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Pattern Formation And Wound Healing

Abstract

One of the main immediate challenges in the biomedical sciences is the synthesis of the vast amount of data now available at the molecular and cellular levels for development, regulation and repair. This, in turn, requires an understanding of the interaction and coordination of a myriad of complex inter-related processes occurring on very different spatial and temporal scales. Mathematics provides the obvious language in which to develop and interpret these interactions, and a number of mathematical models have already been proposed to account for certain observed biological and medical phenomena. Here, we consider two areas of modelling, namely spatial patterning, and wound healing, both sharing the common underlying processes of cells creating and responding to signalling cues.

Introduction

Recent technological advances in molecular and cellular biology have led to an explosion of data in the biomedical sciences. We have a complete mapping of the human genome; we can determine when in development certain genes are switched on; we can accurately follow the fate of single cells. The list is endless. However, we are in danger of falling into the practices of the nineteenth century, when biology was steeped in the mode of classification and there was a tremendous amount of list-making activity. This was recognised by D'Arcy Thompson, in his classic work "On Growth and Form", first published in 1917 (see Thompson, 1992 for the abridged version). He was the first to develop theories as to how certain forms arose, rather than simply cataloging different forms, as was the tradition at that time.

Of course, we have come a long way since then. The identification of a gene that causes a certain disease or deformity has huge benefits for medicine. We must

recognise, though, that genes only specify the properties of proteins and cells. It is the physio-chemical interaction of these cells that lead to, for example, the development of structure and form in the early embryo. Cell fate can be determined by environmental factors and cells respond to signalling cues. Therefore, a study at the molecular level alone will not help us to understand how cells interact.

Such interactions are highly nonlinear and may be nonlocal and therefore they must be couched in a language that is designed to compute the results of complex interactions. At the moment, the best language we have for doing such calculations is mathematics. Mathematics has been extremely successful in helping us to understand physics. It is now becoming clear that mathematics, and computation, have a similar role to play in the life sciences.

In this paper, I will focus on two major problems – the development of pattern formation in the early embryo, and the processes involved in wound healing. Although seemingly very different, these two areas are connected by a unifying underlying theme, which is that both depend crucially on cellular response to signalling cues. Section 2 contains a brief review of the role that modelling has played in pattern formation and morphogenesis in early embryonic development. This is a field with a history stretching back to the days of D'Arcy Thompson. In section 3, I consider wound healing, a much more recent application of mathematics in the life sciences, and focus on a model that investigates scar tissue formation. Finally, section 4 discusses other areas in the life sciences where similar mathematical models have been used.

2. Models For Developmental Biology

Cell fate and position within the embryo can be strongly influenced by environmental factors. Therefore, to answer questions on pattern formation, one must really address the issue of how the embryo organises the complex spatiotemporal sequence of signalling cues necessary to develop structure in a controlled and coordinated manner. Structure can form through tissue movement and rearrangement. Theoretical studies in this area include the early purse-string model of Odell *et al.* (1981) for tissue folding in which, in response to a large deformation, cells were proposed to actively contract and in so doing cause a large deformation in neighbouring cells which, in turn, also contract, setting up a propagating contraction wave which leads to tissue folding. This model was applied to a variety of developmental problems, and provided the precursor to the "mechanochemical theory" of developmental patterning, developed by Murray, Oster and coworkers (for review, see Murray, 1993). This approach emphasised the link between tissue mechanics and chemical regulation, and has been applied

widely in both developmental biology and medicine. Subsequently, Weliky and Oster developed a discrete-cell modelling approach in which morphogenesis occurs via mechanical rearrangement of neighbours in an epithelial sheet. They assume that the boundary of the epithelial sheet is being pulled over the surface of the egg and show that the resultant model can produce many experimentally observed aspects of both *Fundulus* epiboly and notochord morphogenesis in Xenopus laevis (Weliky and Oster, 1990; Weliky *et al.*, 1991). More recently, Davidson *et al.* (1995) used a computational finite element model to test various explanations for sea urchin invagination.

In all these models individual cell movements within the tissue are determined by the balance of mechanical forces acting on the cell. Such models can exhibit tissue folding, thickening, invagination, exogastrulation and intercalation, and have been shown to capture many of the key aspects of processes such as gastrulation, neural tube formation, and ventral furrow formation in *Drosophila*, as well as those mentioned above.

