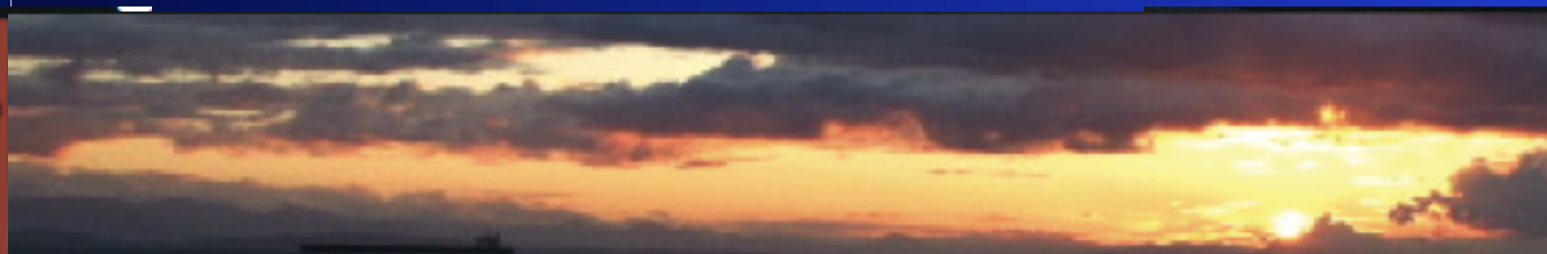
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Cell polarity models

mprime



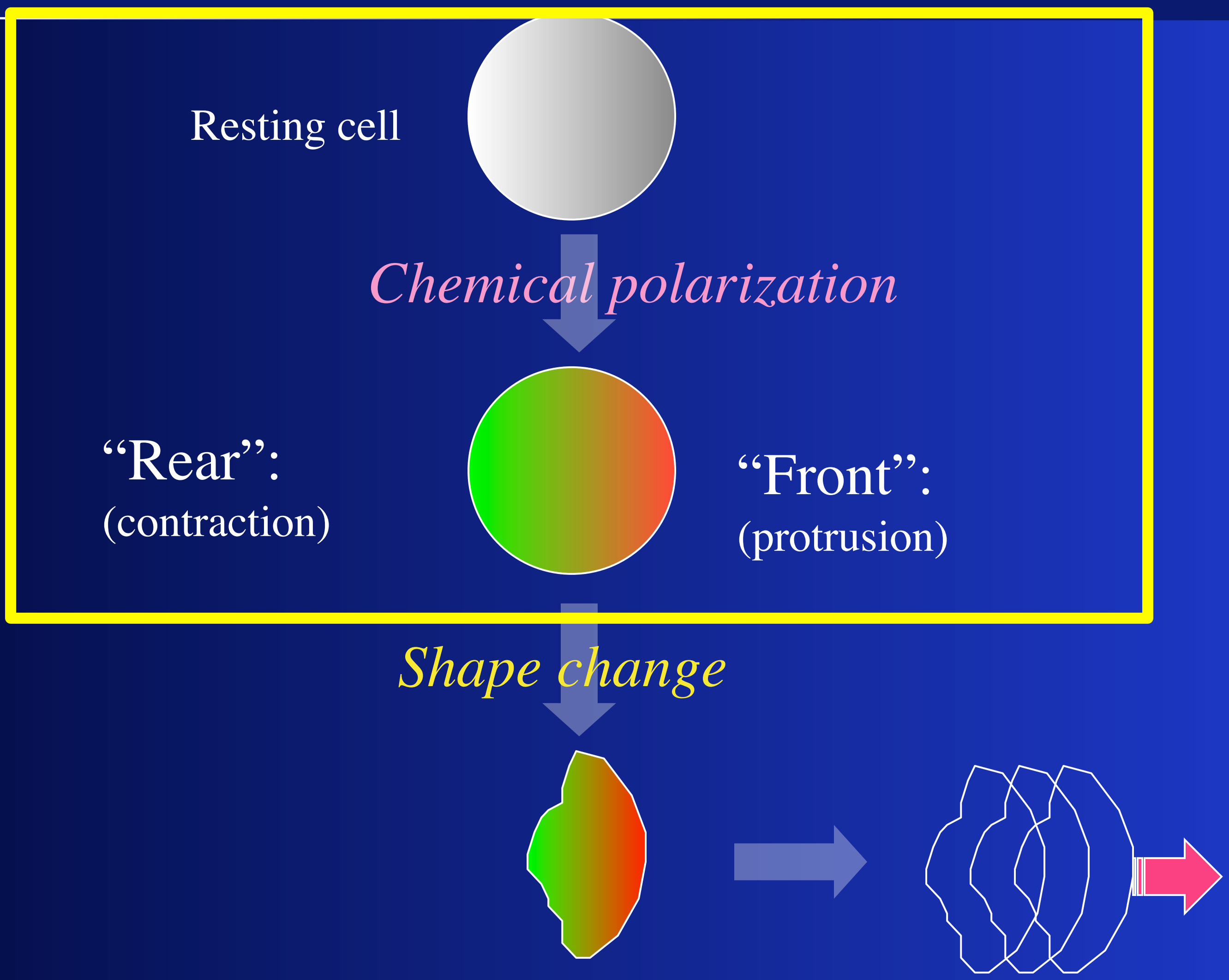
PIMS

www.math.ubc.ca/~keshet/MCB2012/

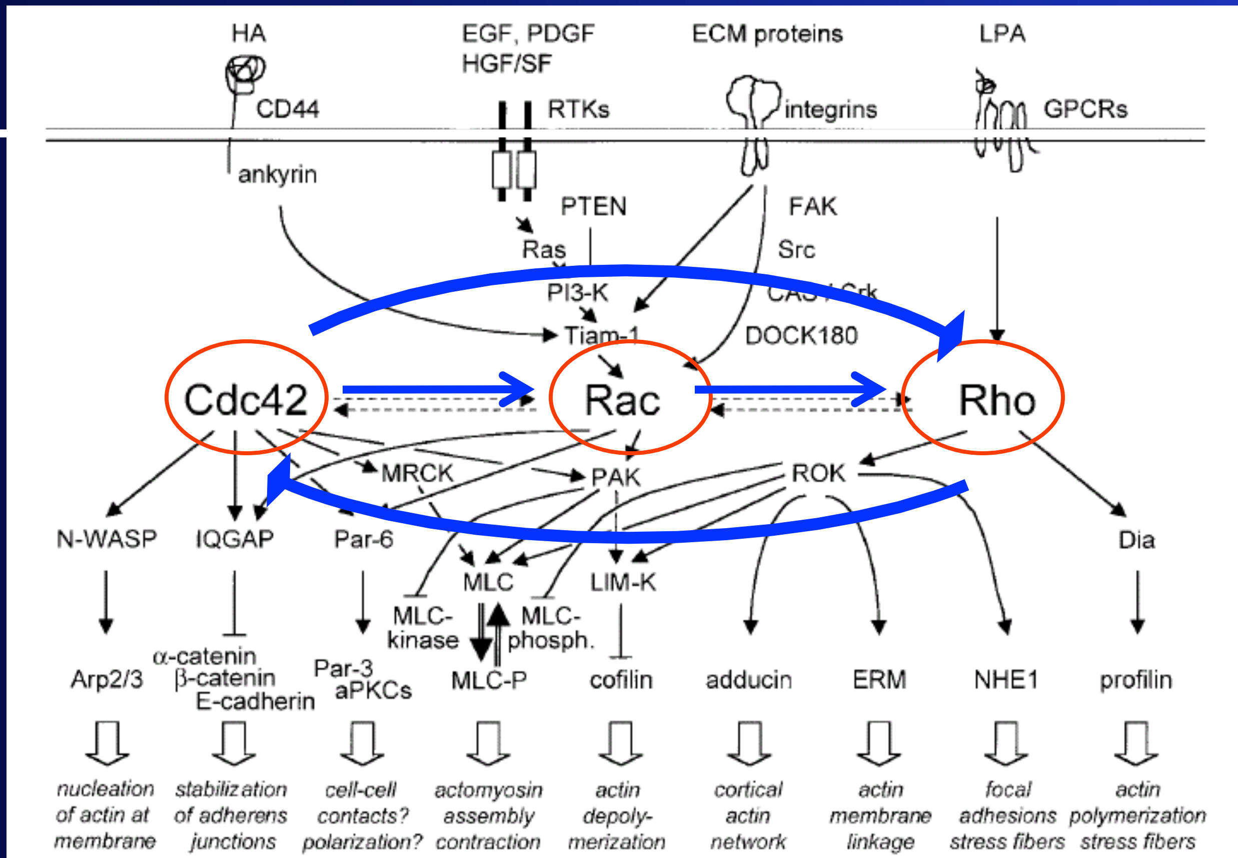
Universal features of polarizing cells

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*).

