Pattern Selection in Biological Pattern Formation Mechanisms

D. E. BENTIL* AND J. D. MURRAY*

Centre for Mathematical Biology
Mathematical Institute, University of Oxford
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Abstract. Realistic pattern formation models in biology usually have several parameters. The determination of sets of parameter values which generate specific patterns is not an easy problem. We describe a simple, systematic method for choosing such parameter values and, by way of example, apply it to one of the new mechanochemical models for biological pattern formation which has nine parameters.

1. INTRODUCTION

Several mechanisms for the generation of pattern and form have been suggested by various authors, such as reaction diffusion models (see, for example [1]) and the new biologically realistic Oster-Murray mechanochemical approach [2–5]. Such pattern formation models usually have several parameters. To test the robustness of such models, a primary step is to examine specimen patterns associated with these models using various sets of parameter values. Although at this stage parameter values which give rise to specific patterns are normally chosen without any experimental basis, the results nevertheless provide an insight as to how certain experiments should be performed to help elucidate the underlying biological process.

Perelson et al. [5] presented a numerical study of one of the mechanochemical models of morphogenesis and proposed a method for determining parameter values associated with specific wave numbers. Their technique for pattern selection allowed particular wave numbers to be isolated when the number of parameters is large. It was based on nonlinear least squares fitting to a desired or idealised dispersion relation. The dispersion relation was obtained by introducing a complex Fourier series representation for the dependent variables of the linearised model. Fourier analysis of the equations usually gives precise information about what type of solution may be expected. The procedure then chose values for the parameters which minimised an objective function.

When a dispersion relation qualitatively indicates exponential growth of a particular wave number, the selection of specific parameter values to isolate such a wave number is far from trivial, especially when the number of parameters involved is more than two or three, as is the case with mechanochemical models. Mapping out complete regions of parameter space which correspond to a particular pattern remains a challenging problem. Murray [6] investigated this problem analytically with respect to reaction diffusion mechanisms which generate spatial patterns.

As shown in Figure 1(a–d), the Perelson et al. [5] technique, namely solving the inverse problem by choosing the desired form of dispersion relation and fitting the actual dispersion relation to it using Levenberg–Marquardt algorithm [1], yields imprecise results. Sometimes negative parameter values were indicated; these are not biologically relevant. We observed from a critical study of [5] that for dispersion relations which gave complex roots, negative values arose within the region of bifurcation which is crucial for both linear and nonlinear

*Current address: Dept. of Applied Mathematics, FS-20, Univ. of Washington, Seattle, WA 98195, USA.
analyses. Thus, when we are dealing with a cubic or even a more complex dispersion relation, it is usually impossible to write out explicit roots before any minimisation procedure is implemented, the least squares method used in [5] is unreliable. There is thus a need for an alternative method. We describe here a systematic procedure for choosing parameter values for a specific pattern selection. The procedure—The Logical Parameter Search Method (LPS)—is easy to use and does not give rise to negative parameter values.

2. The Logical Parameter Search Method

The method uses a search procedure which involves the following general steps:

S1 Choose a hypothetical parameter space for the governing equations. The parameter space should be chosen so as to be biologically realistic and in keeping with what was obtained from the mathematical analysis.

S2 Choose parameter ranges for each of the parameters in question. The ranges should be confined to the parameter space in S1 and may possibly be obtained from experiments.

S3 Set up iterative procedures to cover the parameter ranges for each of the parameters in question. It may be reasonable to fix some parameters or use large iterative steps if several parameters are to be scanned.

S4 Solve the equation or system of equations or find the roots of the polynomial in question for each of the computer generated parameter sets.

S5 Logically test whether what is required of the governing equations has been achieved for every search step.

S6 Note the sets of parameter values which satisfy the set up conditions and continue the search procedures.

S7 If no sets of parameter values are generated go to S1 and adjust the parameter space or check the well-posedness of the governing equations.

By way of example, we apply our technique to the mechanochemical model studied numerically in [5]. The model consists of conservation equations for mesenchymal cell and extracellular matrix (ECM) densities, \( n(x, t) \) and \( \rho(x, t) \) respectively, where \( x \) is the spatial coordinate and \( t \) the time. These are coupled with a force balance equation for the mechanical interaction of cells with the matrix; this equation involves the displacement, \( u(x, t) \), of the material point of ECM located at position \( x \).

