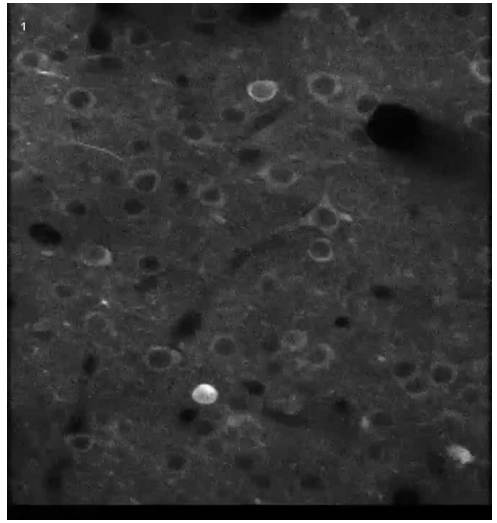
Modellierung dynamischer zellulärer Prozesse

Timo Betz
Institut für Zellbiology, ZMBE
timo.betz@uni-muenster.de

Appetizers…

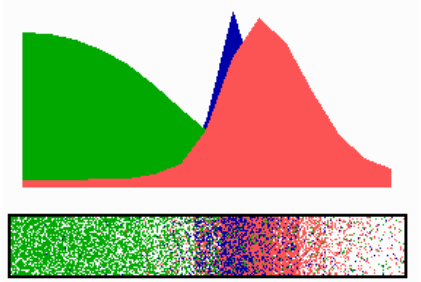
- Why should we care about modelling?
- What can we understand?
- And why is a physicists good at modelling?

Appetizers…



Calcium oscillation are used to transmit information.
How can we model this information transmission?
(Example, neuronal excitation)

Engineering a genetic switch. Here toggle switch, bacteria. (Gerdner et al, 2000, Nature)



How finds a bacteria its center?
Oscillation of a protein complex. (de Boer, PNAS, 2000)

Green: MinD; Red: MinE; Blue: FtsZ

Cells are chemical enterprises, that constantly transform and use energie in chemical reactions.

