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Waves and propagation failure in discrete space models with nonlinear coupling and feedback

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Abstract

Many developmental processes involve a wave of initiation of pattern formation, behind which a uniform layer of discrete cells develops a regular pattern that determines cell fates. This paper focuses on the initiation of such waves, and then on the emergence of patterns behind the wavefront. I study waves in discrete space differential equation models where the coupling between sites is nonlinear. Such systems represent *juxtacrine* cell signalling, where cells communicate via membrane bound molecules binding to their receptors. In this way, the signal at cell j is a nonlinear function of the average signal on neighbouring cells. Whilst considerable progress has been made in the analysis of discrete *reaction-diffusion* systems, this paper presents a novel and detailed study of waves in *juxtacrine* systems.

I analyse travelling wave solutions in such systems with a single variable representing activity in each cell. When there is a single stable homogeneous steady state, the wave speed is governed by the linearisation ahead of the wave front. Wave propagation (and failure) is studied when the homogeneous dynamics are bistable. Simulations show that waves may propagate in either direction, or may be pinned. A Lyapunov function is used to determine the direction of propagation of travelling waves. Pinning is studied by calculating the boundaries for propagation failure for sigmoidal and piecewise linear feedback functions, using analysis of 2 active sites and exact stationary solutions respectively. I then explore the calculation of travelling waves as the solution of an associated n -dimensional boundary value problem posed on $[0, 1]$, using continuation to determine the dependence of speed on model parameters. This method is shown to be very accurate, by comparison with numerical simulations. Furthermore, the method is also applicable to other discrete systems on a *regular* lattice, such as the discrete bistable reaction-diffusion equation.

Finally, I extend the study to more detailed models including the reaction kinetics of signalling, and demonstrate the same features of wave propagation. I discuss how such waves may initiate pattern formation, and the role of such mechanisms in morphogenesis.

Key words: Bistable, Delta-Notch, Discrete Space, Juxtacrine, Pinning, Propagation Failure

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1 Introduction

The development of spatial organisation is a fundamental requirement for the construction of every multicellular organism, from fruit flies to humans. A collection of cells must be able to arrange themselves in some way to form organs, limbs, digits, and so on. A key component of this process of organismal development is the determination of cell fate, whereby cells adopt a particular program of gene activation. Cell fates are regulated by a variety of mechanisms, typically mediated by the production and transport of signalling molecules which induce a response by binding to specific sites. Whilst experimentalists have been able to identify a large number of such proteins and their targets, it is difficult to determine how they act in concert to generate appropriate structures.

Mathematical and theoretical approaches have a long history in the effort to unravel this complex web of regulatory pathways. An important early contribution was made by Turing [1,2], who showed that chemicals can react and diffuse in such a way that spatial patterns of concentration are established, consequently specifying cell fate. In contrast, Wolpert proposed that positional information is encoded by a gradient in morphogen concentration, which could be established by the diffusion of morphogen from a fixed source [3]. A number of potential morphogens which act in this fashion have been identified, but recent research indicates that direct diffusion alone may not be able to set up appropriate gradients due to the binding of morphogen to its membrane receptors [4]. On the other hand, the same theoretical study shows that the interaction of different forms of receptor may release bound morphogen, allowing gradient formation [4]. Recent work also suggests that the details of receptor processing (rather than interaction) can allow the establishment of gradients by a diffusive mechanism [5]. A variety of other mathematical approaches have also been proposed [6,7]. A common feature is that the majority of models do not take account of the intrinsically discrete nature of cells. There is much evidence that a crucial role is played by direct signalling from a cell to its neighbour via membrane-bound proteins, or juxtacrine signalling [8,9]. Such systems have the advantage that they are relatively well characterised experimentally—a number of key proteins and their receptors have been identified [10,11]. On the other hand, the analysis of such systems presents considerable mathematical challenges due to their spatially discrete nature.

Many developmental processes involve a wave of initiation of pattern formation, for example the movement of the morphogenetic furrow in *Drosophila* retinal development, behind which a uniform cell layer is transformed into a regular pattern that determines cell fates [12]. In this paper I focus on the initiation of such waves, and then on the possibility of patterns emerging behind

the wavefront.

The first model to consider juxtacrine signalling was formulated in terms of the activity of a single protein (Delta) and its receptor (Notch) [13], incorporating a negative feedback loop termed lateral inhibition. Models have also been developed that more accurately reflect the elementary events of proteins binding to receptors on neighbouring cells [14,15]. It has been shown that such models with positive feedback can generate patterns [15,16]. Similar models with positive feedback have also been studied [17], where the focus is on signal ranges (see also [18]).

In Section 2 I introduce a simplified model for a juxtacrine cell relay, based upon that first studied by Monk [17]. In that paper, graded signals established by a fixed perturbation at a boundary were studied, and compared to signals given by a diffusive mechanism. In addition, it is noted that travelling fronts may also propagate signals over long distances, but the direction of waves, their speed, and the possibility of propagation failure is not addressed [17]. In Section 3 I show that when the homogeneous dynamics have a single stable steady state, the speed of such waves is governed by the linearisation about the wave front—specifically there is a minimum wave speed, and numerical simulations suggest that biologically relevant initial data give rise to waves with that speed.

