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Lateral Induction by Juxtacrine Signaling Is a New Mechanism for Pattern Formation

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Many signaling molecules in epithelia are now known to function in a membrane-bound form, binding to receptors on immediately neighbouring cells. This "juxtacrine" mode of communication has been well studied in the case of lateral inhibition, where ligand binding at the cell surface downregulates ligand and receptor expression, and is known to generate spatial patterns with a wavelength of exactly two cells. However, recent evidence shows that a number of juxtacrine signals can lead to the opposite phenomenon of lateral induction. Here, we use mathematical modeling to show that such positive feedback, in combination with juxtacrine communication, provides a novel mechanism for the generation of spatial patterns, with wavelengths that vary with parameters and can be many cell lengths.

Key Words: **development; juxtacrine; lateral induction; pattern formation.**

INTRODUCTION

Fine-grained spatial patterns are a ubiquitous feature of epithelia in early animal development. An important mechanism for the generation of such patterns is the expression of neurogenic gene products, the prototype system being the ligand Delta in *Drosophila*, which binds to the receptor Notch on adjacent cells (Lewis, 1998; Muskavitch, 1994; Whitfield *et al.*, 1997). Ligand-receptor interactions such as Notch-Delta are known as juxtacrine: both ligand and receptor are anchored in the cell membrane, so that signaling occurs only between directly neighbouring cells (Bosenberg and Massagué, 1993). This type of signaling has been best studied for Notch-Delta in situations where high Delta expression in a cell downregulates Delta in its neighbours, via the receptors Notch on their surface (Lewis, 1996; Kimble and Simpson, 1997; Haddon *et al.*, 1998). This lateral inhibition has been shown to be a robust mechanism for the formation of spatial patterns: small differences in Notch/Delta expression are amplified by the lateral inhibition, leading to a large amplitude spatial pattern (Collier *et al.*, 1996). Detailed investigation of this pattern-forming process has shown that in all cases, the patterns have a wavelength of exactly two cells, with alternating high/low levels of Delta/Notch expression. Although patterns of this type are common in early animal development, longer wavelength patterns are also observed and cannot be attributed to lateral inhibition.

Recent evidence has shown that in some contexts, the Notch-Delta interaction can generate the opposite phenomenon of lateral induction, with ligand binding upregulating production of new ligand and receptor (de Celis and Bray, 1997; Huppert *et al.*, 1997; Lewis, 1998; Panin *et al.*, 1997). Such induction is well established for some other juxtacrine signals (Reilly and Melton, 1996), in particular TGFα and EGF binding to EGF-R (Clark *et al.*, 1985; Coffey *et al.*, 1987); these growth factors exist as extracellular, diffusible molecules, but are also active in their membrane-bound precursor forms (Brachmann *et al.*, 1989), with the latter dominant when the rate of cleavage is lower than that of decay, as is the case for TGFα (Massagué, 1990). It should be noted that recent evidence suggests that Delta may also exist in a cleaved, diffusible form (Qi *et al.*, 1999). Intuitively, lateral induction appears to be a mechanism leading to homogeneity within a tissue, and it has been widely dismissed as a pattern-forming mechanism. However, we show here that lateral induction is in fact a highly effective genera-

