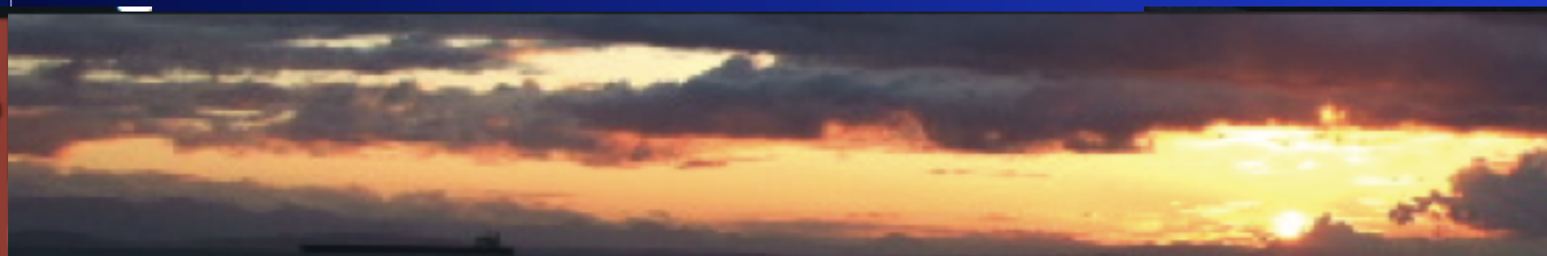
Mathematical Cell Biology Graduate Summer Course
University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Diffusion, Reaction, and Biological pattern formation, cont'd



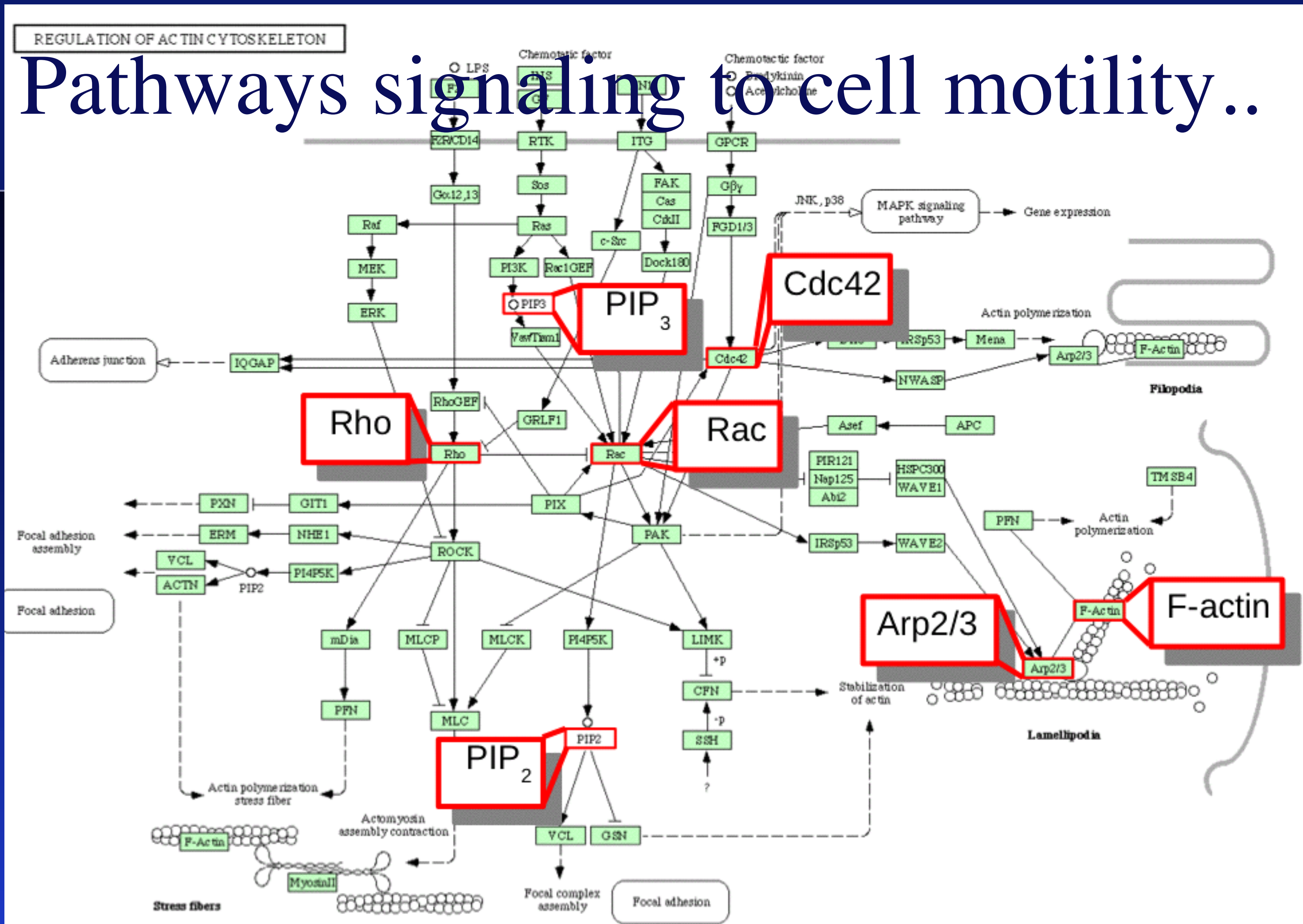
mprime

PIMS

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

Motivation for
"Local pulse analysis":
Why do we need another method?

Pathways signaling to cell motility..

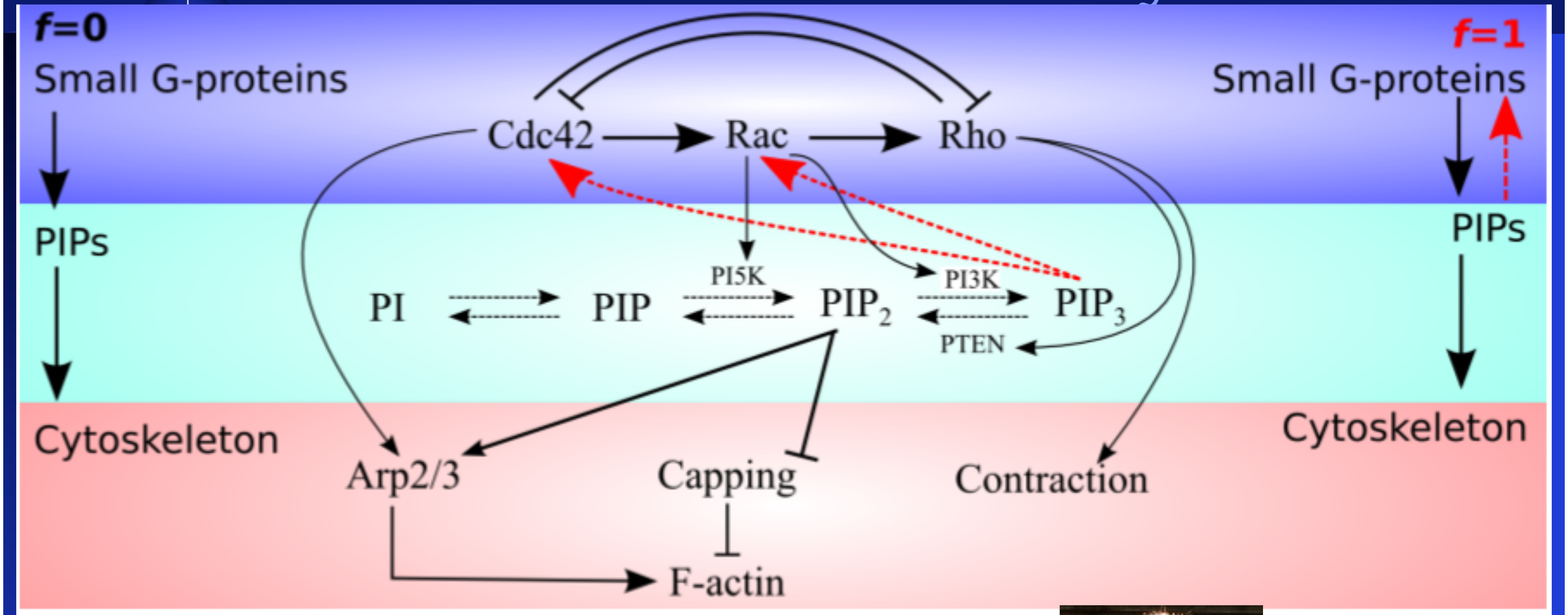


Signaling to actin (KEGG): www.genome.ad.jp/kegg highlights credit: A T Dawes

We want to study these in "layers"