The main focus of this paper is then on bistable systems. Bistability is a more likely scenario for signal propagation, since waves which spread into a region at an *unstable* steady state (as is the case when linear analysis is valid) may be dominated by the effects of random fluctuations in initial data. When the system is bistable, small perturbations ahead of (and behind) the wave front will die out, and not significantly affect wave propagation (unless there is an instability to patterned perturbations—see Section 5). Page *et al* [19] briefly consider the wave speed when the feedback is a step function with threshold v^* , and a delay is also included. They derive an expression for the speed of waves, which shows that waves may move in either direction, and that zero speed waves are only possible for a single value of v^* . In Section 4 I consider more general feedbacks, and construct a Lyapunov function which is used to show that the direction of waves is determined by an integral condition similar to that for diffusive models—even though in the relay model considered here the local dynamics and coupling are not separate. This approach also indicates how *pinned* solutions arise—stationary fronts correspond to local minima of the Lyapunov function. I go on to construct stationary solutions for specific cases, and demonstrate their agreement with numerical simulations. Travelling wave solutions are calculated in a novel way by noting that the advanced and retarded terms in the travelling wave equation may be dealt with by considering a vector of variables v_j defined on $[0, 1]$, where $u(\xi \pm 1) = v_{j \pm 1}$, and boundary conditions ensure continuity. This technique is also applicable to the

discrete bistable reaction diffusion equation which has been extensively studied previously [20–23]. In Section 5 I demonstrate the behaviours outlined for the simple relay model in a more detailed model which includes ligand-receptor binding. As well as forward and reverse waves, this system also exhibits pattern formation, and the interaction between waves and patterns is studied. These results and directions for future work are discussed in Section 6.

2 Juxtacrine cell relay

I consider the following model for juxtacrine communication in a string of cells, where the signal U_j decays with rate δ , and is generated in response to the average signal of neighbouring cells:

$$\frac{dU_j}{dT} = -\delta U_j + f\left(\frac{U_{j-1} + U_{j+1}}{2}\right), \quad j \in \mathbb{Z}, \quad U_j \in \mathbb{R}. \quad (1)$$

$f(U)$ is monotonically increasing, with $f(0) = 0$, so that $U_j \equiv 0$ is a homogeneous (inactive) steady state, and there are either one or two positive roots of $U = f(U)$. The largest of these is denoted by U^{max} , and the rescalings $u = U/U^{max}$ and $t = \delta T$ then give the dimensionless system

$$\frac{du_j}{dt} = -u_j + f\left(\frac{u_{j-1} + u_{j+1}}{2}\right), \quad (2)$$

where $f(0) = 0$, and $f(1) = 1$.

In particular, I consider two cases. The first case is $f'(0) > 1$, so that $u \equiv 0$ is unstable to homogeneous perturbations, and one positive steady state $u \equiv 1$ exists (and is stable)—here I expect waves of activity ($u = 1$) spreading into inactive regions ($u = 0$). The second case is when $f'(0) < 1$ so that there are two positive steady states, $u = \hat{u} < 1$ and $u = 1$, the larger of which is stable—here I expect waves connecting $u = 0$ to $u = 1$, with the direction dependent on the nonlinearities.

Numerical evidence (not shown) suggests that initial data converges to travelling wave solutions in which each cell follows the same temporal trajectory subject to a delay which determines the speed of propagation. Simulations were carried out with a finite number of cells, N , and initial conditions with $u_j = 1$ for $1 \leq j \leq N/2$, and $u_j = 0$ otherwise (boundary conditions, which have no significant effect on wave propagation provided the number of cells is sufficiently large, were $u_0 = u_1$ and $u_{N+1} = u_N$). Thus forward waves take cells from $u_j = 0$ to $u_j = 1$, and introducing the travelling wave co-ordinate

$\xi = j - ct$, with $u_j(t) = u(j - ct) = u(\xi)$:

$$-c \frac{du}{d\xi} = -u(\xi) + f\left(\frac{u(\xi - 1) + u(\xi + 1)}{2}\right) \quad (3)$$

with

$$\lim_{\xi \rightarrow -\infty} u(\xi) = 1, \quad \lim_{\xi \rightarrow \infty} u(\xi) = 0. \quad (4)$$

Travelling wave solutions now correspond to heteroclinic connections between $u = 1$ and $u = 0$. Linearising about a steady state u^* , and seeking solutions $\tilde{u}(\xi) = \bar{u} \exp(\lambda \xi)$ gives

$$1 - c\lambda = f'(u^*) \cosh(\lambda). \quad (5)$$

Similarly to the situation with travelling waves in reaction diffusion equations, the wave speed may or may not be determined by this linear analysis. For example, when $f'(0) > 1$, $u = 0$ is unstable, and travelling waves connecting to $u = 1$ are similar in nature to those for the Fisher equation [6]. The above dispersion relations clearly give a pair of real eigenvalues for $c \geq c_{min}$, which determines the minimum speed of travelling waves. However, in the bistable case, $f'(0) < 1$, and there are real roots for all values of the wave speed c . This is analogous to bistable reaction-diffusion equations, and we expect a unique wave speed to be determined by the nonlinearities.

3 Monostable kinetics

An example of f which gives a single stable state at $u_j \equiv 1$ is

$$f(u) = \frac{(\beta + 1)u}{\beta + u}, \quad (6)$$

which has $f'(0) = (\beta + 1)/\beta > 1$. It is straightforward to see that non-negative initial data for (2) must remain non-negative for all time, and hence travelling wave solutions cannot have an oscillatory approach to $u = 0$. The above dispersion relation (5) at $u^* = 0$ has two equal real roots (corresponding to the minimum wave speed) for some minimum value of c (No real roots when $c = 0$, two negative real roots as $c \rightarrow \infty$, so there is a minimum c for real roots at $c = c_{min}$). The same argument applies to the case of planar waves propagating in a direction normal to the cell face, in arrays of square cells, where the average is now $(u_{j-1} + 2u_j + u_{j+1})/4$, and the amended dispersion relation is

$$1 - c\lambda = f'(u^*) \frac{1 + \cosh(\lambda)}{2}. \quad (7)$$

Figure 1 shows that the predictions of this linear analysis are accurate, and that planar waves in arrays move more slowly than waves in a string of cells.