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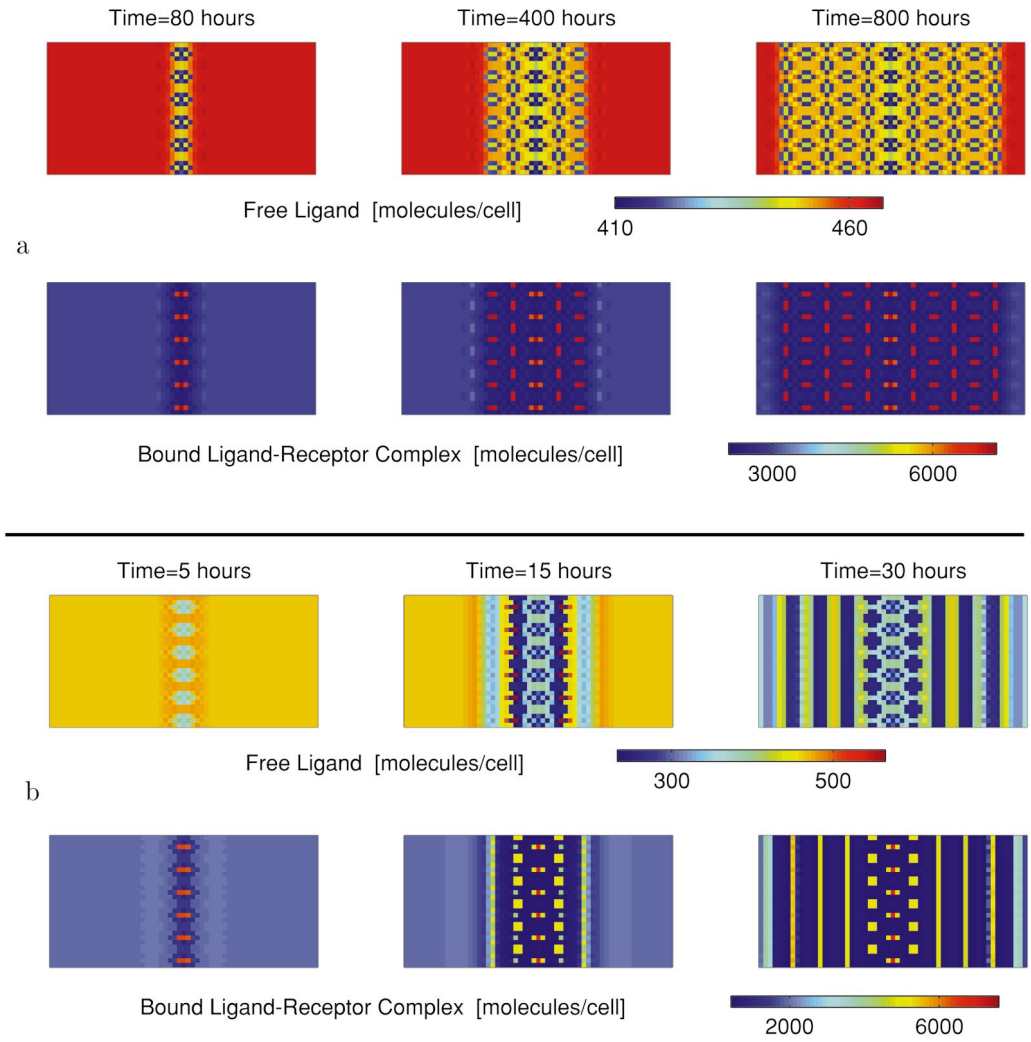

FIG. 1. Different types of spatial patterns in the juxtacrine signaling model [1], solved on a regular grid of cells. (a) Spots. We plot the densities of ligand and bound receptors on a 60×30 grid of cells. Free receptor densities (not shown) have a profile very similar to that for bound receptors. Initially (time zero) all cells are at a homogeneous equilibrium, except for a small perturbation along the midline. The solution is shown at three time points, to illustrate the temporal evolution of the pattern as it spreads across the domain from the initial perturbation. The parameter values are based on experimental data for binding of epidermal growth factor to its receptors (Waters *et al.*, 1990): specifically $k_a = 0.0003$ molecules^{-1} min^{-1}, $k_d = 0.12$ min^{-1}, $k_i = 0.019$ min^{-1}, $d_a = 0.006$ min^{-1}, $d_f = 0.03$ min^{-1}. The feedback functions are given by $P_a(b) = C_1 b/(C_2 + b)$, and $P_f(b) = C_3 + C_4^3 b^3/(C_5^3 + b^3)$, where $C_1 = 110$, $C_2 = 2500$, $C_3 = 90$, $C_4 = 7.4$, $C_5 = 5450$. (b) Stripes. The same initial conditions that gave rise to spots in part a can instead evolve to give stripes for different parameter values. This ability to generate spots or stripes highlights the flexibility of the patterning mechanism. The pattern develops significantly faster in this case than in Fig. 1a; this is simply due to the difference in parameters, which cause the uniform equilibrium to be more strongly unstable. The simulation details are the same as for Fig. 1a, except for $C_1 = 61$, $C_2 = 1000$, $C_3 = 30$, $C_4 = 7.7$, $C_5 = 3600$.

tor of spatial patterns in some contexts, with no restriction on pattern wavelength.