Small GTPAses
Phosphoinositides
Actin

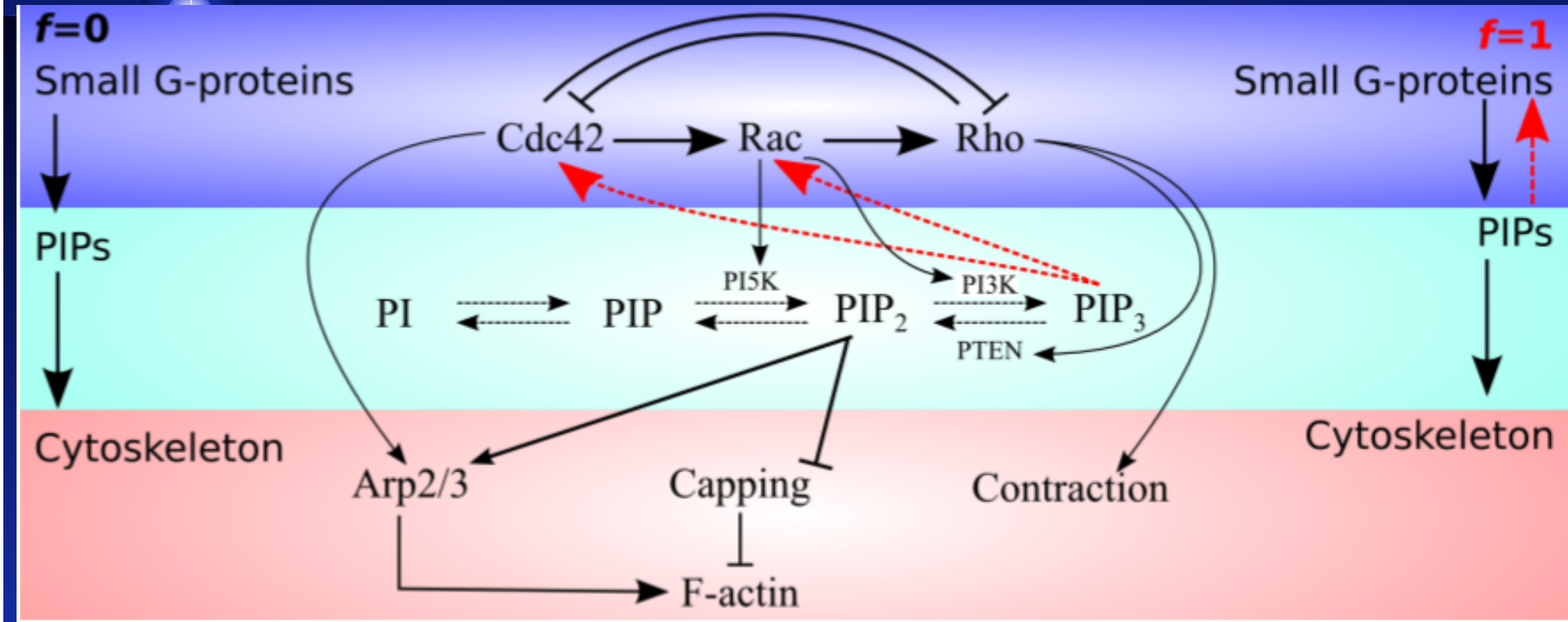
Eventually we need to consider detailed connectivity



AFM Marée

V Grieneisen

These things all diffuse and interact



If we knew all details, this system would be represented by a system of MANY reaction-diffusion equations..

What do we want to know about this system?

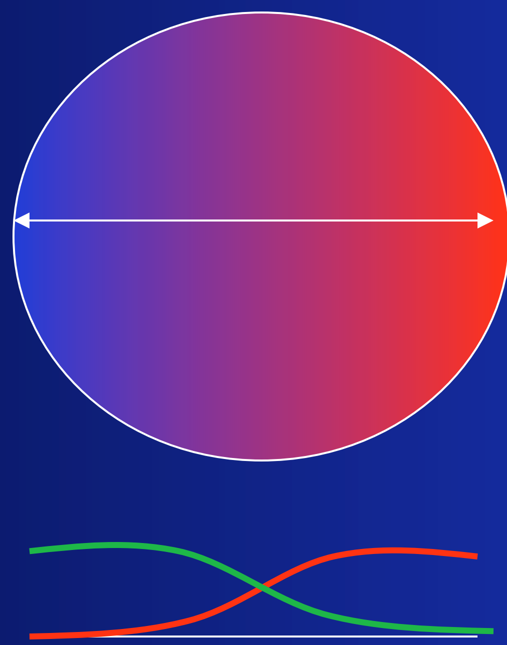
Ans: how does it all work in space & time to produce cell polarization (and motility)

Chemical “pattern” in the (polarizing) cell

Back:

Rho

PTEN



Front:

Rac

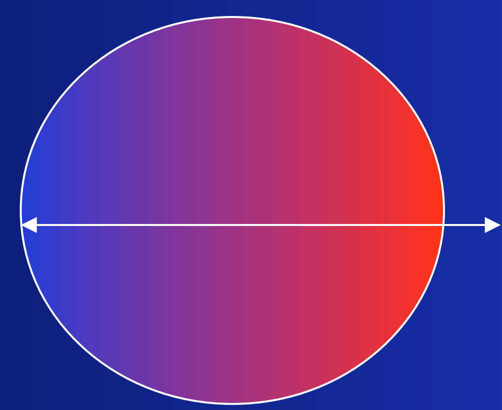
PI3K,

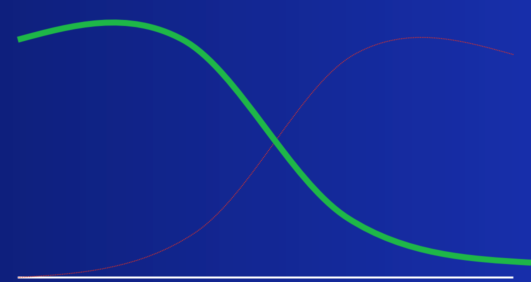
PIP_2, PIP_3

One growing mode leads to polarization

Formation of polarized pattern requires growth of mode:

$$\cos qx \, e^{\sigma t}$$





For $q = n\,\pi / L$

Where $n=1$

(And modes with larger n that have more peaks are inappropriate)

