2国际生物数学会议
INTERNATIONAL CONFERENCE ON BIOMATHEMATICS
REPUBBLICA DI SAN MARINO 5-6-7 OCTOBER 1992

TOPICS ON BIOMATHEMATICS

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World Scientific
Singapore • New Jersey • London • Hong Kong

Published by

World Scientific Publishing Co. Pte. Ltd.
P O Box 128, Farrer Road, Singapore 9128
USA office: Suite 1B, 1060 Main Street, River Edge, NJ 07661
UK office: 73 Lynton Mead, Totteridge, London N20 8DH

TOPICS ON BIOMATHEMATICS
2nd International Conference on Biomathematics

ISBN 981-02-1490-1

Printed in Singapore by Utopia Press.

REPUBBLICA DI SAN MARINO

2 INTERNATIONAL CONFERENCE ON BIOMATHEMATICS

Under the Auspices:
Dicastero Sanità e Sicurezza Sociale - Repubblica di San Marino
Dicastero Pubblica Istruzione e Cultura - Repubblica di San Marino
Consiglio Nazionale delle Ricerche - Roma - Italy

October 5-6-7 1992
Repubblica di San Marino

PATTERN FORMATION IN TURING SYSTEMS WITH MIXED BOUNDARY CONDITIONS

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1 INTRODUCTION

A central issue in developmental biology is the formation of pattern and form in the early embryo. From the apparently homogeneous mass of dividing cells that exists in the earliest stages of development emerges the vast range of pattern and structure observed in the adult. The formation of structure is termed morphogenesis, and pattern generation models are known as morphogenetic models. The role of modelling in morphogenesis is to suggest possible scenarios as to how various physical and chemical processes conspire to produce pattern.

Broadly speaking, there are two main types of models in embryology: chemical prepattern models, which propose that a spatially heterogeneous pattern in some chemical is set up, and in reponse to this the cells differentiate according to some interpretation mechanism; and mechanical models, which propose that a spatial pattern in cell density is set up due to the physicochemical interactions between cells and their environment. In mechanical models cells in high density aggregates then differentiate to form structures (see Murray, 1989, for a review).

In this paper we concentrate on a chemical prepattern model. Turing (1952) showed that a system of reacting and diffusing chemicals could be unstable given a suitable balance between reaction and diffusion, and could evolve to a spatially heterogeneous pattern in the chemical concentrations. In this way a chemical prepattern could be set up which could be interpreted by the cells, resulting in spatially-patterned cell differentiation. Turing's mechanism provides one means of generating positional information (Wolpert, 1969).

Turing's model for pattern formation has been extensively studied analytically and numerically for the case in which all reacting species are assumed to satisfy the same type of boundary condition pointwise on the boundary. Typically, these are either zero flux or fixed at the uniform steady state concentration. The former models an impermeable membrane, the latter a source of chemical at the boundary. We call these boundary conditions scalar boundary conditions. In this paper, we describe some

results for the case of non-scalar boundary conditions, wherein each species satisfies different boundary conditions at any point on the boundary. More details are given in Dillon, *et al.* (1992). In Section 2 we compare the properties of the solutions of the scalar case with those of the non-scalar case, and in Section 3 we consider an application to skeletal development in the limb.

2 COMPARISON OF THE SCALAR AND NON-SCALAR CASES

The two species Turing model in one space dimension takes the form

$$u_t = \nu u_{\xi\xi} + f(u,v,p), \quad v_t = \nu\delta v_{\xi\xi} + g(u,v,p), \tag{1}$$

where $u(\xi,t)$ and $v(\xi,t)$ are nondimensionalised chemical concentrations at position ξ and time t, with $\xi \in (0,1)$; $\nu = D_1/\omega L^2$, $\delta = D_2/D_1$, where D_1 and D_2 are the diffusion coefficients of u and v respectively, ω^{-1} is a typical reaction time scale, and L is a measure of the domain length. The functions f and g are rational polynomials which model the reaction kinetics and p denotes the vector of kinetic parameters.

Many properties of the solutions of the Turing model for scalar boundary conditions are well known (Othmer, 1977). For comparison with the non-scalar case we focus on a particular reaction diffusion system, the simplified glycolysis model (Ashkenazi and Othmer, 1978), for which the reaction kinetics take the form

$$f(u,v,p) = \beta - \kappa u - uv^2, \quad g(u,v,p) = \kappa u + uv^2 - v, \tag{2}$$

where β and κ are fixed parameters.

We analyse the system with the numerical package AUTO (Doedel, 1986), which calculates the steady states and their stability. To analyse the time evolution problem we use a combination of linear analysis, bifurcation analysis and numerical integration. We refer the reader to the paper by Dillon, *et al.* (1992) for full details. Here we simply summarize the main results:

1. Behaviour at small L: For the scalar case, a minimum domain length is required for a non-uniform steady state to exist. For the non-scalar case, however, it is possible to show that a stable, non-constant, steady state can exist at arbitrarily small length.

2. Complexity of the bifurcation diagram: For the scalar case, the bifurcation diagram becomes very complex as the parameter L increases. However, for the non-scalar case, the range of admissible solutions decreases and hence the complexity of the bifurcation diagram is greatly reduced.