The nondimensional version of the governing equations we consider, by way of example, are, in one dimension,

\[
\begin{align*}
\mu \frac{\partial^3 u}{\partial t \partial x^2} + \frac{\partial^2 u}{\partial x^2} + \frac{\partial}{\partial x} \left[ \frac{\tau n}{1 + \lambda n^p} \left( \rho + \beta \frac{\partial^2 \rho}{\partial x^2} \right) \right] &= s u \rho \\
\frac{\partial n}{\partial t} &= D \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left( n \frac{\partial u}{\partial t} \right) - \alpha \frac{\partial}{\partial x} \left( \frac{\partial \rho}{\partial x} \right) + r n (1 - n) \\
\frac{\partial \rho}{\partial t} &= -\frac{\partial}{\partial x} \left( \rho \frac{\partial u}{\partial t} \right)
\end{align*}
\]

(1)

where the nine parameters \{\( r, \mu, \beta, \lambda, D, \alpha, s, r, p \)\} are discussed in detail in [3–5].

Carrying out a Fourier analysis for qualitative solution behaviour (linear stability analysis) about the nontrivial steady state, namely \( n = 1 = \rho, u = 0 \), we get a dispersion relation of the form

\[
\sigma A(\sigma) = 0
\]

(2)
where

\[ A(\sigma) = \mu k^2 \sigma^2 + b(k^2) \sigma + c(k^2) \]

\[ b(k^2) = \left( \mu D + \frac{\tau \beta}{1 + \lambda} \right) k^4 + \left( 1 - \frac{\tau}{1 + \lambda} \right) \left[ \frac{\lambda p}{1 + \lambda} + \mu r \right] k^2 + s \]

\[ c(k^2) = \left( \frac{\tau \beta D}{1 + \lambda} \right) k^6 + \left( D + \frac{\tau}{1 + \lambda} \right) \left[ r \beta - D - \alpha \left( 1 - \frac{\lambda p}{1 + \lambda} \right) \right] k^4 \]

\[ + \left( s D + r - \frac{\tau \beta}{1 + \lambda} \right) k^2 + rs. \]

This biologically relevant steady state will be unstable to spatial perturbations of any wave number, \( k_m \), for which the growth rate, \( \sigma \), of that wave number is positive. That is at least one of \( \text{Re}[\sigma_i(k_m^2 r)] > 0 \), where \( \sigma_i(k_m^2) \) are the \( i \) complex roots of (2) and \( m \) is the mode for that particular wave number. On the domain \([0,1]\), for example, the steady state will be unstable at any of the modes if, for an appropriately chosen set of parameter values, there exists a non-negative integer \( j \) such that

\[ \text{Re} \sigma_i(2j\pi) \begin{cases} > 0, & j = m/2, \\ < 0, & \text{otherwise}. \end{cases} \]  

(3)

If we neglect cell division, that is set \( r = 0 \) in (1), and assume \( p = 2 \) as in [3], the bifurcation between spatially stable and unstable mode is when \( c_{\text{min}}(k_m^2) = 0 \), where \( c_{\text{min}} \) is the minimum of \( c(k^2) \) given above. For a derivation of this, see [2–4]. This gives from (2) conditions for instability as

(i) \[ \frac{\tau}{1 + \lambda} \left[ D + \alpha \left( 1 - \frac{2\lambda}{1 + \lambda} \right) \right] - D > 0 \]

(ii) \[ \left( \frac{\tau}{1 + \lambda} \left[ D + \alpha \left( 1 - \frac{2\lambda}{1 + \lambda} \right) \right] - D(1 + \lambda) \right) > 2D \sqrt{s\beta r(1 + \lambda)} \]

(4)

To isolate a specific mode which gives rise to a particular pattern, we need to choose biologically realistic parameter ranges for each of the parameters in question. The choice of parameter ranges depends on the conditions for instability (constraints on the objective function) which are given in (4). We set up iterative procedures for the parameter ranges and evaluate the roots of the dispersion relation by Newton’s method. Any appropriate root finding procedure could be used. The procedure then checks whether condition (3), that is the objective function, is satisfied at specific modes for particular sets of parameter values within the parameter space. The logical check was carried out as follows. Here, we are concerned with the quadratic polynomial \( A(\sigma) \) which has two roots only:

Let \( \text{flag} \ k = 1 \Rightarrow \text{true} \) and \( \text{flag} \ k = 0 \Rightarrow \text{false} \)

If \( j = m/2 \) and \( \text{Re} \ \sigma_1 \geq 0.0 \) or \( \text{Re} \ \sigma_2 \geq 0.0 \), \( \text{flag} \ 1 = 1 \)

If \( j \neq m/2 \) and \( \text{Re} \ \sigma_1 \geq 0.0 \), \( \text{flag} \ 2 = 1 \)

If \( j \neq m/2 \) and \( \text{Re} \ \sigma_2 \geq 0.0 \), \( \text{flag} \ 3 = 1 \)

If \( \text{flag} \ 1 = 1 \) and \( \text{flag} \ 2 = 0 \) and \( \text{flag} \ 3 = 0 \) write the set of parameter values.

The iteration is continued until all the parameter ranges are scanned. The logical conditions could be changed to suit one’s requirements.

As an illustration, we compare our approach to that of Perelson et al. [5]. Figure 1(a–d) shows dispersion relations for the parameter values used in [5], and those obtained with sets of values from our LPS method—Figure 1(a1–d1). Table 1 compares the parameter values obtained.

These four arbitrary sets of parameter values \( a_1, b_1, c_1, d_1 \) are the results of our approach which isolated the second, fourth, sixth and eighth modes. They were used when we solved
Figure 1. Comparison of dispersion relations at specific modes as obtained in [3] and by our LPS method. On the left (a, b, c, d) are the dispersion relations for Fig. 3.1(a-d) in [5] and on the right (a1, b1, c1, d1) are curves using our LPS approach. Although the method in [5] is more sophisticated, the simple procedure here gives better results and smooth dispersion relations.

Table 1. The various sets of parameter values obtained from the LPS method gave very good results (see a1, b1, c1, d1). Those indicated here are just random choices from the sets. It is possible to pick wider regions around specific modes by choosing large iterative steps.

<table>
<thead>
<tr>
<th>mode</th>
<th>τ</th>
<th>μ</th>
<th>β</th>
<th>λ</th>
<th>D</th>
<th>α</th>
<th>s</th>
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<tr>
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<td>0.015</td>
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<td>0.001</td>
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<tr>
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<td>0.020</td>
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<td>0.0021</td>
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<td>0.200</td>
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<td>1.00</td>
<td>0.70</td>
<td>0.005</td>
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<td>0.001</td>
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</tr>
<tr>
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<td>1.00</td>
<td>0.001</td>
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<td>0.001</td>
</tr>
<tr>
<td>c1</td>
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<td>1.20</td>
<td>0.002</td>
<td>0.10</td>
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<td>0.004</td>
</tr>
<tr>
<td>d</td>
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<td>1.00</td>
<td>0.001</td>
<td>0.12</td>
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<tr>
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</table>

system (1) numerically with periodic boundary conditions. Initial conditions consisted of $u$ and $p$ at their uniform steady states, $u(x,0) = 0$ and $p(x,0) = 1$, and $n$ randomly perturbed from its steady state, that is $n(x,0) = 1 + f(x)$, where $f(x)$ was chosen from a uniform
distribution between -0.05 and 0.05. We used the method of lines and Gear's method, and also by a fully implicit method with small time steps in one space dimension. To ensure that the numerical approximations had converged, different but equivalent substitutions were used. The results are as illustrated in Figure 2. Our results compare well with earlier work on this problem but with a marked decrease in effort in determining the appropriate parameter values through use of this simple, straightforward logical parameter search (LPS) method.

![Graphs showing cell density and concentration distributions](image)

Figure 2. Heterogenous steady state solutions of (1). The solution for the cell density equation $n(x,t)$ is almost identical to that of the matrix density equation $\rho(x,t)$ as we would expect because from (1) convection is the major form of motion for $D$ and $\alpha$ small.

**References**


Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford OX1 3LB, UK.