MATERIALS AND METHODS

Pattern formation by lateral induction was investigated using a mathematical model, which provides a representation of nearest neighbour ligand-receptor interactions in an epithelial sheet. The model is expressed in terms of the numbers of ligand molecules $a(x, t)$, free receptors $f(x, t)$, and bound receptor-ligand complexes $b(x, t)$ on the surface of a cell at time t and position x. We assume a generic kinetic scheme (Waters *et al.*, 1990) with association, dissociation, and receptor internalisation constants k_a, k_d, and k_i, respectively, giving the equations

$$\partial a/\partial t = -k_a a\langle f\rangle + k_d\langle b\rangle - d_a a + P_a(b)$$
$$\partial f/\partial t = -k_a\langle a\rangle f + k_d b - d_f f + P_f(b) \quad [1]$$
$$\partial b/\partial t = k_a\langle a\rangle f - k_d b - k_i b.$$

Here d_a and d_f are the decay rates of ligand and receptor, and P_a and P_f are increasing, saturating functions of b, representing the induction of ligand and receptor production by binding. The notation $\langle\ \rangle$ indicates an average over neighbouring cells; thus the receptors on the surface of a given cell may only be bound by ligand present on adjacent surfaces of neighbouring cells. We represent the epithelium as a regular array of identical square cells, with x = (i, j) a discrete variable indicating position in this array; then $\langle\ \rangle$ denotes an average over the four immediately neighbouring cells.

We used a simple forward Euler scheme to calculate solutions of this model, and linear analysis to predict the circumstances in which patterns should form.

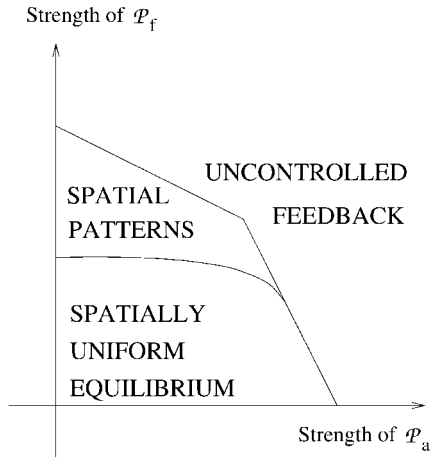

FIG. 2. An illustration of the dependence of model behaviour on the feedbacks in ligand and receptor production. This classification is determined by linear stability analysis of the homogeneous equilibrium, with the strengths of P_a and P_f measured by their slopes at the homogeneous equilibrium levels of bound ligand-receptor complexes b.

RESULTS

Numerical simulations of this model show that for appropriate parameter values, permanent spatial patterns do form in this system, consisting of either spots or stripes (Fig. 1). Here, a localised disturbance is applied along the midline of the domain to an otherwise uniform equilibrium state, initiating a pattern that spreads across the domain. The capacity to form patterns of both spots and stripes illustrates the flexibility of this pattern-generating system: note that in Fig. 1b, the one-dimensional symmetry of the striped pattern is not imposed initially.

The key regulators of model behaviour are the functions P_a and P_f, which represent the strength of upregulation in production of ligand and receptor, as induced by ligand-receptor binding. Calculation of the linear stability of spatially homogeneous equilibria (for details see Owen and Sherratt, 1998) shows that these functions determine which of three possible long-term behaviours occurs (Fig. 2). When the responses are very strong, an uncontrolled feedback loop is set up, causing both ligand and receptor numbers to increase until maximal expression is achieved in every cell. Lower upregulation can stabilise more moderate, spatially uniform ligand and receptor levels. However, the combination of low and moderate feedback in ligand and receptor expression respectively causes a homogeneous equilibrium to be stable to spatially homogeneous perturbations, but unstable to inhomogeneous perturbations, leading to spatial patterns.