Models for tissue motion are not amenable to a mathematical analysis and tend to be highly computation-based. However, models for how cells differentiate can be addressed mathematically. Broadly speaking, there are two classes of such models. In one class, the *chemical pre-pattern models*, it is hypothesized that a chemical (morphogen) signal is set up in some way and cells respond to this signal by differentiating. In the other class, *the cell movement models*, it is hypothesized that cells respond to mechanochemical cues and form aggregates. Cells in high density aggregates are then assumed to differentiate.

The simplest chemical pre-pattern model is the gradient model proposed by Wolpert (1969) in which a source-sink mechanism, coupled with diffusion and degradation, leads to a spatial gradient in a single morphogen. He proposed that this provided *positional information* for cells, which differentiated according to a series of threshold values. More complicated spatial patterns can be generated due to the reaction and diffusion of a number of chemicals. This phenomenon is known as *diffusion-driven instability* and was first proposed by Turing in a remarkable paper (Turing, 1952). The reaction kinetics he considered were stabilizing and diffusion is, of course, a homogenizing process. Yet combined in the appropriate way, these two stabilizing influences conspire to produce an instability which can result in spatially heterogeneous chemical profiles – a spatial pattern. This is an example of an *emergent property*. Such models can be described in partial differential equation form, or discretized and analysed as cellular automata (Bard, 1981).

Turing's original model considered linear reaction kinetics, with the result that any instability would lead to unbounded solutions. Since his seminal paper, many reaction-diffusion models have been proposed with different types of kinetics. These models take the general form:

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + f(u,v) \tag{1}$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 u + g(u,v) \tag{2}$$

where $u(\underline{x},t)$, $v(\underline{x},t)$ denote chemical concentrations at position $\underline{x}$ and time t, D_u, D_v are diffusion coefficients and f, g are reaction kinetics. These equations are solved subject to certain initial conditions, typically random perturbations about a uniform steady state, and boundary conditions, which are typically periodic, zero flux, or fixed. Many different reaction kinetics have been proposed, for example, in the Gierer-Meinhardt model (1972):

$$f(u,v) = \alpha - \beta u + \gamma u^2/v, \quad g(u,v) = \delta u^2 - \mu v, \tag{3}$$

where α, β, γ, δ and μ are constants. For the Schakenberg (1979) model,

$$f(u,v) = k_2 a - k_1 u + k_4 u^2 v, \quad g(u,v) = k_3 b - k_4 u^2 v, \tag{4}$$

where $k_1,\ldots,k_4$ are (positive) rate constants, and a and b can be considered to be approximately constant. The Thomas (1976) model has the form

$$f(u,v) = \alpha(u_0 - u) - \frac{V_m uv}{K_m + u + u^2/K_s}, \quad g(u,v) = \beta(v_0 - v) - \frac{V_m uv}{K_m + u + u^2/K_s}, \tag{5}$$

where α, β, U_0, V_0, V_m, K_m and K_s are positive constants. These are only a few examples. Such model kinetics are, in the main, hypothetical.

After many years of experimental effort, the first Turing patterns were finally observed in the chlorite-iodide-malonic acid starch reaction (CIMA reaction) (Castets *et al.*, 1990; De Kepper *et al.*, 1991). This has now been extensively modelled and one simplified version of the model (Lengyel and Epstein, 1991) takes the form:

$$\frac{\partial u}{\partial t} = k_1 - u - \frac{4uv}{1+u^2} + \nabla^2 u \tag{6}$$

$$\frac{\partial v}{\partial t} = k_2 \left[k_3 \left(u - \frac{uv}{1+u^2} \right) + c\nabla^2 v \right] \tag{7}$$

where u, v are the concentrations of iodide and chlorite, respectively and k_1, k_2, k_3 and c are positive constants (see Maini *et al.*, 1997, for review and references

therein). General results on the patterning properties of reaction-diffusion equations can be found in the books by Britton (1986), Edelstein-Keshet (1988), Fife (1979), Grindrod (1996), Murray (1993) and Segel (1984).