Polarization



GTPases

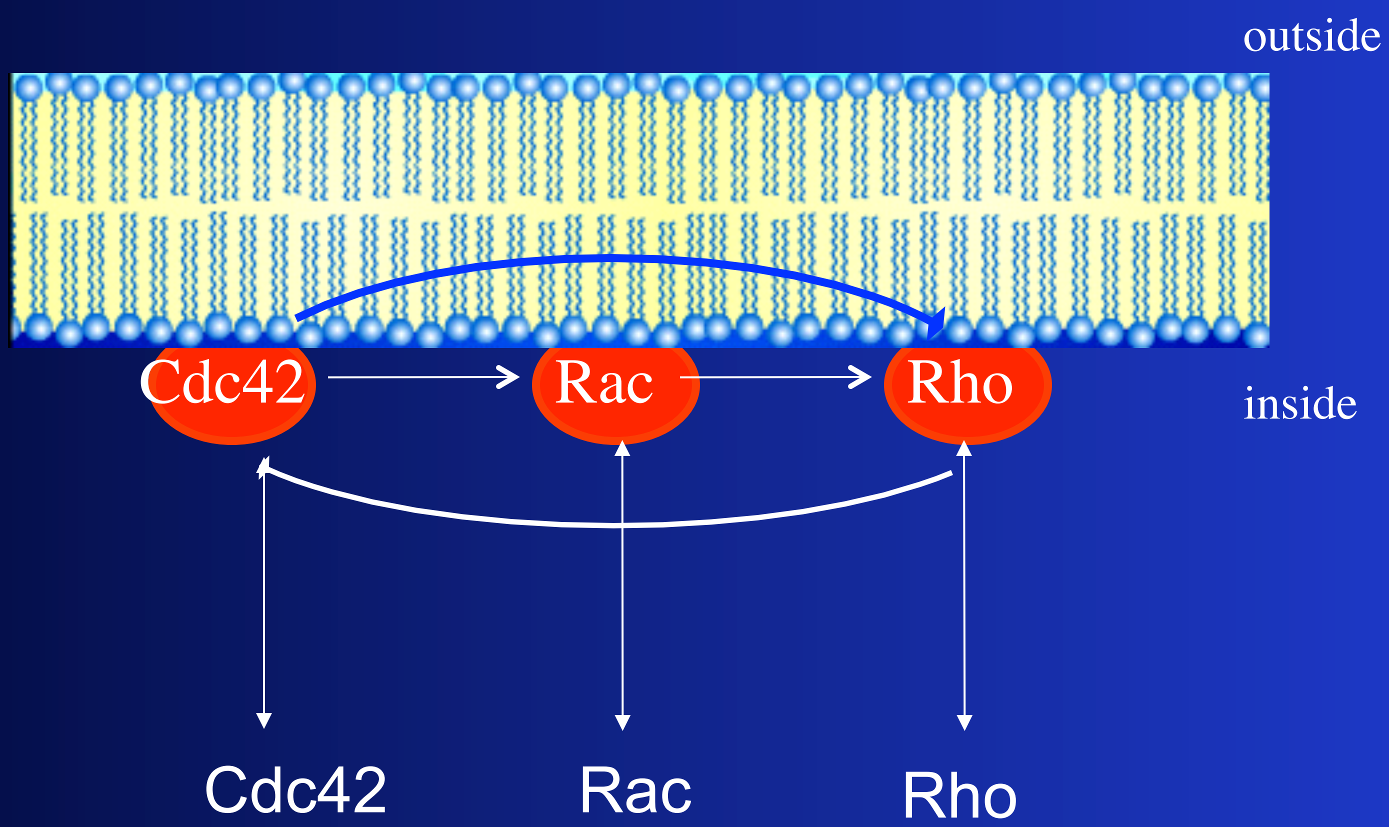


out

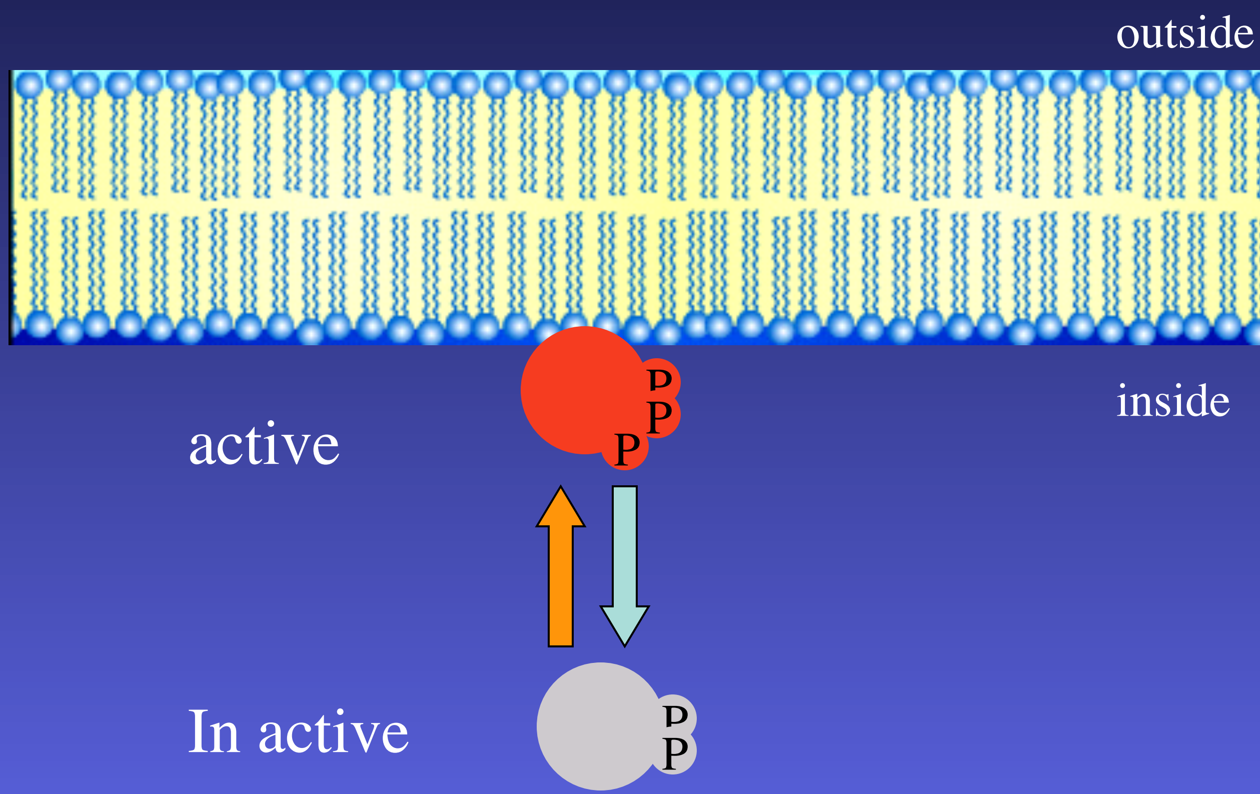
in

Schmitz et al (2000) Expt Cell Res 261:1-12