Note that these minimum speeds are for initial conditions with a step from 1 to 0. Initial conditions which decay slowly ahead of the wave front are expected to have faster speeds, but are not considered relevant.

Fig. 1. Analytically and numerically calculated speeds for (2) with $f(u) = (\beta + 1)u/(\beta + u)$. The solid curve and asterisks is for a string, and the dashed curve and crosses is for an array, with average signal $(u_{j-1} + 2u_j + u_{j+1})/4$. Simulations used MATLAB's ODE solver `ode45` for 400 cells and 100 time units, with speeds calculated every 10 time units and the final speed plotted. The predicted speeds are given by solving (5) for a string of cells, and (7) for an array, subject to $u^* = 0$ and there being two equal roots for λ .

These predictions extend to the case where the feedback is delayed (for example due to the time taken for protein synthesis). The model (2) becomes

$$\frac{du_j}{dt} = -u_j + f(\langle u_j(t - T) \rangle), \quad (8)$$

which gives the amended dispersion relation (for a string)

$$1 - c\lambda = f'(u^*)e^{c\lambda T} \cosh(\lambda). \quad (9)$$

Again, if $f'(0) > 1$ then there are no real roots when $c = 0$, and two negative real roots as $c \rightarrow \infty$. Provided initial data is non-negative on $[-T, 0]$, solutions must remain non-negative for all time, and hence there must be a minimum wave speed when (9) has two equal real roots. Similar arguments apply for waves in an array of cells.

4 Bistable kinetics

When the homogeneous kinetics are bistable ($f'(0) < 1$) the direction of waves is determined by the full nonlinear system. I will concentrate on the case of a string of cells from now on, but the methods outlined here are straightforward to apply to planar waves in arrays of cells.

Consider the example:

$$f(u) = \frac{(\beta^m + 1)u^m}{(\beta^m + u^m)}, \quad m > 1, \quad (10)$$

which has $f'(0) = 0$. Figure 2 shows contours of wave speed as a function of m and β , calculated from numerical simulations of the model (2). Clearly there is a region of pinned fronts which separates regions of forward and reverse waves. The dash-dotted line, which lies in the pinning region, indicates the

Fig. 2. Wave speed for the relay model (2) with Hill function feedback $f(u)$ given by (10). Numerical simulations were for 100 cells and 1000 time units, and the speed was calculated by measuring the time between successive cells crossing 0.5. Contours are shown at $c = \pm 0.02, \pm 0.05, \pm 0.2, \pm 0.4$ and ± 0.6 , with dashed lines indicating negative speeds. The dash-dotted line indicates when the integral condition $I_f = 0$ is satisfied, where I_f is given by (11). The heavy lines are the boundaries for stationary solutions as calculated by considering 2 active sites in Section 4.2.

condition $I_f = 0$, where

$$I_f = \int_0^1 f(u) - u \, du. \quad (11)$$

It appears that the sign of this integral determines the direction of waves if they are not pinned. In the next subsection I construct a Lyapunov function

which justifies this claim.

4.1 Lyapunov Function

Discrete reaction diffusion systems can typically be written as gradient systems since the potential for the discrete diffusion operator is well known, and that for the local reaction term is simple to evaluate by direct integration. Because the relay model (2) has non-local terms in the nonlinear feedback, it is not possible in general to find a potential function. However, I will show that a Lyapunov function for (2) is given by

$$V(\mathbf{u}) = \sum_j \frac{(u_{j+1} - u_j)^2}{4} + G(u_j) - G(u^*), \quad (12)$$

where $\mathbf{u} = \{u_j : j \in \mathbb{Z}\}$,

$$G(u) = \int_0^u f^{-1}(u) - u \, du, \quad (13)$$

and u^* is the homogeneous steady state which corresponds to the global minimum of $G(u)$. It is a simple matter to check that the minima of V are defined by

$$0 = \frac{u_{j+1} + u_{j-1}}{2} - f^{-1}(u_j), \quad (14)$$

which corresponds precisely to steady states of (2).

The minima of $G(u)$ are 0 and 1, and $G(0) = 0$, so that if $G(1) < 0$, $u^* = 1$ is the global minimum, and otherwise $u^* = 0$ must be (except for equality). Using the fact that $f(0) = 0$ and $f(1) = 1$, it follows that

$$G(1) = \int_0^1 f^{-1}(u) - u \, du = - \int_0^1 f(u) - u \, du = -I_f, \quad (15)$$

either by a simple geometric argument (reflections preserve area), or by the substitution $v = f^{-1}(u)$ and integration by parts.

Hence the global minimum of V is $u_j = 0$ if $I_f < 0$, and $u_j = 1$ if $I_f > 0$. Inhomogeneous states cannot be *global* minima, since the squared term in V is always positive for such states.

