Cell Polarization, a review of Models and Experiments

Jilkine A, Edelstein-Keshet L (2011) A Comparison of Mathematical Models for Polarization of Single Eukaryotic Cells in Response to Guided Cues.

PLoS Comput Biol 7(4): e1001121.

Universal features of polarizing cells

1. Ability to sense both steep and shallow external gradients (as small as 1%–2%) in vast range of concentrations. Polarization leads to an *amplification* of this asymmetry to some macroscopic level.
2. Remain *sensitive to new stimuli*, and can reorient when the stimulus gradient is changed.
3. Polarity maintained after stimulus is removed (*maintenance*) – may require cytoskeleton.

Additional features of some cells

1. *Spontaneous polarization*, in absence of spatial cues.

2. *Adaptation:* a persistent response to a gradient stimulus, but transient response to a spatially uniform stimulus.

3. Response to multiple stimuli: either *multiple "fronts"* or a *unique axis of polarity*.

4. Pseudopods continually extended and retracted. Reorient by splitting a pseudopod, one part becoming dominant.

Cell type comparisons

Cell type	Polarization Behaviors	Scale
Budding yeast	Spontaneous polarization, unique axis of polarity	Size: 5 μm, TP: 3 min
D. discoideum	Gradient sensing (1% and up), adaptation (Lat), spontaneous polarization, high amplification, reorientation, maintenance, multiple fronts (Lat), unique axis (WT)	Size: 10–20 μm, TP: 30–60 s, speed: 3–15 μm/min
Fibroblasts	Gradient sensing, reorientation	Size: 50–150 μm, TP: 30–50 min, speed: 1 μm/min
Keratocytes	Spontaneous polarization, maintenance	Size: 10 μm (fragments), 30–40 μm (cells), speed: 10–40 μm/min,
Neutrophils	Gradient sensing, spontaneous polarization, high amplification, reorientation, unique axis (WT)	Size: 10 μm, TP: 30 s, speed: 10–20 μm/min
Neurons	Attractive/repulsive turning, gradient detection, adaptation	