The gradient models and the Turing-type models differ in two crucial aspects (Nagorcka, 1989): In the gradient model, the chemical pre-pattern is set up by a simple process which can only produce a simple gradient. To use this gradient to generate complicated pattern, it is hypothesized that a complex series of thresholds exist and cells have the machinery to interpret multiple thresholds. In Turing's model, complex spatial patterns arise due to a complex chemical interaction, but the interpretation of the pre-pattern is via a single threshold and is therefore simpler than that in the gradient model.

The other class of models, namely cell movement models, assume that a spatial pattern arises in cell density, and cells then differentiate in a density-dependent manner. Cell aggregation occurs when the cell dispersing factors (for example, diffusion) are overcome by aggregating factors such as chemotaxis (movement up chemical gradients), or factors generated by the mechanical interaction of cells with the extracellular matrix (ECM) on which they move. These include haptotaxis (movement up adhesive gradients) or passive convection arising as the result of deformation of the ECM due to cell traction. Chemotactic models have been analysed by a number of authors and shown to lead to spatial pattern formation (see, for example, Keller and Segel, 1971; Maini *et al.*, 1991). These models involve reaction and diffusion, but spatial patterning arises in this case due to the advective term introduced by chemotaxis. The typical model takes the form:

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + g(n,u), \tag{8}$$

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \nabla.(\chi(u) n \nabla u) + f(n,u) \tag{9}$$

where $n(\underline{x},t)$, $u(\underline{x},t)$ denote cell density and chemoattractant concentration, respectively, at position $\underline{x}$ and time t, D_n, D_u are diffusion coefficients, f, g are terms incorporating production and degradation and $X(u)$ is the chemotactic sensitivity.

The first partial differential equation model incorporating the role of mechanical cues in the formation of cell aggregation was proposed by Oster *et al.*, (1983) and since then such models have been extensively studied (Murray, 1993). The mathematical equations of these models are quite different. They consist of conservation equations for cells and extracellular matrix, which take the general form of the equations above, but the main difference is the force-balance equation, which is that for a visco-elastic material.

Other movement models hypothesize that cells move to minimize energy (Cocho *et al.*, 1987a,b; Steinberg, 1970; Sulsky, 1984). Such models can be set up mathematically and solved to show cell sorting and patterning behaviour consistent with a number of experimentally observed phenomena.

Turing considered the chemicals in his model to be growth hormones, so that the spatial pattern in chemical concentrations would result in spatially non-uniform growth and hence pattern. He applied his theory to account for whorled leaves and to growth-induced shape changes in the early embryo which he proposed could account for gastrulation. Since his seminal paper, reaction-diffusion models have been proposed to account for a vast number of patterning processes in nature, too great to be completely reviewed here, so we consider a few examples to give a flavour of the applications.

Gierer and Meinhardt (1972) used their model to account for pattern formation in *Hydra* and showed that it was consistent with several of its regenerative properties. Reaction-diffusion models have been proposed to account for compartmentalisation in insect development and to provide an explanation for the occurrence of various mutants (see Meinhardt, 1982, for review). However, for *Drosophila* it now appears that patterning is due to a cascade of protein interactions that are consistent with the gradient-type models and are not of Turing-type.

Reaction-diffusion models have been applied to shell patterns (Meinhardt, 1995) and to butterfly wing pigmentation patterns (Nijhout, 1990). Reaction-diffusion and cell movement models have been applied to animal coat markings (Bard, 1981; Cocho *et al.*, 1987a,b; Murray, 1981; Murray and Myerscough, 1991) and to skeletal patterning in the limb, for which gradient models have also been proposed (see Maini and Solursh, 1991, for a critical review). In most of these cases it is difficult, biologically, to distinguish between models. For example, if one observes a chemical pattern or a cell aggregation pattern, is it the cause of cell differentiation or a result of it?

Although these models are based on very different biological assumptions, many of them share common properties. For example, the patterning in reaction-diffusion and in many cell movement models arises from the interaction of the processes of short-range activation, long-range inhibition. On the one hand, this has the disadvantage of making it very difficult to use models to distinguish between mechanisms, on the other hand, it does mean that one can make general conclusions and predictions that are mechanism-independent. This leads to the idea of *developmental constraints* which proposes that only certain patterns are possible, regardless of the mechanism (Oster and Murray, 1989). Figure 1 illustrates one such developmental constraint.