To see that $\dot{V} \leq 0$:

$$\begin{aligned} \dot{V}(\mathbf{u}) &= \nabla V \cdot \dot{\mathbf{u}} \\ &= \sum_j \left[f^{-1}(u_j) - \frac{u_{j+1} + u_{j-1}}{2} \right] \left[f \left(\frac{u_{j+1} + u_{j-1}}{2} \right) - u_j \right]. \end{aligned} \quad (16)$$

Since f is monotonic increasing, if $f(a) \geq b$ then $a \geq f^{-1}(b)$. It follows that for each term in the above series, the product is either of two terms of opposite sign, or zero, so clearly $\dot{V} \leq 0$. Thus V is indeed a Lyapunov function for (2), with (homogeneous) global minima determined by the sign of I_f , and inhomogeneous stationary states (pinned solutions) must correspond to a set of local minima of V which are identical up to a shift in index. The loss of such local minima corresponds to the so-called “depinning transition”, when solutions must evolve to the global minimum. It follows that the direction of waves with $c \neq 0$ is determined by I_f , with

$$\begin{cases} c > 0 & \text{if } I_f > 0, \\ c < 0 & \text{if } I_f < 0. \end{cases} \quad (17)$$

For diffusive discrete bistable systems, the potential formulation has been used to predict depinning by perturbing analytical solutions by a shift, and determining the loss of energy minima (and therefore stationary fronts) as a function of that shift [23]. However, this method relies upon an analytical expression for solutions which is not currently available for models of the form (2). The analytical solution used by Kladko *et al.* [23] is constructed as a perturbation of the solution to the continuum reaction diffusion system, but here there is no equivalent continuous model. The continuation of previously known steady solutions (in the zero coupling limit) has also been proved using the implicit function theorem [24], but the juxtacrine relay model cannot be considered as a network of weakly coupled bistable units. In the next subsection I analyse the depinning transition by considering a finite number of active sites in the wave front.

4.2 Stationary fronts with n active sites

Conditions for stationary fronts in discrete *diffusive* bistable systems have been derived by considering a limited number of “active sites”, where only those sites feel nonlinearity, and all other sites are close enough to the homogeneous steady states to be in the linear regime [23,25], or to be considered as at those states [20]. With Hill functions (10) there is no linear approach of u_j to zero, rather, all sites experience nonlinearity unless they are at zero. Thus I consider two active sites, u_0 and u_1 , where u_1 is fully nonlinear, and u_0 is related to all points further left by linearisation:

$$\begin{cases} u_j = 1 + Ae^{\lambda_1 j} & \text{for } j = -\infty \dots 0, \\ u_0 = f\left(\frac{1 + Ae^{-\lambda_1} + u_1}{2}\right), \\ u_1 = f\left(\frac{u_0}{2}\right), \\ u_j = 0 & \text{for } j = 0 \dots \infty, \end{cases} \quad (18)$$

where λ_1 is the positive root for λ of (5) with $u^* = 1$ and $c = 0$, and hence $e^{-\lambda_1} = (1 - \sqrt{1 - f'(1)^2})/f'(1)$.

Matching at $j = 0$ means that $u_0 = 1 + A$, and stationary solutions are given by

$$u_0 = f\left(\frac{1 + (u_0 - 1)e^{-\lambda_1} + f(u_0/2)}{2}\right). \quad (19)$$

This may have 3 roots or 1 root, and transitions between these cases correspond to the loss of stationary fronts through a fold bifurcation. These bifurcations were tracked for the case of Hill function feedback (10), as the exponent m and threshold β varied. The results are plotted on Figure 2, indicating very good agreement with the results of numerical simulations of the full system. The same approach with 3 active sites gives almost identical results (not shown). In both cases the agreement is not so good for small m , where the pinning region is very small and the number of active sites is larger.

This idea may be extended to piecewise linear bistable kinetics given by

$$f(u) = \begin{cases} 0 & \text{if } u < \beta \\ \alpha(u - \beta) & \text{if } \beta \leq u \leq \beta + \frac{1}{\alpha} \\ 1 & \text{if } u > \beta + \frac{1}{\alpha}. \end{cases} \quad (20)$$

Stationary states consisting of finite sequences $\{u_i\}$, connecting $u = 1$ to $u = 0$, require the following to be satisfied:

$$\begin{aligned} \frac{1 + u_1}{2} &\geq \beta + \frac{1}{\alpha} \\ u_j &= \alpha \left(\frac{u_{j-1} + u_{j+1}}{2} - \beta \right) \quad \text{for } 1 \leq j \leq n \\ \frac{u_n}{2} &\leq \beta \end{aligned} \quad (21)$$

For example, a one step stationary solution must satisfy

$$\frac{\alpha}{2(\alpha + 2)} \leq \beta \leq \frac{2\alpha + \alpha^2 - 4}{2\alpha(\alpha + 2)}, \quad \text{subject to } \alpha \geq 2, \quad (22)$$

and 2 step stationary solutions satisfy

$$\frac{\alpha^2}{4(\alpha + 2)} \leq \beta \leq \frac{-\alpha^3 + 4\alpha + 4\alpha^2 - 8}{4\alpha(\alpha + 2)}, \quad \text{subject to } \sqrt{2} \leq \alpha \leq 2. \quad (23)$$

These regions are shown in Figure 3, as well as contours of wave speed calculated from simulation of the ODEs (2) with (20). Regions for 3 and 4 step solutions are also shown, valid for $-1 + \sqrt{5} \leq \alpha \leq \sqrt{2}$ and $2\sqrt{3}/3 \leq \alpha \leq -1 + \sqrt{5}$ respectively. These analytical boundaries for stationary solutions agree well

with simulations. Regions for n -step stationary solutions with $n > 4$ are easy to calculate, but do not give rise to the relatively simple expressions seen for $n \leq 4$. The regions are disjoint except for single points of intersection which

Fig. 3. Wave speed for the relay model (2) with piecewise linear $f(u)$ given by (20). Contours are shown at $c = \pm 0.02, \pm 0.05, \pm 0.2, \pm 0.4, \pm 0.6$ and ± 0.8 , with dashed lines indicating negative speeds. The heavy curves indicate the boundaries of regions with n -step stationary solutions, determined analytically from (21) for $n = 1, 2, 3, 4$ (from right to left). For larger n the regions get progressively smaller (not shown).

