

Supplementary Material for Wave-pinning and cell polarity from a bistable reaction-diffusion system

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1 Model Comparisons

We concentrate here the three systems to compare:

Wave-pinning (WP)

$$\frac{\partial a}{\partial t} = b \left(k_0 + \frac{\gamma a^2}{K^2 + a^2} \right) - \delta a + D_a \frac{\partial^2 a}{\partial x^2}, \quad (1a)$$

$$\frac{\partial b}{\partial t} = -b \left(k_0 + \frac{\gamma a^2}{K^2 + a^2} \right) + \delta a + D_b \frac{\partial^2 b}{\partial x^2}. \quad (1b)$$

Local excitation global inhibition (LEGI)

$$\frac{\partial A}{\partial t} = k_a S(t, x) - k_{-a} A, \quad (2a)$$

$$\frac{\partial I}{\partial t} = D \frac{\partial^2 I}{\partial x^2} + k_I S(t, x) - k_{-I} I, \quad (2b)$$

$$\frac{\partial R}{\partial t} = k_R A (R_T - R) - k_{-R} I R. \quad (2c)$$

Activator depleted substrate model (ASDM)

$$\frac{\partial a}{\partial t} = b \left(\frac{sa^2}{1 + sa^2} \right) - r_a a + D_a \frac{\partial^2 a}{\partial x^2}, \quad (3a)$$

$$\frac{\partial b}{\partial t} = b_b - b \left(\frac{sa^2}{1 + sa^2} \right) - r_b b + D_b \frac{\partial^2 b}{\partial x^2}. \quad (3b)$$

1.1 The LEGI model

In Eqs. 2, A is the activator, I is the inhibitor and R is the response element, and $S(t, x)$ is the external stimulus (1, 2). For a time-invariant stimulus such as $S(t, x) = (c_0 + c_1 x)$, a (unique) steady state value can be computed (1). The response to constant, spatially uniform $S = c_0$ (i.e. for $c_1 = 0$) is independent of S . To generate Fig 1, we first set $S = c_0$ to obtain the steady state levels, and then used transient stimuli described in the Appendix of our paper (e.g., $S = c_0 + c_1 x$), together with parameter values $k_R = k_{-R} = 1$, $k_a = k_{-a} = 2$, $k_I = k_{-I} = 1$, $R_T = 1$, $D = 10$. To represent the removal of stimulus we reset the value of S to c_0 .

In Figure 1, we demonstrate prototype responses of the LEGI model to the same repertoire of stimuli used in our wave-pinning tests. As seen in Fig. 1(a), a transient stimulus of the left edge of a cell, k_S^{loc} . causes a transient response in R at $t = 20$, but that response decays rapidly after the signal is turned off.

(Note return to homogenous distribution of R by $t = 200$). The same phenomenon is observed in Fig. 1(b) in response to a transient graded stimulus, k_S^{grad} . A direct result of the LEGI’s passive “readout” property, a model cell rapidly shifts polarity in response to gradient reversal, demonstrated in Fig. 1(c). However, a spatially noisy stimulus (“perturbed rest state”) fails to produce spontaneous polarization, regardless of its amplitude. This is illustrated in Fig. 1(d), and stems from earlier comments about the absence of a pattern-forming mechanism in the LEGI model.

Eqs. 2 have a unique spatially homogeneous steady state A_s, I_s, R_s when $S = c_0$. As shown in Fig. 3, the LEGI model has an increasing response to stronger gradients, without a threshold. When a stimulus is first turned on, the initial time behaviour before inhibition kicks in is approximated by $\gamma \approx k_R A_s$ (units of seconds).

1.2 The ASDM system

For Eqs. 3, typical parameter values, $s = 0.004, s_a = 0.1, b_a = 0, r_a = 0.004, b_b = 0.006, r_b = 0, D_u = 0.002, D_v = 0.4$ were kindly suggested by Prof. H. Meinhardt (personal communication), who also noted that r_b can be set to zero with no loss of functionality. With these parameters, the spatially uniform steady state of the system, a stable spiral, occurs at $u = 1.5, v = 0.81667$. It is easy to check that this set of parameters satisfy the conditions for Turing pattern formation on a periodic domain as assumed in most simulations of cell polarity by Meinhardt.