The separation of the peaks depends crucially on the feedback strengths; numerical investigation demonstrates that increasing the strength of ligand production induces longer range patterns. Figure 3 shows the results of simulations in which the strength of receptor upregulation is kept fixed while the strength of ligand feedback is allowed to vary. This parameter variation gives rise to patterns with wavelengths of between 5 and 15 cells as ligand feedback is increased. The outcome of these numerical studies agrees qualitatively with our linear stability analysis, which gives a theoretical prediction for the wavelength expected to dominate in the solution of the model [1]. If the strength of receptor feedback is also increased then numerical results (not shown) indicate that the average wavelength decreases. Therefore, patterns with longer range wavelengths are generated by the strongest feedback in ligand production and the weakest feedback in receptor production that still enable patterns to evolve.

Pattern formation does not depend on particular initial conditions, and small random perturbations applied across a domain also evolve to patterns, usually of spots (Fig. 4a); these also have a characteristic wavelength, but with some irregularities. Crucially, this characteristic wavelength still varies with parameters and can be many cell lengths. This is confirmed in Fig. 4b, which shows a simulation with parameters which should give a much longer characteristic wavelength; this is indeed the case. In all cases the pattern consists of sharp peaks in the expression of free receptors and bound ligand-receptor complexes, separated by longer plateaus.

A detailed sensitivity analysis shows that the pattern formation mechanism is robust, with patterns relatively insensitive to small variations in the model parameters. Figure 5 illustrates the effect of varying each model parameter by ±20% from a fixed set of reference parameters, and with initial conditions of the form of small perturbations about a homogeneous equilibrium. We calculated the change in the mean wavelength and amplitude of the patterns and plotted their change relative to that in the parameter. Our results confirm the robustness of the patterning mechanism. In particular the mean wavelength of the pattern, which is its key feature, varies very little with