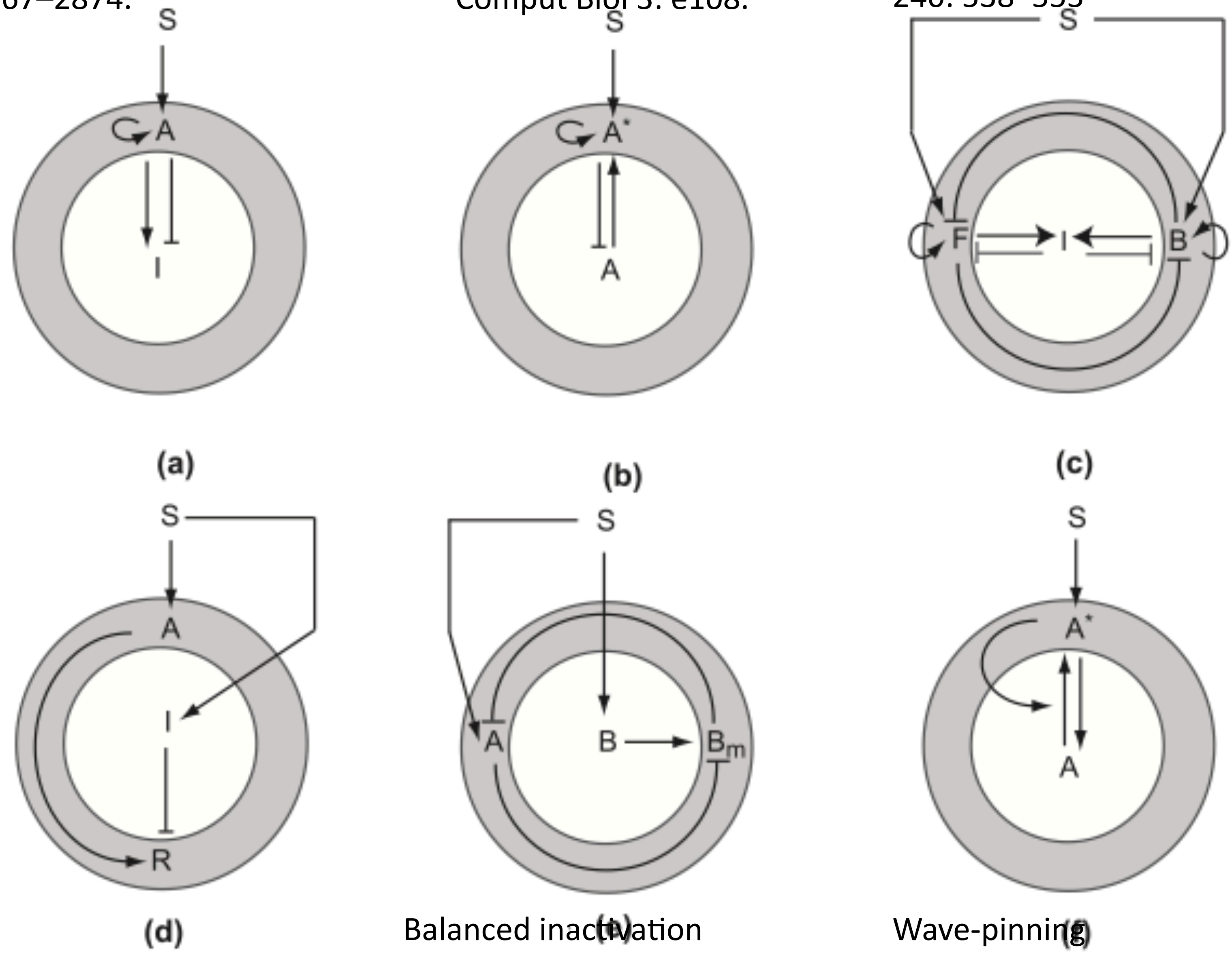
Stimuli and signaling proteins

Cell type	Feedback Loops	Stimulus	Cytoskeleton
Budding yeast	Cdc42→Cdc24→Cdc42, Cdc42→actin→Cdc42	Bud1	Actin (MO)
D. discoideum	Amplification upstream of PI3K	cAMP	Actin (MO)
Fibroblasts	Cdc42→Rac→RhoA	PDGF, fibronectin, interleukins	Actin, MT, FA
Keratocytes		Mechanical	Actin
Neutrophils	Front/back mutual inhibition PIP3→actin→PIP3	fMLP, interleukins, others	Actin
Neurons	Rac/Rho mutual inhibition	Netrins, semaphorins, ephrins	Actin, MT

Lateral Inhibition, Turing
Meinhardt (1999). J Cell Sci 112: 2867–2874.

Substrate depletion
Otsuji et al. (2007) PLoS Comput Biol 3: e108.