To choose a set of parameters for this system that would permit a reasonable comparison of behaviours to be made to the WP model, we scaled the system so that rates of diffusion match those of the active and inactive Rho proteins, as in our wavepinning model (since these parameters can be reasonably determined from known biology.) Scaling time by a factor of 25 leads to the new set of parameters $s = 0.1, r_a = 0.1, r_b = 0$ (units s^{-1}), $b_b = 0.15$ (conc/s), $s_a = 0.1$ (conc), $D_u = 0.05, D_v = 10$ (units of $\mu\text{m}^2/\text{s}$). The parameter s_a is not changed by this rescaling, as it has units of $[\text{concentration}]^{-2}$. This set of parameters is ideally suited to a periodic domain, as it leads to unstable wavenumbers of the form $q = n\pi/L$ for $n = 1, 2, 3$, implying that not only the polar pattern, but others with up to 2 peaks could occur. By adjusting the slow diffusion to $D_u = 0.1\mu\text{m}^2/\text{s}$, while retaining all other values, we found that the system was even better suited to a no-flux 1D domain. It has identical rates of diffusion as our wavepinning model and is thus suitable for numerical comparisons. Our final choice for parameters was consequently $s = 0.1, r_a = 0.1, r_b = 0, b_b = 0.15, s_a = 0.1, D_u = 0.1, D_v = 10$.

The requirement that a polar pattern can be excited (wavenumber of the form $q_1 = n\pi/L$ for $n = 1$ on a 1D domain of length $L = 10\mu\text{m}$ with no-flux boundaries) imposes strict constraints on rate constants. The resulting system was consistent with polar patterns on this 1D domain, but the mode $n = 2$ was also Turing unstable, and so occasionally a higher mode (with two peaks, one at each edge) would also appear. Observe that rates s, r_a are one order of magnitude slower than the corresponding rates γ, δ in the wave-pinning model. This choice was not arbitrary. Rather, it was a requirement for Turing instability of Eqs. 3 as explained in Section 3.3 of our paper.

Stimuli were applied in two ways, either by adding $k_S^{\text{loc}}, k_S^{\text{grad}}$, etc. to the term in large braces in Eqs. 3, or by setting $s = S(t, x) = k_S^{\text{loc}}, k_S^{\text{grad}}$. Similar results were obtained for both methods. Supplementary Figure 2 illustrates the distinct temporal and spatial behaviours of the ASDM mechanism tested with the same repertoire of stimuli in these ways. Panels (a,b) show that polarity evolves in response to both localized and graded transient stimuli, $k_S^{\text{loc}}, k_S^{\text{grad}}$. Qualitative features of the response are distinct from those of wavepinning (Fig 2a,b in the paper): first, in the substrate-depletion model, the relative chemical levels at the two “ends” of the cell ($x = 0$ vs $x = L$) change gradually, taking many tens of seconds to create an appreciable “macroscopic” polarization. By $t = 40\text{s}$, the polarity is still weak. By $t = 120\text{s}$, the polarity response begins to approach its maximal amplitude. By comparison, in wavepinning, a very fast initial response creates a strong chemical difference between the cell ends (by $t = 20$ or earlier) and later the propagating activation front moves further into the cell. Second, a comparisons of panels (c) in Supplementary Figure 2 and Fig. 2 in the paper shows that polarity generated by the ASDM system tends to “freeze” once created, and fails to respond by reversing when the stimulus gradient is reversed, unlike the wave-pinning model. (Generically, a third intermediate with longer time-constant is assumed to inhibit the activator and unfreeze the system in chemotactic models, e.g. (3).) Finally, comparison of the sensitivity of the two models to spatially noisy initial conditions (Panels d in the two figures) shows that ASDM is highly sensitive to signals of arbitrarily

low amplitude (related to its Turing instability). By comparison, response in the wavepinning model is “triggered” only by stimuli above some threshold. In response to random initial conditions, both models occasionally produce a non-polar pattern, with either more than one peak (ASDM), or a peak in the center of the domain (WP) that is a metastable state.

