Mathematics Applied to Biology and Medicine

J Demongeot* & V Capasso**

*   TIMC-IMAG-CNRS UJF-INPG
        Faculté de Médecine
        38700 La Tronche, France

**   Dipartimento di Matematica
        Universita' di Milano IRMA
        (Istituto per Ricerche di Matematica Applicata)-CNR
        Bari, Italy

Wuerz Publishing Ltd

© Copyright 1993 by Wuerz Publishing Ltd

Mathematics Applied to Biology and Medicine
J Demongeot and V Capasso, editors

ISBN 0-920063-63-2

Printed in the United Kingdom

Bifurcating Spatial Patterns in a Cell-Chemotaxis Model

P. K. Maini[1] , K. H. Winters[2] , M. R. Myerscough[3], J. D. Murray[4]

[1] Centre for Mathematical Biology, Mathematical Institute, 24-29 St. Giles', Oxford OXl 3LB, UK

[2] Theoretical Studies Department, Harwell Laboratory, Didcot OXll 0RA, UK

[3] School of Mathematics and Statistics, F07, University of Sydney, NSW 2006, Australia,

[4] Applied Mathematics, FS-20, University of Washington, Seattle WA 98195, USA

1. Introduction

Spatial pattern formation is a key issue in early embryonic development. Embryonic cells divide, migrate, and differentiate to form the various structures, markings and organs of the body. Perhaps the most spectacular manifestation of this process is animal coat markings. These patterns are formed by melanin-secreting cells which migrate from the neural crest to the epidermal and dermal layers of the skin. Several models have been proposed for skin patterning. For example, reaction-diffusion models [1, 2, 3] hypothesise the existence of chemicals (morphogens) which react and diffuse and, under appropriate conditions, generate spatially heterogeneous patterns. Cells are then assumed to be pre-programmed to differentiate according to the level of the chemical they experience. Much of the justification for such models is still circumstantial. An alternative class of models are the mechanochemical models [3, 4], which propose that initially a spatial pattern in cell density is set up and cells then differentiate according to their local density. One such model takes account of cell-chemotaxis, the process by which cells migrate up a chemical gradient [5]. Under appropriate conditions this model can exhibit spatial patterns in cell density. The hypothesis that cells in high density aggregates will differentiate and produce melanin then suggests that the observed pigment patterns simply reflect patterns in cell density. This model was recently proposed for the stripe and shadow patterns on the alligator *(Alligator Mississipiensis)* [6]. Experimental results unequivocally show that higher densities of melanin forming cells are found in the dark stripe regions of

the alligator.

Here, we illustrate some of the spatial patterns exhibited by the cell-chemotaxis model. We briefly describe the model in Section 2. In Section 3 we present a selection of spatially patterned solutions found using the finite element package ENTWIFE. We also illustrate the effect on the patterns of domain growth since in many developmental situations spatial organisation of pattern takes place on a time scale commensurate with significant growth of the embryo [6].

2. Model Equations

Chemotaxis is a major factor in many developmental processes and this is the key aggregation force in the model. The model involves two dependent variables, the cell density, $n(\underline{r},t)$, and the chemoattractant concentration, $c(\underline{r},t)$, where $\underline{r}$ and t are the spatial coordinate and time respectively. The model consists of a pair of coupled nonlinear partial differential equations which describes the motion of the cells and the production, diffusion and degradation of the chemoattractant. The nondimensionalised model equations are:

$$\partial n / \partial t = \quad D\nabla^2 n \quad - \quad \alpha \nabla.(n\nabla c) \quad + \quad srn(N-n) \quad\quad (1)$$
$$\text{diffusion} \quad\quad\quad \text{chemotaxis} \quad\quad\quad \text{cell growth}$$

$$\partial c / \partial t = \quad \nabla^2 c \quad + \quad sn/(1+n) \quad - \quad sc \quad\quad\quad\quad (2)$$
$$\text{diffusion} \quad\quad \text{production} \quad\quad \text{degradation}$$

where D, α, s, r, and N are all positive, non dimensional, constants.