coincide to so-called *anomalous pinning* [20], i.e. there is no pinning region as such, but rather a pinning point, which is analogous to continuous space systems. Anomalous stationary solutions are continuous functions of the index, which means that they must be degenerate minima of the Lyapunov function. For example, at $\alpha = 2, \beta = 1/4$, there is a family of stationary solutions given by $u_j = U(j + \gamma)$ where $\gamma \in \mathbb{R}$ is an arbitrary shift and

$$U(x) = \begin{cases} 1 & \text{if } x < 0 \\ 1 - x/2 & \text{if } 0 \leq x \leq 2 \\ 0 & \text{if } x > 2. \end{cases} \quad (24)$$

4.3 Travelling waves as a boundary value problem

The calculation of n -step stationary solutions suggests a way to numerically compute trajectories of the travelling wave equations for waves with $c \neq 0$. Given the travelling wave equation for a string of cells (3), I consider $z \in$

$[0, 1]$, $k \in \mathbb{Z}$ and identify $u(\xi) = u(k+z)$ with $v_k(z)$, and $u(\xi \pm 1)$ with $v_{k \pm 1}(z)$. Truncating the range of k to be a finite number of segments, n , and using a linear approximation at either end:

$$\begin{aligned} -c \frac{dv_1}{dz} &= -v_1 + f\left(\frac{1 - (1 - v_1)e^{\lambda_1} + v_2}{2}\right) \\ -c \frac{dv_k}{dz} &= -v_k + f\left(\frac{v_{k-1} + v_{k+1}}{2}\right) \quad \text{for } 2 \leq k \leq n-1 \\ -c \frac{dv_n}{dz} &= -v_n + f\left(\frac{v_{n-1} + e^{-\lambda_0}v_n}{2}\right) \end{aligned} \quad (25)$$

on $z \in [0, 1]$ with boundary conditions

$$v_k(1) = v_{k+1}(0) \quad \text{for } 1 \leq k < n \quad (26)$$

and either

$$v_n(1) = \varepsilon, \quad \frac{dv_n}{dz}(1) = \lambda_0 v_n(1); \quad (27)$$

or

$$v_1(0) = 1 - \varepsilon, \quad \frac{dv_1}{dz}(0) = \lambda_1(1 - v_1(0)). \quad (28)$$

Here, $\varepsilon > 0$ is a small parameter which represents the expectation that for a sufficiently large number of segments the solution should be close to the homogeneous fixed points ($u^* = 0$ and $u^* = 1$) at either end. The derivative conditions ensure compatibility with the linearisation at those fixed points, where λ_0 and λ_1 are determined by (5) at $u^* = 0$ and $u^* = 1$ respectively. The extra boundary condition determines the wave speed. I used numerical simulations to find an initial solution and wave speed for a particular parameter set, and AUTO 97 [26] was then used to continue solutions as feedback parameters and wave speed varied.

This approach is very effective for calculating travelling wave solutions for a range of feedback forms and parameter sets. I have considered Hill function feedback (10), piecewise linear feedback (20) and

$$f(u) = \frac{\tanh(\alpha(u - \beta)) - \tanh(-\beta)}{\tanh(\alpha(1 - \beta)) - \tanh(-\beta)}, \quad (29)$$

which also satisfies $f(0) = 0$, $f(1) = 1$.

All these cases give wave speeds and profiles in excellent agreement with simulations of the full system. Figure 4 demonstrates this for the case of Hill function feedback (10), showing the variation of wave speed with threshold β when the exponent $m = 10$. Propagation failure is clearly indicated (speeds as low as $c = 0.001$ are resolved), and agrees with the evidence of numerical simulations (indicated by asterisks) and the analysis of 2 active sites described

Fig. 4. Wave speed for the relay model (2) with Hill function feedback $f(u)$ given by (10) and exponent $m = 10$. The solid lines show the speed calculated by numerical continuation with AUTO 97 [26] for the boundary value problem (25,26), with (27) for forward waves, and (28) for reverse waves, with $n = 10$ and $\varepsilon = 0.0001$. The asterisks show sample wave speeds calculated from simulations of the ODE system (2), taken from Figure 2. The two large points indicate the boundaries of the pinning region as determined by the analysis of 2 active sites in section 4.2.

above (depinning transition indicated by points). Figure 5 shows an example of the travelling wave profile calculated in this way. The profile is mapped to the time domain by shifting segment v_k from $z \in [0, 1]$ to $\xi = z + k \in \mathbb{R}$, scaling the travelling wave co-ordinate by $-c$, and then applying a shift in order to compare profiles with those from direct numerical simulations of the full ODEs. Formally, if s_j is the relevant shift then $u_j(t)$ for $t \in [s_j, s_j + n/c]$ is given by

$$u_j \left(\frac{n+1-k-z}{c} + s_j \right) = v_k(z), \quad \text{for } k = 1, \dots, n \text{ and } z \in [0, 1]. \quad (30)$$

For a forward wave like that illustrated in Figure 5, all sites move from $u = 0$ to $u = 1$ as the wave propagates. The excellent agreement is clear in this figure, as the difference between profiles from boundary value solutions and full simulations is barely distinguishable.

In the case of forward waves with piecewise linear feedback given by (20), the boundary conditions (27) may be replaced with

$$u_n(1) = 0, \quad \frac{u_n(0)}{2} = \beta. \quad (31)$$

Fig. 5. Wave profile for the relay model (2) with Hill function feedback $f(u)$ given by (10), exponent $m = 10$ and $\beta = 0.474478$. The dashed line shows the temporal evolution of a particular cell as the wave moves forward, from direct numerical simulations. All cells follow this profile. The solid line shows the travelling wave solution calculated by numerical continuation with AUTO 97 [26] for the boundary value problem (25,26,27), with $n = 10$ and $\varepsilon = 0.0001$. The wave speed is $c = 0.0483486$, and the profiles are superimposed by applying (30) with the shift $s_j = 15.4$. They are so close as to be barely distinguishable visually.