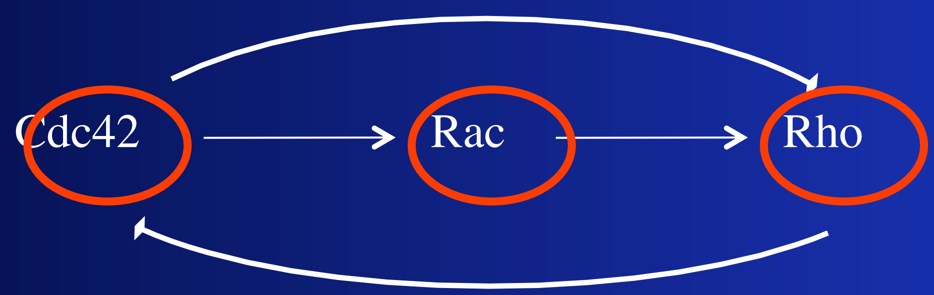
Reduce to one “layer” to simplify

Small GTPAses

Phosphoinositides

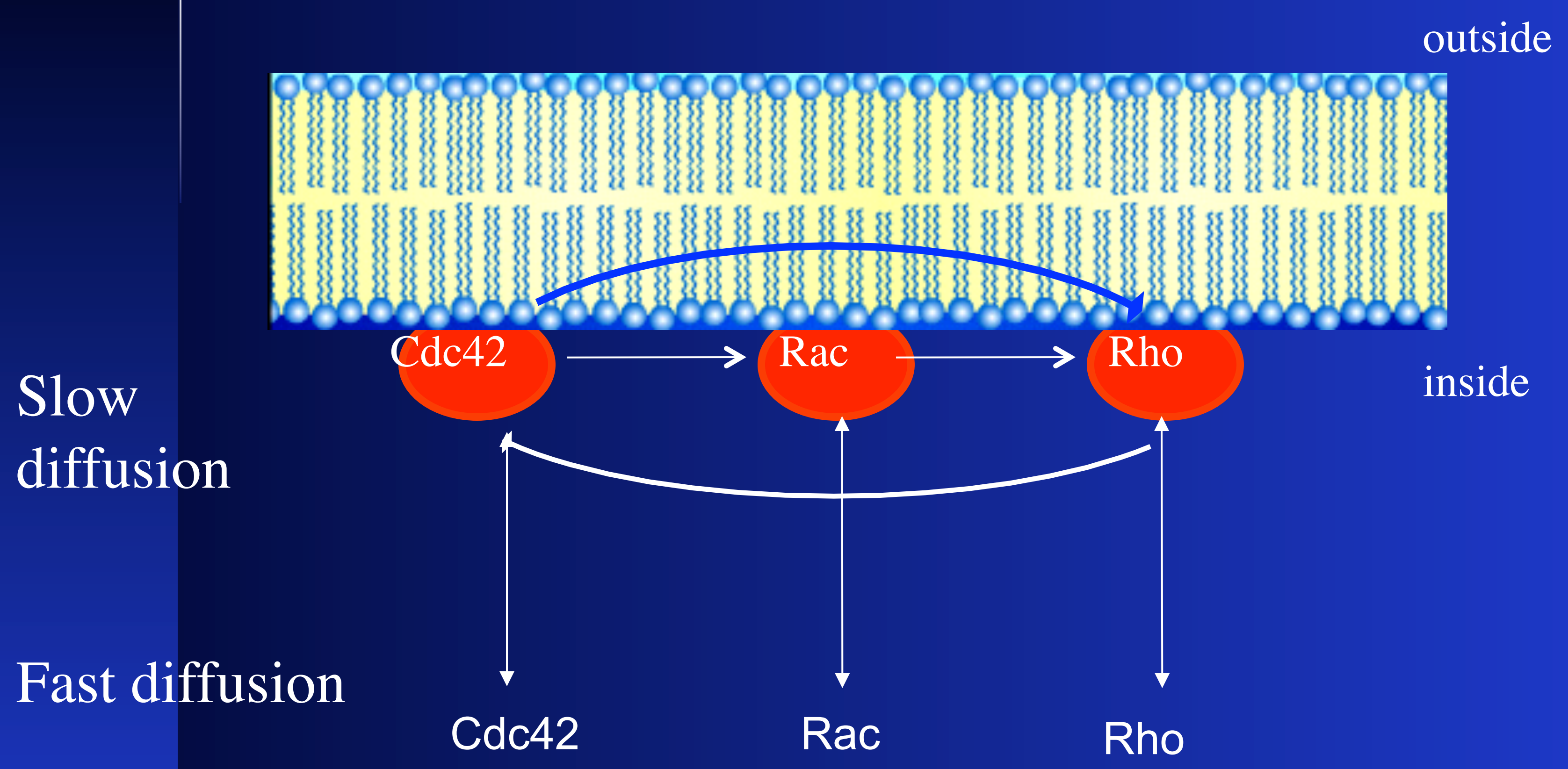
Actin

Chemical interactions in that layer

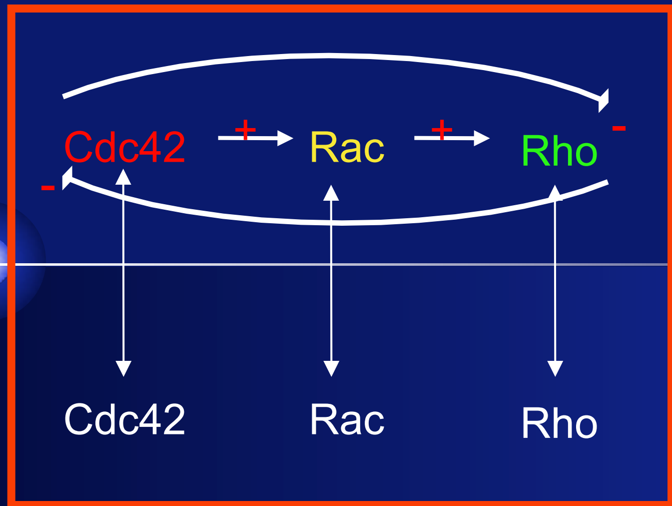


Why? Because Rho GTPases are implicated in setting up that polarization.

Differences in diffusion are inherent to the system



Mathematical model (6 PDEs)



active

$$\frac{\partial C}{\partial t} = f_C(\rho)\left(\frac{C_i}{C_{\mathrm{tot}}}\right) - \delta_C C + D_m \Delta C,$$

$$\frac{\partial R}{\partial t} = f_R(C)\left(\frac{R_i}{R_{\mathrm{tot}}}\right) - \delta_R R + D_m \Delta C R,$$

$$\frac{\partial \rho}{\partial t} = f_\rho(C, R)\left(\frac{\rho_i}{\rho_{\mathrm{tot}}}\right) - \delta_\rho \rho + D_m \Delta \rho,$$

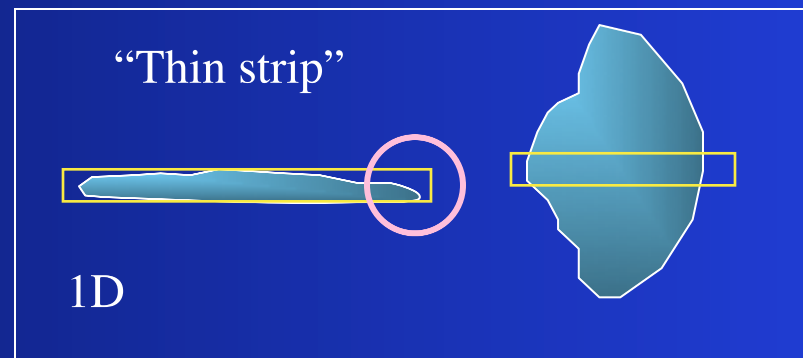
inactive

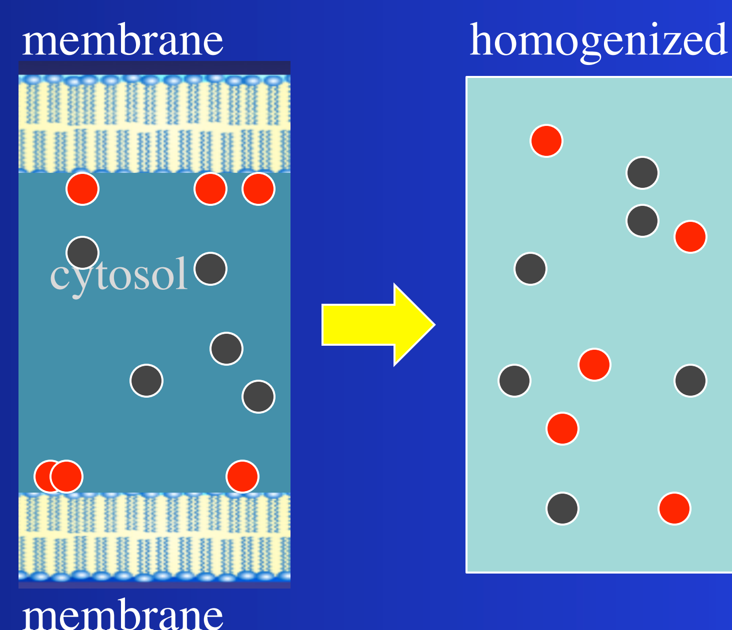
$$\frac{\partial C_i}{\partial t} = -f_C(\rho)\left(\frac{C_i}{C_{\mathrm{tot}}}\right) + \delta_C C + D_{mc} \Delta C_i,$$

$$\frac{\partial R_i}{\partial t} = -f_R(C)\left(\frac{R_i}{R_{\mathrm{tot}}}\right) + \delta_R R + D_{mc} \Delta R_i,$$

$$\frac{\partial \rho_i}{\partial t} = -f_\rho(C, R)\left(\frac{\rho_i}{\rho_{\mathrm{tot}}}\right) + \delta_\rho \rho + D_{mc} \Delta \rho_i.$$

$D_{mc} > D_m$





Can we analyse this mathematically?

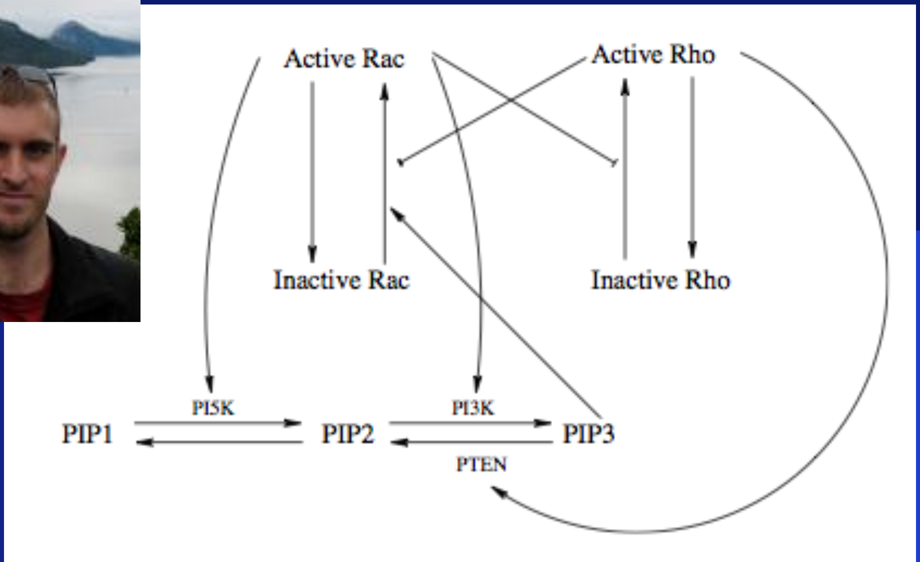
As is, a system of 6 PDEs is challenging to understand analytically. This is one motivation for easier method (LPA)

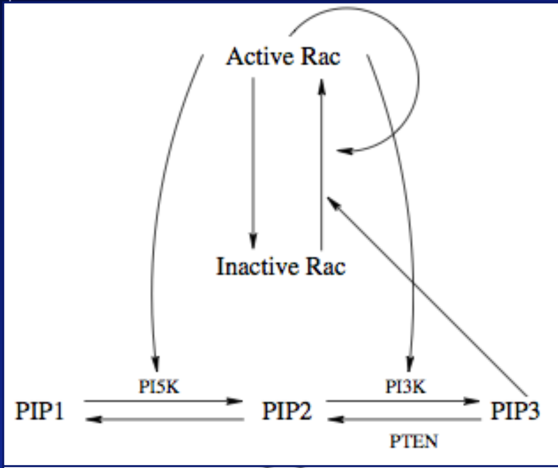
Models develop in response to experiments.