We are interested in pattern formation on finite two-dimensional domains - the model for the skin of developing vertebrates - so we consider these equations on a finite domain Ω with zero flux boundary conditions, namely

$$\underline{n}.\nabla c(\underline{r}) = \underline{n}.\nabla n(\underline{r}) = 0 \quad \text{for} \quad \underline{r} \in \partial\Omega \quad\quad\quad (3)$$

where $\underline{n}$ is the unit outward normal to the boundary $\partial\Omega$. The mathematical problem consists of equations (1) and (2), with boundary conditions (3).

The system has two uniform steady-states; $n = 0$, $c = 0$ and $n = N$, $c = \dfrac{N}{1+N}$ and a linear analysis about these uniform states shows that the trivial steady state is always unstable but that in certain parameter regimes the nontrivial spatially homogeneous solution can be driven unstable by spatially heterogeneous perturbations and evolve to in homogeneous spatial patterns in n and c. The form of the pattern is determined primarily by the non-dimensional parameter set (D, α, r, N) and the size and shape of the domain. The model and analysis are discussed in detail in [5, 7].

3. Two-Dimensional Spatial Patterns

We investigate possible steady states of the full nonlinear system using the software package ENTWIFE, which solves nonlinear problems by discretisation in the finite-

element approximation using a standard Galerkin formulation. The package locates the critical values of a chosen parameter for which the uniform steady state bifurcates to a nonuniform steady state and continues this solution as the bifurcation parameter changes [8]. Here we present a selection of the results of applying ENTWIFE to the steady-state problem where the domain Ω is taken to be a 1 x 4 rectangular domain (Figures 1 - 3).

4. Discussion

We have presented a cell-chemotactic model for biological pattern generation and have illustrated some of the spatial patterns obtained by solving the model equations using ENTWIFE. A more detailed discussion of the numerical procedure used and the patterns obtained can be found in [7, 8]. This simple model exhibits a surprisingly complex and diverse range of patterns. In its application to the formation of snake skin markings, the model exhibits several of the patterns commonly observed on snakes [9]. Testable predictions made by the model are discussed in [7].
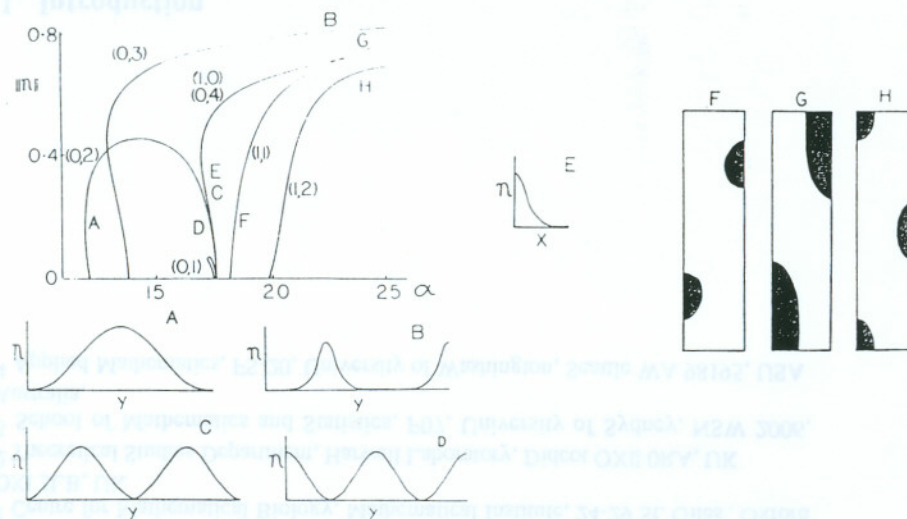

Fig.1: Bifurcation diagram for fixed r, N, D and s and varying α on a 1 x 4 domain. This diagram only shows the upper branches of primary bifurcations, secondary bifurcations from these branches were observed but not studied in detail. The letters A to H on the state diagram denote the patterns in cell density (the chemical concentrations exhibit similar patterns). The linearised system has eigenfunctions $\cos(n\pi x)\cos(m\pi y/4)$ denoted by mode (n,m). Note that modes $(0,4)$ and $(1,0)$ are degenerate. Shaded regions denote high cell density