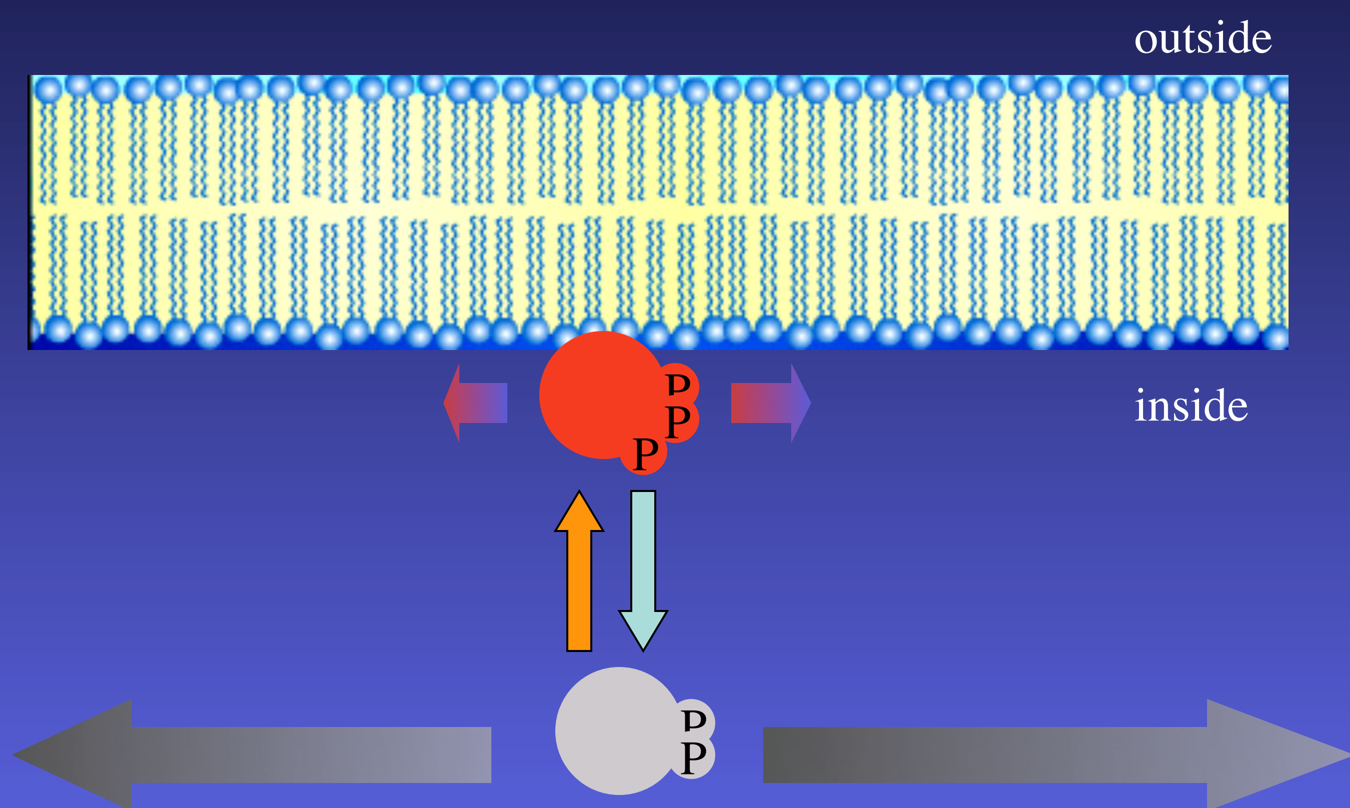
Active and inactive forms



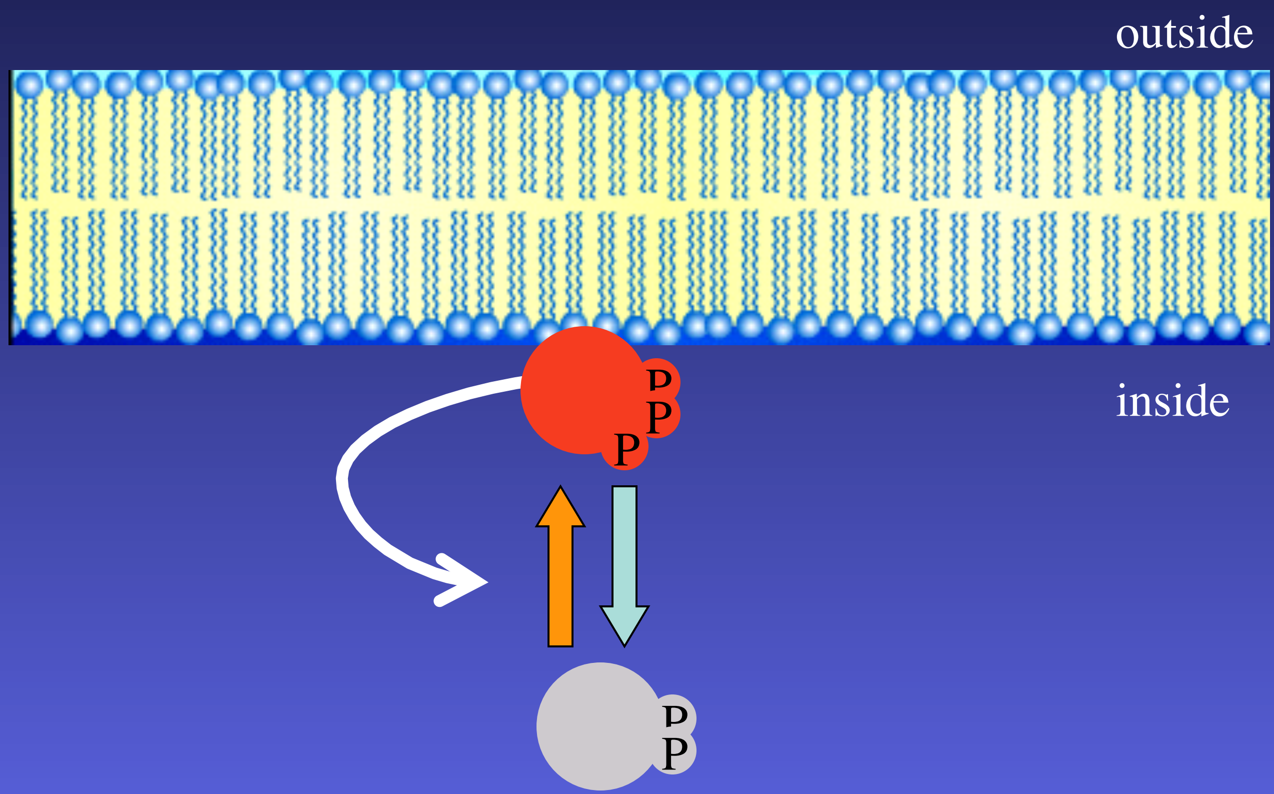
Simplified view:



100-1000 fold difference in rates of diffusion

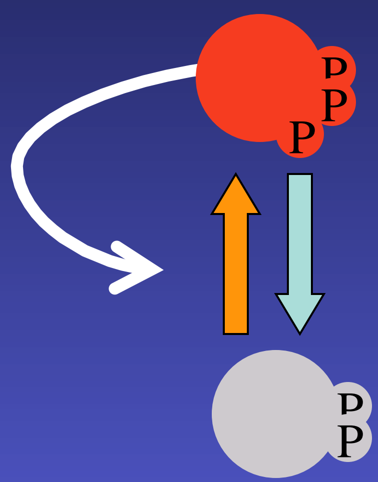


Caricature model



Only two variables

Active

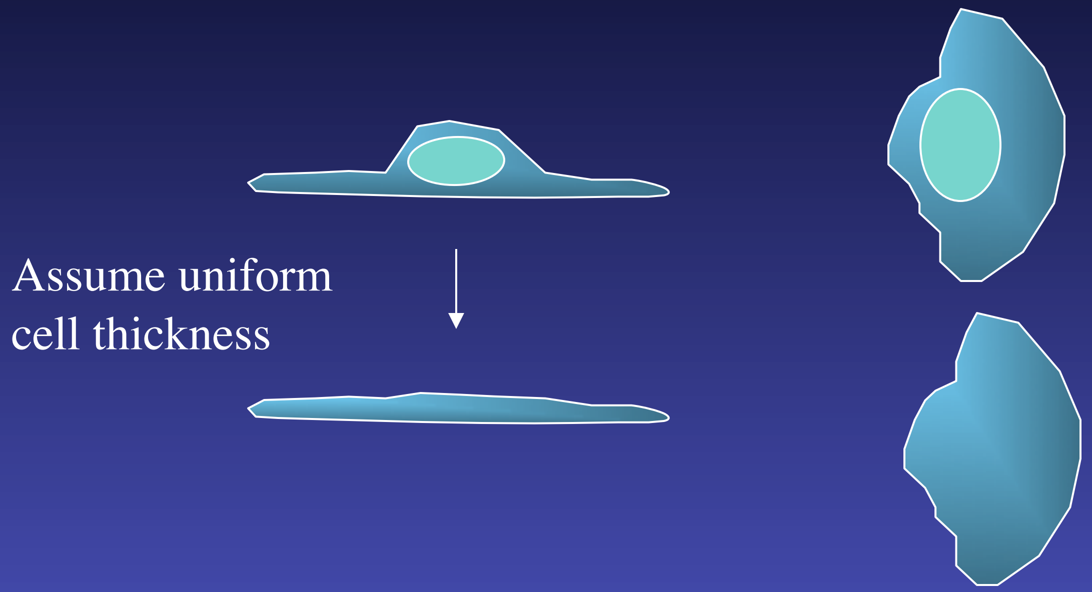


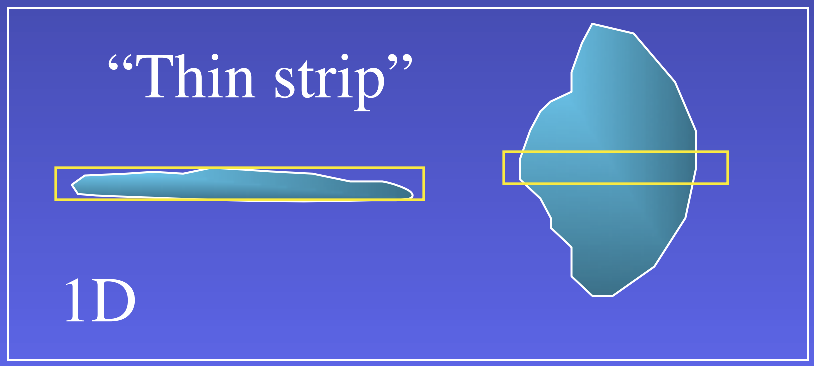
Slow diffusing

Inactive

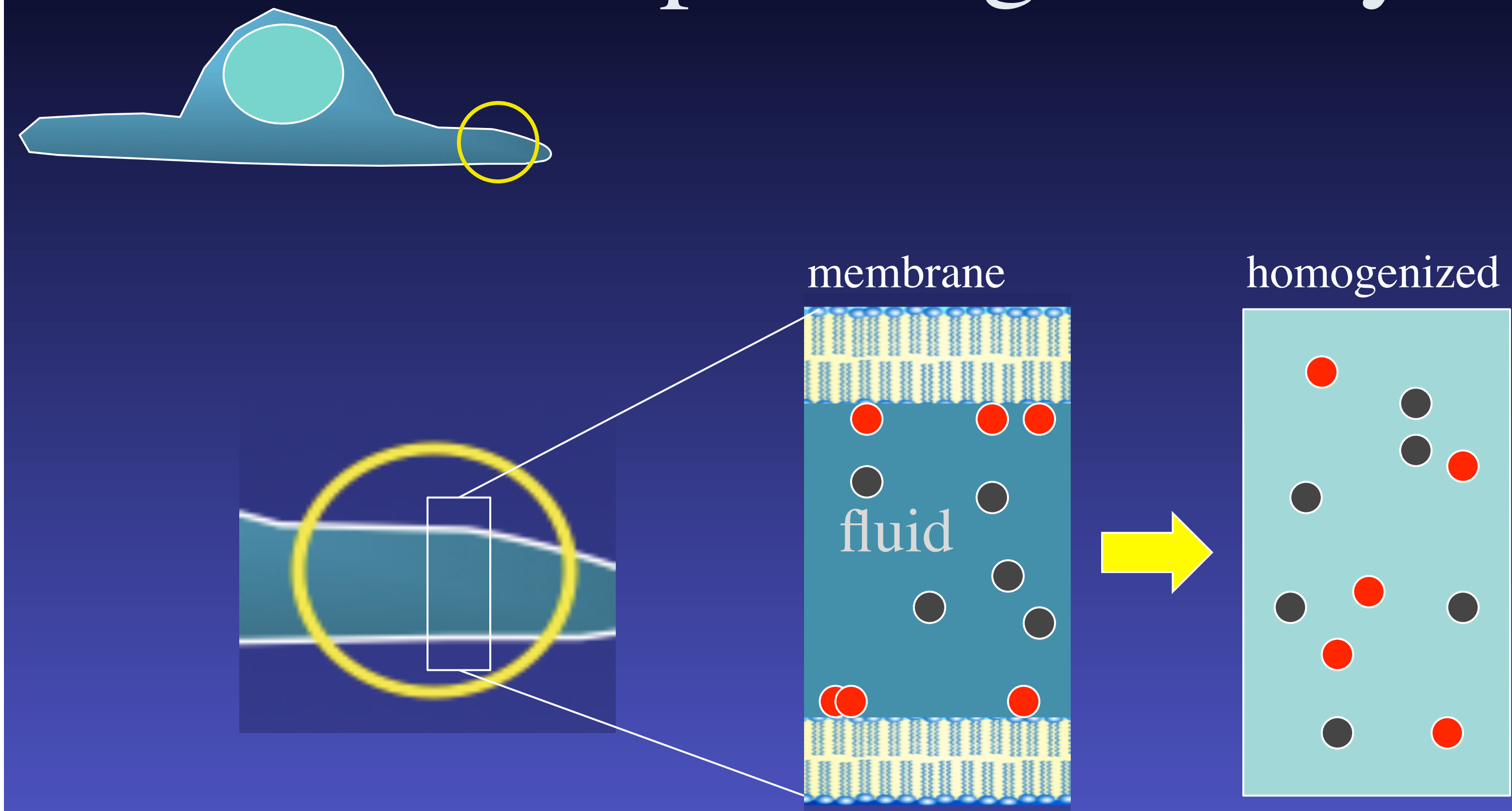
fast diffusing

Geometry

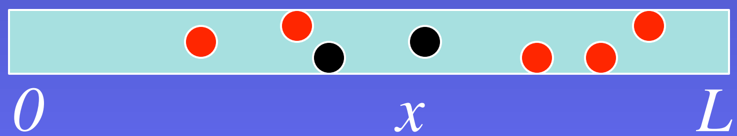




Simplified geometry



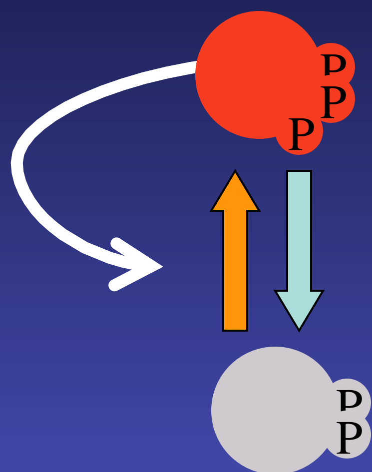
1D thin strip:



RD model

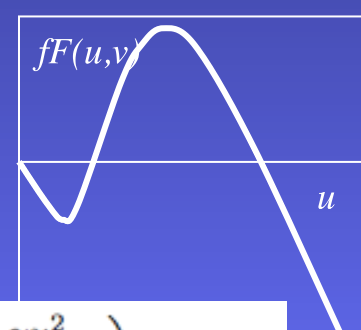
Active

Inactive



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

$$D_u << D_v$$

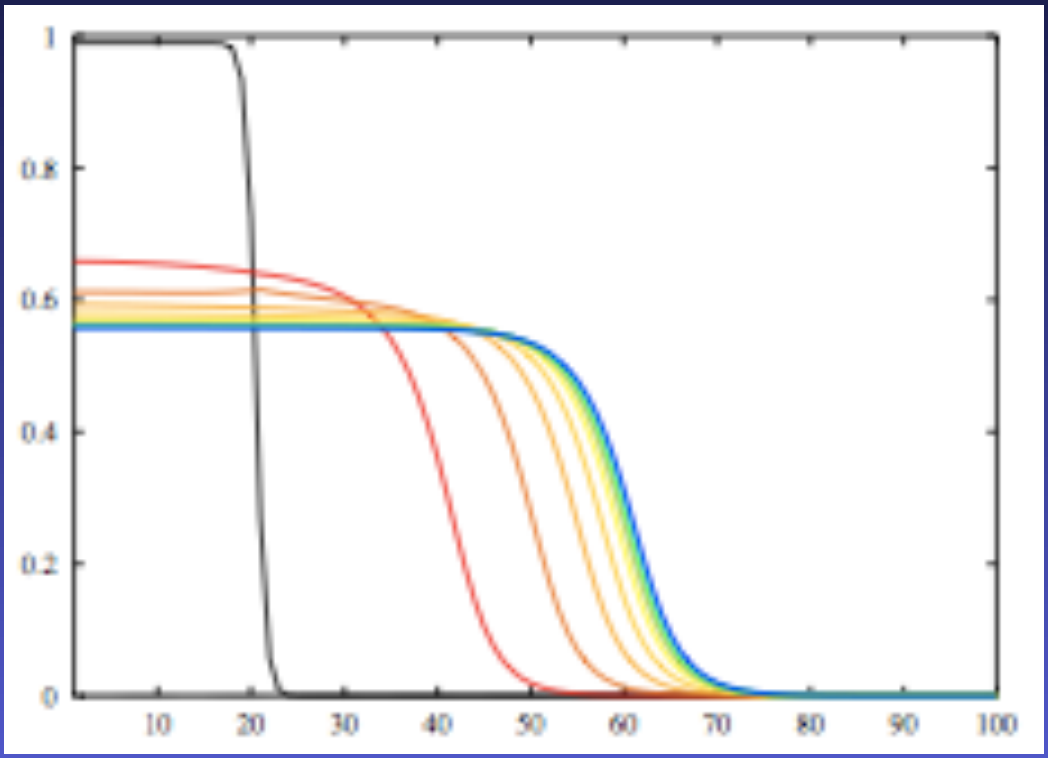


$$f(u,v) = \eta\left(\delta + \frac{\gamma u^2}{m^2+u^2}\right)v - \eta u$$

A Jilkine

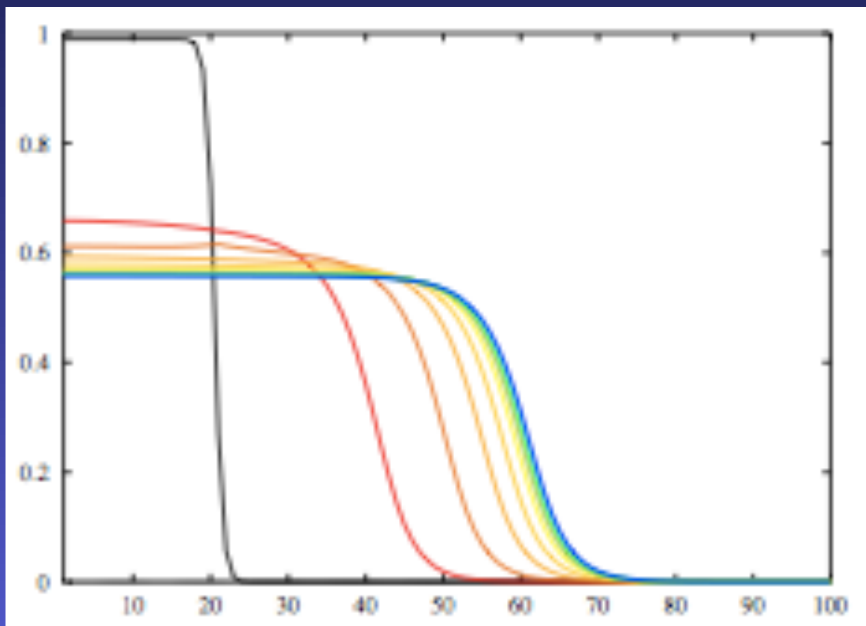
Y Mori

Behaviour: Wave-pinning

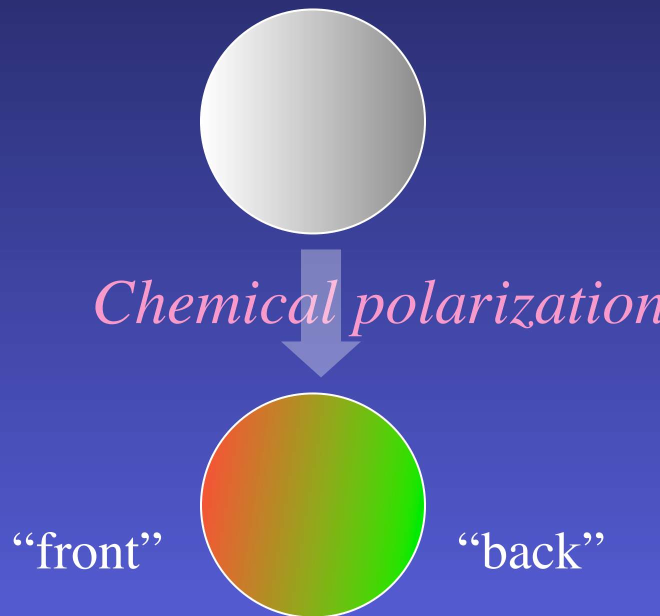


Mori Y, Jilkine A, LEK (2008) Biophys J, 94: 3684-3697.
Mori Y, Jilkine A, LEK (2011) in press SIAM J Appl Math

WP = polarization



"front" "back"



Rescaled (there is a small parameter)

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

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

$$f(u,v) = \left(\delta + \frac{\gamma u^2}{1+u^2}\right) v - u.$$

$D_u << D_v$

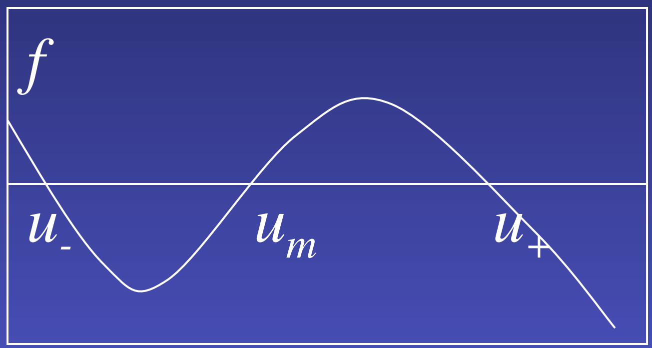
$$\epsilon^2 = \frac{D_u}{\eta L^2}, \quad D = \frac{D_v}{\eta L^2}$$

Analyse location and speed of wave front using matched asymptotic expansions..

Conditions for Wave-pinning:

1. For v fixed in some range, $v_{min} < v < v_{max}$, $f(u,v)=0$ has 3 roots

Shape of f:



2. There is a v_c in the above range such that $$\int_{u_-}^{u_+} f(u,v_c)\,du = 0$$

3. Conservation of $u+v$

4. $D_u << D_v$

Methods of analysis

$$\frac{\partial u}{\partial t}(x,t) = f(u,v) + D_u \Delta u,$$
$$\frac{\partial v}{\partial t}(x,t) = g(u,v) + D_v \Delta v,$$

Linearization,
Linear stability analysis of full PDE, look for +ve eigenvalues

$D_u \ll D_v$

Local pulse analysis

Methods of analysis, RD systems

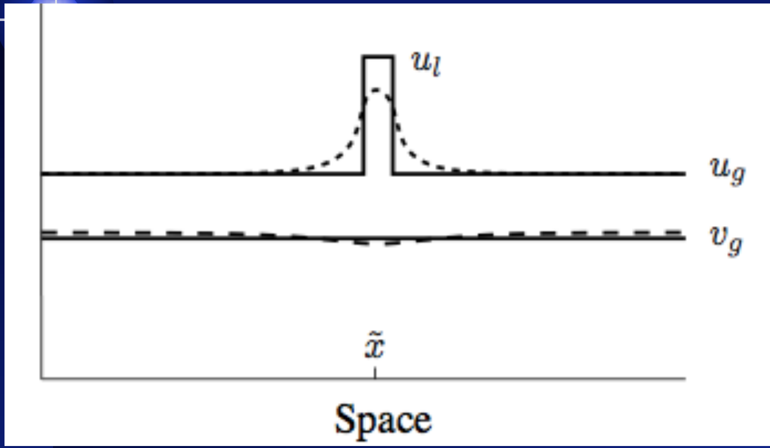
$$\frac{\partial u}{\partial t}(x,t) = f(u,v) + D_u \Delta u,$$
$$\frac{\partial v}{\partial t}(x,t) = g(u,v) + D_v \Delta v,$$