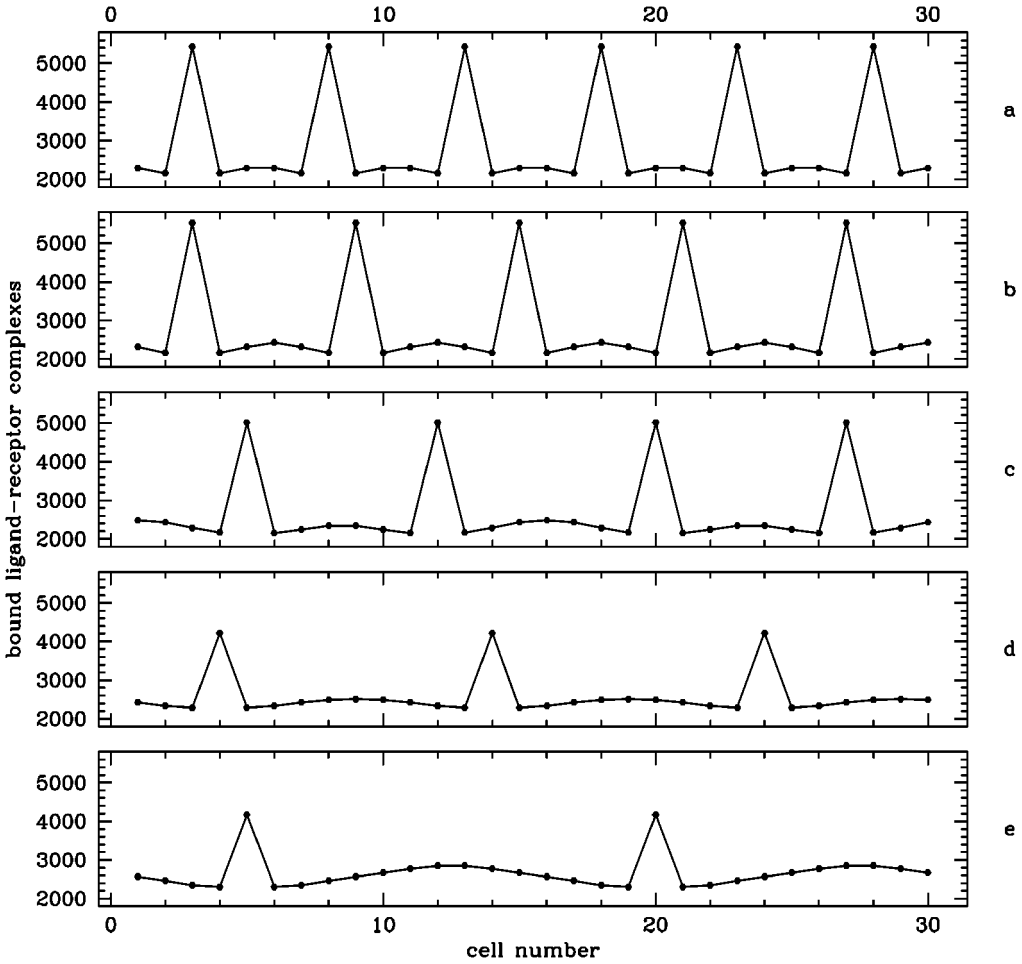

FIG. 3. Lateral induction gives rise to spatial patterns of longer wavelengths: five different simulations of the juxtacrine signaling model [1]. For brevity, we show only the density of bound-ligand receptor complexes. The distance between the peaks in bound receptors increases as the strength of the ligand production increases, the weakest feedback being in a and the strongest in e. Simulations were for a one-dimensional domain of 30 cells, with initial conditions of small random perturbations about the homogeneous equilibrium. Parameter values are as in Fig. 1 except that the ligand feedback function is given by $P_a(b) = C_1^m b^m/(C_2^m + b^m)$, where C_1 is determined by m, $C_2 = 2500$ and m varies in each simulation as follows: (a) 0.8, (b) 1.0, (c) 1.5, (d) 1.87, (e) 1.95. As m increases, the strength of ligand upregulation increases.

small parameter changes. Moreover, the patterns are robust to the removal of individual cells: if one of the cells with a peak in bound receptor number is removed, a new peak forms in one of the remaining cells (not illustrated). This further confirms the robustness of our patterning mechanism and may explain the experimental observation of new neuroblast formation following removal of cells already committed to the neuronal pathway (Technau *et al.*, 1998).

DISCUSSION

Our numerical simulation and analysis of a model for juxtacrine signaling demonstrate that lateral induction is an important mechanism by which patterns may form. Intuitively, patterning in this system arises via spatially localised positive feedback. Suppose that receptor expression is increased on one cell relative to its neighbours. This leads to additional binding of ligand to these receptors, and the positive feedback mechanism causes further receptor expression on the surface of this cell; it is this self-reinforcing process that generates the high peaks of free and bound receptor levels in the patterns. Free ligand expression will also increase somewhat on this cell, although the level remains relatively constant because of the weak feedback and the tendency of free ligand to bind to available receptors. However, on neighbouring cells, ligand expression is actually reduced, via binding to the high number of recep-

