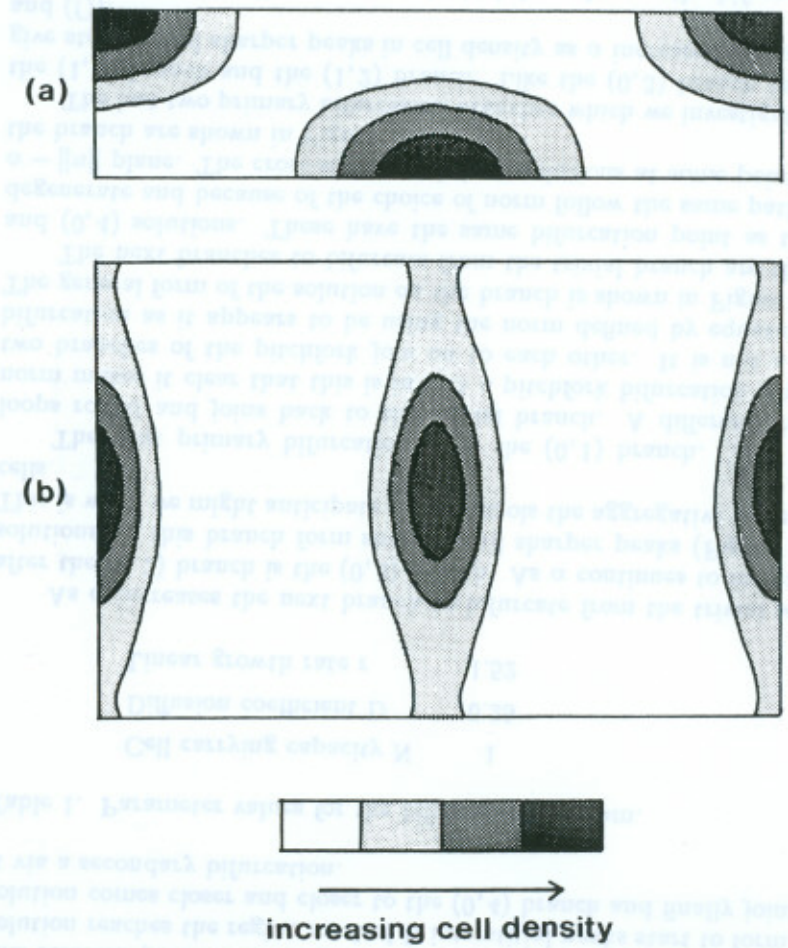

Figure 8. Effect of changing domain width L_x on $(1,2)$ mode: (a) $L_x = 1$; (b) $L_x = 2.7$.

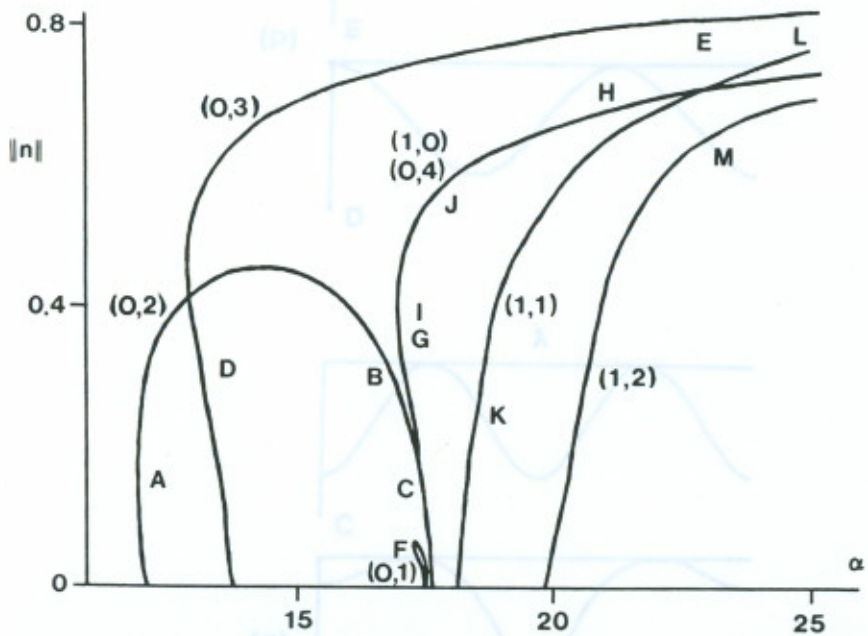

Figure 9. Bifurcation diagram. Ordered pairs refer to the mode on that branch. Letters A-M refer to Figure 10 which shows solutions on the branches.