$D_u \ll D_v$

Local pulse analysis

Due to: Stan Maree, Veronica Grieneisen, with Bill Holmes

Local Pulse Analysis



Approximate PDEs by ODEs for local and global variables:

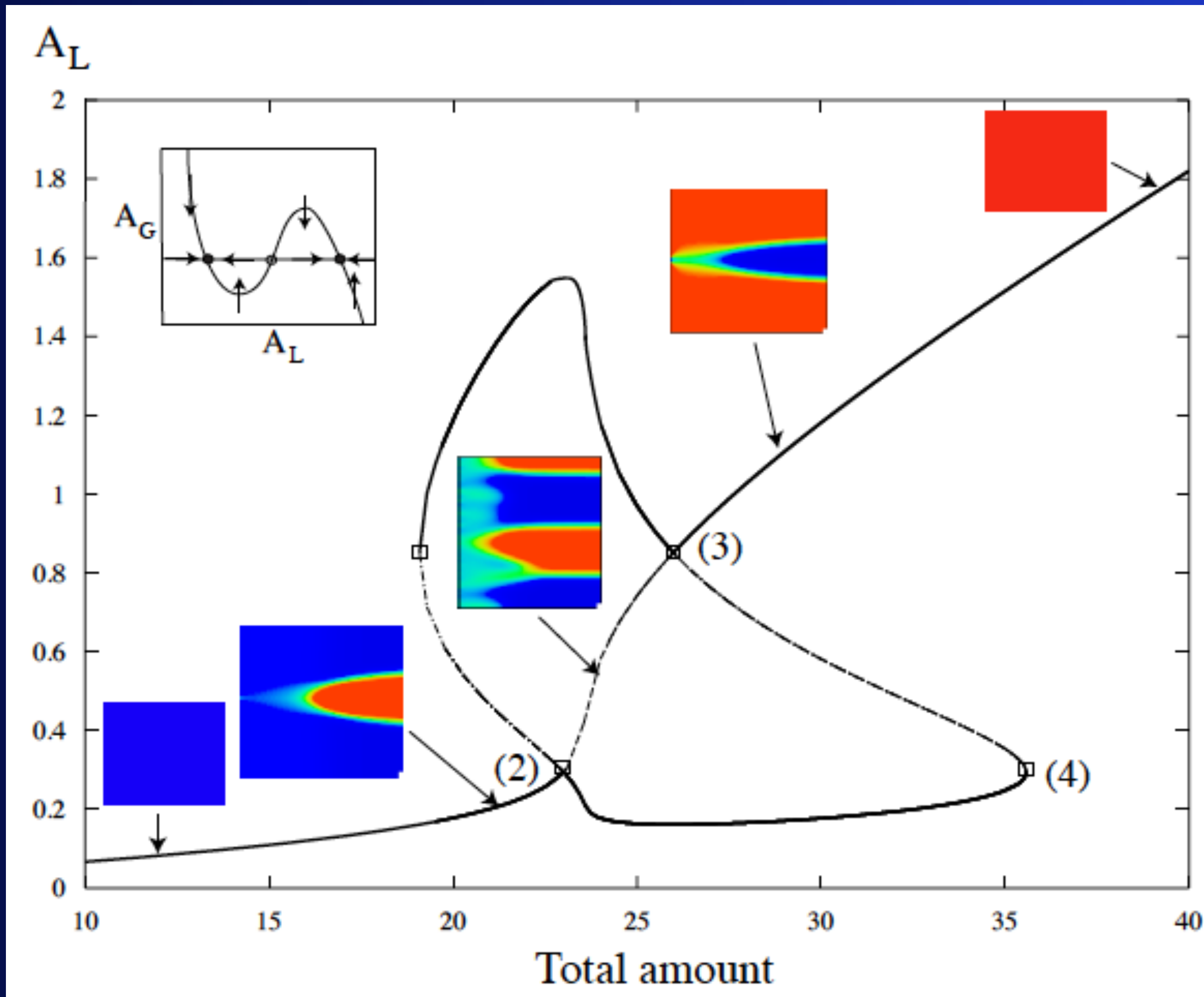
$$\frac{\partial u}{\partial t}(x,t) = f(u,v) + D_u \Delta u,$$
$$\frac{\partial v}{\partial t}(x,t) = g(u,v) + D_v \Delta v$$

$D_u << D_v$

$$\frac{du^g}{dt}(x,t) = f(u^g, v^g),$$
$$\frac{dv^g}{dt}(x,t) = g(u^g, v^g),$$
$$\frac{du^l}{dt}(x,t) = f(u^l, v^g)$$

$D_u \to 0 \quad D_v \to \infty$

LPA bifurcation and patterns



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.

(Images on next slides taken from this source)

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	

PLoS Comput Biol 7(4): e1001121

Stimuli and signaling proteins

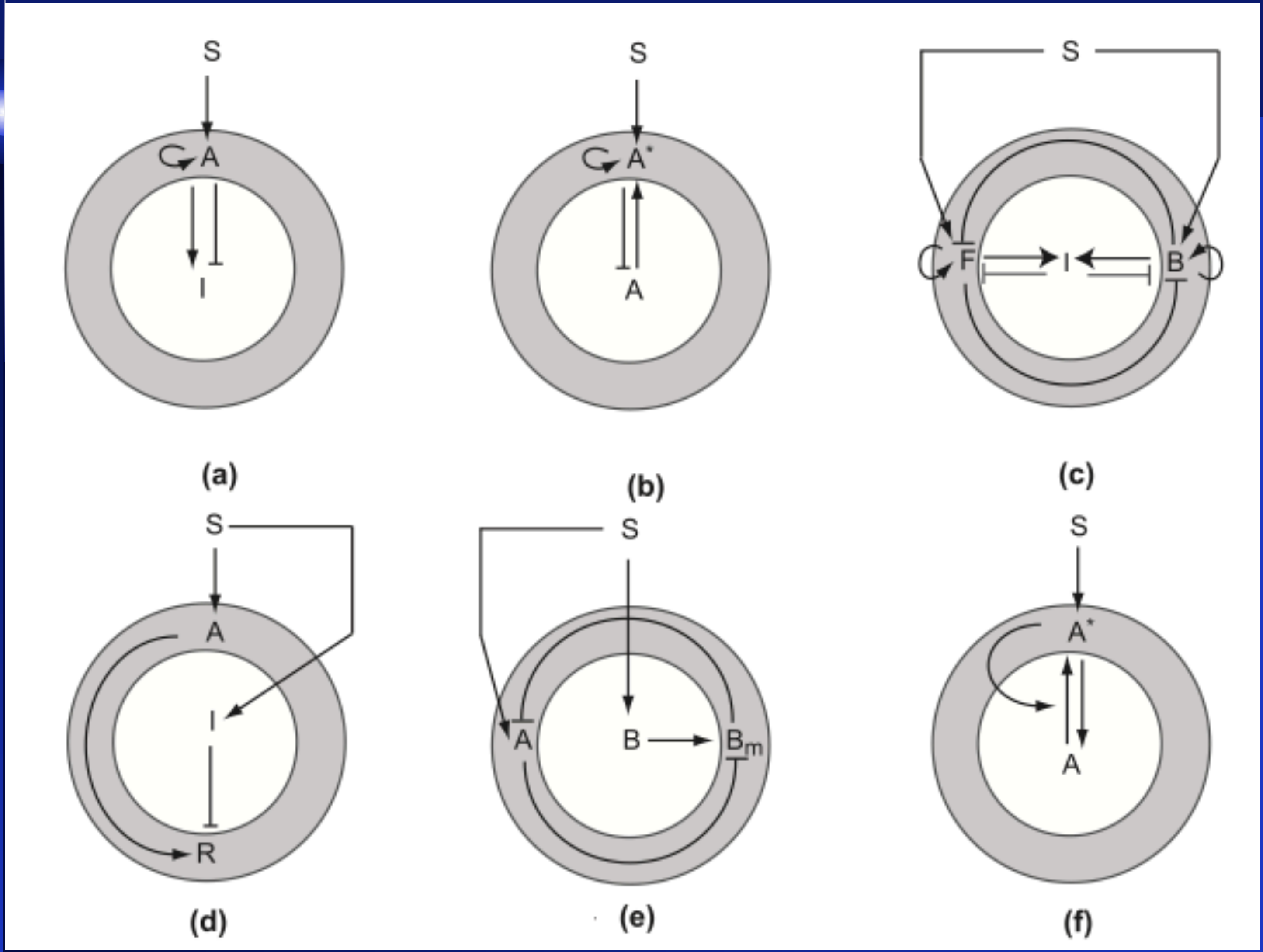
Cell type	Feedback Loops	Stimulus	Cytoskeleton
Budding yeast	Cdc42→Cdc24→Cdc42, Cdc42→actin→Cdc42	Bud1	Actin (MO)
D. discoideum	Amplification upstream of PI3K	cAMP	Actin (MO)
Fibroblasts	Cdc42→Rac→RhoA	PDGF, fibronectin, interleukins	Actin, MT, FA
Keratocytes		Mechanical	Actin
Neutrophils	Front/back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