Turing, mutual inhibition
Narang A (2006) J Theor Biol 240: 538–553

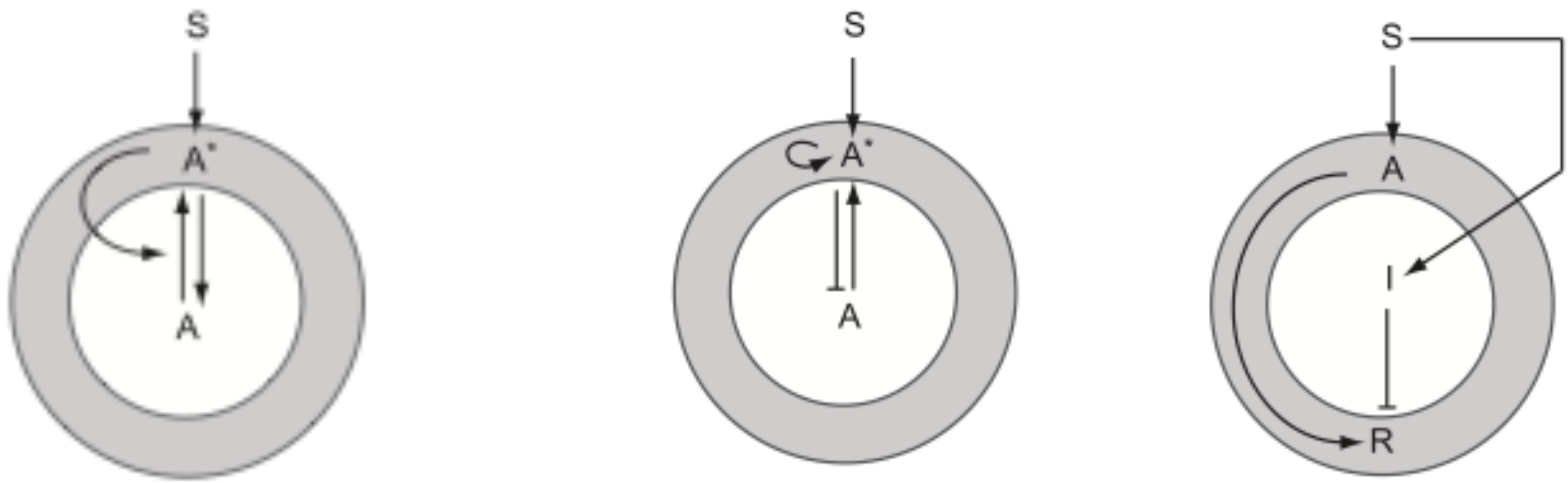


LEGI
Levchenko A, Iglesias P (2002). Biophys J 82: 50–63

Balanced inactivation
Levine H, Kessler DA, Rappel WJ (2006) PNAS 103: 9761–9766

Wave-pinning
Mori Y, Jilkine A,LEK (2008) Biophys J 94: 3684–3697

Testing four models



Wave-Pinning Goryachev Otsuji LEGI

Types of models

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

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

- Wave-pining

$$f(u,v) = -g(u,v) = v\left(k_0 + \frac{\gamma u^2}{K^2 + u^2}\right) - \delta u.$$

- Otsuji

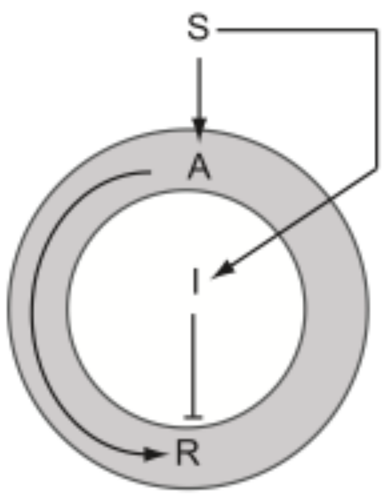
$$f(u,v) = -g(u,v) = a_1\left[v - \frac{u+v}{(a_2 s(u+v)+1)^2}\right],$$

- Goryachev

$$f(u,v) = -g(u,v) = \alpha E_c u^2 v + \beta E_c uv - \gamma u, \quad E_c = \frac{E_c^0}{1 + \int_S f(u)\,ds}.($$

- LEGI: see over

LEGI



$$\frac{\partial A}{\partial t} = k_A S(t,x) - k_{-A} A,$$

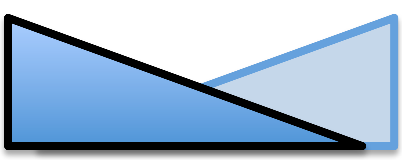
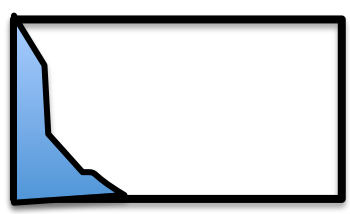
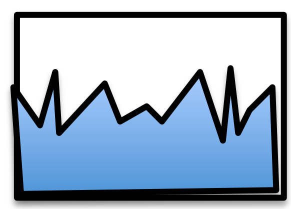
$$\frac{\partial I}{\partial t} = D \frac{\partial^2 I}{\partial x^2} + k_I S(t,x) - k_{-I} I,$$