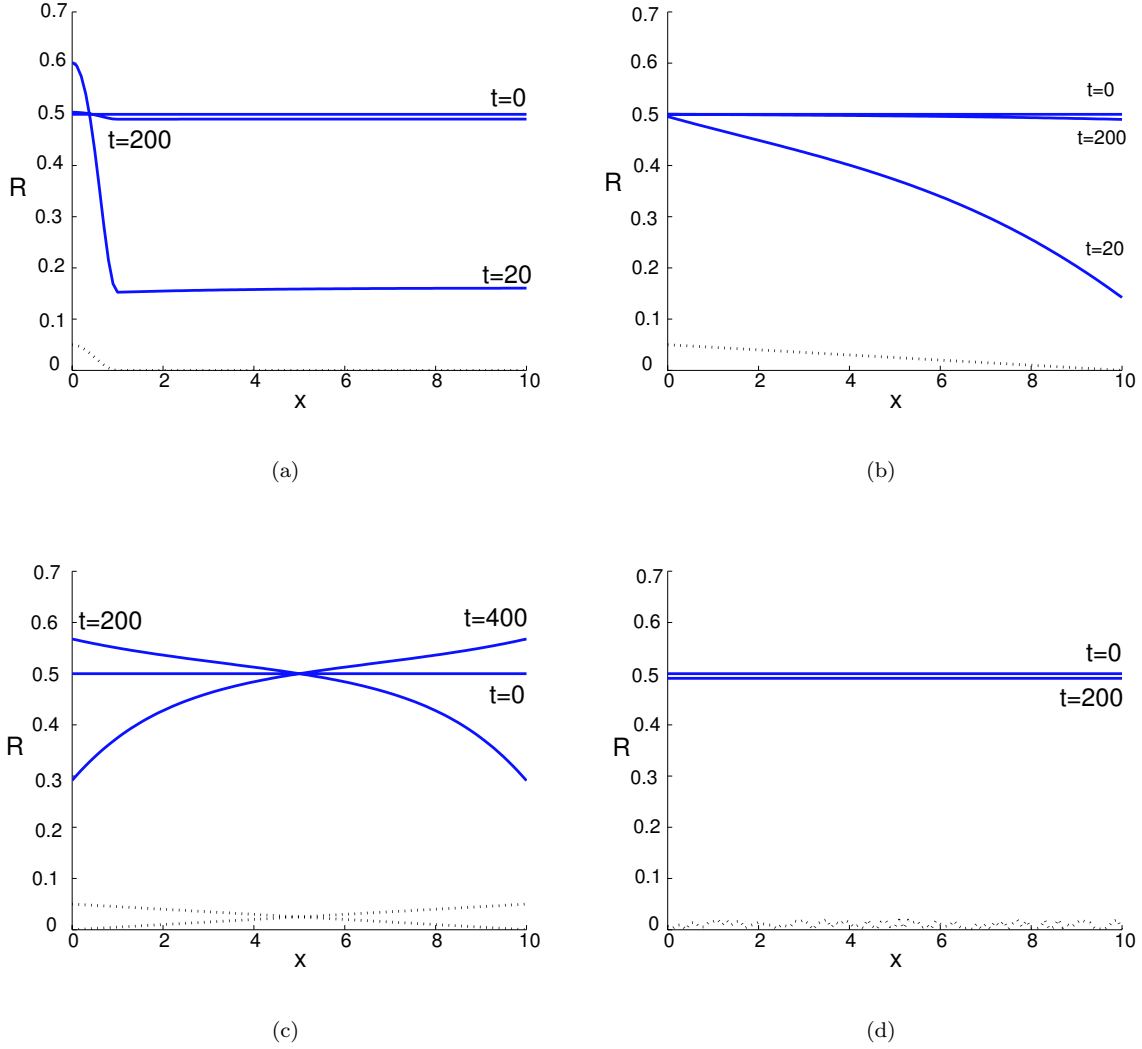


Figure 1: The LEGI model (Eqs. 2), showing responses (solid lines) to the same four types of stimuli and/or initial conditions (dotted lines) as for the wave-pinning model. In each case, starting at $t = 0$ with the steady state, a transient stimulus k_S^{loc} , applied at the left cell edge in (a), or as a gradient, k_S^{grad} across the cell in (b) leads to a transient response at $t = 20$ that disappears by $t = 200$, after the stimulus is turned off. Reversing the gradient leads to a reversal of polarization (c). Random initial conditions (d) do not lead to any spontaneous polarization, regardless of noise amplitude.

2 Sensitivity and persistence

In Fig. 3, we compare the responses of all three models to both persistent (left) and transient (right) stimuli of various gradient strengths. Several differences are noteworthy. The WP model (top) requires gradients larger than some threshold to respond, unlike both ASDM and LEGI. The LEGI model (middle) responds

