Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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Introduction

What are some of the major questions in cell biology?

(That require quantitative methods and reasoning)

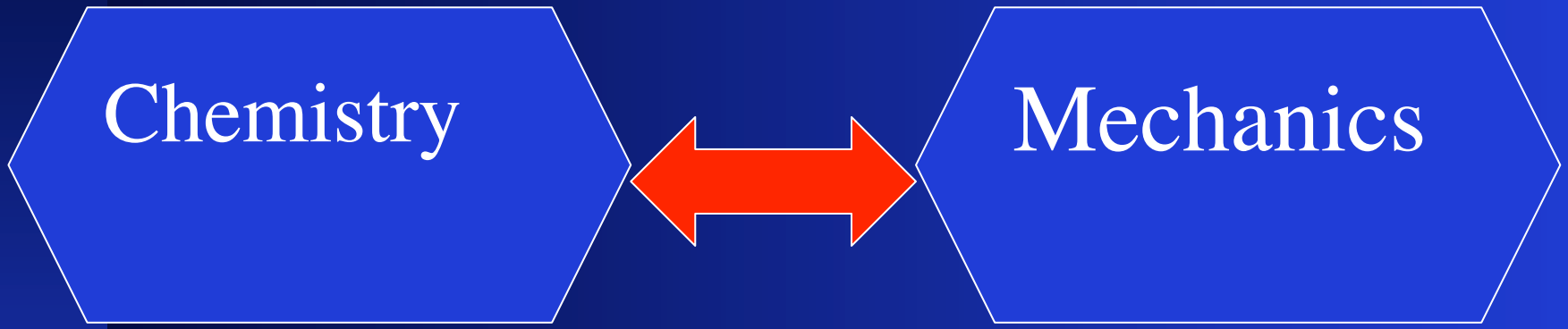
Big questions

- How does a cell know when to divide?
- How does it coordinate the process of division ("cytokinesis")?

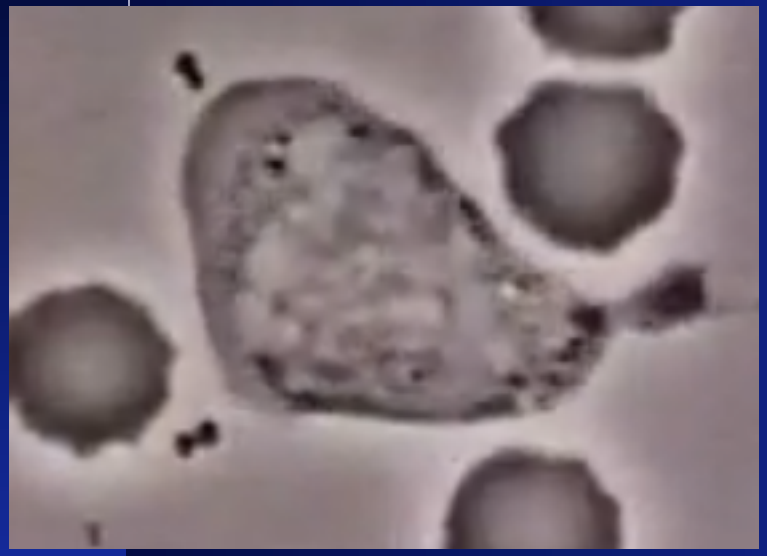
- How do cells move? What guides them?
- How do cells sense "directional cues"?

- How does a multi-cellular organism get its form/shape? ("morphogenesis")

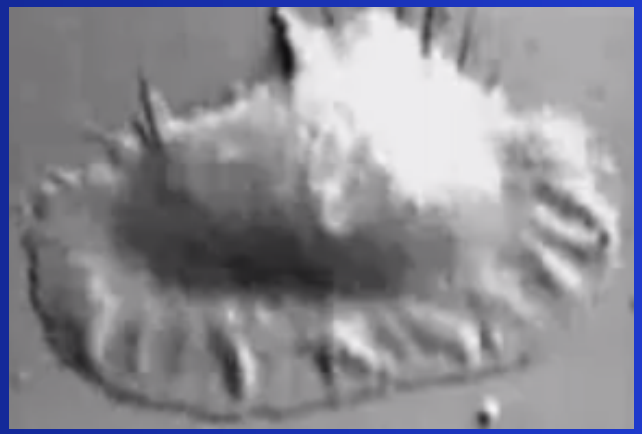
The mechanisms:



Some movies..



http://www.youtube.com/watch?v=I_xh-bkiv_c&feature=fvsr



http://www.youtube.com/watch?v=HGkxo2mmLXY

Neutrophil chemotaxis

http://www.youtube.com/watch?v=ZUUfdP87Ssg

Cells that can crawl

Neutrophils:

Orion Weiner: http://cvri.ucsf.edu/~weiner/

Slime mold amoeba

Figures removed for copyright reasons

Tumor

Huang et al
Nature 2003

keratocytes:

Svitkina TM, Borisy GG. (1999).J Cell Biol. 31;145(5):1009-26.

Dictyostelium discoideum (WT and Latrunc)
Sasaki et al (2004) JCB, Volume 167, Number 3, 505-518

What's "under the hood"?

Fish
keratocyte

cytoskeleton

(actin)

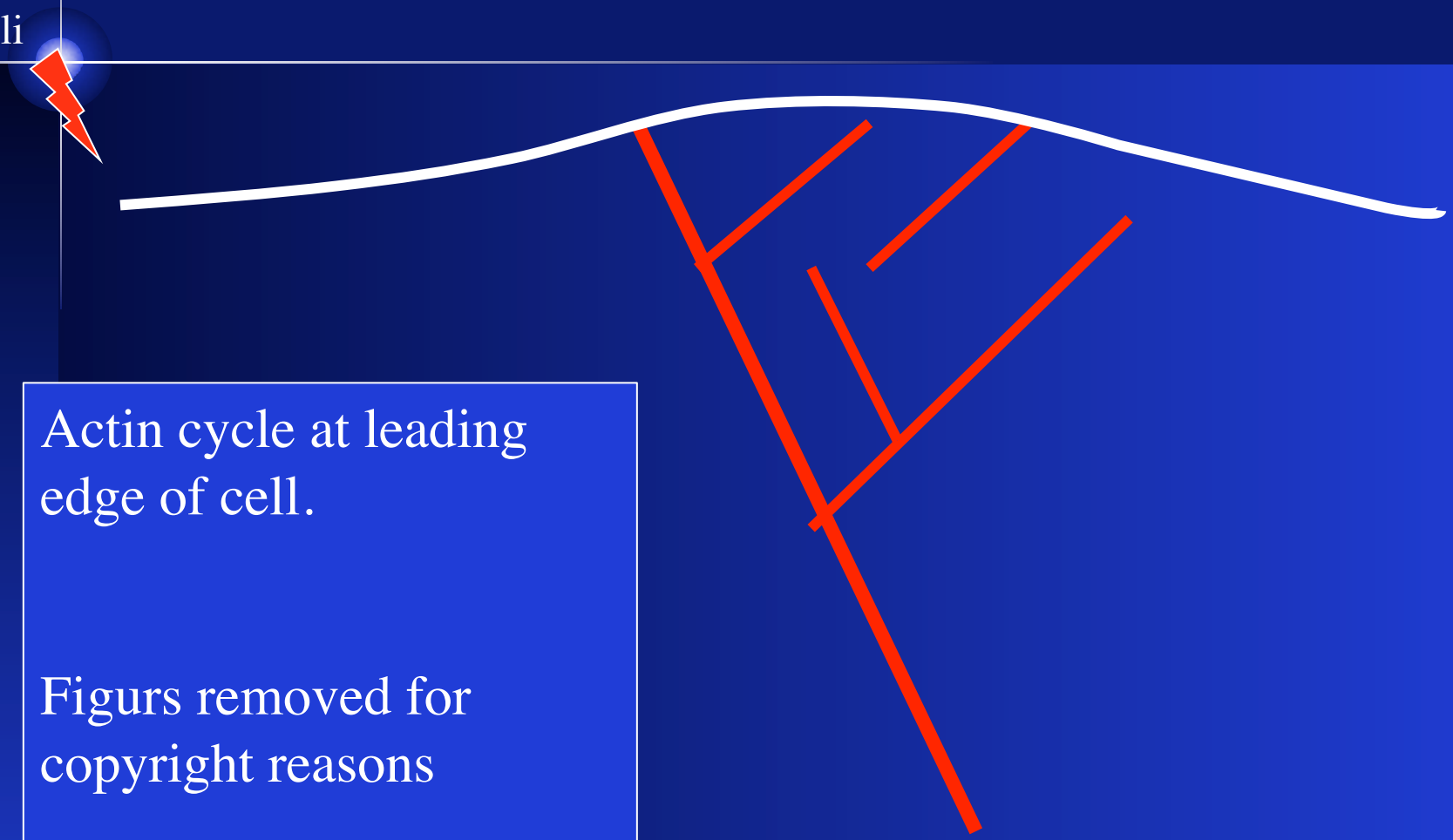
Figures removed for copyright reasons

Actin meshwork at cell edge

)

Pollard & Borisy (2003) Cell 112: 453-465

The cytoskeleton is dynamic



Actin cycle at leading edge of cell.

