A Local Activator-Inhibitor Model of Vertebrate Skin Patterns

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ABSTRACT

A model for vertebrate skin patterns is presented in which the differentiated (colored) pigment cells produce two diffusible morphogens, an activator and an inhibitor. The concentrations of these two substances at any point on the skin determine whether a pigment cell at that point will be colored or not. Computer simulations with this model show many realistic features of spot and stripe patterns found in vertebrates.

INTRODUCTION

The color patterns on vertebrate skin are of great importance to the survival of the organism because they are involved in camouflage, species identification, and warning patterns. The theoretical problem of the morphogenesis of these patterns is therefore of interest from an evolutionary point of view as well as being a fascinating mathematical problem in its own right.

Typical skin patterns are spots or stripes which are formed by specialized pigment cells (melanocytes). Innumerable variations of spot and stripe patterns are found in fish [2] and mammals [12]. The problem of how skin patterns are formed becomes a description of how the colored pigment cells are distributed on the embryonic skin.

The prevailing theoretical answer to this question is that pattern formation is governed by reaction-diffusion processes of the Turing type [1,8]. In this scheme, the uniformly distributed pigment cells produce two or more species of morphogen molecules which react with each other and diffuse in space to produce a pattern of concentrations with a characteristic wavelength. These morphogen concentration "prepatterns" then induce the differentiation of the pigment cells, producing a permanent pattern similar to the prepattern. The calculated patterns are dependent on initial and boundary conditions, and show many of the characteristic forms observed in vertebrates.

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The Turing model for skin patterns has not yet been tested experimentally, but evidence is accumulating from studies on cold-blooded vertebrates that there are several types of pigment cells which can interact with one another and change each other's properties [5,6,11]. This evidence suggests, contrary to the Turing model, that the intercellular interaction is local, possibly due to short-range diffusion of morphogen molecules or to direct cell contact. In this paper I explore an alternative to the Turing model which involves local cell interactions and which also gives rise to an interesting spectrum of pigment patterns.

THE MODEL

I propose an activator-inhibitor diffusion theory developed originally by Swindale [13] for the study of patterns in the visual cortex of the brain. As a simplified initial condition, I imagine on the early embryonic skin a uniform distribution of pigment cells, containing a mixture of differentiated (colored) cells (DCs) and undifferentiated cells (UCs). A simple mechanism for the production of this mixture might be a slow random process of differentiation in the UC cell population. Each DC produces an inhibitor morphogen which stimulates the dedifferentiation of other nearby DCs, and an activator morphogen which stimulates the differentiation of nearby UCs. The two substances are diffusible, with the inhibitor having the longer range. The UCs are passive and produce no active substances. The fate of each pigment cell, UC or DC, will be determined by the sum of the influences on it from all neighboring DCs.

The processes of production, diffusion, and decay of morphogens can be modeled by a generalized diffusion equation:

$$\frac{\partial M}{\partial t} = \nabla \cdot \mathbf{D} \cdot \nabla M - KM + Q. \tag{1}$$

Here $M = M(\mathbf{r}, t)$ is the morphogen (either inhibitor or activator) concentration, and the terms on the right are diffusion, first-order chemical transformation, and production, respectively.

Each DC produces at constant rate two morphogens, an activator $M^{(1)}$ and an inhibitor $M^{(2)}$, which diffuse away from their source and are uniformly degraded by the neighboring cells, according to Equation (1). The resulting steady-state distributions of the morphogens about a DC are shown schematically in Figure 1(a). Together, the two morphogens constitute a "morphogenetic field" $w(R)$, where R is the distance from the DC, which is "read" by nearby pigment cells in the skin. The "reading" process is modeled by assuming that the net activation effect found close to the DC is represented by a constant positive field value, and the net inhibition effect found further from the DC is represented by a constant negative field value.

This is shown in Figure 1(b). The activation region is a small circular area about the DC with a large constant positive field value. The inhibition region is the outer circular annulus with a small negative field value. The integrated field over the cells in the whole circular area must be close to zero in order to avoid the complete dominance of either activator or inhibitor.