PLoS Comput Biol 7(4): e1001121

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

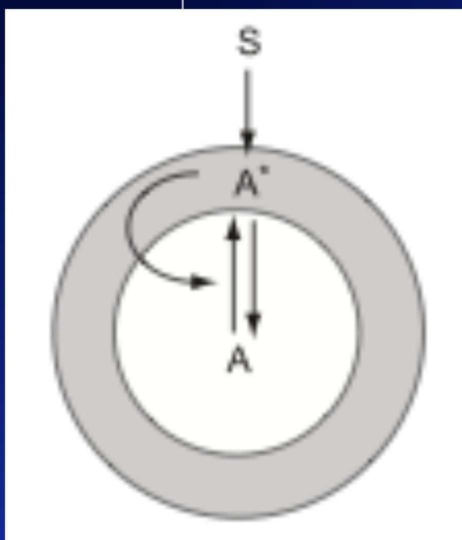


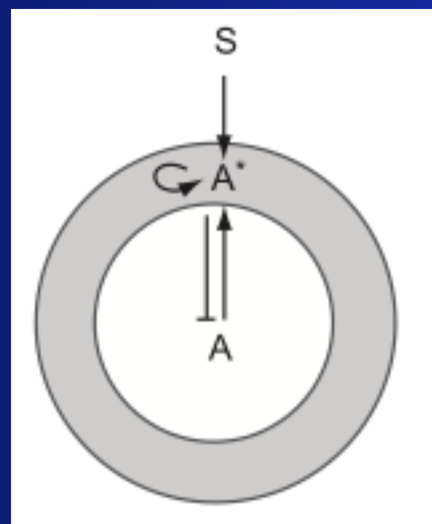
LEGI
Levchenko A, Iglesias P (2002). Biophys J 82: 50–63

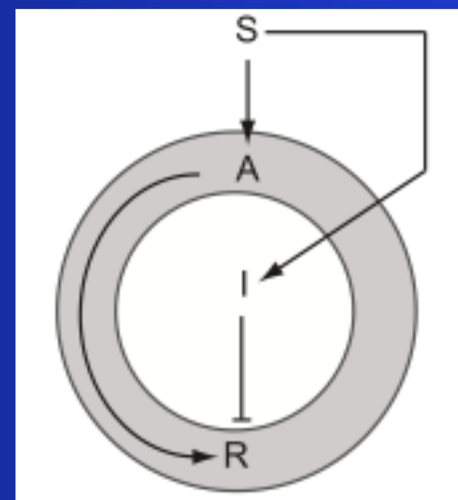
Balanced inactivation
Levine H, Kessler DA, Rappel WJ (2006) PNAS 103: 9761–9766

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

Testing four models







Wave-Pinning Goryachev Otsuji LEGI

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Types of models

- Reaction-diffusion with slow and fast variables

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

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

- Wave-pining

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

- Otsuji

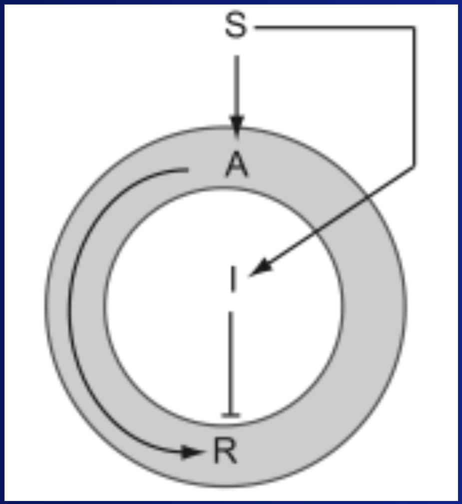
$$f(u,v) = -g(u,v) = a_1\left[v - \frac{u+v}{(a_2 s(u+v)+1)^2}\right],$$

- 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

Local excitation global inhibition (LEGI)



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

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

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

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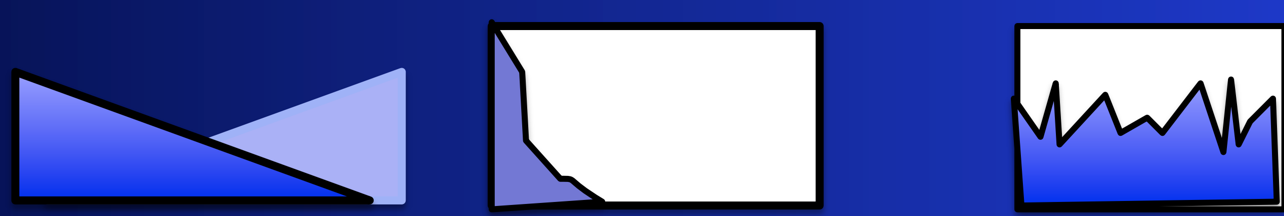
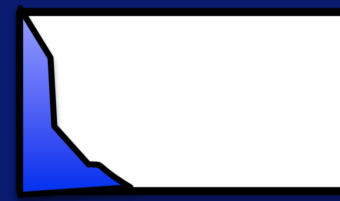
Stimuli

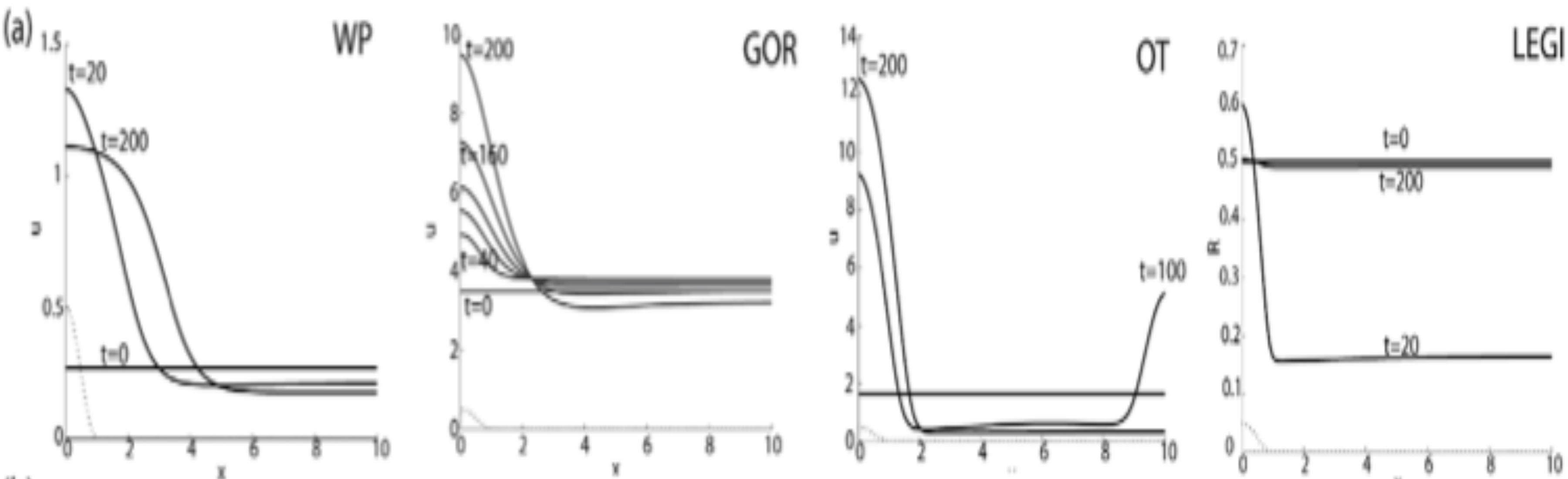
$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u,v) + k_S v,$$