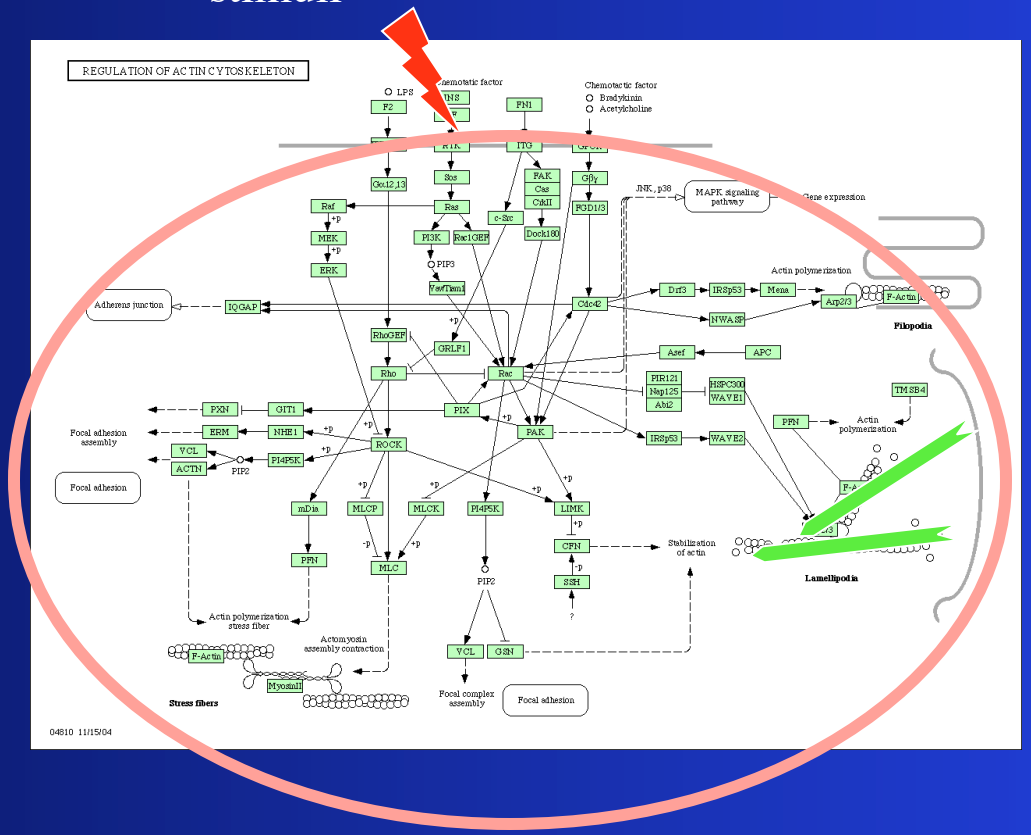
Figurs removed for copyright reasons

Pollard (2003) **The cytoskeleton, cellular motility and the reductionist agenda** *Nature* **422**: 741-745

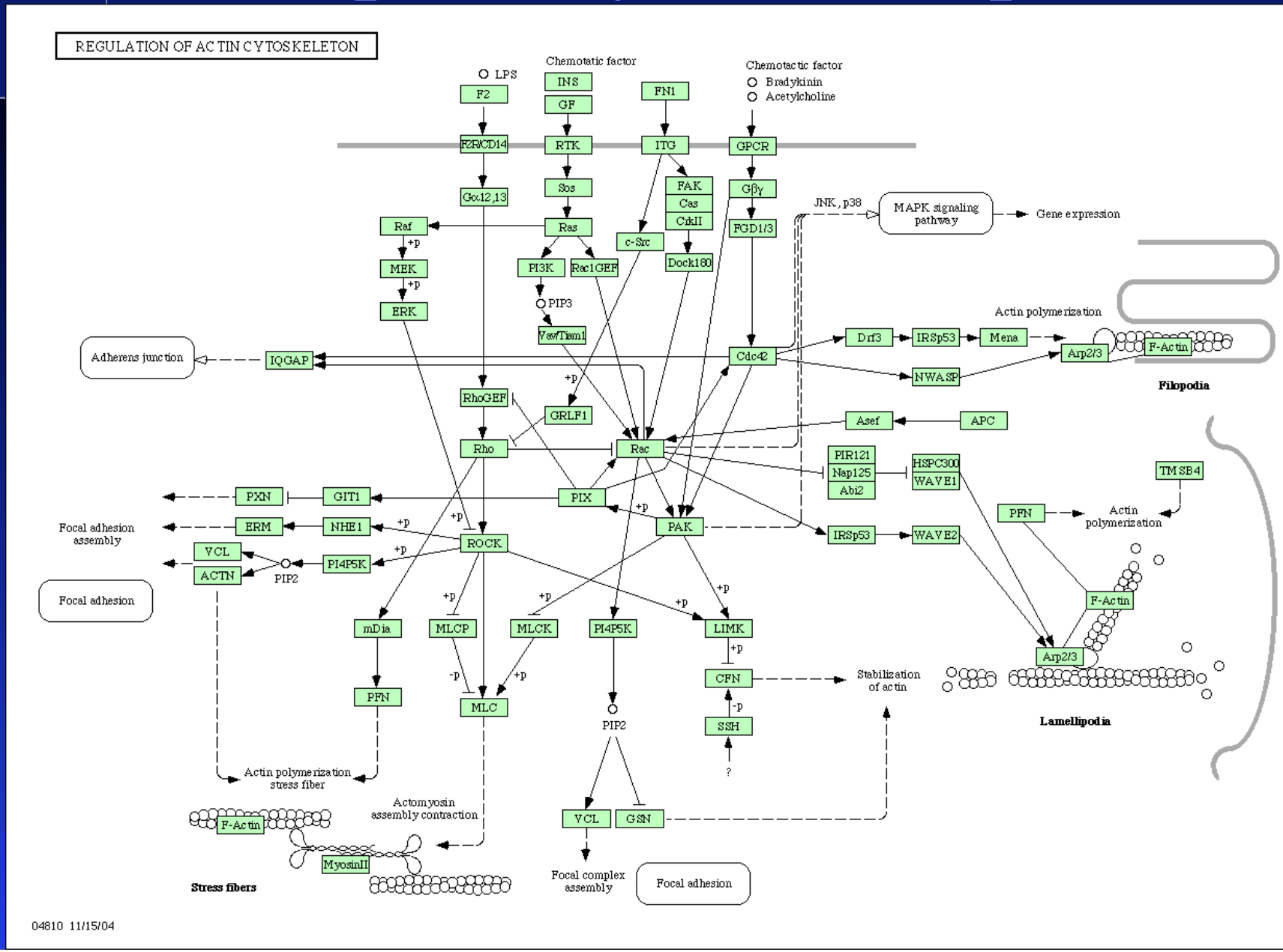
It is regulated by biochemical pathways:

Intricate internal biochemistry channels stimuli to actin.