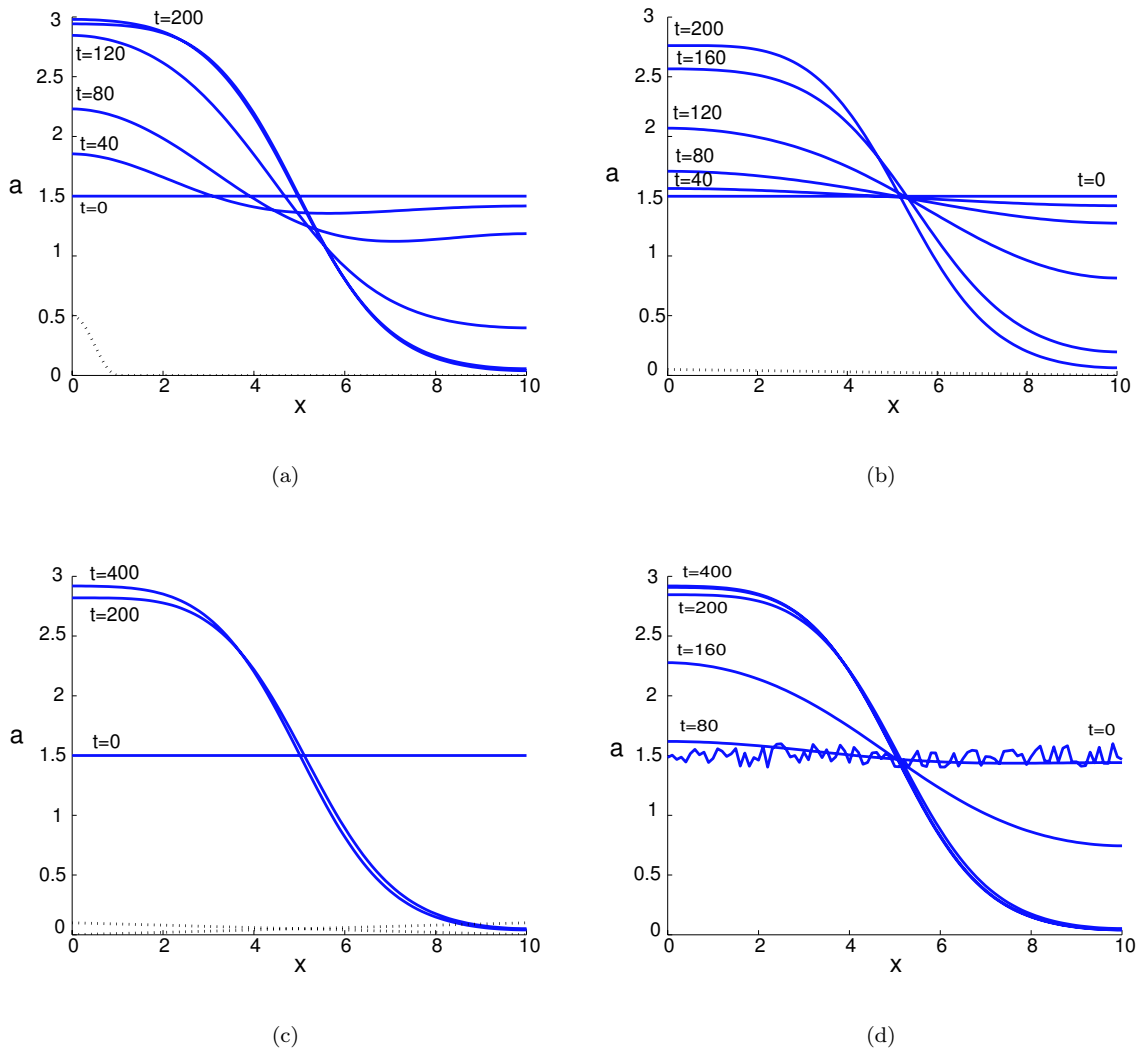


Figure 2: The ASDM system (Eqs. 3) showing responses to the same four types of stimuli used in the wave-pinning model and in Supplementary Fig. 1. Spatial profiles for the activator (solid lines) at various times ($t = 0, 40, \dots, 400$ s) are shown here to emphasize and compare the time scale taken for macroscopic polarization to be evident. In (a), it takes well over 40s for the stimulus at the left cell edge to create a noticeable chemical difference between “front” and “back” of the cell, and the magnitude of polarization creeps to its full amplitude only by about $t = 200$ s. A similar outcome occurs for a spatial gradient (b). (Compare timescale with plots on Fig. 2a,b in the text.) The polarization persists even when the stimulus is removed (in both (a) and (b)). Unlike both wave-pinning and LEGI models, once formed, the polarized pattern is “frozen” and does not respond by repolarizing when the gradient is reversed as shown in (c). The model admits a Turing RD instability and is sensitive to (arbitrarily) small perturbations of the homogenous steady state, unlike the previous two models.

in a way that increases with stimulus strength, but forgets the stimulus once it is turned off.