The results are illustrated in Figure 9. The first branch to bifurcate from the trivial solution was the $(0,2)$ mode solution. The cross-sections of this solution parallel to the y direction are shown in Figure 10(a). As the solution reaches the region marked B interstitial peaks start to form. This solution comes closer and closer to the $(0,4)$ branch and finally joins onto it via a secondary bifurcation.

Table 1. Parameter values for the bifurcation diagram.

Cell carrying capacity N	1
Diffusion coefficient D	0.25
Linear growth rate r	1.52

As α increases the next branch to bifurcate from the trivial solution after the $(0,2)$ branch is the $(0,3)$ branch. As α continues to increase the solutions on this branch form sharper and sharper peaks (Figure 10(b)). This is what we might anticipate as α controls the aggregative force on the cells.

The next primary bifurcation gives the $(0,1)$ branch. This branch loops round and joins back to the trivial branch. A different choice of norm makes it clear that this is in fact a pitchfork bifurcation where the two branches of the pitchfork join on to each other. It is not a double bifurcation as it appears to be using the norm defined by equation (14). The general form of the solution on the branch is shown in Figure 10(c).

The next branches to bifurcate from the trivial branch are the $(1,0)$ and $(0,4)$ solutions. These have the same bifurcation point as they are degenerate and because of the choice of norm follow the same path in the $\alpha - \|n\|$ plane. The cross-sections of these solutions at some points along the branch are shown in Figure 10(d).

The last two primary bifurcation branches which we investigated were the $(1,1)$ branch and the $(1,2)$ branch. Like the $(0,3)$ branch these just give steeper and sharper peaks in cell density as α increased (Figure 10(e) and (f)).

We have given no indication of which branches on the bifurcation diagram are unstable and which are stable. At least some of the branches will be unstable. We shall investigate this question in a future publication. In other parameter regimes they may produce stable pattern. This diagram is also incomplete in that secondary bifurcations may occur which we have not investigated. Nevertheless this bifurcation diagram highlights and gives a useful insight into the complexities of pattern produced by this model and the way the different modes may interact with themselves and each other.

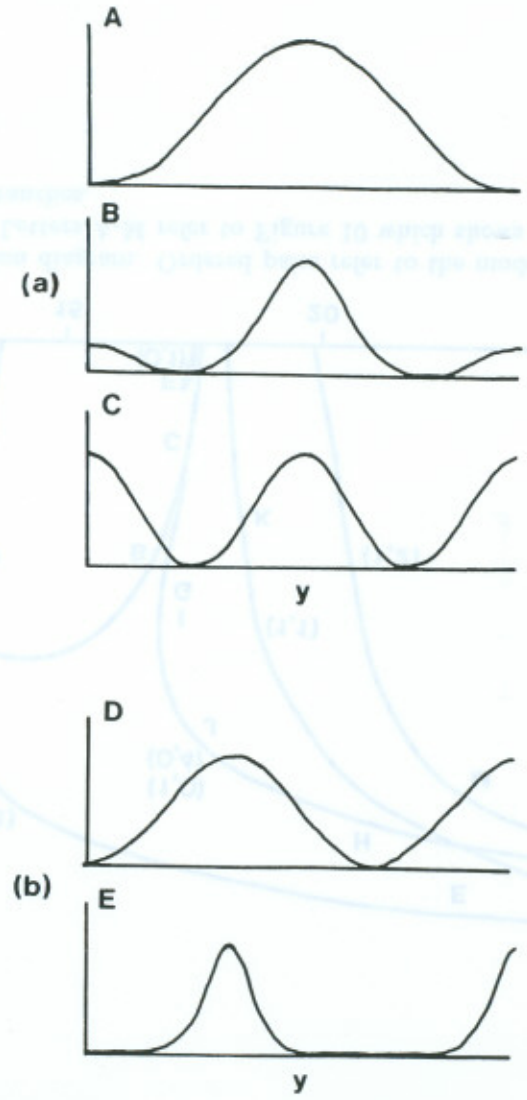

Figure 10. Cross-sections and shaded diagrams of solutions on the non-trivial branches in Figure 9: (a) $(0,2)$ branch; (b) $(0,3)$ branch; (c) $(1,0)$ branch; (d) $(0,4)$ branch; (e) $(1,0)$ branch; (f) $(1,1)$ branch; (g) $(1,2)$ branch.