To see why, consider travelling waves from 1 to 0, with $c > 0$ and that are non-increasing. If there exists an interval $[a - 1, a]$ on which $0 < u(\xi) < \beta$ then, since $f(u) = 0$ if $u \leq \beta$,

$$\frac{du}{d\xi}(a) = \frac{u(a) - f\left(\frac{u(a-1) + u(a+1)}{2}\right)}{c} = \frac{u(a)}{c} > 0, \quad (32)$$

which contradicts monotonicity. Thus, travelling wave solutions must reach zero at some finite value of ξ , with zero derivative, which is guaranteed by the above condition (31). A similar argument for reverse waves shows that (28) can be replaced by

$$u_1(0) = 1, \quad \frac{u_1(1) + 1}{2} = \beta + \frac{1}{\alpha}, \quad (33)$$

which ensures that the wave trajectory leaves $u = 1$ with zero derivative. Figure 6 shows an example of the trajectory calculated with these amended boundary conditions. The match between numerical simulation and this boundary value approach is again very good. The dependence of speed on parameters, and the depinning transition, are also well resolved (not shown).

Fig. 6. Wave profile for the relay model (2) with Piecewise linear feedback $f(u)$ given by (20), and $\alpha = 4, \beta = 0.3322425$. The dashed line shows a simulation trajectory, and the solid line that calculated by numerical continuation with AUTO 97 [26] for (25,26,31), with $n = 10$. The wave speed is $c = 0.1$, and the profiles are superimposed by applying (30) with the shift $s_j = 3.95$.

The same technique also works very well for the discrete bistable equation (with cubic nonlinearity for convenience)

$$\dot{u}_j = D(u_{j-1} - 2u_j + u_{j+1}) + u_j(1 - u_j)(u_j - a). \quad (34)$$

Travelling waves and propagation failure in this system have been studied extensively, including different forms of nonlinearity [20–23]. Numerical techniques have been developed which consider the advanced and retarded terms in the travelling wave equation as forcing terms, allowing the iterative use of standard boundary value solvers [21]. These approaches typically require the introduction of a small diffusive term in order to specify enough boundary conditions. In addition, methods are currently being developed to deal with such functional differential equations directly [27]. The results presented here complement these methods by showing that existing tools can also be used without modification, and without the introduction of diffusive terms (AUTO 97 allows the overspecification of boundary conditions provided additional parameters can be varied [26]—the wave speed is just such an additional parameter). The corresponding ordinary differential boundary value problem for

travelling wave solutions is:

$$\begin{aligned}
-c \frac{du_1}{dz} &= D(e^{-\lambda_-} u_1 - 2u_1 + u_2) + u_1(1 - u_1)(u_1 - a) \\
-c \frac{du_k}{dz} &= D(u_{k-1} - 2u_k + u_{k+1}) + u_k(1 - u_k)(u_k - a) \quad \text{for } 2 \leq k \leq n-1 \\
-c \frac{du_n}{dz} &= D(u_{n-1} - 2u_n + 1 - (1 - u_n)e^{\lambda_+}) + u_n(1 - u_n)(u_n - a)
\end{aligned} \tag{35}$$

on $z \in [0, 1]$, with boundary conditions (26), and (27) when $c > 0$ or (28) when $c < 0$, where

$$c\lambda_l - 2D(\cosh \lambda_l - 1) + f'(l) = 0, \quad \text{for } l = 0, 1. \tag{36}$$

Figure 7 shows a comparison between numerical simulation and the travelling wave profile calculated in this way with AUTO 97 [26]. Again, a very close match is achieved, and the dependence of wave speed on parameters is well resolved. Other combinations of boundary conditions also work, for example

Fig. 7. Wave profile for the discrete bistable reaction diffusion equation (34) with $D = 0.1$ and $a = 0.45505$. The dashed line shows the temporal profile of a particular cell as the wave moves forward. All cells follow this profile. The solid line shows the profile calculated by numerical continuation with AUTO 97 [26] for the boundary value problem (35,26,27), with $n = 20$ and $\varepsilon = 10^{-6}$. The wave speed is $c = 0.001$, and the profiles are superimposed by applying (30) with the shift $s_j = 70$. Ten sections are shown (3 to 12) with vertical lines indicating their boundaries.

enforcing compatibility with the linearisation at $z = 0$ and $z = 1$.

5 Ligand Receptor model

The following dimensionless model represents the binding of ligand to receptors on neighbouring cells, and the consequent feedback. The full details of the model derivation can be found in [14,15]. a_j represents the number of signal molecules (ligands), f_j the number of free receptors, and b_j the number of bound receptors on cell j . $P_a(b_j)$ and $P_f(b_j)$ are the feedback terms, which depend on the number of bound receptors on a cell. The remaining terms represent binding, dissociation, and decay:

$$\frac{da_j}{dt} = -k_a a_j \langle f_j \rangle + k_d \langle b_j \rangle - a_j + P_a(b_j) \quad (37)$$

$$\frac{df_j}{dt} = -k_a \langle a_j \rangle f_j + k_d b_j - d_f f_j + P_f(b_j) \quad (38)$$

$$\frac{db_j}{dt} = k_a \langle a_j \rangle f_j - k_d b_j - k_i b_j, \quad (39)$$

and $\langle u \rangle = (u_{j-1} + u_{j+1})/2$, corresponding to a string of cells. I assume that $P_a(0) = 0$, so the model has an unstimulated (homogeneous) steady state ($a_j = 0, f_j = f_0, b_j = 0$), where $f_0 = P_f(0)/d_f$. P_a and P_f are monotonic, increasing functions of b . Typically there will be one or two additional homogeneous steady states, determined by $A_0 = P'_a(0)$ which also determines the stability of the unstimulated state.