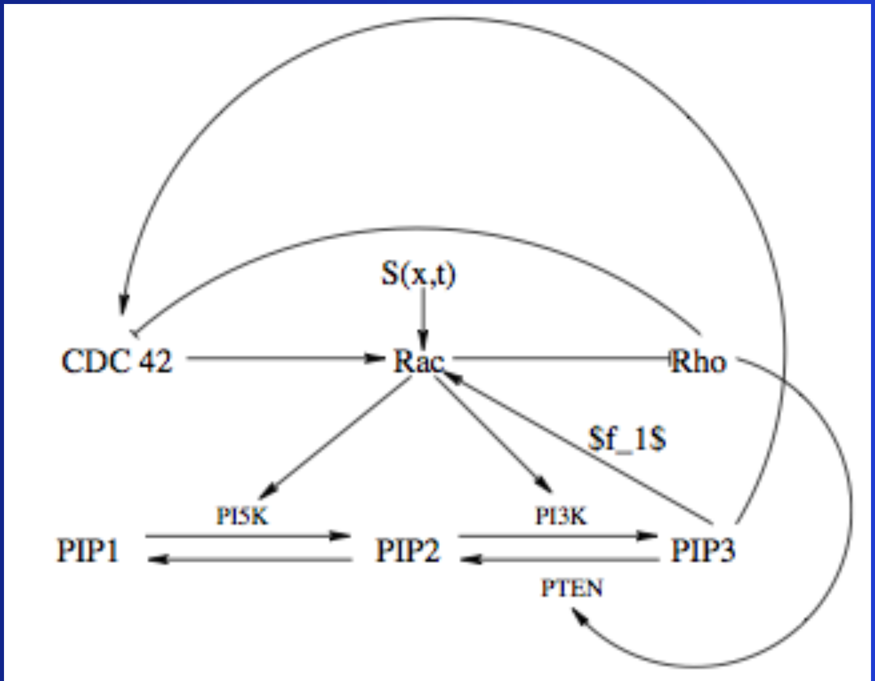
We want a handy way to understand them

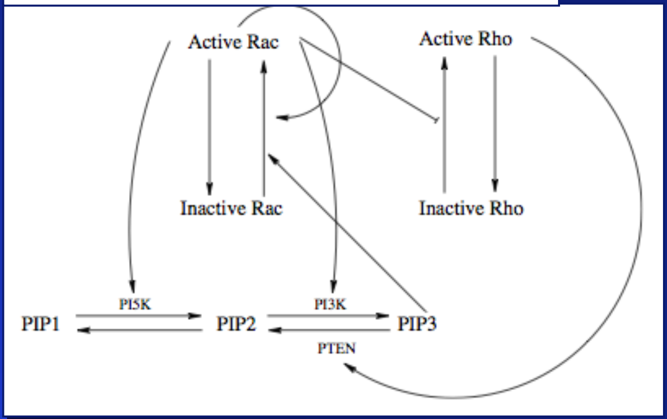
New Models

Bill Holmes, Ben Lin, Andre Levchenko, LEK







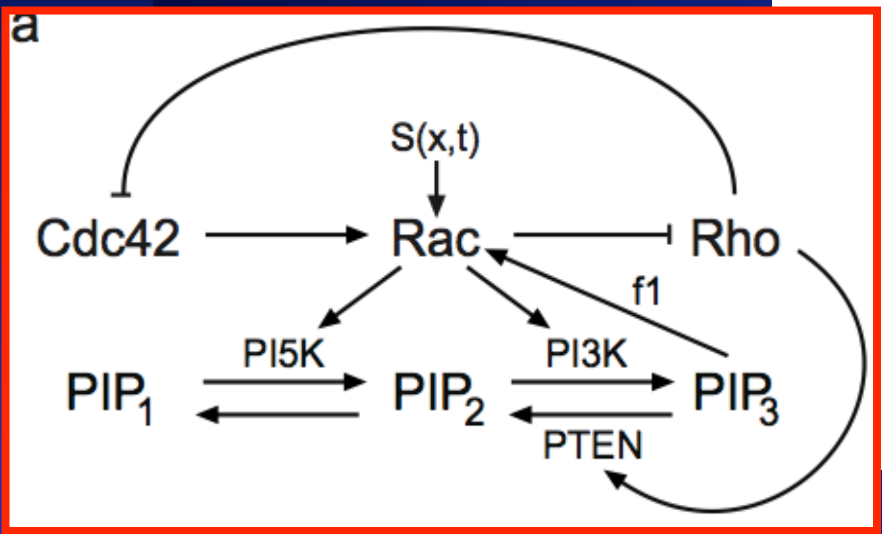


Typical sets of equations

$$\frac{\partial C}{\partial t} = h + D_m \Delta C \qquad \frac{\partial C^i}{\partial t} = -h + D_{mc} \Delta C^i$$

$$\frac{\partial R}{\partial t} = f + D_m \Delta R \qquad \frac{\partial R^i}{\partial t} = -f + D_{mc} \Delta R^i$$

$$\frac{\partial \rho}{\partial t} = g + D_m \Delta \rho \qquad \frac{\partial \rho^i}{\partial t} = -g + D_{mc} \Delta \rho^i$$



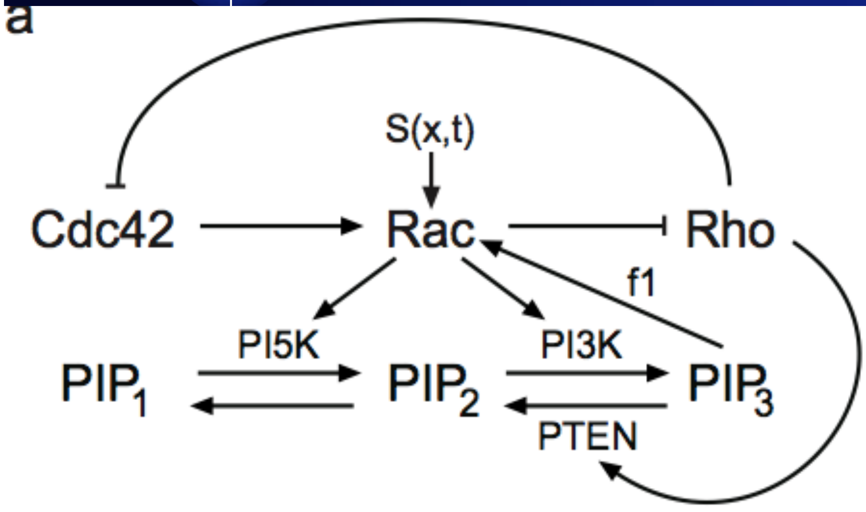
$$h = \left(\frac{I_c}{1 + \left(\frac{\rho}{a_1}\right)^n} + f_2 \frac{P3}{P3b} \right) \frac{C_i}{C_t} - \delta_C C$$

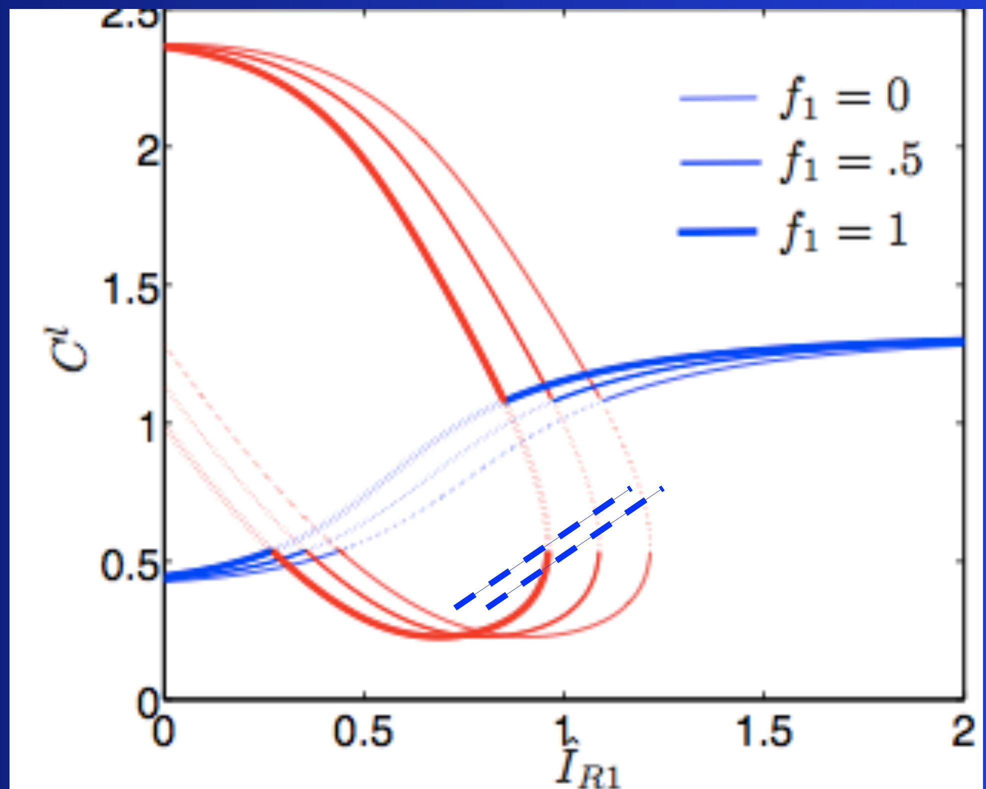
$$f = \left((I_R + \alpha C) + f_1 \frac{P3}{P3b} + S(x,t) \right) \frac{R_i}{R_t} - \delta_R R$$

$$g = \frac{I_\rho}{1 + \left(\frac{R}{a_2}\right)^n} \frac{\rho_i}{\rho_t} - \delta_\rho \rho$$