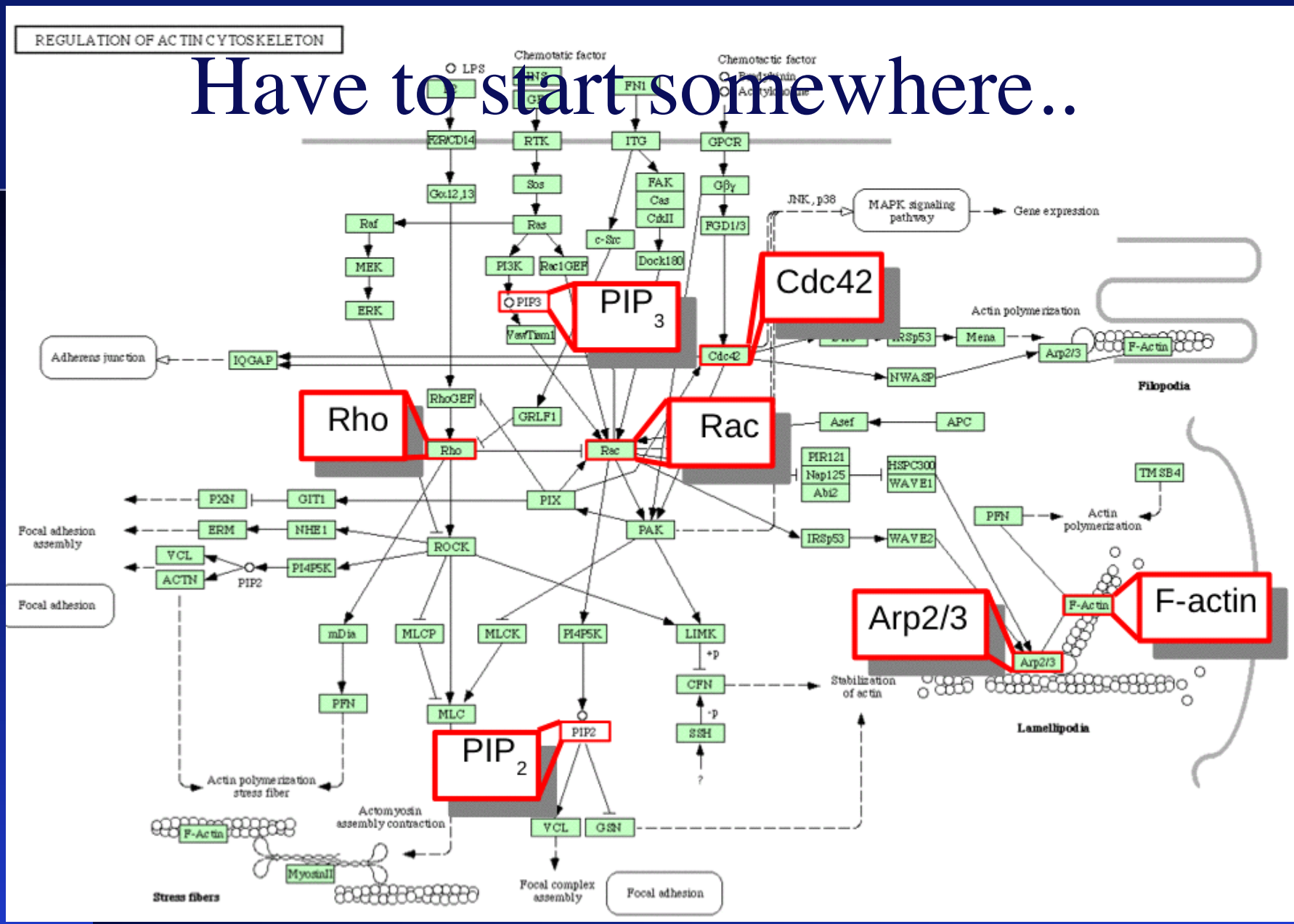
stimuli



The pathways are complex



Have to start somewhere..



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

Consider signaling “layers”

Small GTPAses

Phosphoinositides

Actin

First understand each layer well..

Small GTPAses

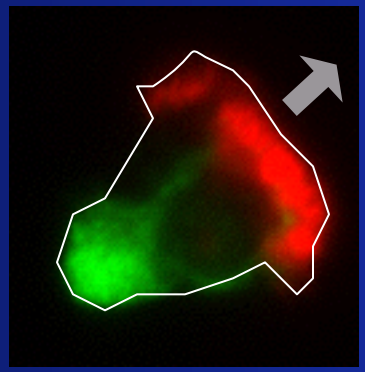
Phosphoinositides

Actin

Biochemical polarization

Rear

Front



Henry Bourne's Lab

RhoA actin

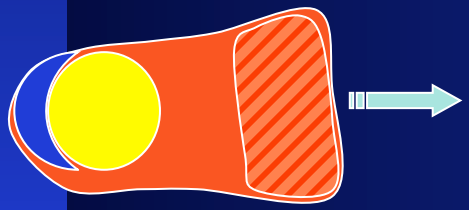
Polarized distribution in stimulated cells

Figurs removed for copyright reasons

Cdc42 (red) in front
Nabant et al (2004) Science

Rac (green) in front
(FRET, fibroblast)
Krayanov et al (2000), *Science*.

Rho (green) in back
actin (red) in front
(neutrophil)
Bourne lab
http://www.cmpharm.ucsf.edu/bourne/