$$\frac{\partial R}{\partial t} = k_R A(R_T - R) - k_{-R} IR,$$

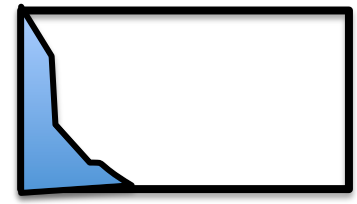
Stimuli

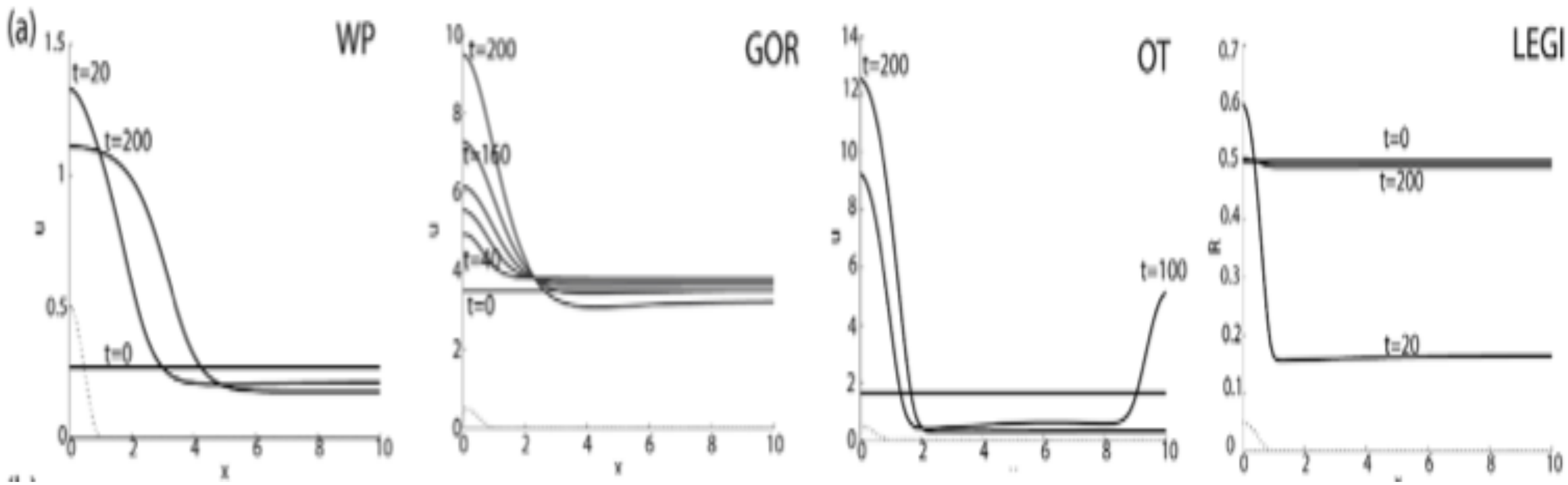
$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u,v) + k_S v,$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} - f(u,v) - k_S v,$$

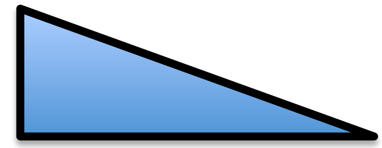
Single localized stimulus at left edge of the cell