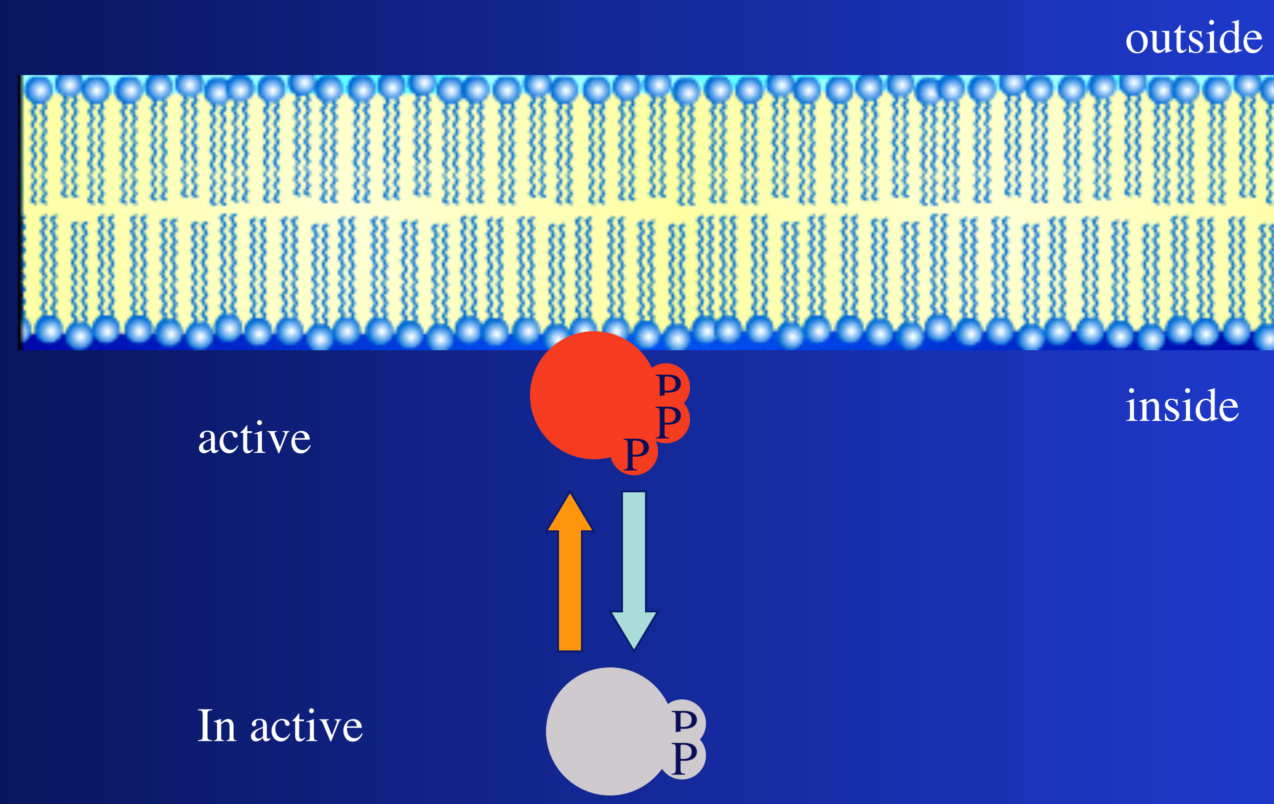
… Plus equations for P_1, P_2, P_3

LPA helps to understand how these models behave

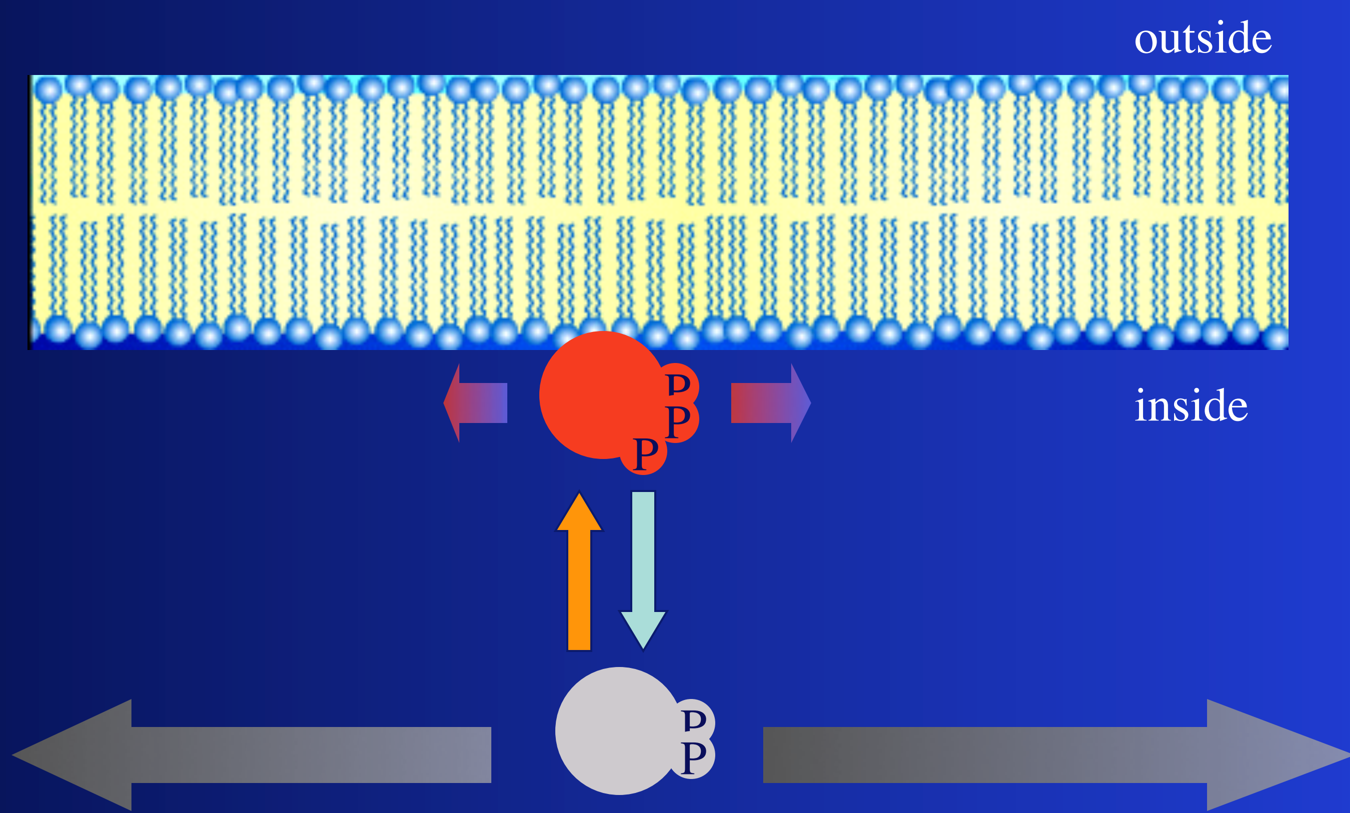




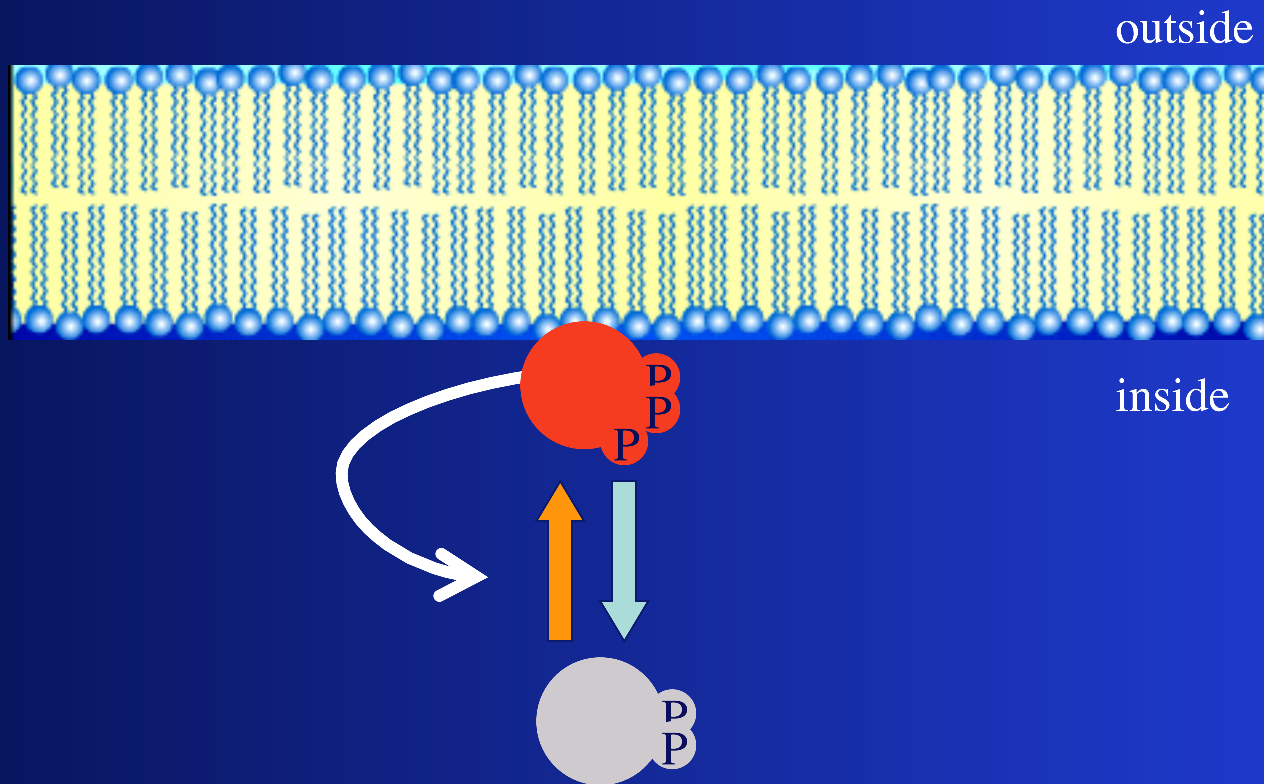
Simplified view:



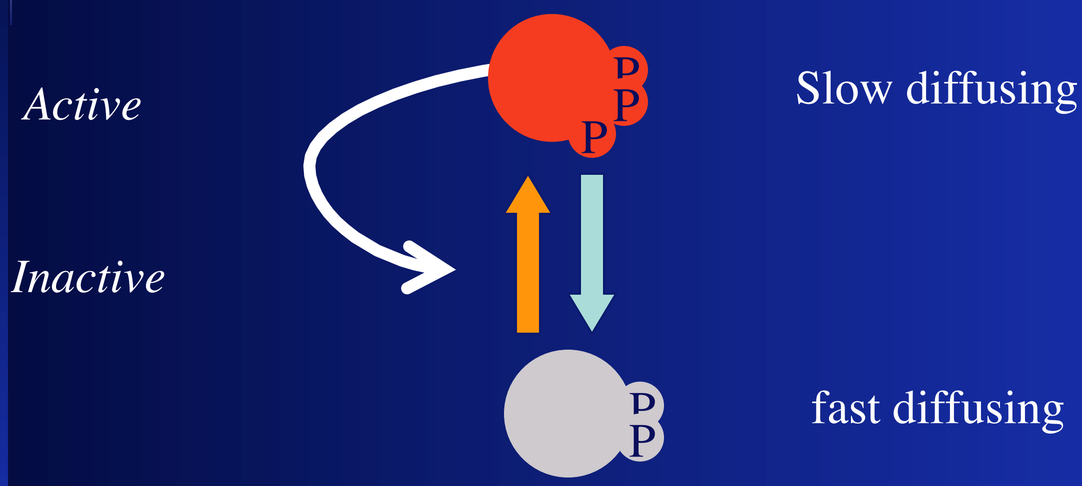
100-1000 fold difference in rates of diffusion



Caricature model



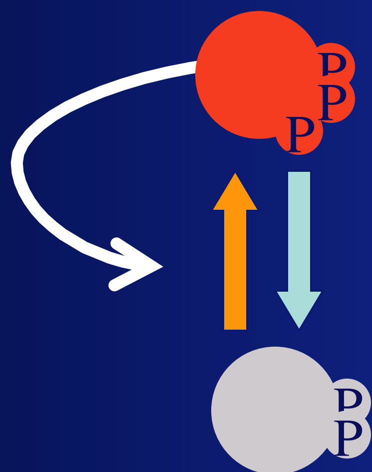
Only two variables



RD model

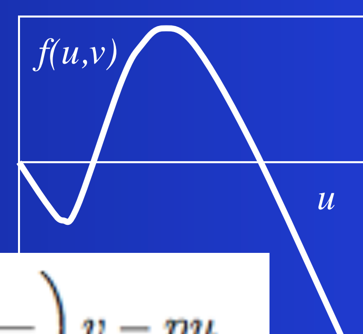
Active

Inactive



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

$D_u << D_v$

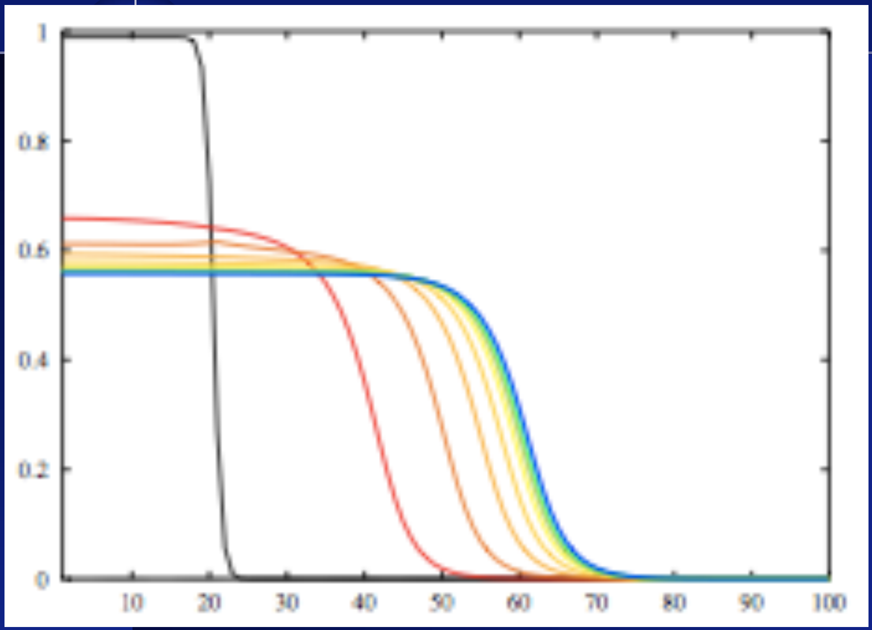


$$f(u,v) = \eta\left(\delta + \frac{\gamma u^2}{m^2+u^2}\right)v - \eta u$$

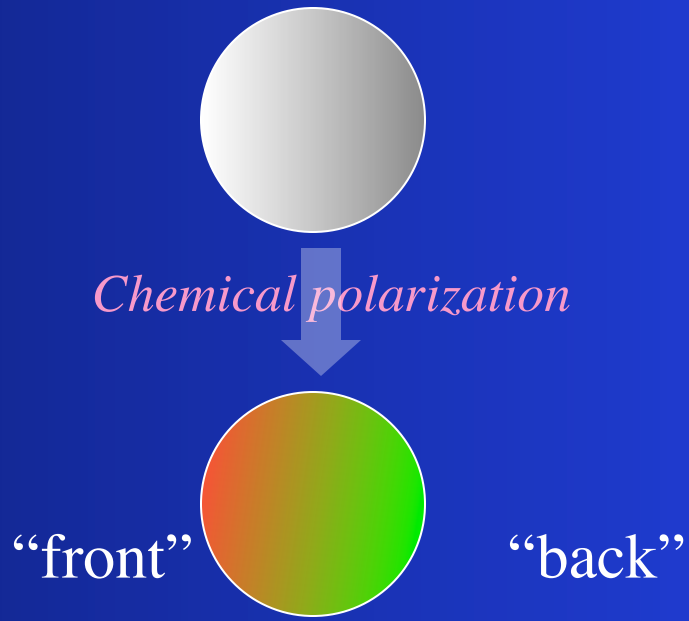
A Jilkine

Y Mori

WP = polarization



“front” “back”



A stable, robust way to chemically distinguish front from back.

Methods of analysis, RD systems

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

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

$D_u << D_v$

Local pulse analysis

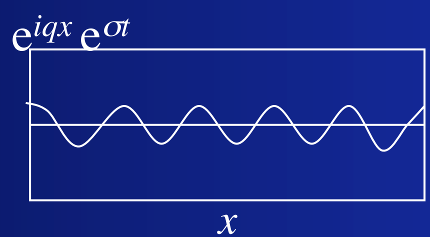
(Traditional) Linear Stability analysis

Linearized PDEs:

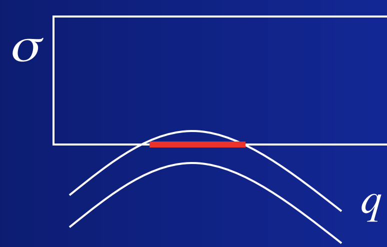
$$\frac{\partial a}{\partial t} = c_{11}a + c_{12}b + D_A \frac{\partial^2 a}{\partial x^2}$$

$$\frac{\partial b}{\partial t} = c_{21}a + c_{22}b + D_B \frac{\partial^2 b}{\partial x^2}$$

Perturbations:



Growing Modes:



Methods of analysis, RD systems

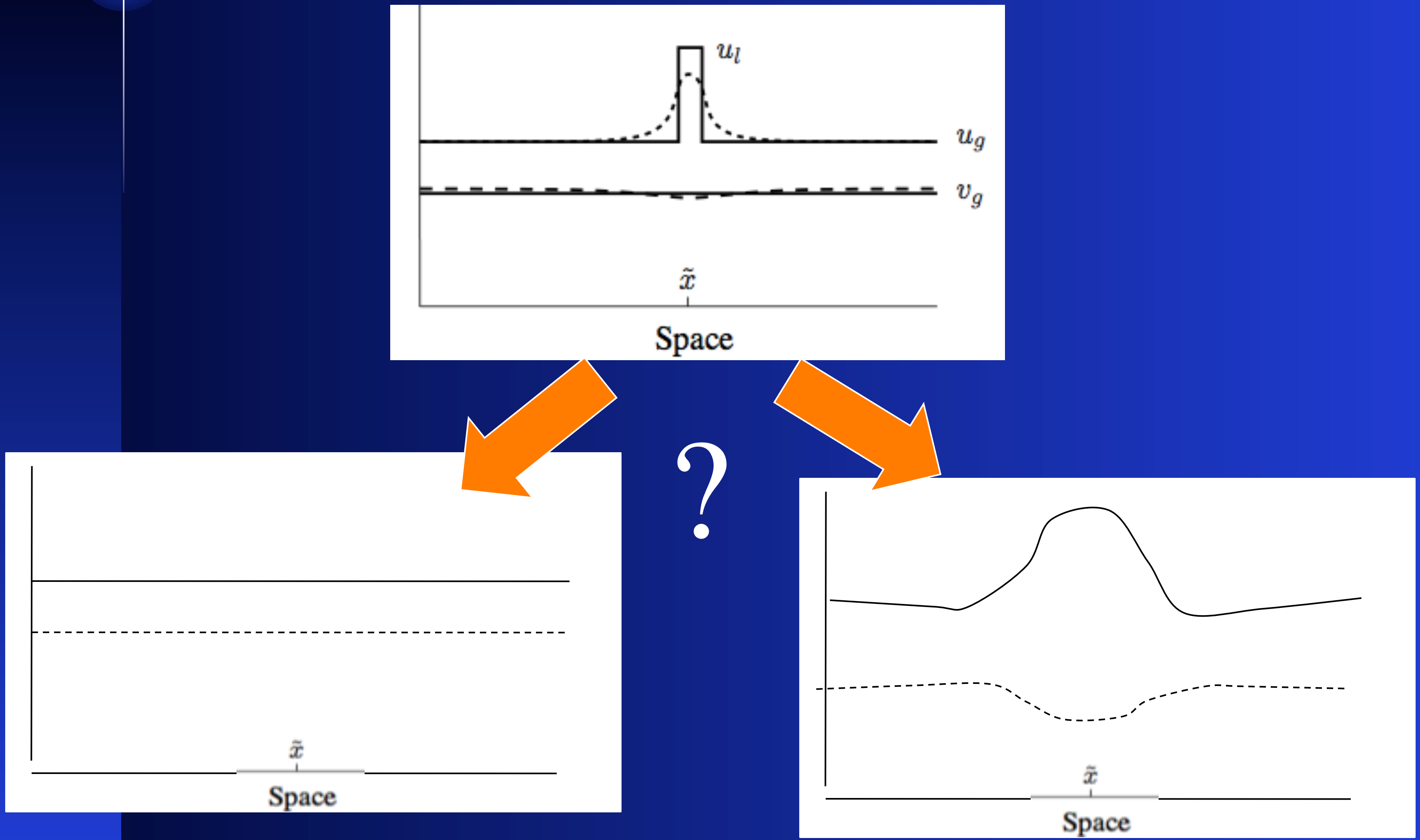
$$\frac{\partial u}{\partial t}(x,t) = f(u,v) + D_u \Delta u,$$
$$\frac{\partial v}{\partial t}(x,t) = g(u,v) + D_v \Delta v,$$