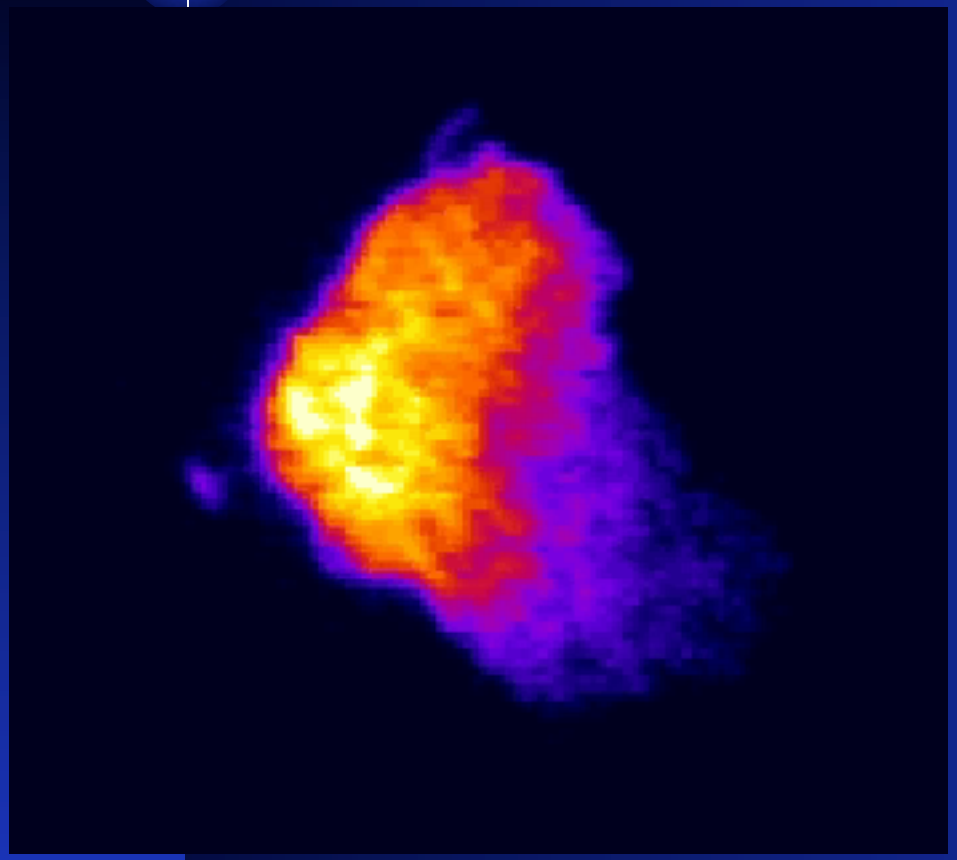


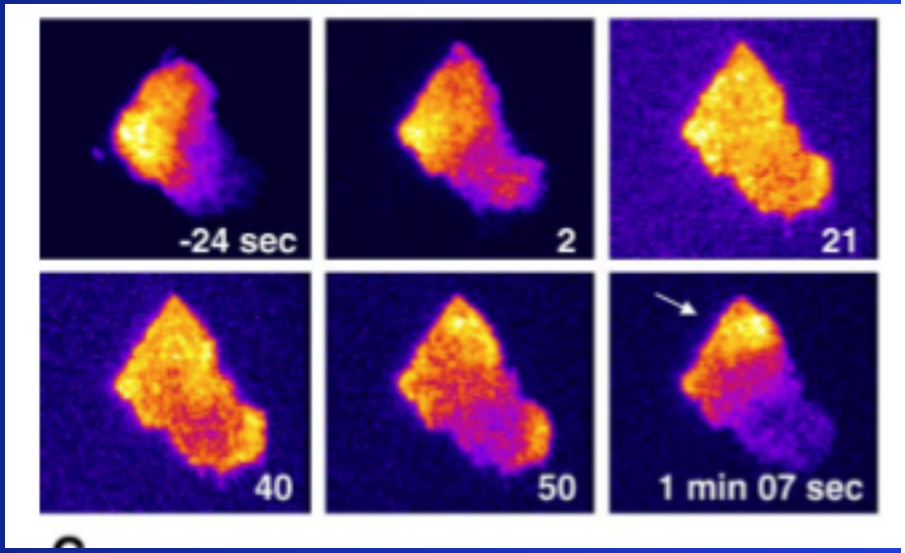
Rho Cdc42, Rac

Mutual exclusion: Cdc42 vs Rho

Fig panels credit: Jilkine

Signaling proteins

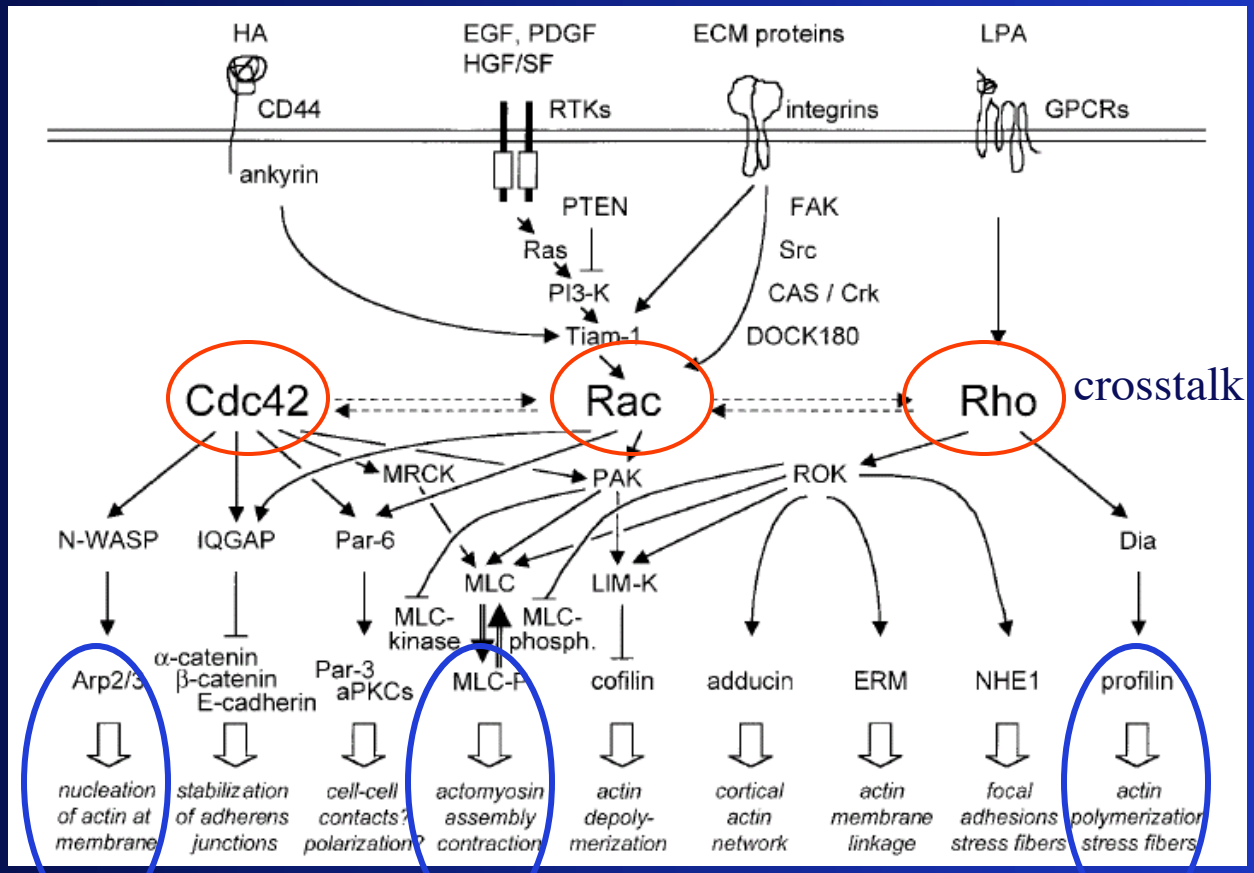




Rac in stimulated cells

Weiner et al (2007) PLoS Biology 5

Rho GTPases (Cdc42, Rac, Rho)



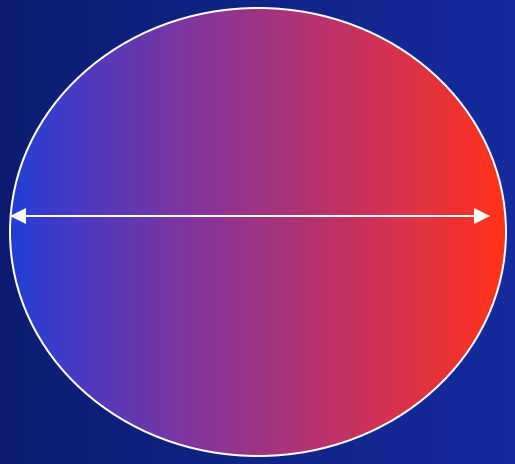
Schmitz et al (2000) Expt Cell Res 261:1-12

"Front vs Back"

Back:

Rho

PTEN

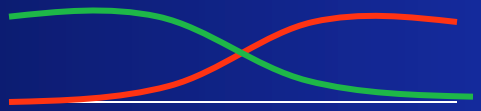


Front:

Rac

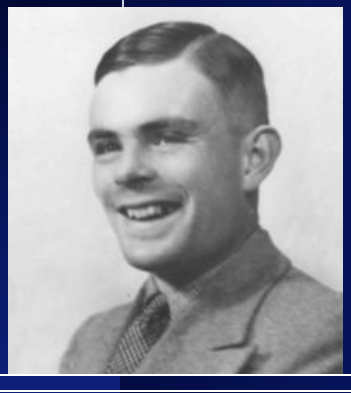
PI3K,

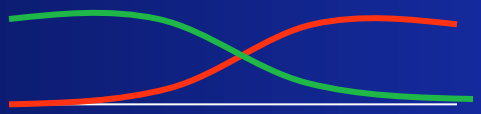
PIP_2, PIP_3



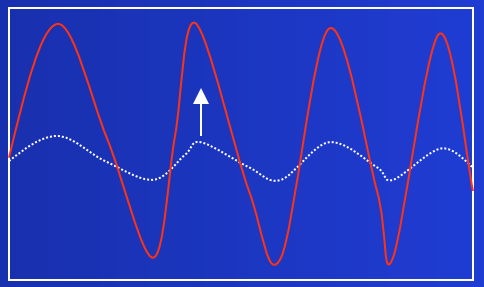
What process(es) account for segregation of chemicals?