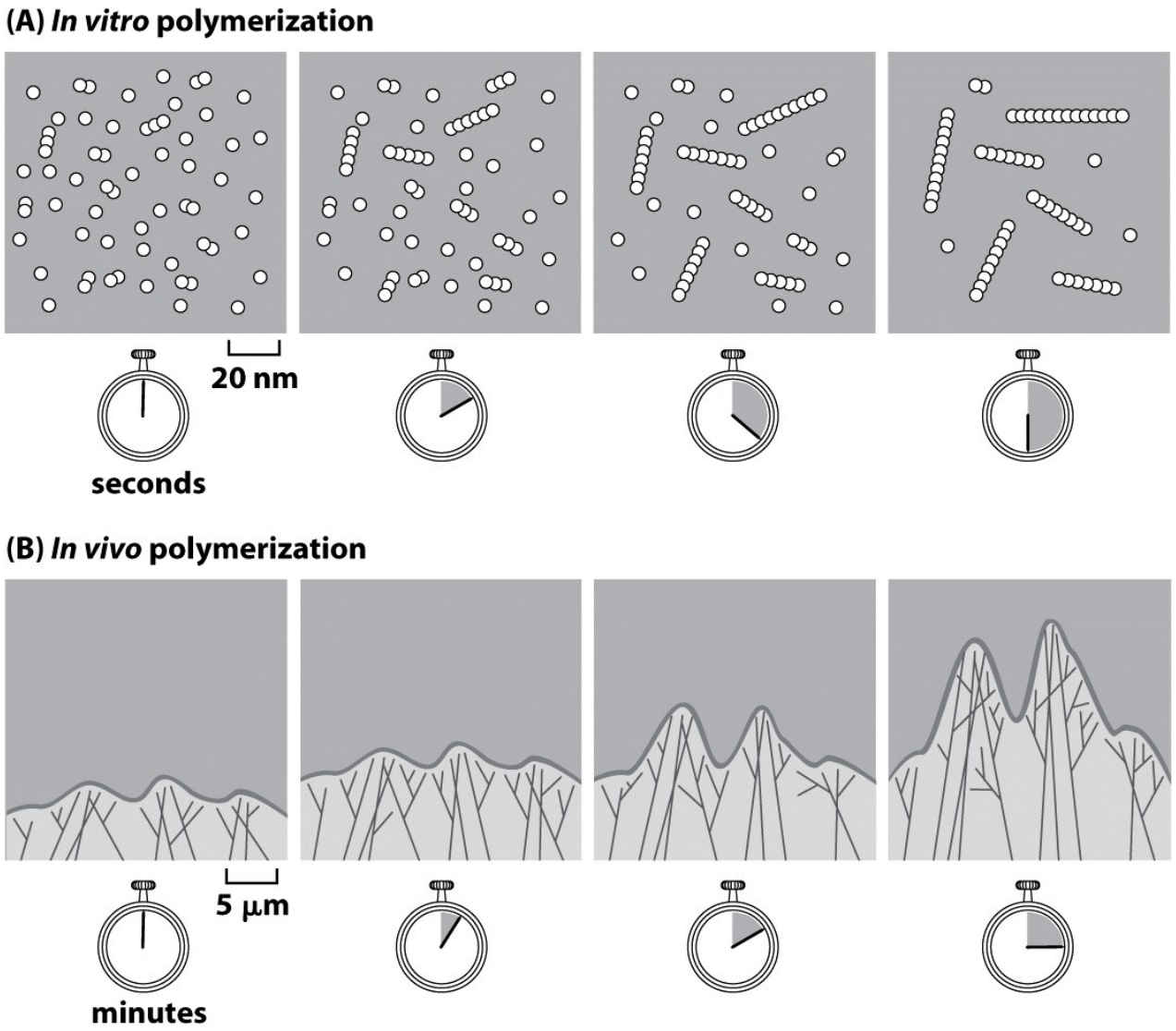


Figure 15.1 Physical Biology of the Cell (© Garland Science 2009)