The jacobian at $(0, f_0, 0)$ is

$$M = \begin{pmatrix} -k_a f_0 - 1 & 0 & k_d + A_0 \\ -k_a f_0 & -d_f & k_d + F_0 \\ k_a f_0 & 0 & -k_d - k_i \end{pmatrix}. \quad (40)$$

Clearly $\lambda_1 = -d_f$ is an eigenvalue of M , and the remaining two are those of the 2×2 matrix given by the corner elements. Thus, standard conditions on the trace and determinant mean that the unstimulated state is stable if

$$-k_a f_0 - 1 - k_d - k_i < 0 \quad (41)$$

and

$$k_a f_0 (k_i - A_0) + k_d + k_i > 0. \quad (42)$$

When $k_a f_0 A_0 > k_a f_0 k_i + k_d + k_i \geq 0$, $(0, f_0, 0)$ is unstable, there is typically one other steady state $(a_e, f_e, 1)$ which is stable, and waves correspond to those

analysed in Section 3, with speed governed by linear analysis. Otherwise, both $(0, f_0, 0)$ and $(a_e, f_e, 1)$ are stable, separated by an unstable state—in these circumstances bi-directional propagation and pinning are to be expected.

I choose Hill function feedbacks of the form

$$P_a(b) = \frac{C_2^m b^m}{(C_2^m + b^m)}, \quad P_f(b) = C_3 + \frac{C_4^n b^n}{(C_5^n + b^n)}, \quad (43)$$

and for convenience I fix the kinetic parameters, the unstimulated state, the level of free receptors at the stable stimulated state, and the threshold for receptor feedback:

$$k_a = 100, d_f = 3, k_d = 10, k_i = 2, f_0 = 0.3, f_e = 1, C_5 = 1.5 \quad (44)$$

These values are based on those used in previous studies of Transforming Growth Factor- α binding to its receptor [14]. However, the phenomena illustrated here are by no means confined to these particular choices.

Given that these parameters are specified, the threshold for ligand feedback, C_2 , determines a_e , C_1 , C_3 and C_4 as follows:

$$a_e = \frac{(k_d + k_i)b_e}{k_a f_e}, \quad C_1^m = (k_i b_e + a_e) \frac{C_2^m + b_e^m}{b_e^m}, \quad (45)$$

and

$$C_3 = d_f f_0, \quad C_4^n = (k_i b_e + d_f f_e - C_3) \frac{C_5^n + b_e^n}{b_e^n}. \quad (46)$$

I then let C_2 , m and n vary to illustrate the different possibilities.

Linearising about $(0, f_0, 0)$ and looking for travelling wave solutions proportional to $\exp \lambda(j - ct) = \exp \lambda \xi$, gives nontrivial solutions for $\det(M + c\lambda I) = 0$, where M is given by (40). Expanding about the second column gives the dispersion relation:

$$D(c, \lambda) = (k_a f_0 + 1)(k_d + k_i) - c\lambda(k_d + k_i + k_a f_0 + 1) + c^2 \lambda^2 - k_a f_0 \cosh \lambda(k_d \cosh \lambda + A_0) = 0. \quad (47)$$

Similarly to the relay model, if $k_a f_0 A_0 > k_a f_0 k_i + k_d + k_i$ there are only real roots for $c \geq c_{min}$, where c_{min} is determined by solving (47) subject to $\partial D(c, \lambda)/\partial \lambda = 0$, which ensures a double root. Based upon experience with similar systems (such as the continuous space Fisher equation), I expect “sharp front” initial conditions to give waves with this minimum speed, and this is supported by numerical simulations, as illustrated in Figure 8.

Fig. 8. Simulation of the ligand-receptor signalling model (37) with Hill function feedbacks given by (43), showing progression of the wave front at a speed determined by linear analysis, and much slower propagation of pattern behind the wave front. Only the bound receptor level, b_j , is shown— f_j has a similar profile, while the variation in a_j is similar but smaller in amplitude. The minimum speed predicted by the dispersion relation (47), derived from linear analysis, is 6.37 compared to a simulation speed of 6.24. The simulation was for 200 cells and 30 dimensionless time units, with $m = 1$, $n = 2$ and $C_2 = 1$, and the other parameters are as given in the text by (44,45,46). Simulations for much longer times approach the predicted speed of 6.37, for example at $t = 120$ with 1000 cells the simulation speed is 6.34. The pattern is not a boundary effect, and also continues to propagate.

The model (37) also supports pattern formation in arrays of square cells when the local average is $\langle u \rangle = (u_{j-1} + 2u_j + u_{j+1})/4$ [14–16,28]. A simple extension shows that the average for a string used here supports the same pattern-forming bifurcation, and this is apparent some way behind the wavefront in Figure 8. These previous investigations only addressed pattern formation as a bifurcation from the homogeneous stimulated steady state, and not the establishment of the stimulated state in the first place. The relative speeds at which the front moves and patterns develop will to a large extent determine the efficacy of such waves as inducers of pattern.

When $A_0 = 0$, for example whenever $m > 1$ in (43), the unstimulated state is stable, and the local dynamics are bistable. Thus, the speed and direction of travelling waves will be determined by the nonlinearities. In particular, waves in either direction are expected, and possibly pinning. This is illustrated in Figure 9, with $m = 20$ and $n = 1$ giving a relatively wide pinning region. For this choice of parameters patterns do not form behind the wave front.