$$\left[\|n\| = \frac{\int_\Omega |N-n| dxdy}{\int_\Omega dxdy}\right].$$
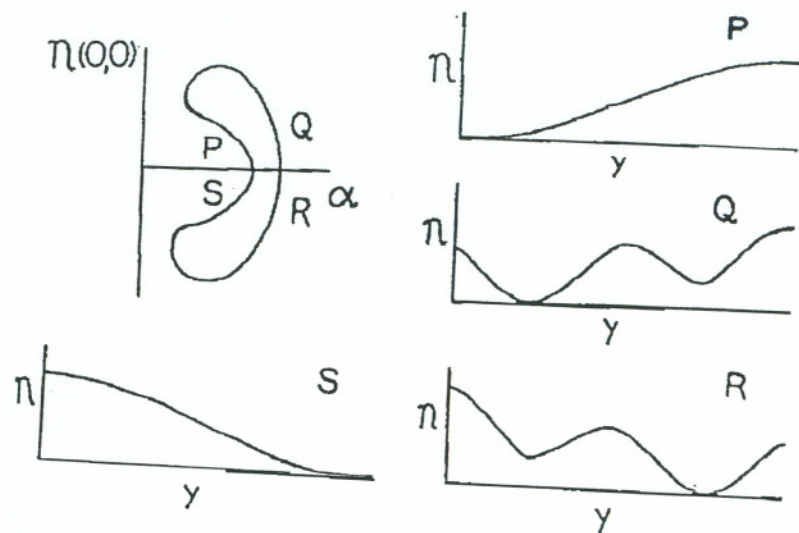
Fig. 2: Magnified view of the bifurcation of mode (0,1) in Figure 1 with the value of n at the origin plotted against α. The letters P to S denote the patterns indicated.
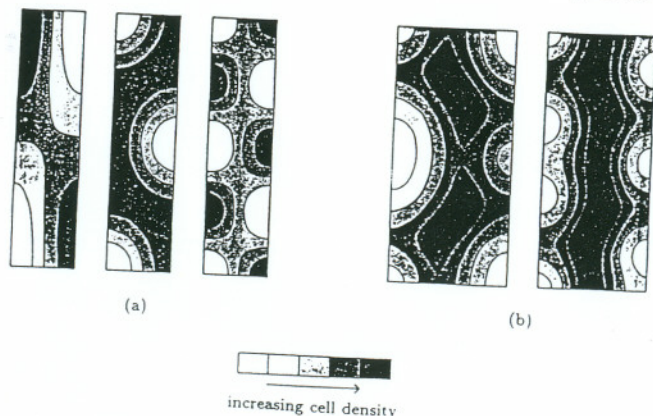

Fig. 3 : (a) A selection of patterns in cell density. (b) The effect of changing the width of the domain.

References

1. J. D. Murray. A prepattern formation mechanism for animal coat markings. *J. Theor. Biol.*, **88**:161-199, 1981.

2. J. B. L. Bard. A model for generating aspects of zebra and other mammalian coat patterns. *J. Theor. Biol.*, **93**:363-385, 1981.

3. J. D. Murray. Mathematical Biology. *Springer-Verlag*, Heidelberg, 1989.

4. J. D. Murray, P. K. Maini, and R. T. Tranquillo. Mechanochemical models for generating biological pattern and form in development. *Physics Reports*, **171**:59-84, 1988.

5. G. F. Oster and J. D. Murray. Pattern formation models and developmental constraints. *J. Exp. Zool.*, **251**:186-202, 1989.

6. J. D. Murray, D. C. Deeming, and M. J. W. Ferguson. Size dependent pigmentation pattern formation in embryos of *alligator mississipiensis*: time of initiation of pattern formation mechanism. *Proc. Roy. Soc. (London)*, B **239**:279-293, 1990.

7. P. K. Maini, M. R. Myerscough, K. H. Winters, and J. D. Murray. Bifurcating spatially heterogeneous solutions in a chemotaxis model for biological pattern generation. *Bull. Math. Biol.*, 1991. (in press).

8. K. H. Winters, M. R. Myerscough, P. K. Maini, and J. D. Murray. Tracking bifurcating solutions of a model biological pattern generator. *Impact Comp. Sci. Eng.*, **2**:355-371, 1990.

9. J. D. Murray and M. R. Myerscough. Pigmentation pattern formation on snakes. *J. Theor. Biol.*, **149**:339-360, 1991.