Consider mathematics of pattern formation



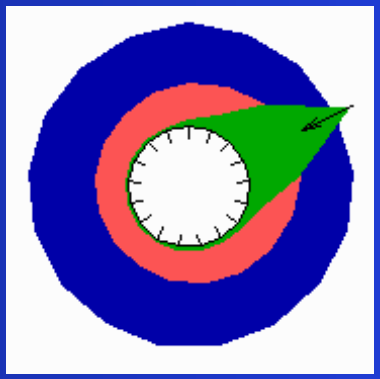


Turing: RD systems
diffusive instability



Local activation
Long-range inhibition

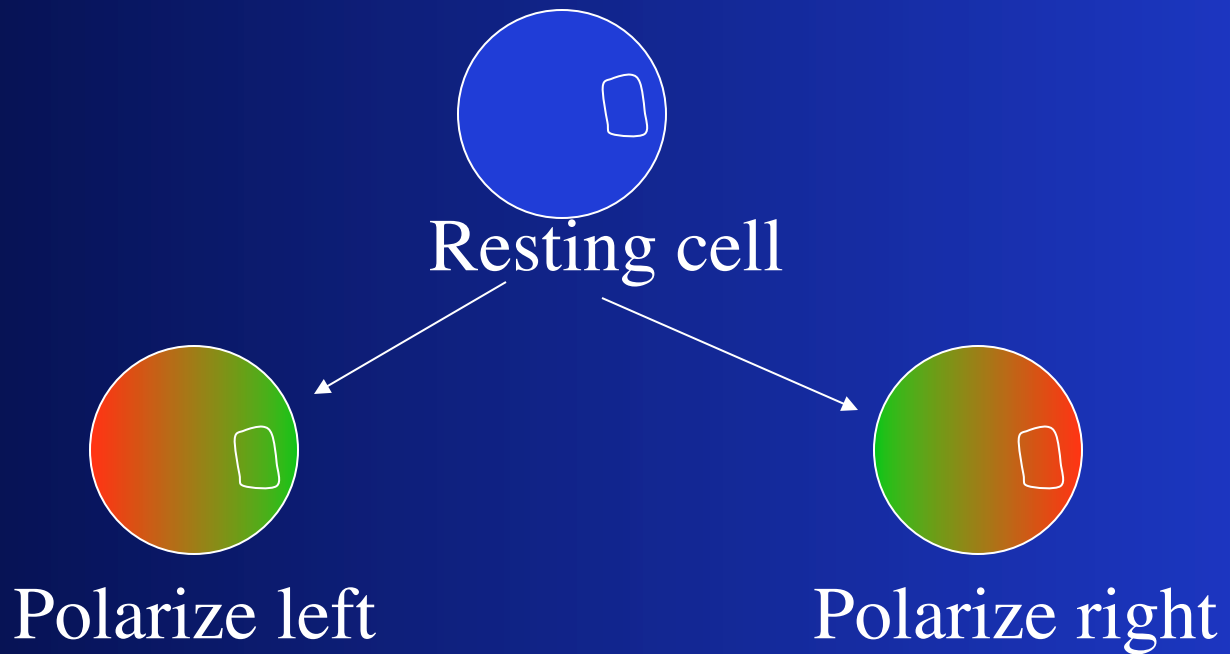
Meinhardt: Lateral inhibition



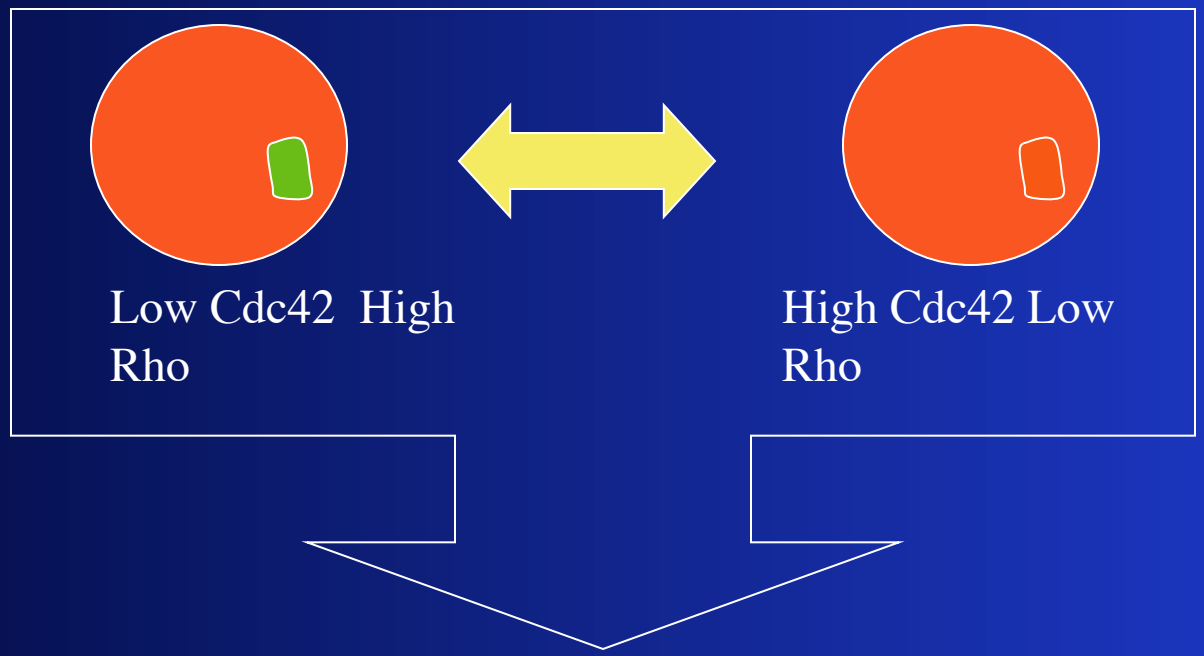
A.M. Turing, *(1952)* Phil. Trans. R. Soc. London B237, pp.37-72, 1952

Meinhardt, H. (1999). J. Cell Sci. **112**, 2867-2874.

What can we suggest?



Multiple states

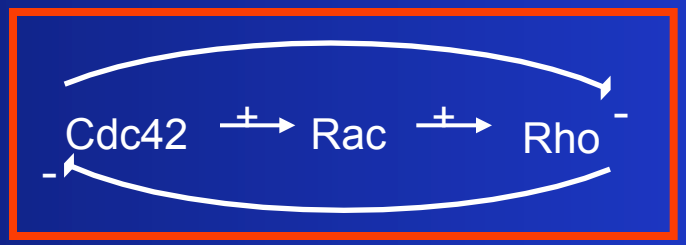


More than one persistent state possible:
"bistability"

Hypothesized crosstalk schemes

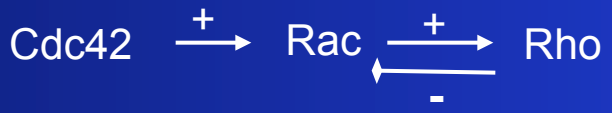
1) Hall (1995):

2) Giniger (2002):



3) Evers (2000), Sander (1999)

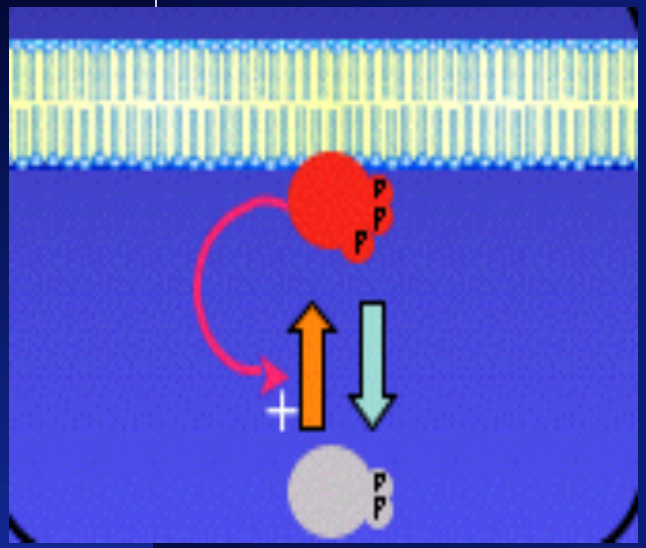
4) van Leeuwen (1997)

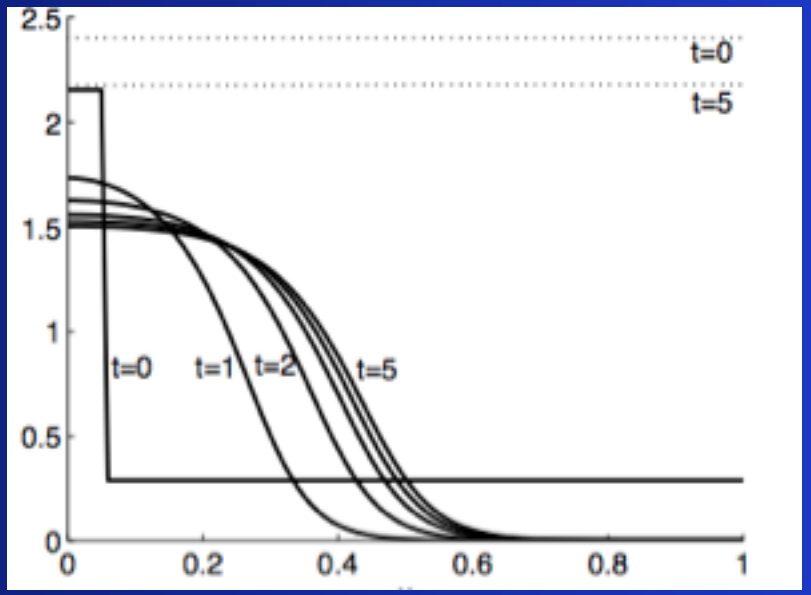


5) Li (2002)