A key property of many development processes is their robustness in the face of naturally occuring random fluctuations. This has been a major problem

for reaction-diffusion theory, as it is well-known that the patterns it produces are not robust (Bard and Lauder, 1974). In other words, Turing-type models can exhibit multiple stable solutions in large regions of parameter space. Recently it has been shown that boundary conditions can play a crucial role in stabilizing patterns. For example, if one chooses fixed boundary conditions for one chemical and zero flux boundary conditions for the other, then this reduces the number of admissible solutions and thus diminishes the regions in parameter space in which one obtains multiple stable solutions. In effect, the boundary conditions serve to select only certain patterns (Dillon *et al.*, 1994).

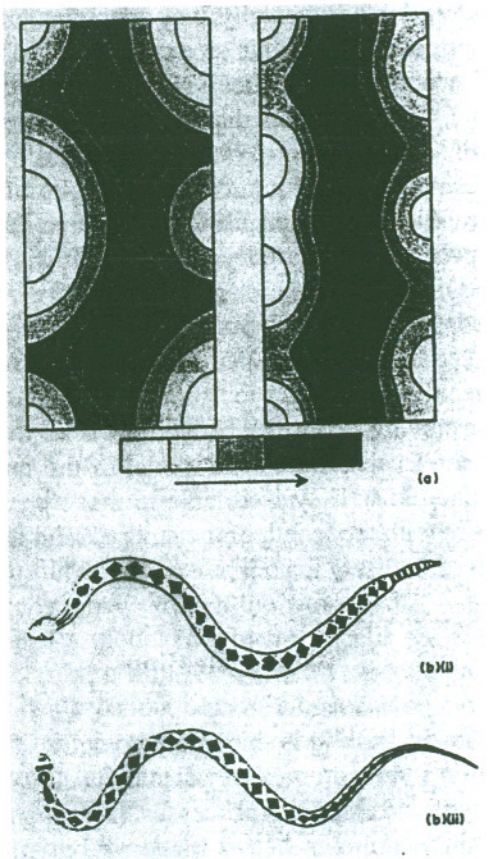

Figure 1. (a) Simulation of the cell-chemotaxis model (8)-(9) showing the effect of domain size on cell density concentration (arrow denotes increasing cell density). As the domain narrows, the diamond pattern changes to a simpler, wavy stripe pattern. This is an example of a developmental constraint. (b) Examples of diamond patterns on snakes (i) Crotalus adamanteus; (ii) Coluber hippocrepis (note the effect of the tapering domain). (Reproduced from Murray and Myerscough, 1991, with permission).

In higher dimensions, this problem becomes more acute as one now has the added problem of degeneracy. For example, for certain parameters, there may be two or more admissible solutions with the same linear growth rate and it is then not clear which solution is selected. Using nonlinear bifurcation analysis, Ermentrout (1991) showed that the nonlinear terms play a key role in pattern selection, with quadratic terms favouring spots, while cubic terms favour stripes. More recently, Benson *et al.*, (1998) have shown how a spatially-varying parameter can unravel such degeneracies and select one pattern over another. The role of spatially-varying parameters has received little attention but they can play a crucial role in the patterning process. For example, Wolpert and Hornbruch (1990) showed experimentally that double-anterior chick limb buds gave rise to two humeri, even though the size of the bud was the same as that of a normal limb bud, which only produces one humerus. This contradicts the standard Turing model, which predicts that patterning complexity is initimately linked to domain size. Maini *et al.*, (1992) showed that a Turing model with spatially-varying diffusion coefficients could give rise to results that are consistent with Wolpert and Hornbruch's experiments. Results of dye-spreading experiments suggest that the hypothesis of spatially-varying diffusion is very plausible (Brümmer *et al.*, 1991).

In all the above applications, patterns occur simultaneously throughout the whole domain. However, in some cases, patterns arise as the result of propagation. For example, in the alligator embryo, the pigmentation stripes occur as a propagating pattern moving down the body from head to tail. Murray *et al.*, (1990) have shown that a cell-chemotactic model of the form discussed above can give rise to such patterns. They were able to make predictions on how the number of stripes varies with the length of the embryo, and these were confirmed experimentally.