This model is similar to inhibitor theories of patterns formation, for example of hair follicles in mammalian skin [3], or of leaf primordia on the shoot apex of a green plant [7]. However, pure inhibition theories are only capable of producing spatial patterns of pointlike structures. In our case, we need connected regions of differentiated pigment cells, and this requires short-range activation as well as long-range inhibition.

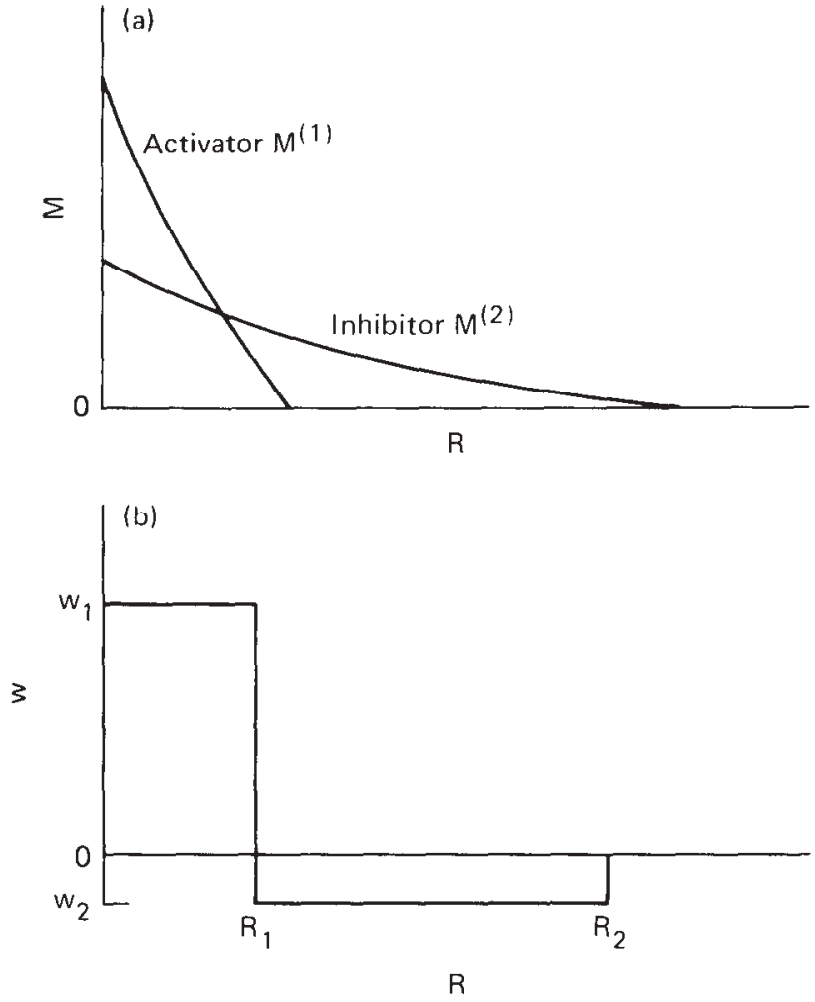

FIG. 1. A schematic illustration of the local activator-inhibitor model. In (a) the steady-state activator and inhibitor concentrations about a differentiated pigment cell are shown. The inhibitor has a longer range than the activator. In (b) the combined (field) effect of activator and inhibitor is modeled with constant positive and negative circular regions.