Slide courtesy: A. Jilkine

Underlying core idea



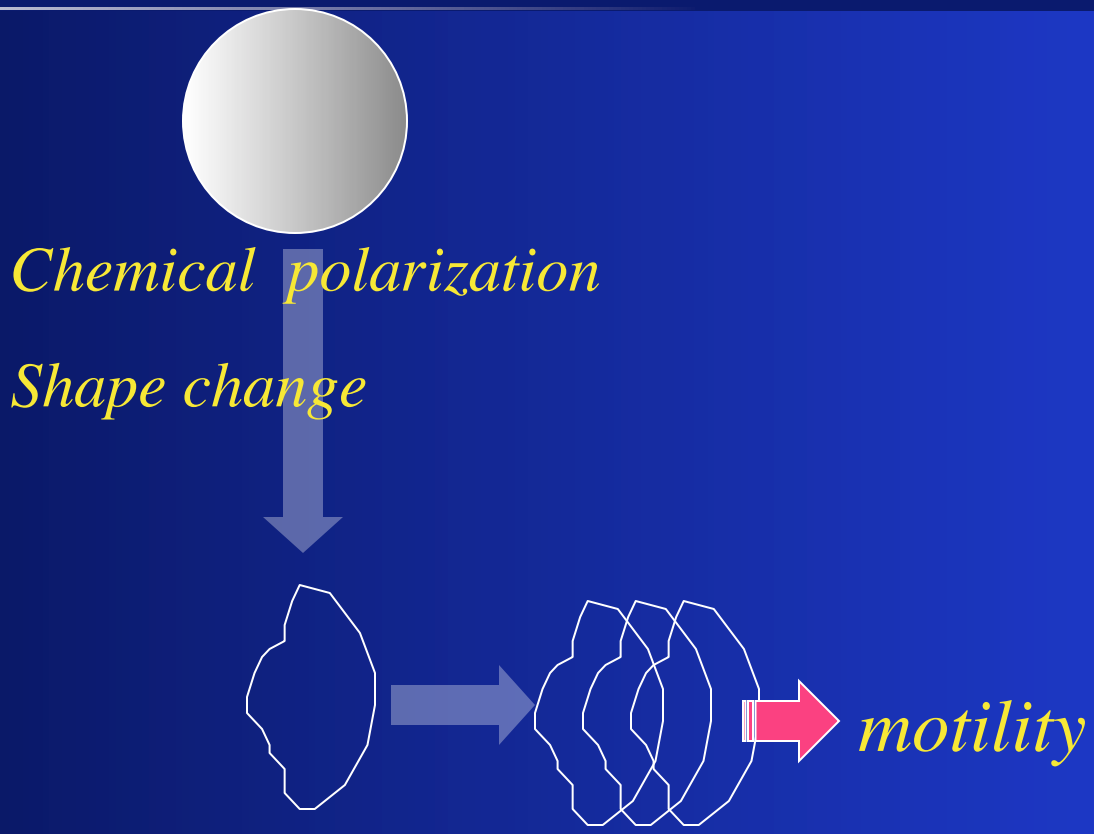


"Wavepinning"

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

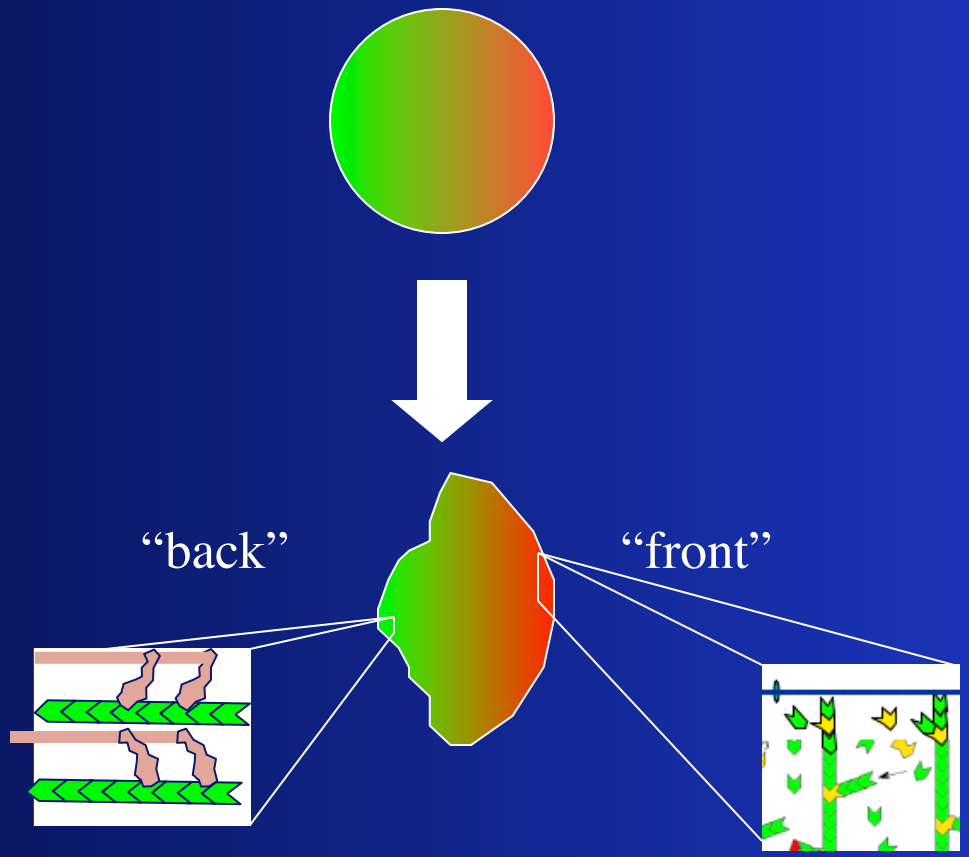
Mori Y, Jilkine A, LEK (2011) SIAM J Appl Math

What do we want to understand?



Mechanics biochemistry

Role of cytoskeleton, forces, and regulation in cell shape and motion



Pay attention to rates and biological parameters, where available

	Fraction in active (GTP form), resting cell	3-25%		Benard et al (1999)
$\delta_C, \delta_R, \delta_\rho$	Decay rates of activated small G-proteins	1	s^{-1}	Sako et al. (2000)
D_m	Membrane diffusion coefficient	0.1	$\mu m^2\, s^{-1}$	Postma et al. (2004)
D_{mc}	Cytosolic diffusion coefficient	10	$\mu m^2\, s^{-1}$	Postma et al. (2004)
C_{tot}	Effective total Cdc42 concentration	2.4	μM	Michaelson et al. (2001)
R_{tot}	Effective total Rac concentration	7.5	μM	Michaelson et al. (2001)
ρ_{tot}	Effective total Rho concentration	3.1	μM	Michaelson et al. (2001)

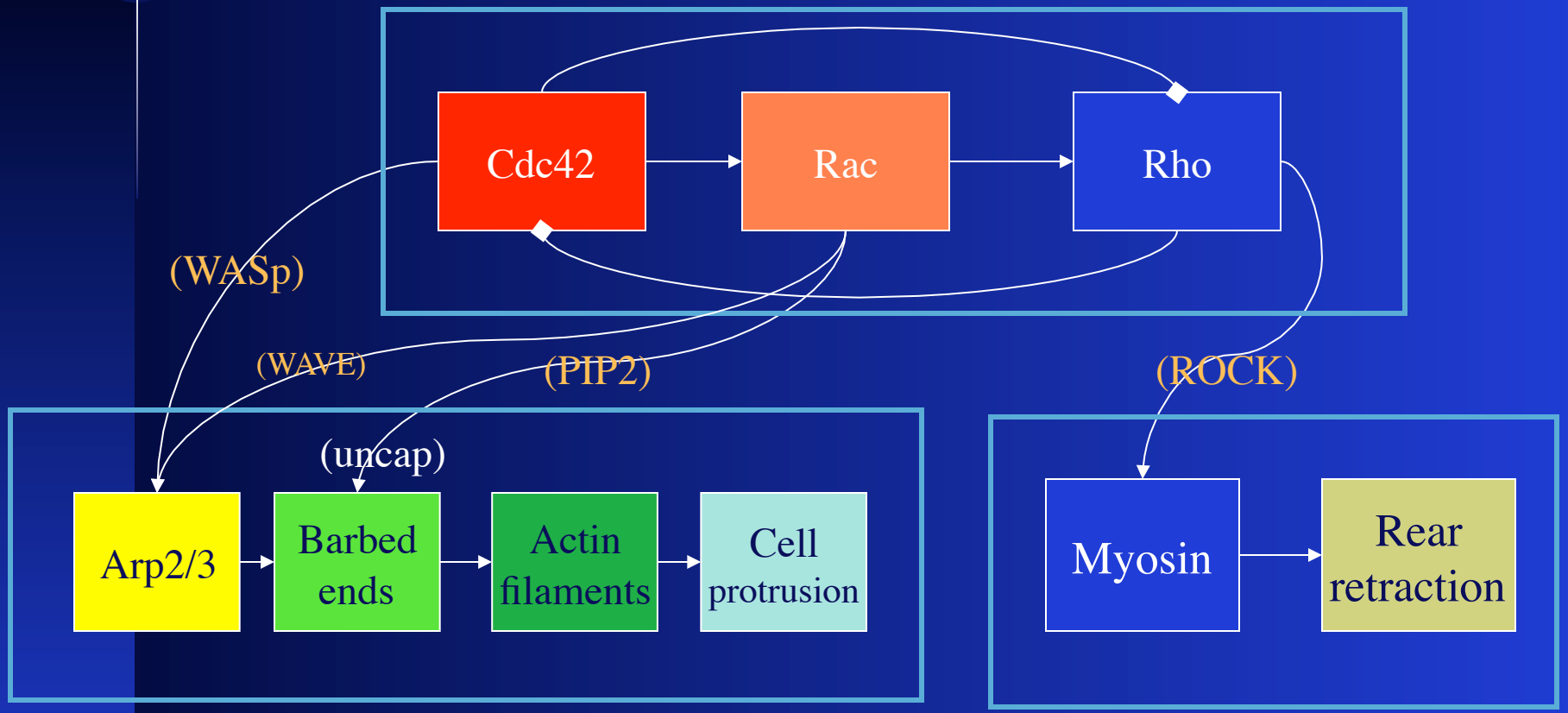
What can we calculate from this?