References

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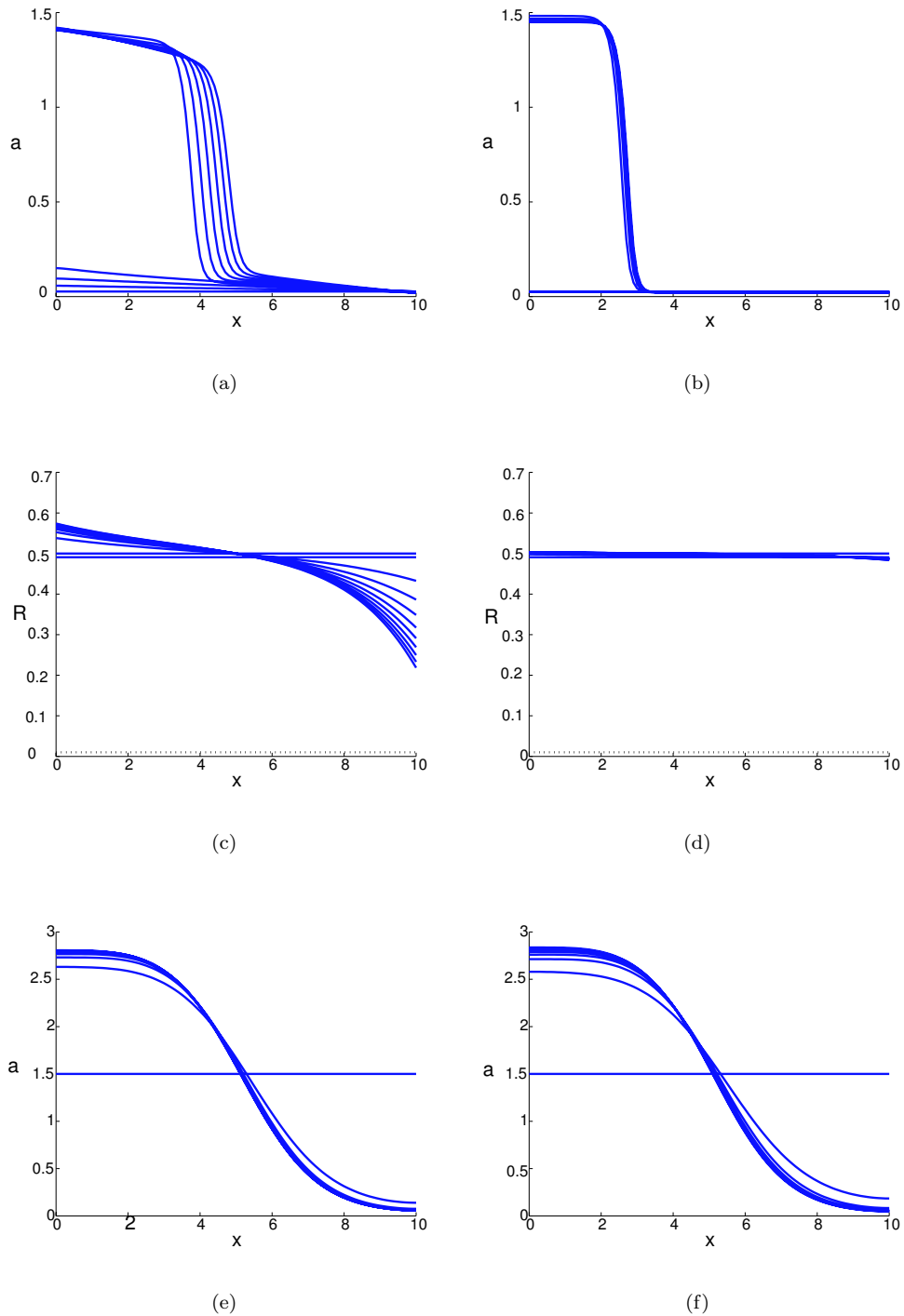


Figure 3: Comparison of sensitivity and persistence of the wave-pinning model (WP) (top), the LEGI model (center) and the substrate-depletion model (ASDM) (bottom) in response to uniform and successively stronger graded stimuli. In each panel we show the profile (of the active form a in Eqs. 1, of the response element R in Eqs. 2, and of the activator a in Eqs. 3) at $t = 200$ in response to the stimuli $S(x) = 0.01(1+m)x$ where $m = 0, 1, \dots, 9$. Left panels: gradient on for entire duration; Right panels: transient gradient, turned off at $t = 50$. The ASDM (e,f) is most sensitive: it responds to all but the uniform stimulus by polarizing. The wave-pinning system (a,b) exhibits a threshold, and LEGI produces a response that increases with signal. Both WP (b) and ASDM (f) but not LEGI (d) persist after the stimulus is removed.