Lamellipodium uses actin polymerization to move cells forward

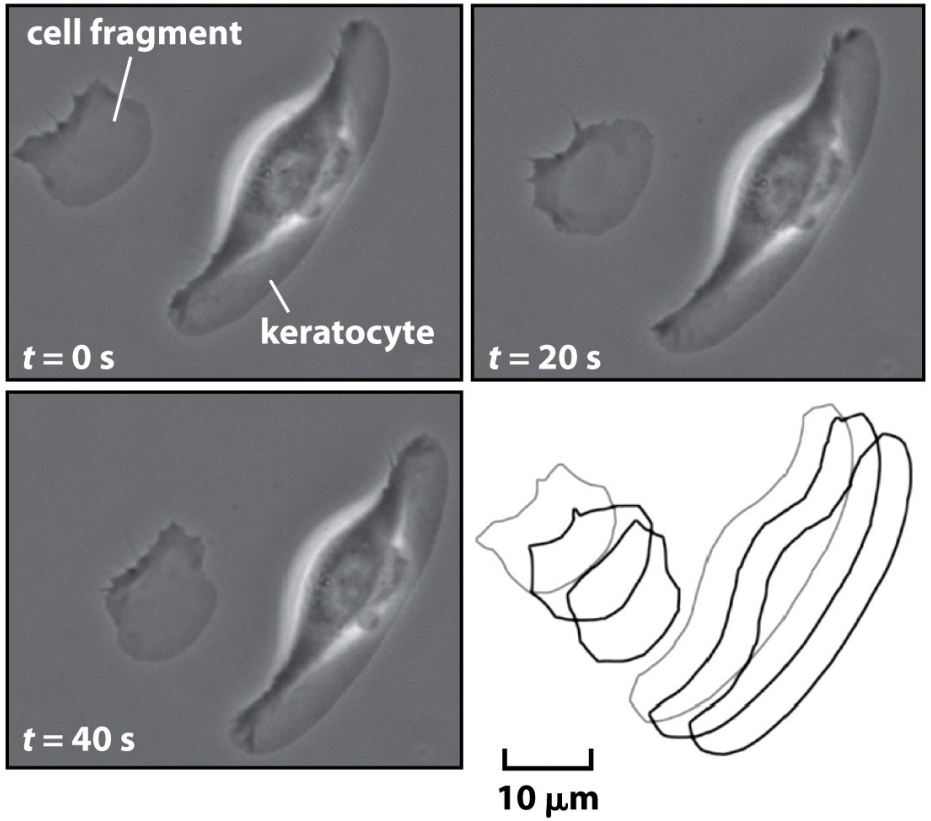
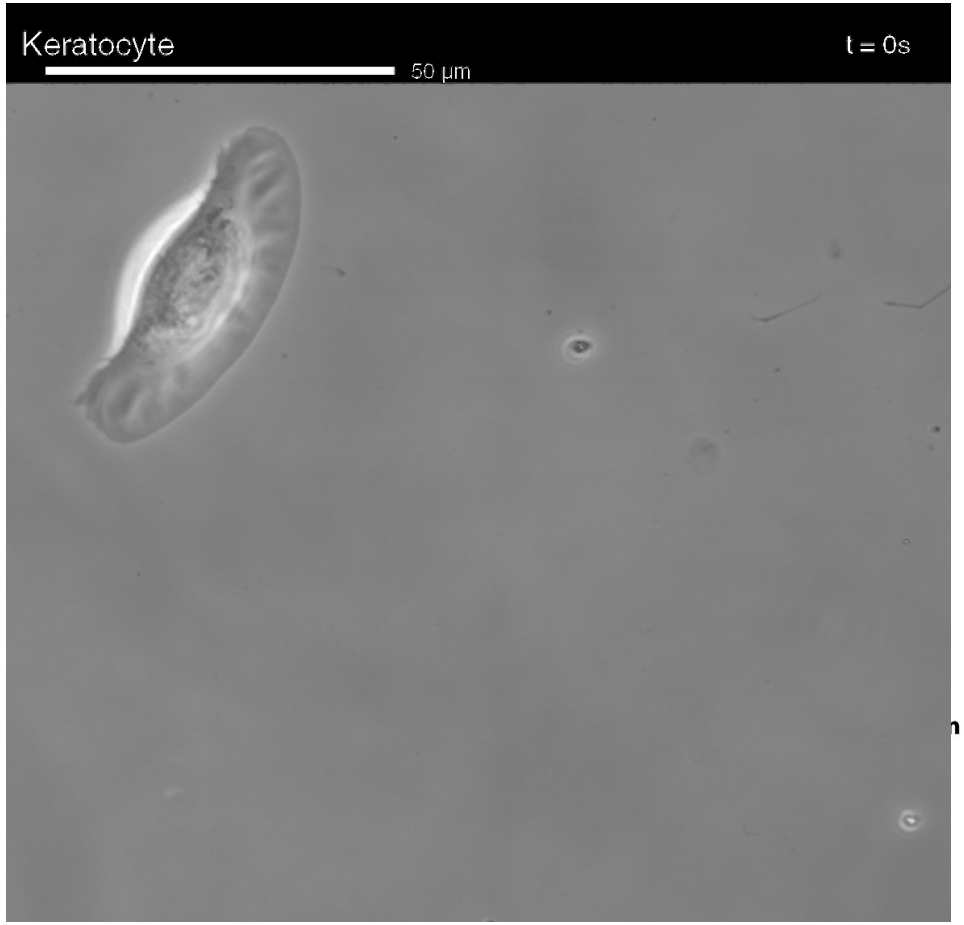


Figure 15.2a Physical Biology of the Cell (© Garland Science 2009)



Plan of the class today:

- How can we mathematically describe a chemical reaction?
- What happens in complex situations?
- Modelling Michaelis-Menten enzyme kinetics
- Example 1: Modelling calcium oscillations

Rate equation on the example of retinal, that switches between the -trans and -cis conformation depending on photon absorption