3. Multiplicity of stable steady states: For the scalar case there are regions in parameter space wherein more than one stable steady state solution exists. For the non-scalar case the problem of multiplicity of solutions is greatly reduced. Solutions are less sensitive to changes in domain size and are more robust to changes in other parameters.

3 APPLICATION

Here we consider the application of Turing models to the formation of skeletal patterning in the vertebrate limb. Figure 1 shows the sequence of bifurcations in the limb as it grows out. Although limb development is a three-dimensional process, the patterning in each dimension can be decoupled to a first approximation (see Maini and Solursh 1991 for a review). The development of pattern along the proximal-distal axes is through a 1-2-3 transition sequence. In Figure 2 we compare the transition sequence for the scalar Turing system with that of the non-scalar case as the parameter L increases.

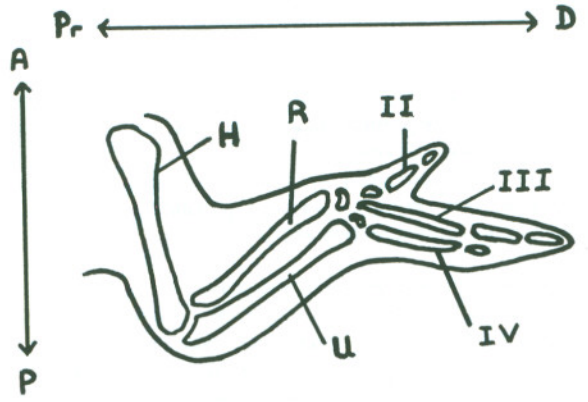

Figure 1. Diagrammatic representation of the chick limb showing the skeletal elements. H - humerus, R - radius, U - Ulna, II, III, IV - digits, A - anterior, P - posterior, Pr - proximal, D - distal.

4 DISCUSSION

A great number of Turing-type models have been proposed for spatial pattern formation and their properties have been extensively studied analytically and numerically. They have been proposed as morphogenetic models for a wide range of developmental phenomena. It is well-known that the patterns exhibited by Turing models are very sensitive to initial conditions, scale, geometry and parameter variation. Hence, as they stand, Turing models are inadequate to account for robust patterning mechanisms such as those which underlie, for example, skeletal development in the tetrapod limb.

In this paper we have summarized the effects of boundary conditions on an one-dimensional reaction diffusion system. From this, we can see that imposing non-scalar boundary conditions can lead, in a robust and controlled manner, to a sequence of transitions that closely resembles those observed in skeletal patterning in the developing limb. Here we took domain length L as our bifurcation parameter. However, as this parameter occurs in the dimensionless parameter $\nu = D_1/\omega L^2$, the sequence of transitions observed above could be generated by changes, for example, in diffusion coefficients. This could arise due to a change in gap junction permeability (Mehta *at al.*, 1989; Brümmer *et al.*, 1991). Some results from a model that incorporates this are analyzed in Dillon and Othmer (1993).

Our model does not capture the anterior-posterior asymmetry of the limb. However,

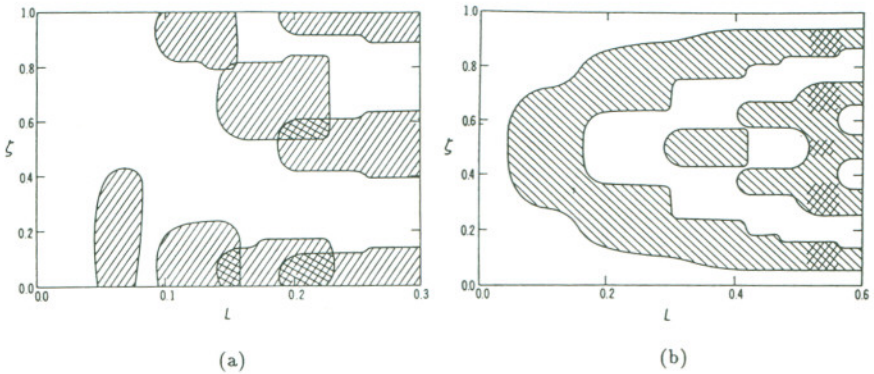

Figure 2. The subintervals of $(0,1)$ in which the v-component of the solution to the glycolysis model exceeds a fixed threshold concentration, as a function of L. (a) The scalar case where u and v satisfy zero flux boundary conditions; (b) The non-scalar case in which u satisfies zero flux boundary conditions and the concentration of v is fixed to zero on the boundary. Clearly for (b) a simple threshold mechanism can reliably produce the sequence 1-2-3- ... of pattern elements as the parameter L increases, whereas this is impossible for the standard case with scalar boundary conditions.

recently Maini *et al.* (1992) have shown that introducing biologically realistic spatial variation in chemical diffusion coefficients can reproduce this asymmetry.

In summary, boundary conditions have a marked effect on the steady state patterns exhibited by reaction-diffusion models in one-dimension. We would expect this effect to be even more pronounced in two- and three- dimensions, in part because there are more combinations of the different types of boundary conditions.

Acknowledgements This work (RD and HGO) was supported in part by NIH Grant No. GM29123.

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