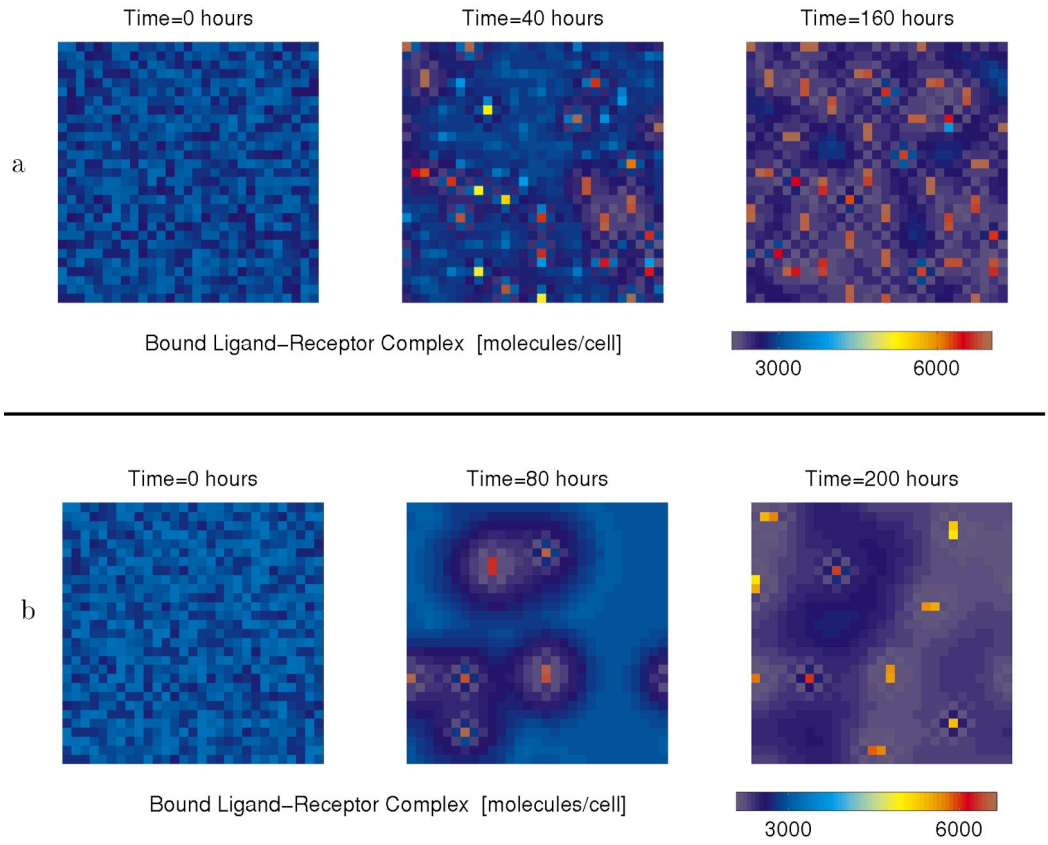

FIG. 4. Random initial distributions of ligand and receptor also give rise to patterns with a characteristic wavelength. (a) A spatial pattern generated from random perturbation of a homogeneous equilibrium applied throughout a 30×30 grid of cells. For brevity, only the density of bound ligand-receptor complexes is illustrated. The pattern has a characteristic wavelength, but with some irregularities. The parameter values are the same as for Fig. 1a. (b) For parameter values as in Fig. 3e, the characteristic wavelength arising from random initial conditions is much longer, as expected.

tors. Thus the initially increased receptor expression in one cell does not propagate widely, leading to the localised peaks in free and bound receptors observed in the patterns. More specifically, the sharpness of the peaks arises because it is not possible for a cell with very high receptor expression to have more than two neighbours with similarly high expression: the weak feedback in ligand production means that there is insufficient ligand to sustain binding to very high receptor numbers on more than two adjacent cells. Patterns with long wavelengths, such as those illustrated in Fig. 3, arise when receptor feedback is relatively low, with relatively high ligand feedback. In such cases, the self-reinforcement discussed above is less pronounced, and though it is strong enough to generate spatial patterns, these have longer wavelength and smaller amplitude. In such patterns, formation of additional peaks is prevented by relatively high ligand levels between the peaks, which inhibit the self-reinforcement mechanism.

The pattern formation mechanism thus depends on feedback that is relatively strong for receptor expression and weak for ligand—indeed, as indicated in Fig. 2, patterns can form with zero feedback in ligand expression. Quantitative comparisons of feedback effects in particular ligand-receptor systems are difficult with existing data, and for Notch-Delta at least, feedback activity is context-dependent; however, one recent study of *Drosophila* wing vein morphogenesis (Huppert *et al.*, 1997) indicates that Delta-Notch binding can induce Notch while inhibiting Delta, strongly suggesting that Delta-Notch can exhibit the conditions required for our patterning mechanism.

Spatial patterning in this system is a direct consequence of two key biological ingredients: juxtacrine signaling and positive feedback in receptor and ligand production. Nearest neighbour signaling has previously been implicated in alternating patterns (wavelength of two cells), but our demonstration of longer wavelengths and of both striped and spotted configurations shows that in combination with positive feedbacks, it is a quite general patterning mechanism. The particular feedback functions used here are only representative of the whole class of positive feedbacks, and