CALCULATIONS

The calculation begins by distributing DCs randomly on a rectangular grid of points representing pigment cells. Then for each grid point at position $\mathbf{R}$, the field values due to all nearby DCs at positions $\mathbf{R}_i$ are added up. If $\sum_i w(|\mathbf{R}-\mathbf{R}_i|) > 0$, then the point at $\mathbf{R}$ becomes (or remains) a DC. If $\sum_i w(|\mathbf{R}-\mathbf{R}_i|) = 0$, the point does not change state, and if $\sum_i w(|\mathbf{R}-\mathbf{R}_i|) < 0$, the point becomes (or remains) a UC. By simplifying the morphogenetic field as shown in Figure 1 and by discretizing the cell positions, I have converted a continuum model [Equation (1)] into a cellular automaton [14]. Cellular automata are very useful for computational purposes because they simplify the problem at hand while retaining the essential features required for exhibiting self-organization phenomena. This is justified by the observation that very nearly the same results are obtained [13] when $w(R)$ is a continuous function, as in Figure 1(a). The process of summing the morphogenetic fields and changing states for each grid point is repeated until the resulting pattern no longer changes. I find that five iterations suffice for convergence to a stable pattern, and that the general form of the final pattern is not sensitive to the initial DC distribution.

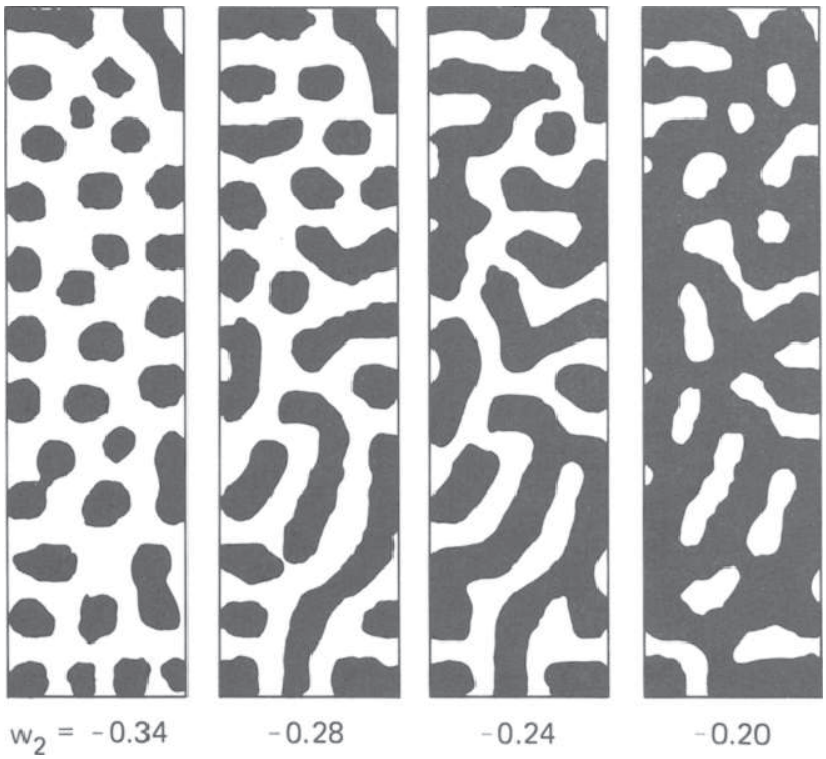

FIG. 2. Patterns produced with the activator-inhibitor model. The activation area has a radius of 2.30, and the inhibition area has an outer radius of 6.01. The activation field value w_1 is $+1.0$, and the inhibition field value w_2 is varied as indicated in the four examples. As inhibition is decreased (left to right), the spot pattern connects up into a pattern of stripes. Each panel is 25×100 in the arbitrary grid units.

One useful demonstration with the model is the close relationship of spot and stripe patterns. Many vertebrate species are spotted or striped, and some tropical fish genera show combinations of these patterns on the same individual [2]. Since it is unlikely that stripes and spots arise from wholly different mechanisms, a useful theory must be able to generate both patterns. This is done in Figure 2. Here the outer radius of the inhibitor area is 6.01, the radius of the activator area is 2.30, and the spacing between adjacent grid points is 1.0 in arbitrary units. The activator field value is fixed at 1.0, and the inhibitor field value is varied to produce different patterns. When the inhibitor is strong (Figure 2, $w_2 = -0.34$), the DCs cannot form connected masses, and instead form isolated spots. As the inhibitor weakens, the spots connect up with each other until well-developed stripes appear. With very strong inhibition, the pattern will consist of isolated DCs on an uncolored

FIG. 3. Pattern produced with an anisotropic activator-inhibitor model. The activator area is an ellipse ($x^2/a^2 + y^2/b^2 = 1$) with axes $a_1 = 2.30$, $b_1 = 1.38$, and the inhibitor area is an ellipse with axes $a_2 = 3.61$ and $b_2 = 6.01$. The panel is 60×100 in the arbitrary grid units.

background. With very weak inhibition, the pattern will be a solid mass of color. All of these patterns are found in the vertebrates.