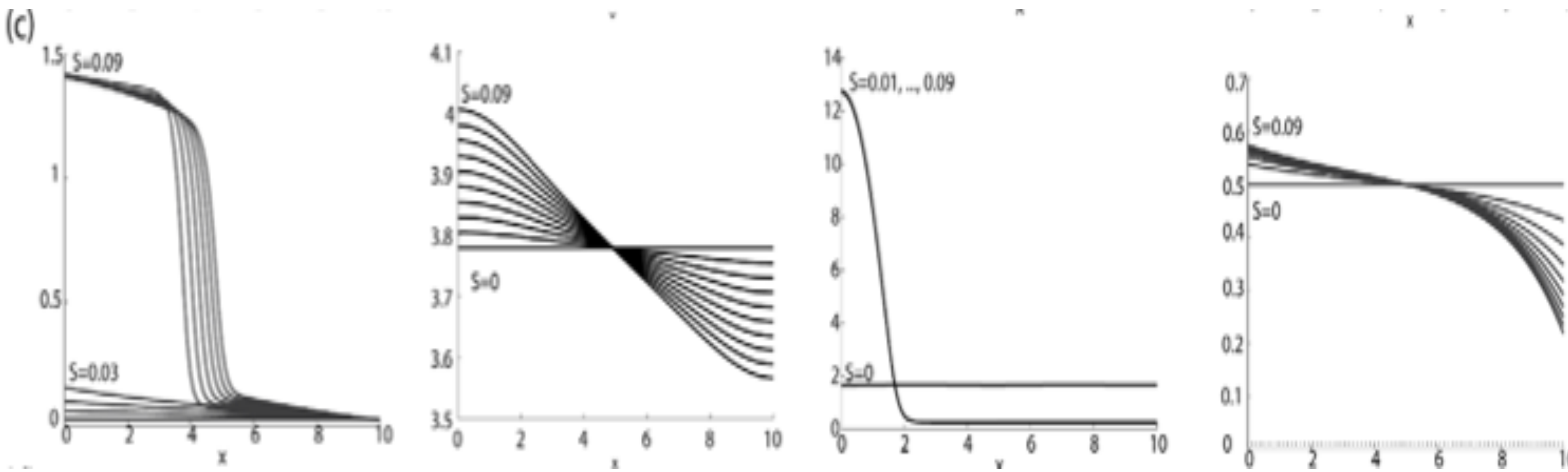




Wave-Pinning Goryachev Otsuji LEGI

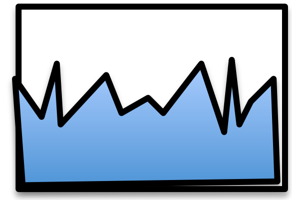
Gradient stimulus

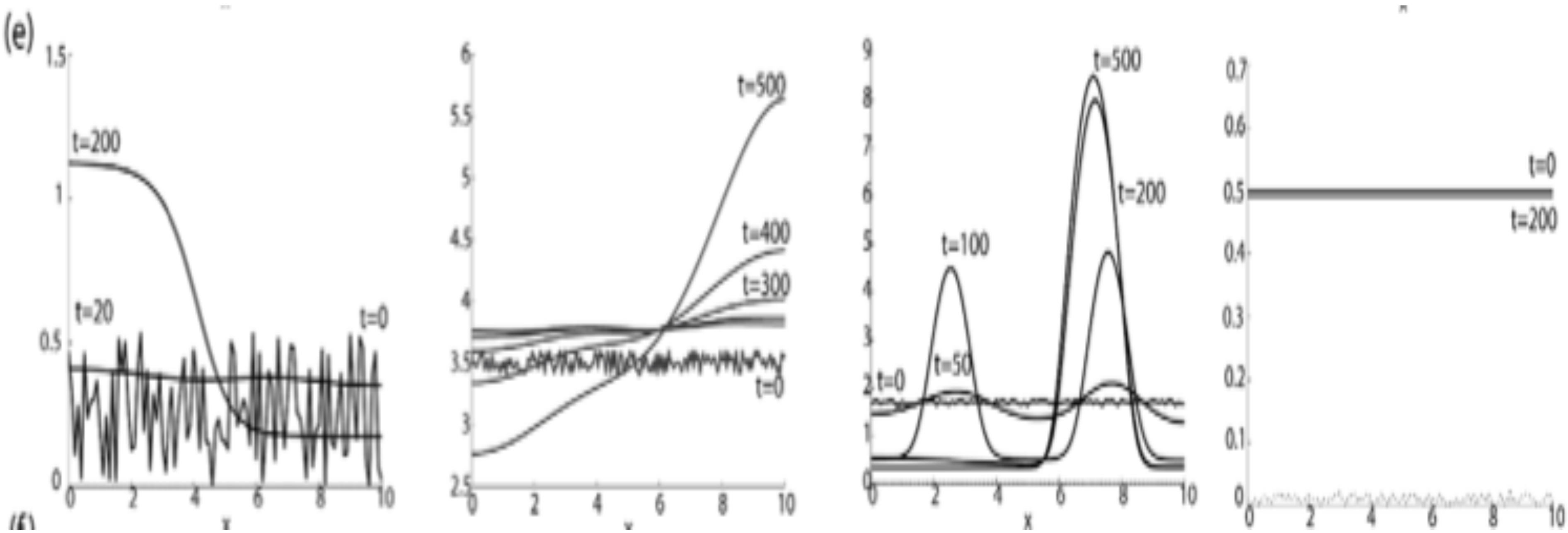




Wave-Pinning Goryachev Otsuji LEGI

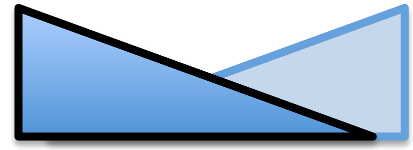
Noisy initial conditions

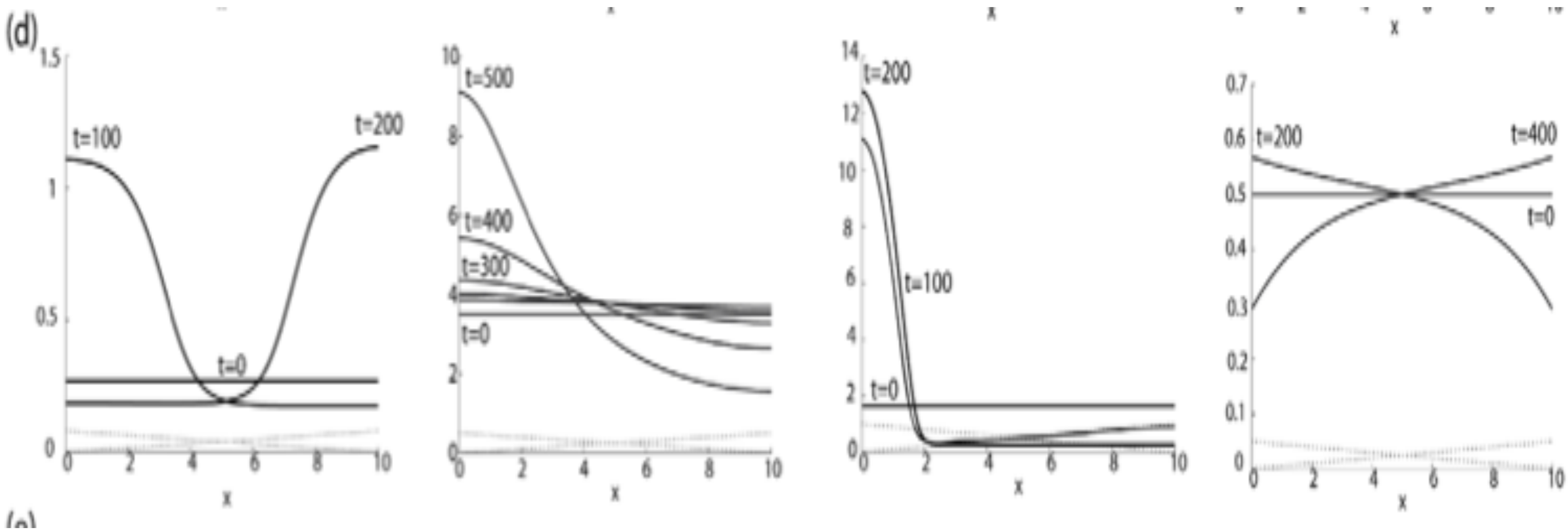




Wave-Pinning Goryachev Otsuji LEGI

Gradient + reversal





Wave-Pinning Goryachev Otsuji LEGI

In such Turing-type models, the pattern will not reverse when a new gradient of opposite polarity is applied

Features that models can explain

Behavior	"Turing Type"	Wave-Based	Gradient Sensing
Maintenance of polarity	Yes	Yes	No
Multi-stimuli response	Yes (transient)	Yes (long time-scale)	Yes
High amplification	Yes	Yes	No
Adaptation	No	No	Yes
Spontaneous polarization	Yes	Yes	No
Reversible asymmetry	No	Yes	Yes