I_C	Typical Cdc42 activation rate	3.4	$\mu M\, s^{-1}$
I_R	Typical Rac activation rate	0.5	$\mu M\, s^{-1}$
I_ρ	Typical Rho activation rate	3.3	$\mu M\, s^{-1}$

Simplify to get mathematical insights

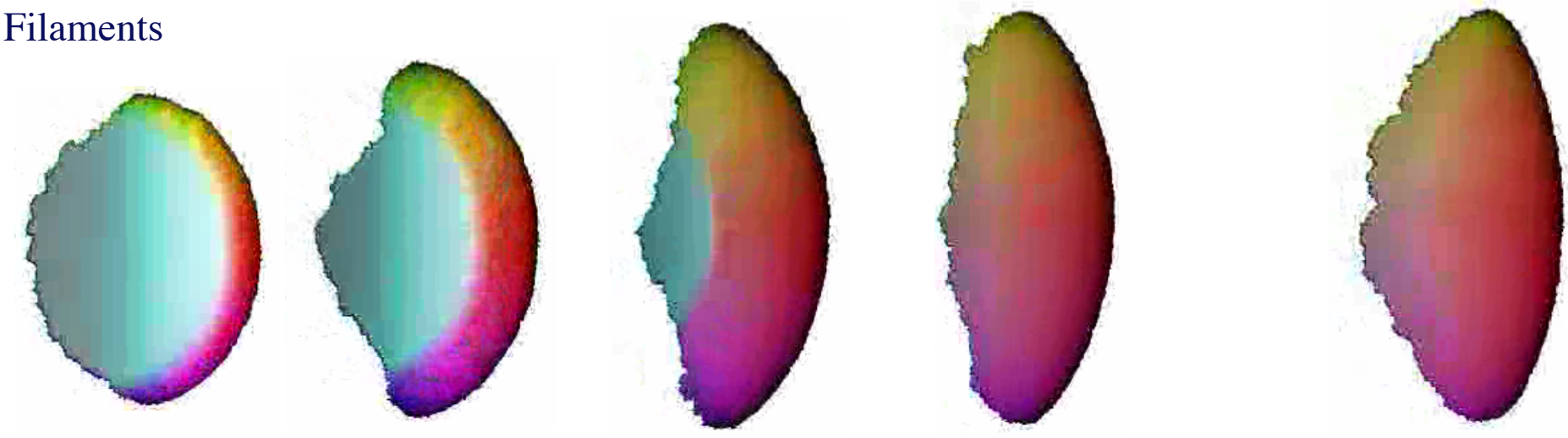
Then go back to more detail..

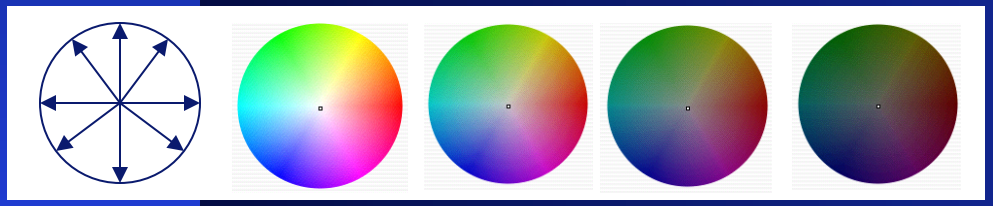
Rho & actin modules

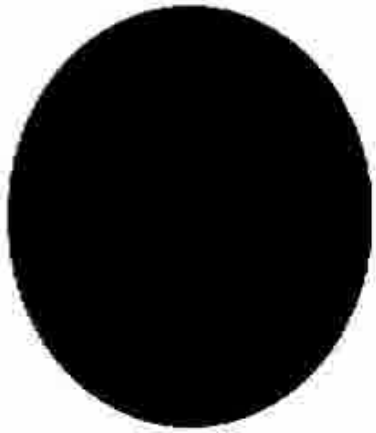


Ask if your hypothesized network can explain some cell behaviour

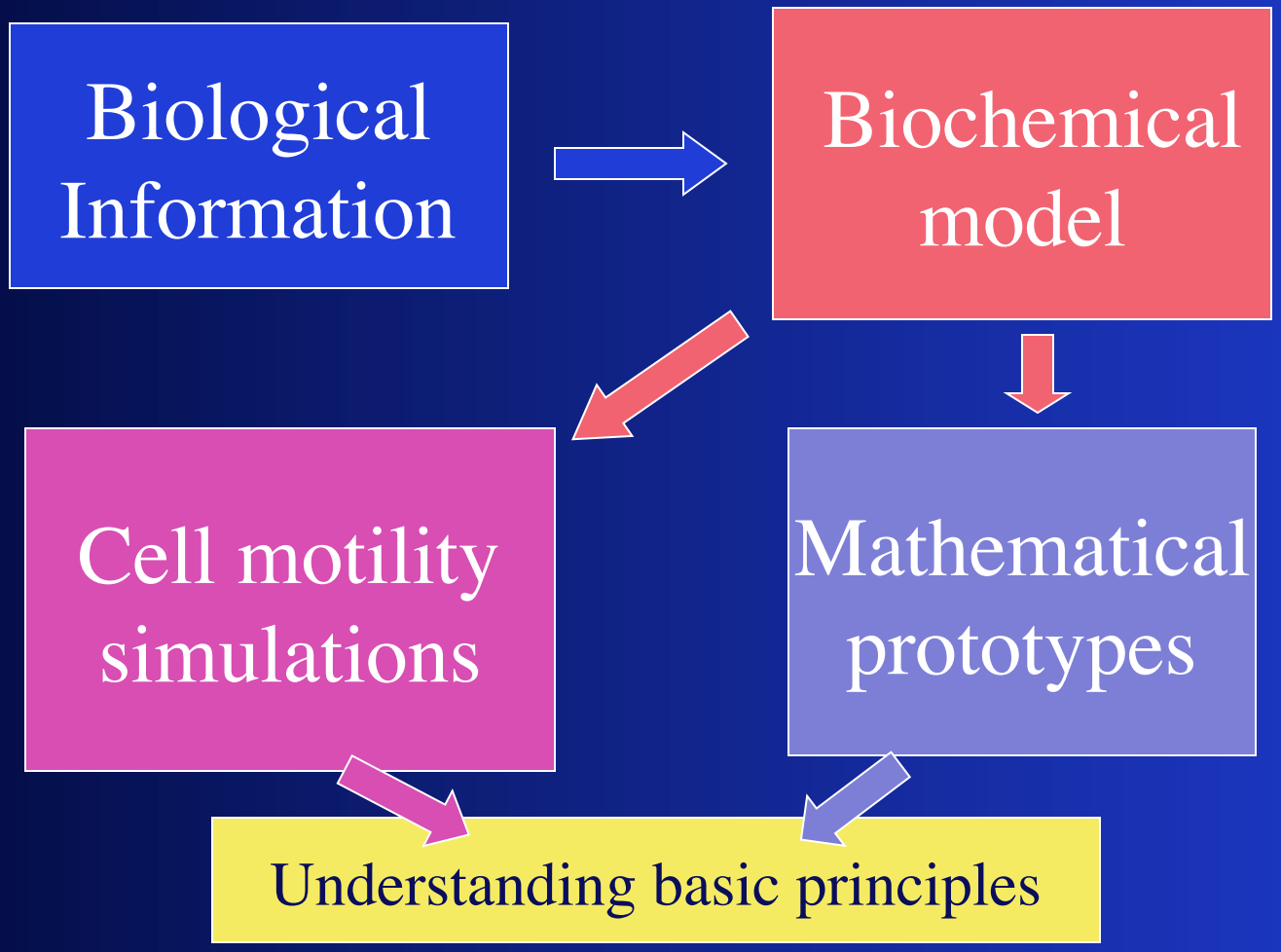
Filaments







Methods:


Biological Information
Biochemical model
Cell motility simulations
Mathematical prototypes
Understanding basic principles

Where is math needed?

- Analyse and interpret data.
- Put data into context of some hypotheses
- Rigorously formulate hypothesis so as to make testable predictions
- Rule out impossible mechanisms based on model predictions…
- [FILL IN…]

What kinds of math?

- Simple models and analysis (ODEs)
- Nonlinear dynamics, bifurcations
- Spatiotemporal models (PDEs, particle-based)
- Simulations..

What are some challenges

- Gradually building up complexity
- Figuring out what is important.. And what are distracting (unimportant) details
- Finding good data/biologists to work with

Mathematical tools

Can be used in some powerful ways to draw strong conclusions that would otherwise be difficult or impossible to obtain.

Example: scaling arguments…

Final example for today..