3. Wound Healing

The process of wound healing is extremely complex. For example, dermal wound healing involves the interaction of many cell types and occurs as a sequential cascade of overlapping processes (Jennings and Hunt, 1992). Immediately after injury, there is heavy bleeding but further blood loss is prevented by the constriction of blood vessels. The process of coagulation releases active substances and eventually a fibrin clot forms. Subsequently, fibroblasts begin to infiltrate the wound and dissolve the clot, replacing it with a collagen matrix. Wound closure occurs due to cell invasion and wound contraction. The latter may be enhanced by fibroblasts differentiating into myofibroblasts, a phenotype that can exert stronger traction forces. Cell movement, traction, and

secretion of collagen can all be influenced by chemical signals which, in turn, can be modifed by the cells. Epithelial wound healing tends to occur mainly due to cell invasion and proliferation and differs from dermal healing in that there is no scar tissue formation.

Wound healing is obviously a highly complex nonlinear process and to gain insight to the whole, one has to start by focussing on particular aspects of the healing process. For example, we have explored the role of epidermal growth factor, and of electrical signalling in corneal wound healing (Dale *et al.*, 1994, Gaffney *et al.*, 1999a, 1999b), and have shown how the increase in the rate of healing depends on topical application of growth factor. We have considered a mechanochemical model for dermal wound contraction with the aim of understanding how fibroproliferative and fibrocontractive abnormal healing occurs. The model has been used to make predictions on how keliod scarring may be reduced (Olsen *et al.*, 1996).

Here, we review the results of some recent work (Dallon *et al.*, 1999) which focusses on the role of alignment in wound healing. In normal, unwounded skin, collagen fibres are aligned in a cross-linked (basketweave) arrangement. Scar tissue, however, is characterised by a high degree of matrix alignment. Therefore, not only can scar tissue be disfiguring, it is also a weakness in the skin and can be easily damaged again. As fibroblasts enter the wound, they degrade the fibrin within the clot and secrete collagen. Collagen is extruded from cells so its orientation is determined by the direction of cell movement. At the same time, cells are encountering collagen fibres deposited by other cells and receiving directional cues in the form of contact guidance, causing cells to align with the fibres. However, cells also exert forces on the fibres, causing the fibres to change their orientation. Hence there is a complex feedback between cell direction and alignment of collagen fibres. Moreover, the composition of the matrix will affect the speed at which cells move through the wound.

We have developed a model in which the cells are considered as discrete entities moving in a matrix, which is modelled as a continuum. With each cell is associated a speed and a direction, both of which can be modified by the matrix, as described above. Each point in the matrix has associated with it a density of fibrin, a collagen density and a vector representing collagen direction. These are modified due to interaction with the cell. This modelling framework allows us to examine the roles of each interaction and to investigate how alignment depends on the strength of each interaction. As a result, we can make experimentally testable predictions as to the outcome of varying different parameters.

Figure 2 shows the results of a typical simulation. In this simulation, the effect of different cell speeds is investigated and the results show that increasing the cell speed results in an increase in collagen alignment. Hence, the model predicts that increasing the cell invasion speed will result in a greater degree of

scar tissue formation. This may explain the anti-scarring effect of neutralizing antibody to TGF-β (Shah et al., 1992). TGF-β acts as a chemottractant to fibroblasts and increases the speed at which they enter the wound, so reducing its amount will decrease cell speed and reduce alignment. This possible explanation is more fully explored in Dallon *et al.*, (1999).

This model has also been used to make predictions on the effects on alignment of the source of cells entering the wound (from the sides or from below), cell polarisation, and of including in the wounded region an area of aligned collagen. The model can also be extended to investigate the effects of cell proliferation and cell ageing.