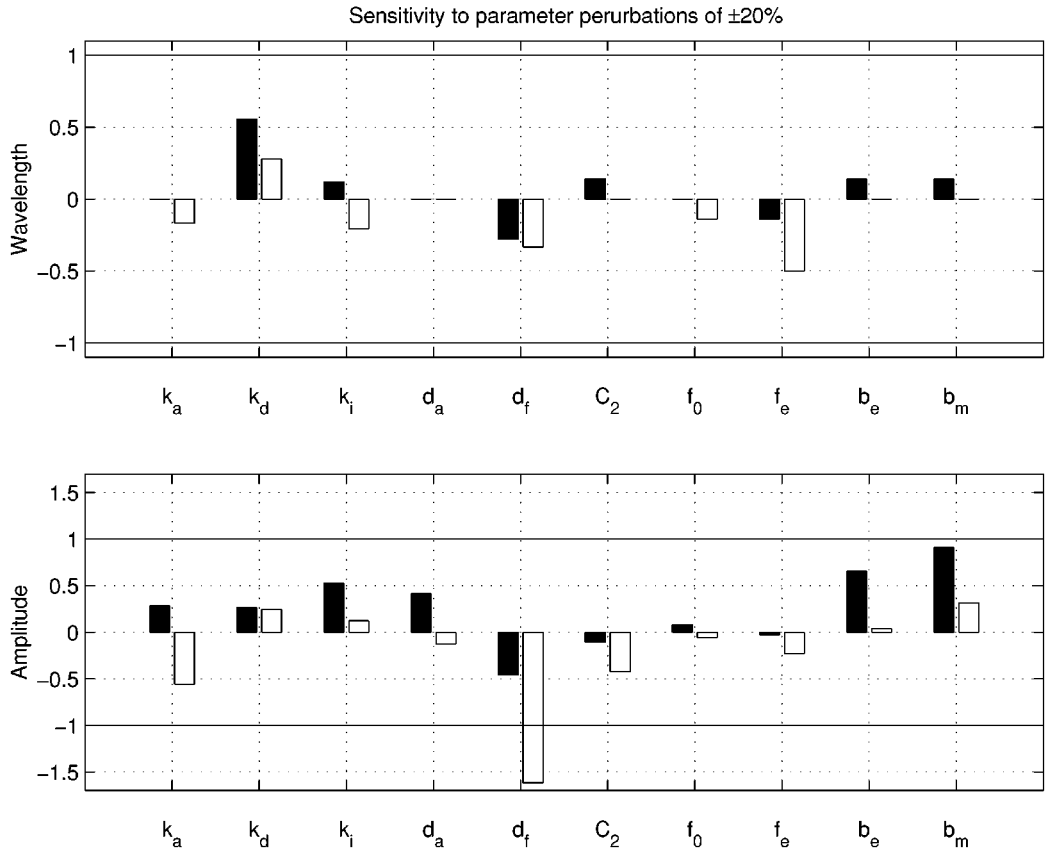

FIG. 5. Sensitivity analysis: Numerical simulations of the juxtacrine signaling model [1] were analysed for their sensitivity to model parameters. The measure of sensitivity is the percentage change in solution measure (mean wavelength or amplitude) divided by the percentage change in parameter. Thus a value of ± 1 indicates a change in output magnitude in equal proportion to the changed input. These results clearly demonstrate that the pattern wavelength, the key feature of any pattern, is highly robust. Simulations were for a one-dimensional domain of 100 cells, with initial conditions such that the whole domain is at the stable homogeneous equilibrium, except for the cell at the left hand boundary which was perturbed by + 10% from this value. This initiates a pattern, which was allowed to develop for 33.33 h and then analysed. Here we illustrate the results for each parameter varying by ± 20% from a set of reference values. This reference parameter set was: $k_a = 0.0003$ molecules^{-1} min^{-1}, $k_a = 0.12$ min^{-1}, $k_i = 0.019$ min^{-1}, $d_a = 0.006$ min^{-1}, $d_f = 0.03$ min^{-1}. The feedback functions are given by $P_a(b) = C_1 b/(C_2 + b)$, and $P_f(b) = C_3 + C_4^3 b^3/(C_5^3 + b^3)$, where $C_2 = 500$, and C_1, C_3, C_4, and C_5 are determined by the following biologically relevant values: receptor level in the absence of any ligand binding, $f_0 = 500$; normal steady-state free and bound receptor levels, $f_e = 1000$, $b_e = 1000$; maximum possible receptor expression, $b_m = 25500$.

we stress that our analysis does apply to this whole class. Moreover, we have shown that the mechanism is robust to small variations in the parameters governing ligand-receptor binding and feedback.