Integrating experiment and theory

James Bailey in the Verchere lab

Islet Amyloid in Type 2 Diabetes

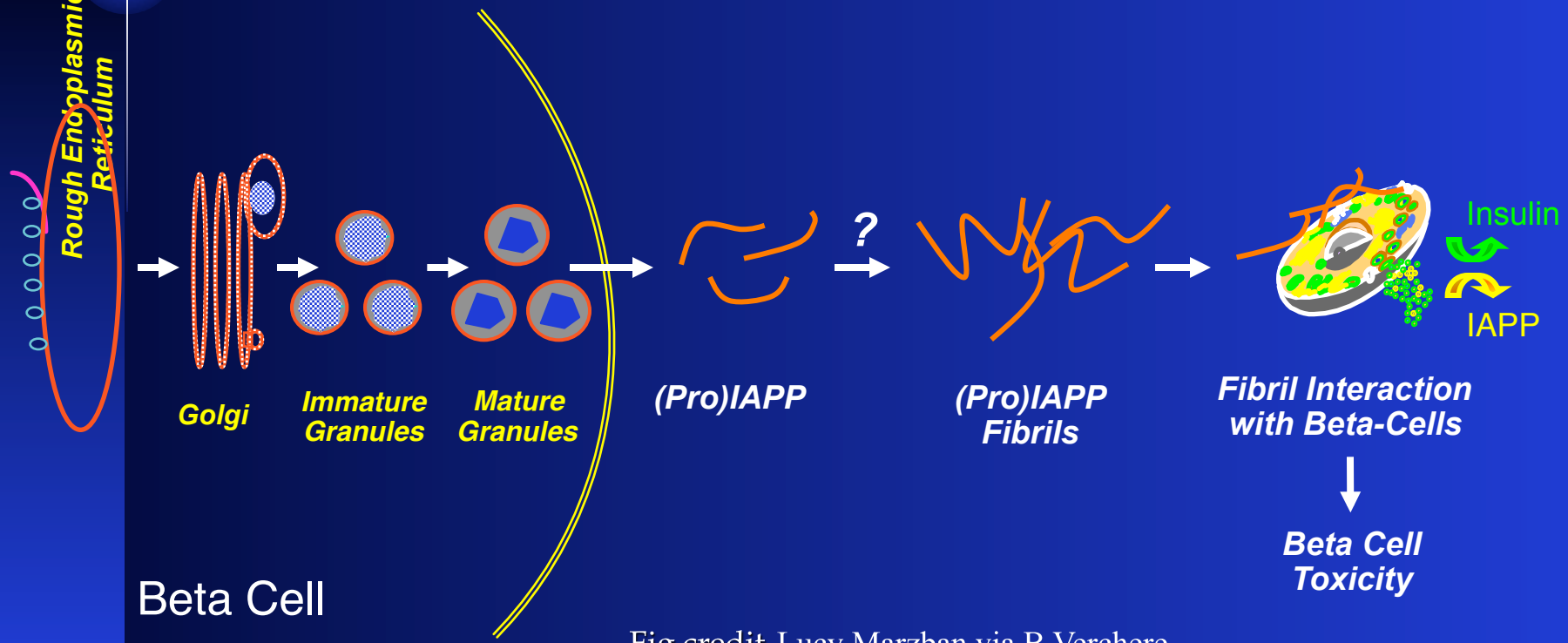
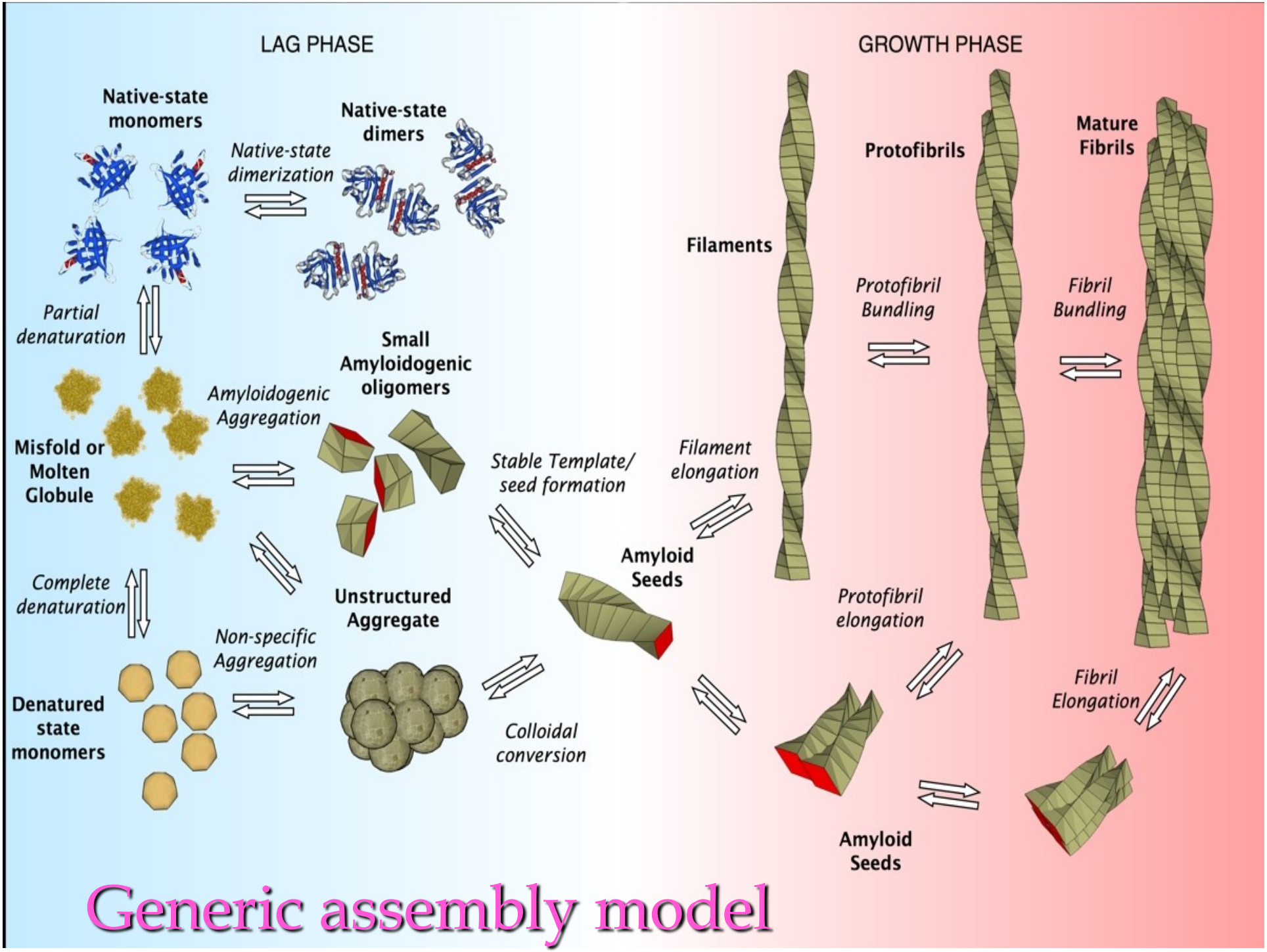
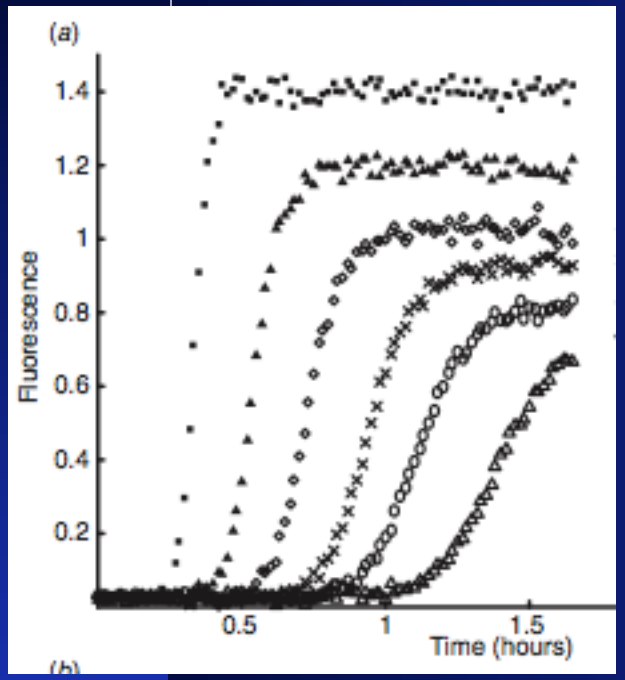


Fig credit Lucy Marzban via B Verchere



Generic assembly model

Macroscopic data to microscopic mechanism



Scaling and model