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



Single localized stimulus at left edge of the cell





Wave-Pinning Goryachev Otsuji LEGI

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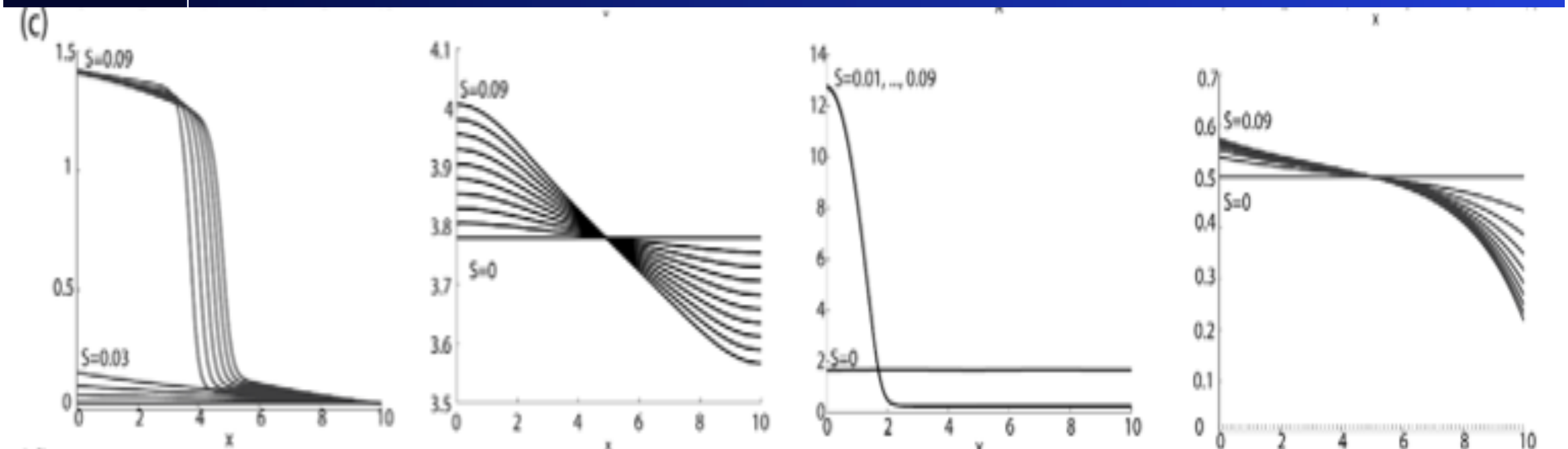
Gradient stimulus



Wave-Pinning Goryachev Otsuji LEGI

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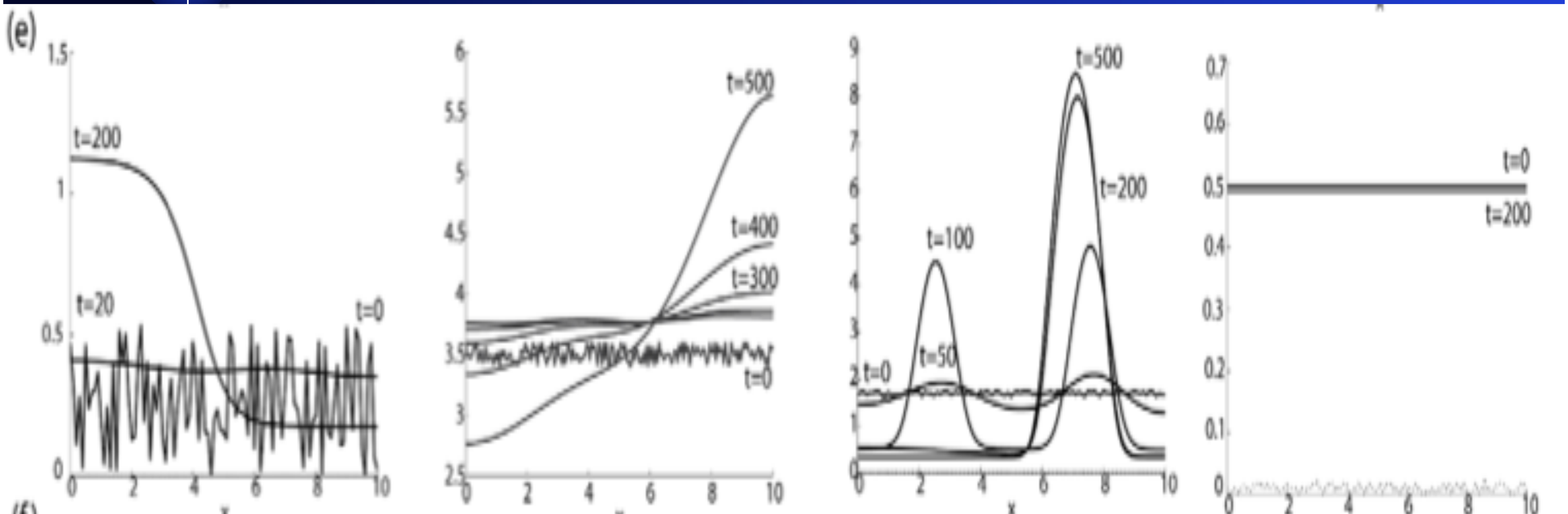
Noisy initial conditions



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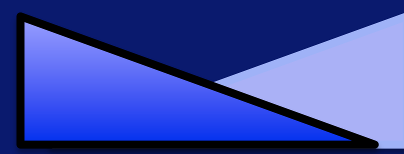
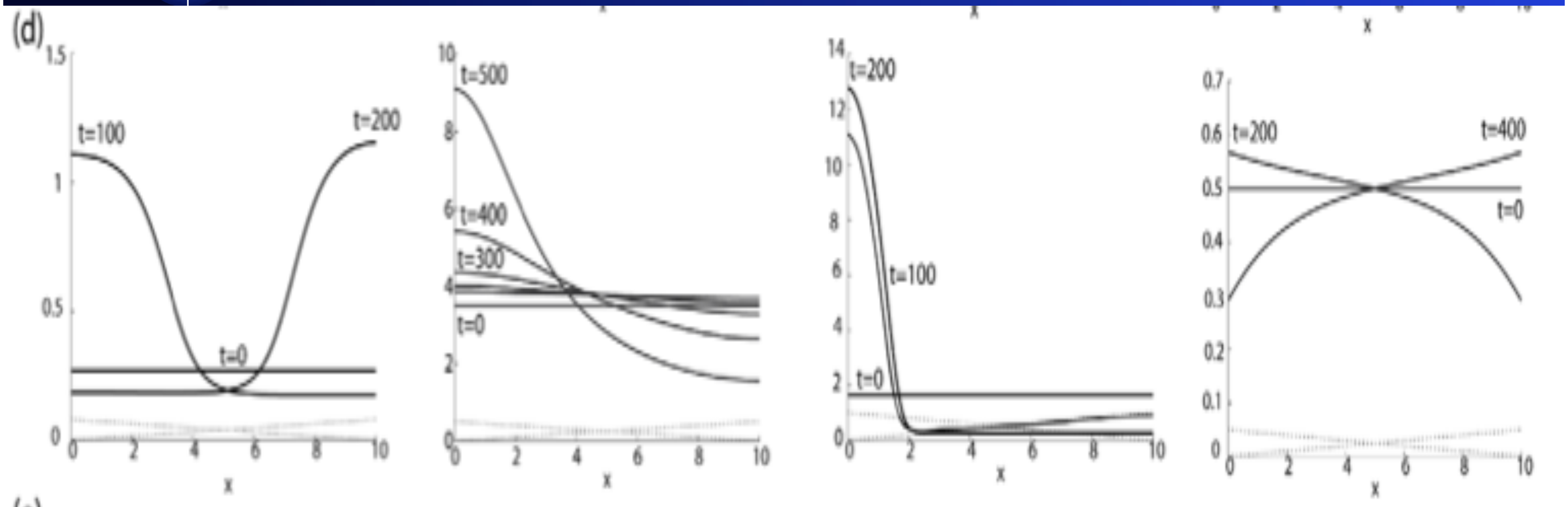
Gradient + reversal





Wave-Pinning Goryachev Otsuji LEGI

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

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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

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End of Part 1