It is important to note that the striped patterns in Fig. 1b are not merely the consequence of initiation by a stripe. In fact, the initial conditions were a row of spots in an otherwise homogeneous domain. These do not give a spreading pattern of spots as in Fig. 1a, but instead generate a planar wave front which lays down a series of stripes. Additional simulations (not shown here) demonstrate that an initial perturbation with a strip of domain given random fluctuations also generates a striped pattern—in this case the stripes are not perfect, but nevertheless clearly recognisable. In a further test, we started with a perturbation in just one corner, which gave a series of concentric rings—typical of such initial conditions for stripe-forming mechanisms. Thus, the key feature here is that stripes do form without being trivially initiated by a stripe. A significant challenge for future research will be to determine under what conditions we expect to see spots or stripes.

There are a number of other theoretical mechanisms that have been proposed for the generation of spatial patterns in developmental biology. The theory of Turing (Turing, 1952; Meinhardt, 1982) shows that the reaction and diffusion of two or more chemical regulators of development, or morphogens, can give rise to spatial prepatterns in the concentration of those chemicals, which may then be translated

into patterns in cell differentiation or growth. Patterns in purely chemical systems have been demonstrated experimentally (Castets *et al.*, 1990; Maini *et al.*, 1997), but not in a biological context, and not with chemicals that have been identified as morphogens. This basic Turing scheme only allows sequential formation of the chemical prepattern and its interpretation by cells, but the inclusion of cell chemotaxis, and the contribution of the cells themselves to chemical production and degradation, allows the simultaneous generation of chemical and cellular patterns (Painter *et al.*, 1999). This type of pattern formation has also been demonstrated theoretically in the context of tumour growth (Owen and Sherratt, 1997). Mechanisms based upon mechanochemical interactions (Murray *et al.*, 1988) propose that the forces exerted by cells on their environment, be that other cells or some substratum, when combined with chemical regulation, can generate spatial patterns in cell density. Applications of this theory to developmental biology include the generation of feather primordia (Oster *et al.*, 1983) and the formation of cartilage condensations (Oster *et al.*, 1985). "Neural" schemes introduce the key property of local activation and long-range inhibition as a direct consequence of the complex neuronal dendritic structure, but are only applicable in very specific contexts (Ermentrout and Cowan, 1979; Swindale, 1980). The juxtacrine mechanism described here has key differences from all these mechanisms: as well as depending on local interactions rather than diffusion, it does not require differences in signal ranges between activator and inhibitor morphogens. Cell movement is not necessary, although its incorporation into our theoretical scheme would be feasible and is an important challenge for future research. Moreover, the biological interpretation of juxtacrine patterns is immediate: the mechanism highlights individual cells without dependency on arbitrary thresholds, and with the pattern expressed directly in terms of the biologically significant property of receptor occupancy.

Our theoretical model is not intended to be a detailed representation of any given developmental situation: rather, it is a generic representation of processes that may contribute to a number of morphogenetic phenomena. Two candidates for such phenomena are the chick feather array and the *Drosophila* wing. In the former case, Notch and Delta have recently been implicated in the initiation of the feather bud pattern, with a regular pattern of Notch developing from the midline prior to epithelial placode formation (Crowe *et al.*, 1998), in a manner strongly reminiscent of Fig. 1a. Many other signaling molecules are of course involved in this process, and recent evidence implicates both tissue interaction (Noramly and Morgan, 1998) and reaction-diffusion (Jung *et al.*, 1998) processes; our results suggest that lateral induction may be an additional key patterning mechanism. In the Drosophila wing, Delta is expressed along developing veins, with sharp bands of Notch expression at the vein-intervein boundaries (de Celis *et al.*, 1997), in a pattern very similar to that illustrated in Fig. 1b; this system has recently been shown to be subject to positive feedback (de Celis and Bray, 1997; Huppert *et al.*, 1997; Panin *et al.*, 1997). Other processes are known to be involved in wing patterning, in particular the interaction between vestigial and scalloped (de Celis, 1999; Bray, 1999), and the secreted growth factor Dpp (de Celis, 1997); again, our results suggest that lateral induction may be an additional key mechanism.

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