$D_u \ll D_v$

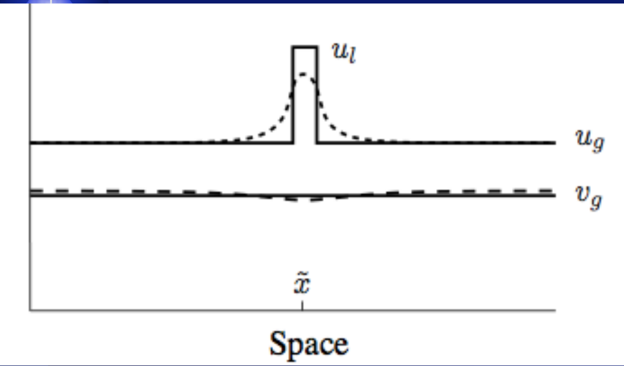
Local pulse analysis

Due to: Stan Maree, Veronica Grieneisen, Bill Holmes

Local pulse analysis



Local Pulse Analysis



Approximate PDEs by ODEs for local and global variables:

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

$D_u << D_v$

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

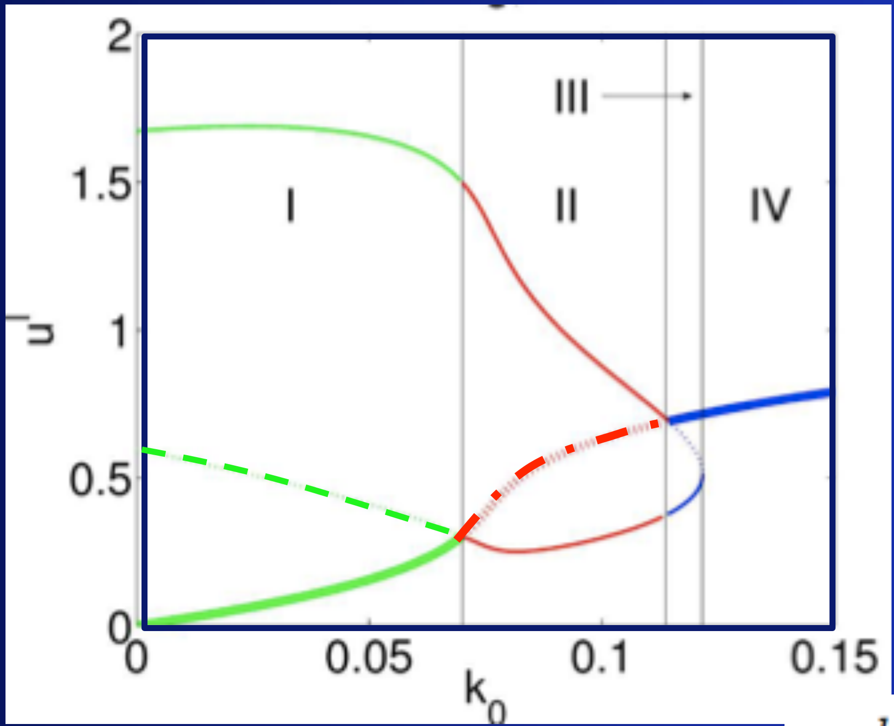
$D_u \to 0 \quad D_v \to \infty$

Bifurcation structure (LPA)

$$u_t(x,t) = v(k_0 + \frac{\gamma u^n}{K^n + u^n}) - \delta u + D_u \triangle u$$
$$v_t(x,t) = -f(u,v) + D_v \triangle v$$

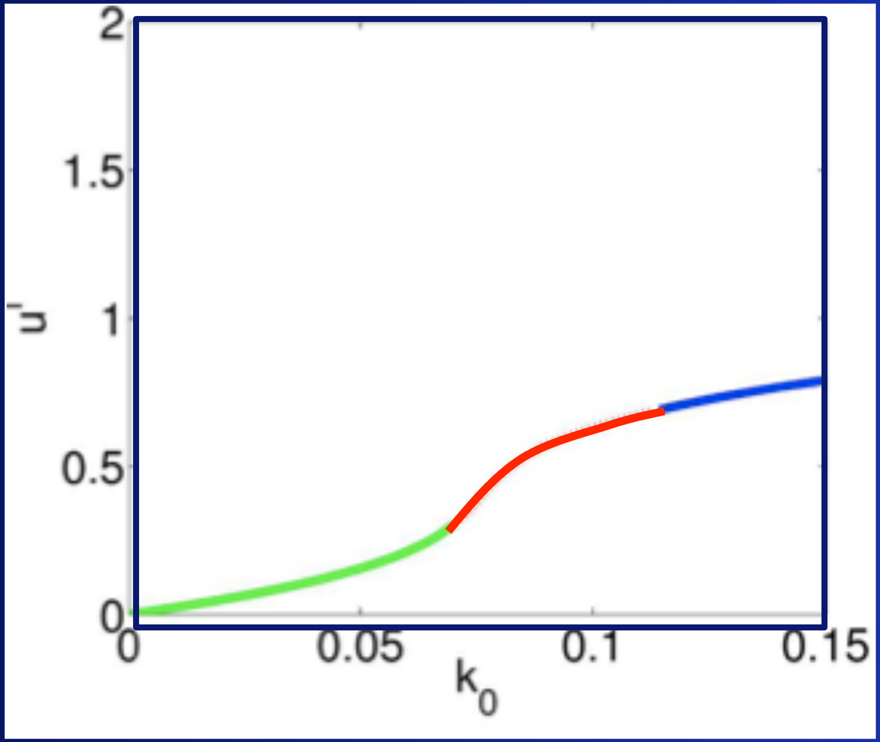
$$\frac{du^g}{dt}(x,t) = f(u^g, v^g),$$
$$\frac{dv^g}{dt}(x,t) = g(u^g, v^g),$$
$$\frac{du^l}{dt}(x,t) = f(u^l, v^g)$$

Bifurcation structure (LPA)



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

Bifurcation structure of well mixed system



$$u_t(x,t) = v(k_0 + \frac{\gamma u^n}{K^n + u^n}) - \delta u$$
$$v_t(x,t) = -f(u,v)$$

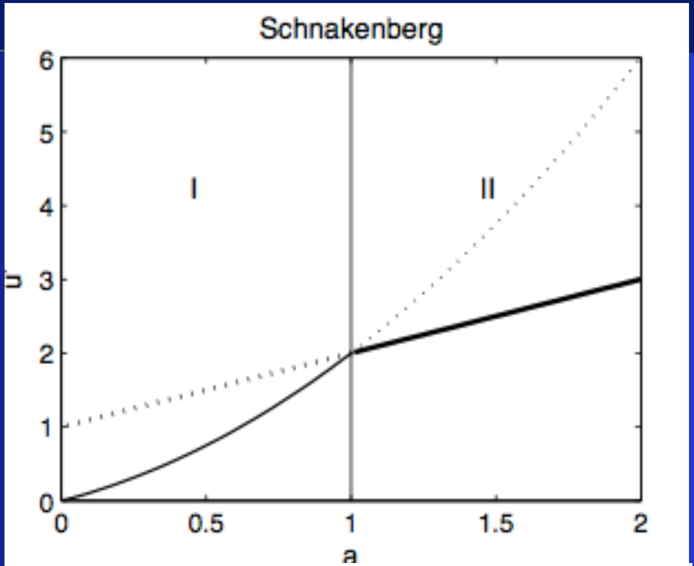
Other sys.