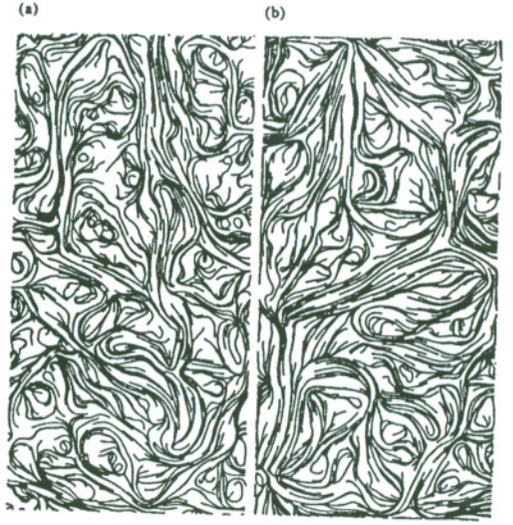

Figure 2. Results of numerical simulations of the model of Dallon *et al.*, (1999) showing collagen fibre alignment as the result of increasing cell speed. Initially, the collagen is aligned randomly throughout the wound and then cells are introduced through the sides and the bottom of the wound. The results are for two different cell speeds, with speed increasing from (a) to (b). Note that there is more alignment in (b) than in (a). (Figure modified from Dallon *et al.*, 1999 — see original paper for fuller details).

Discussion

In this paper my aim has been to show how mathematical modelling can be used to help understand the effects of complex, overlapping biological interactions. I have focussed on two seemingly very different phenomena and shown that they can be studied using similar types of mathematical techniques.

The study of pattern formation in biology has a long tradition, while the use of mathematical models to understand the processes of wound healing is a recent innovation.

Although I have concentrated on two particular applications of mathematical models it is important to note that these types of models have been used in many different areas. Probably the best known example of pattern formation is the Belousov-Zhabotinsky reaction, in which bromate ions oxidise malonic acid in a reaction catalysed by cerium (which has the states Ce^{3+} and Ce^{4+}) resulting in sustained periodic oscillations in the cerium ions. If, instead, the catalyst Fe^{2+} and Fe^{3+} and phenanthroline is used, the periodic oscillations are visualised as colour changes between reddish-orange and blue (for a review, see Johnson and Scott, 1996). This system can also exhibit a number of different types of wave structures such as propagating fronts, spiral waves, target patterns and toroidal scrolls and all these spatiotemporal phenomena have been studied by using models similar in form to (1) and (2) (Zaikin and Zhabotinskii, 1970, Winfree, 1972, 1974, Müller *et al.*, 1985, Welsh *et al.*, 1983, Zykov, 1987). Such oscillatory and wave-like patterns are characteristic of media that are termed *excitable*. Such media have the property that in order to propagate a signal, a sufficiently large stimulus is required to *excite* the system. Once excited, the medium is unable to respond for a period of time, known as the refractory period, to further stimuli.

Excitable media are very common in physiology and one of the most widely-studied and important areas of wave propagation concerns the periodic electrical activity in the heart (Panfilov and Holden, 1997) which controls the muscle contractions that result in the heart beating. If this activity is disrupted, the waves break up and the heart no longer beats efficently, resulting in fibrillation and almost certain death. Understanding this phenomenon through mathematical modelling may help in the design of low voltage defibrillators.

Excitable media also have a role to play in the aggregation of certain amoeboid species, such as the cellular slime mold, Dictyostelium discoideum. Under starvation conditions, these amoebae signal each other via cyclic AMP, resulting in the propagation of spiral waves of chemical. The amoebae, which are chemotactic to the chemical, move up gradients of cyclic AMP, resulting in the formation of aggregations. The formation of aggregates seems to be a vital component of the Dictyostelium discoideum life cycle, as it appears to be necessary to enable the cells to differentiate into a spore type, which can survive harsh conditions.

In section 3, we studied a model for matrix alignment in wound healing. Alignment phenomena occur in a number areas, for example in fish schooling, insect swarming, and in the formation of bands of intercellular actin. These all occur as the result of entities signalling to each other and are therefore amenable to mathematical modelling.

In conclusion, mathematical modelling can be used as a tool to help understand phenomena across a broad range of disciplines within the life sciences. The role of a model is first, to exhibit the phenomena that are being modelled, then to make experimentally testable predictions. The outcome of these experiments can then be fed back into the model resulting in an improved model which can provide further predictions. This iterative process can only be accomplished in a genuinely interdisciplinary collaboration.

The life sciences are the source of an enormous number of novel, exciting and challenging mathematical and computational problems. Can mathematics be as influential in the life sciences as it has been in physics? Only time will tell.

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