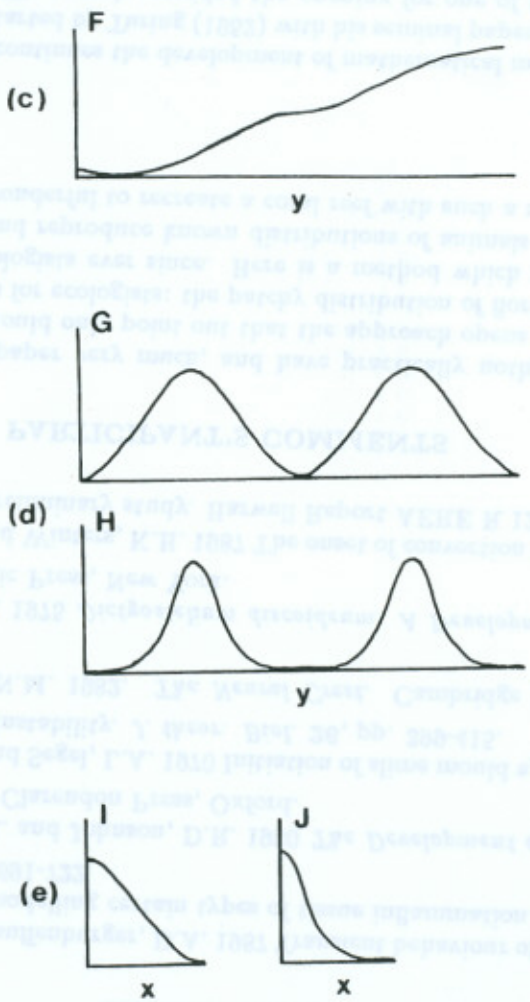

Figure 10. (contd).

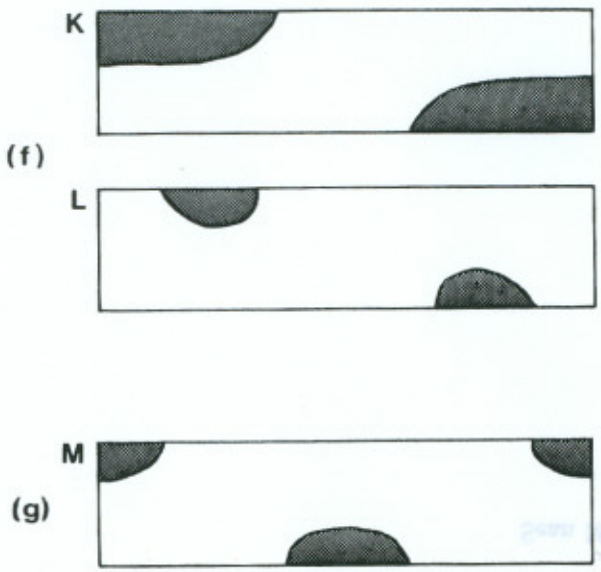

Figure 10. (contd).

5. Conclusion

The model for cell aggregation by chemotaxis which we have used here is a very simple one. We have shown that it produces a number of patterns in cell density. Some of these patterns, for example those in Figure 8 we cannot predict using linear analysis. It seems likely that this system of equations can generate other complex patterns in other parameter regimes and that even this very simple model can produce a rich variety of two dimensional pattern.

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PARTICIPANT'S COMMENTS

I liked this paper very much, and have practically nothing to contribute to it. I should only point out that the approach opens some interesting possiblities for ecologists: the patchy distribution of flora and fauna has intrigued ecologists ever since. Here is a method which may, in the least, describe, and reproduce known distributions of animals and plants. Wouldn't it be wonderful to recreate a coral reef with such a method?

Y. Cohen

This paper continues the development of mathematical models of pattern formation started by Turing (1952) with his seminal paper on chemical morphogenesis. That work provided the opening for one of the most exciting areas of mathematical biology today and Harrison (1987) provides an excellent review of the field. Turing's initial work has been developed by a number of researchers into a more complete mathematical theory and such topics as animal coat markings and the formation of cartilage condensations during early limb morphogenesis are currently areas to which considerable research effort is being directed.

This paper predicts that biological systems in which chemotaxis plays a major rôle can, under certain very reasonable assumptions, display regular

patterns of cell aggregation. The fact that the equations are so relatively simple in character has meant that the authors have been able to carry out a detailed analysis of the bifurcation diagram which enables a much fuller understanding of the way in which one pattern changes into another when the dimension of the region of interest change.

One of the most exciting aspects of mathematical biology is the the interaction between the mathematical modeller and the experimental biologist. Most modelling is carried out after a biologist has completed an experiment and is looking for a mechanism to describe the observations. This paper seems to point the way to a set of experiments on certain pattern formation in chemotactic systems and as such is in the tradition of good Applied Mathematics where, the mathematics enriches the experimental discipline, in this case, biology.

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Sean McElwain