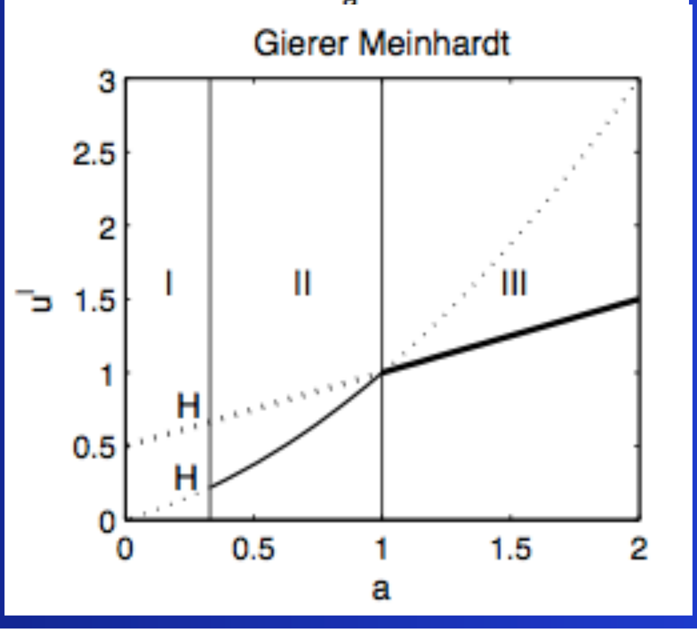
Schnakenberg

$$u_t(x,t) = a - u + u^2 v + D_u \Delta u$$
$$v_t(x,t) = b - u^2 v + D_v \Delta v,$$

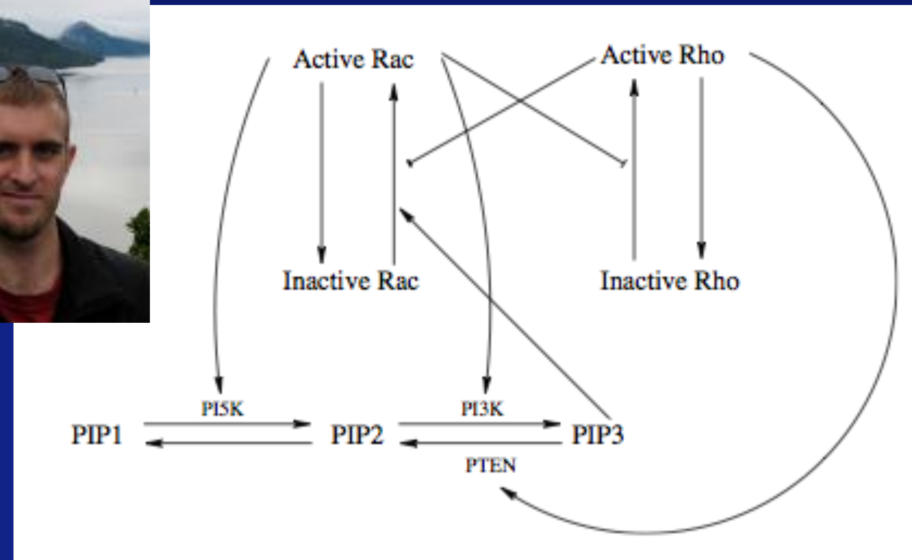
Gierer-Meinhardt

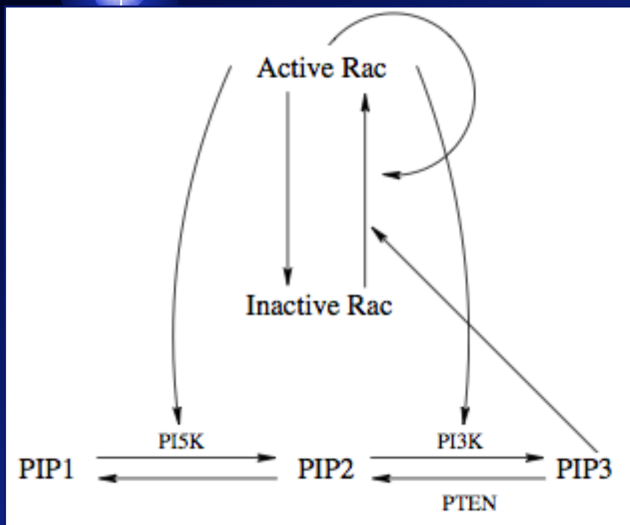
$$u_t(x,t) = a - bu + \frac{u^2}{v(1+Ku^2)} + \Delta u$$
$$v_t(x,t) = u^2 - v + D\Delta v.$$

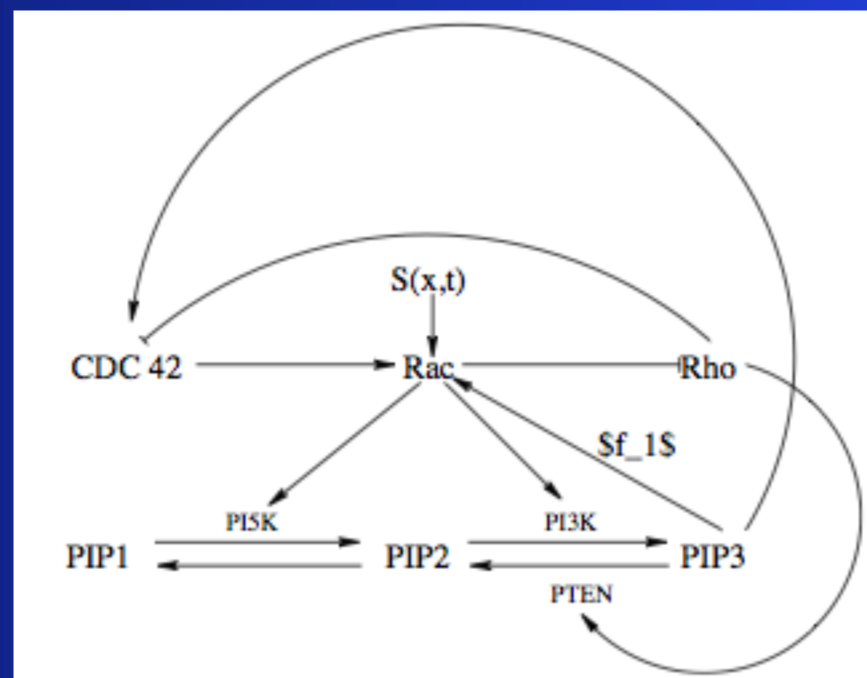


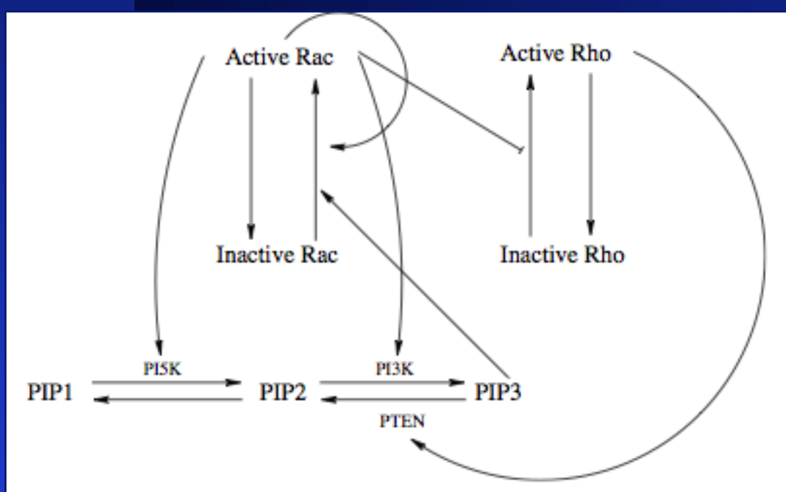


New Models


Active Rac
Active Rho
Inactive Rac
Inactive Rho
PIP1
PI5K
PIP2
PI3K
PIP3
PTEN


Active Rac
Inactive Rac
PIP1
PI5K
PIP2
PI3K
PIP3
PTEN


S(x,t)
CDC 42
Rac
Rho
f_1
PIP1
PI5K
PIP2
PI3K
PIP3
PTEN

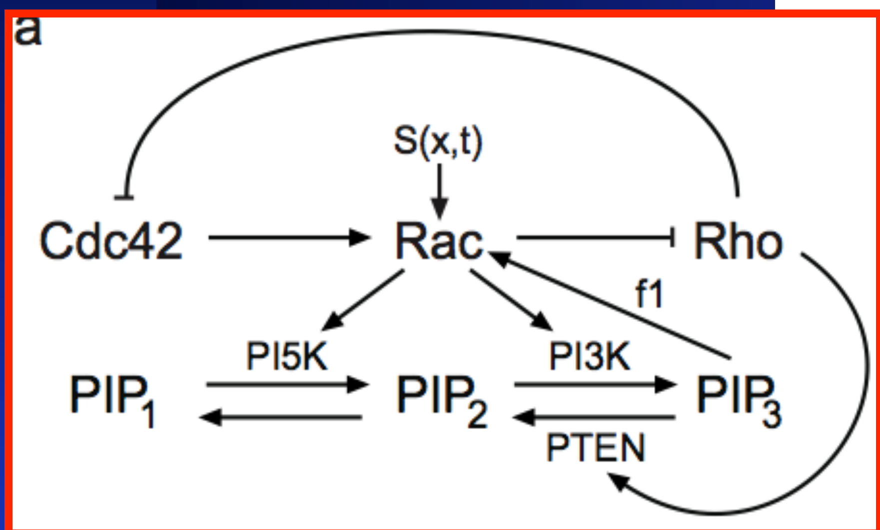

Active Rac
Active Rho
Inactive Rac
Inactive Rho
PIP1
PI5K
PIP2
PI3K
PIP3
PTEN

Revised biochemistry

$$\frac{\partial C}{\partial t} = h + D_m \Delta C \qquad \frac{\partial C^i}{\partial t} = -h + D_{mc} \Delta C^i$$

$$\frac{\partial R}{\partial t} = f + D_m \Delta R \qquad \frac{\partial R^i}{\partial t} = -f + D_{mc} \Delta R^i$$

$$\frac{\partial \rho}{\partial t} = g + D_m \Delta \rho \qquad \frac{\partial \rho^i}{\partial t} = -g + D_{mc} \Delta \rho^i$$



$$h = \left(\frac{I_c}{1 + \left(\frac{\rho}{a_1}\right)^n} + f_2 \frac{P3}{P3b} \right) \frac{C_i}{C_t} - \delta_C C$$

$$f = \left((I_R + \alpha C) + f_1 \frac{P3}{P3b} + S(x,t) \right) \frac{R_i}{R_t} - \delta_R R$$

$$g = \frac{I_\rho}{1 + \left(\frac{R}{a_2}\right)^n} \frac{\rho_i}{\rho_t} - \delta_\rho \rho$$

… Plus equations for P_1, P_2, P_3

Revised biochemistry