Fig. 9. Wave speeds calculated from numerical simulations of the ligand-receptor model (37) as the threshold C_2 varies, illustrating pinning and reversal. Speeds were calculated by measuring the delay between crossings of a_j through $a_e/2$, and continuing until subsequent delays changed by less than 0.1%. $m = 20, n = 1$, and the feedback terms and other parameters are as given in the text by (43,44,45,46).

When patterns do form, bistability allows for the wave speed to be tuned to be similar to the speed of pattern propagation into the stimulated state which is left behind the wave front. Figure 10 shows such an example—this would be an ideal mechanism for laying down a regular developmental pattern. More importantly, bistability means that the unstimulated state would persist even with random fluctuations in initial conditions.

6 Discussion

I have demonstrated that the relay model (2) exhibits travelling wave solutions whose speed is governed by linear analysis when the homogeneous dynamics have a single stable steady state, and activity always propagates into inactive regions. In contrast, when the system is bistable, linear analysis cannot predict the wave speed, and the direction of waves also remains to be determined. By constructing a Lyapunov function I have shown that an integral condition on the feedback function determines the wave direction, in a similar manner to bistable reaction diffusion equations. I then studied the cases when local minima of the Lyapunov function exist, which correspond to *pinned* solutions. Using ideas from the study of reaction-diffusion systems [20,23], stationary fronts were approximated by considering a finite number of active sites. When

Fig. 10. Simulation of the ligand-receptor model (37), showing progression of the wave front when the system is bistable, and the pattern behind the wave front propagates at a similar speed. Note that $b = 0$ ahead of the wave, and f_j and a_j are not shown for the reasons outlined in the legend to Figure 8. The parameters were $m = 2$, $n = 3$, $C_2 = 0.3374$, and other details as given in the text by (43,44,45,46).

the feedback is of Hill function type (10) two active sites are sufficient, and the loss of fixed points through saddle-node bifurcations corresponds to the so-called *de-pinning transition*. This approximation proves to be very accurate across a range of Hill function exponents, which characterise the strength of feedback. A similar approach can be applied to the case of piecewise linear feedback functions (20). Of further interest is the application of AUTO 97 [26] to continue solutions to the travelling wave equation (3) in terms of an associated finite dimensional boundary value problem. This technique accurately tracks the speed of travelling waves as parameters vary, and is applicable to other systems defined on a regular lattice, such as the discrete bistable reaction diffusion equation [22]. Finally, I demonstrated these features of wave propagation and failure in the ligand-receptor relay model (37), as well as their interaction with a pattern forming instability of the activated state behind the wave front.

There are a number of interesting directions for future research suggested by this work. A natural extension is to consider different orientations of plane waves in different lattices (e.g. square and hexagonal). A diagonally propagating plane wave in a square lattice corresponds exactly to waves on a string, but other directions may be possible. Other work on diffusive systems includes directional dependence explicitly in the development of the travelling wave problem [21].

Another interesting question concerns the restriction to monotonic feedback

functions, particularly with respect to the construction of a Lyapunov function. Local Lyapunov stability of homogeneous states to inhomogeneous perturbations can still be established by relaxing this assumption in favour of monotonicity in a neighbourhood of the fixed points (which is required in any case for stability to homogeneous perturbations). Global stability, and hence the direction of waves, would not follow because of the existence of regions between the two locally stable states in which the Lyapunov function (12) is not defined. It remains a challenge to prove the directional dependence for more general feedback functions.

The inclusion of temporal delays, for example due to signal transduction and protein synthesis, also presents important questions. Page *et al* [19] derive an expression for the speed of forward waves for the relay model (2) on a string, when the feedback is a step function of the delayed local average:

$$\frac{du_j}{dt} = -u_j + H\left(\frac{u_{j-1}(t - \sigma) + u_{j+1}(t - \sigma)}{2} - \beta\right), \quad (48)$$

where σ is the delay, H is the Heaviside function, and β is the threshold for feedback. Their expression is easily extended to waves in either direction, so the speed of waves in this system is:

$$|c| = \frac{1}{\sigma - \ln(1 - 2\beta)}. \quad (49)$$

This indicates that the wave speed is zero if and only if $\beta = 1/2$, independent of the delay, and there is only a pinning *point* in this case. This agrees precisely with the analysis in this paper for the case of piecewise linear feedback—as can be seen from (22), as the slope $\alpha \rightarrow \infty$ the pinning range collapses exactly to the point $\beta = 1/2$. Although delays cannot affect the existence of pinned states (which are of course stationary), they will affect wave speeds when $c \neq 0$. In addition, in more complex models with negative feedback terms, delays may lead to oscillatory behaviour.

Wearing *et al* [16] showed that linear analysis would predict the onset of patterning in the juxtacrine system (37), but that linear predictions of solution properties such as wavelength were not borne out in the full nonlinear system. In particular, random initial data typically leads to irregular pattern. Nonlinear analysis has also been used to study patterns in small arrays of cells [28], but it is still not clear which modes should dominate in larger systems. Plahte [29] has also noted this discrepancy in related models, and presents some nonlinear analysis based upon the assumption of switch-like feedbacks—i.e. $m, n \rightarrow \infty$ in (43). The initiation of pattern by travelling waves in the bistable case presents a mechanism for the establishment of regular pattern, even when the initial “receptive-field” is subject to random perturbations. This robustness is an important feature for effective developmental pattern-

ing. However, an open question still remains as to the resulting wavelength. Further avenues of investigation for the ligand-receptor model include the calculation of pinning regions using the analysis of a small number of active sites; the application of the numerical techniques outlined here; and a study of the interaction of pinning, wave reversal and pattern formation.

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