The striping patterns in Figure 2 are isotropic, with no preferred direction, whereas in real skin patterns such as on the zebra, there usually is a preferred direction. Directionality can be introduced by assuming that the diffusion of activator and inhibitor are nonisotropic. This was indicated in Equation (1) by the tensor form of the diffusion constant. Anisotropy has been observed in the morphogenesis of pigment patterns in fish [11], and it is also consistent with the concept of polar transport [15], which has been used to explain the effects of tissue polarity in pattern formation. Thus in tissues showing polarity, we expect that the perpendicular components of the diffusion tensor will be unequal, i.e., $D_{xx} \neq D_{yy}$. In the model calculations, this can be introduced by changing the circular areas in the $w(R)$ field to ellipses. An example is shown in Figure 3. The inhibitor is polarized perpendicular to, and the activator parallel to, the stripes. The idea of preferential diffusion of morphogens in perpendicular directions is not new [4,9,16], but it does not have a clear biophysical explanation and must at present be considered only as an interesting hypothesis.

DISCUSSION

Both this model and the Turing reaction-diffusion model (actually consisting of a large class of specific chemical kinetic models) predict basic features of vertebrate skin patterns. In certain details, however, they are different. For example, the activator-inhibitor model pattern in Figure 3 shows both branching and termination of the colored stripes, features which arise from the random initial distribution of DCs, and which are also observed in zebra coat patterns. The Turing models studied to date [1,8] do not show these features, possibly because of the more deterministic nature of these models.

Although the suggested mechanisms of activation and inhibition in this paper are diffusion processes, this assumption is not necessary. The model when reduced to the morphogenetic field concept shown in Figure 1(b) is a simple logical algorithm involving on-off switching of cell differentiation according to a threshold variable. The variable need not be the concentration of a diffusible substance. It might instead have to do with direct cell contacts or with local elastic strains in the underlying tissues. The tissue polarity indicated in Figure 3 might have more to do with unidirectional macromolecular arrays than with anisotropic diffusion. I believe that the diffusion mechanism is the simplest explanation of the pigmentation process, but it is certainly not the only explanation.

Also, the model construct of a static random mixture of differentiated and undifferentiated pigment cells is an oversimplification. A more realistic model might allow the migration of pigment cells toward or away from other

pigment cells according to "attractive" or "repulsive" interactions. Finally, the assumption of only one type of pigment cell is also an oversimplification, since there are known to be several types [5]. Swindale's original model [13] in fact postulated two cell types. The usefulness of the model is not so much in its detailed assumptions, but rather in its logical structure. The fact that a model with a very simple logical structure can reproduce many of the observed features of a pattern strongly suggests that the actual pattern mechanism is also simple, and this is the principal conclusion to be drawn from the present work.

This model could be generalized to generate multicolored patterns, which are common in vertebrates. Also, the topology of striping patterns has been closely studied in connection with the problem of classifying fingerprints [10], and the formal similarity of the patterns on zebra skin and in fingerprints suggests that the morphogenetic mechanisms may be similar.

More detailed and realistic models of vertebrate skin patterns might best arise from experimental work specifically aimed at elucidating the mechanism which controls pigment-cell differentiation. Specifically, one would like to know whether the mechanism involves chemical waves on a uniform cellular substratum, or short-ranged interactions between pigment cells, or something altogether different. Once this is determined, a computer model can then be constructed to investigate how a color pattern emerges from the multicellular system.

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