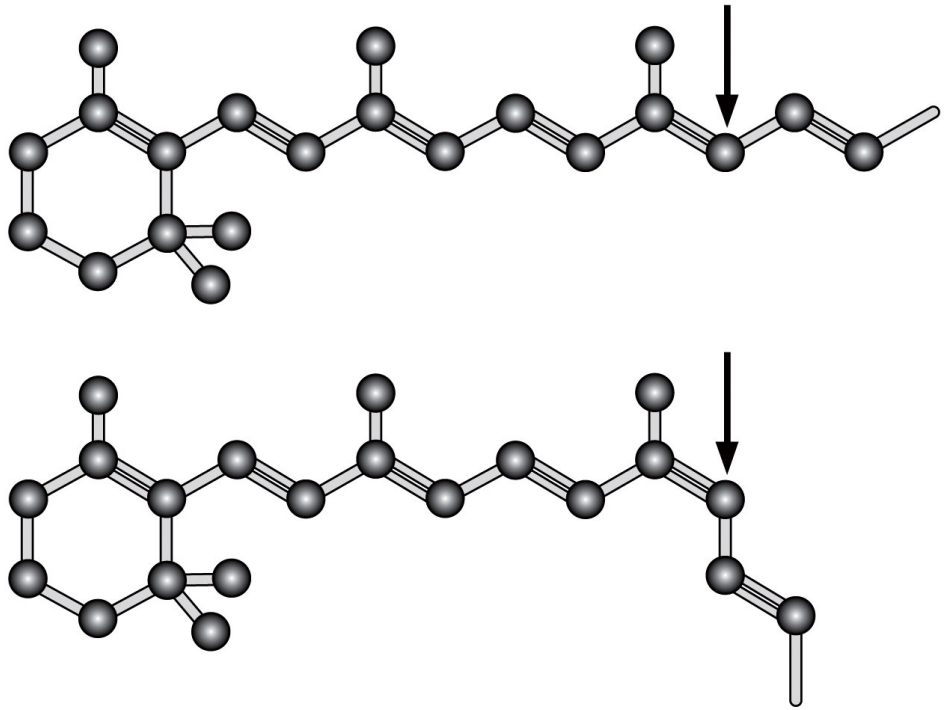


Figure 15.5a Physical Biology of the Cell (© Garland Science 2009)

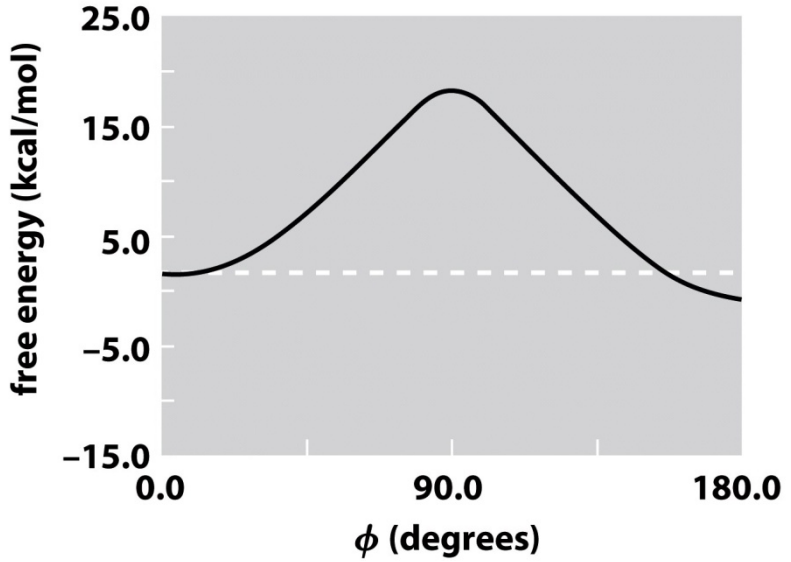


Figure 15.5b Physical Biology of the Cell (© Garland Science 2009)

Strong energy barrier between the two conformations

Hence we can model the reaction as a degradation:

$$A \xrightarrow{k} B$$

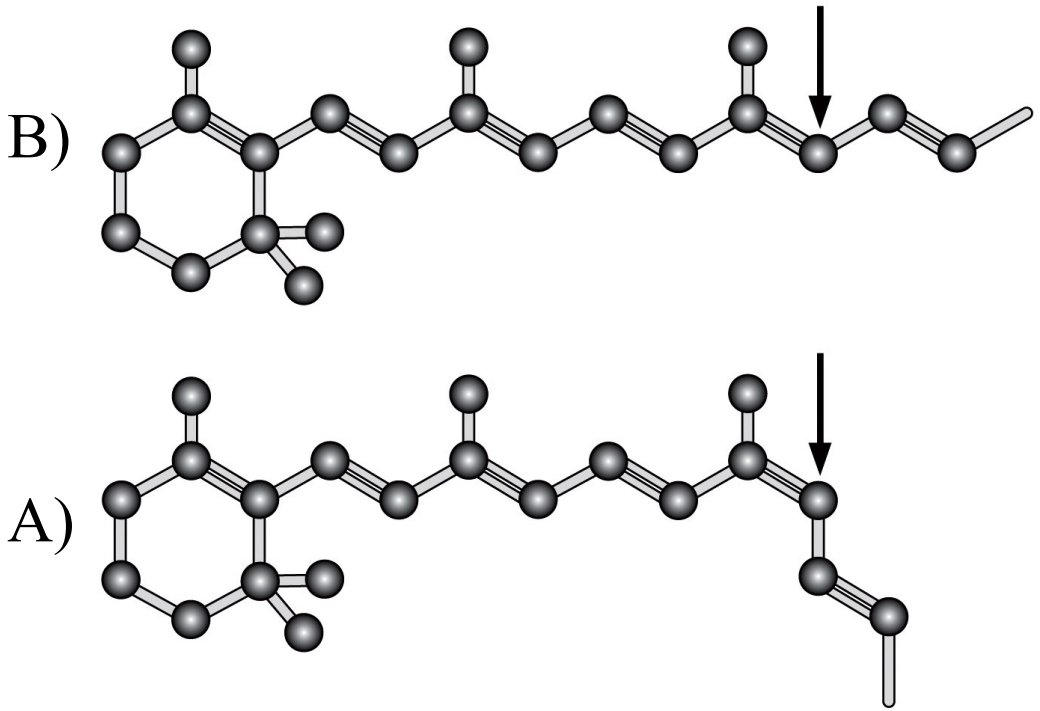


Figure 15.5a Physical Biology of the Cell (© Garland Science 2009)

Hence we can model the reaction as a degradation:

$$A \xrightarrow{k} B$$

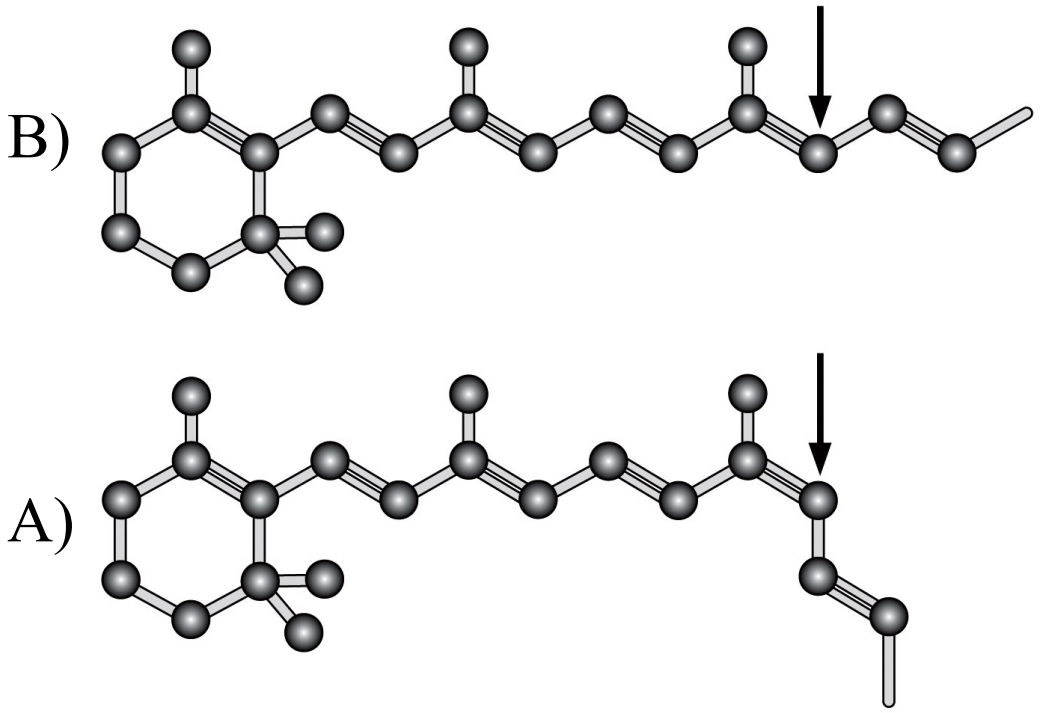


Figure 15.5a Physical Biology of the Cell (© Garland Science 2009)

Differential equation for degradation:

$$\frac{dc(t)}{dt} = -k \times c(t)$$

What is the solution to this equation?

A simple rate equation leads to an exponential decay

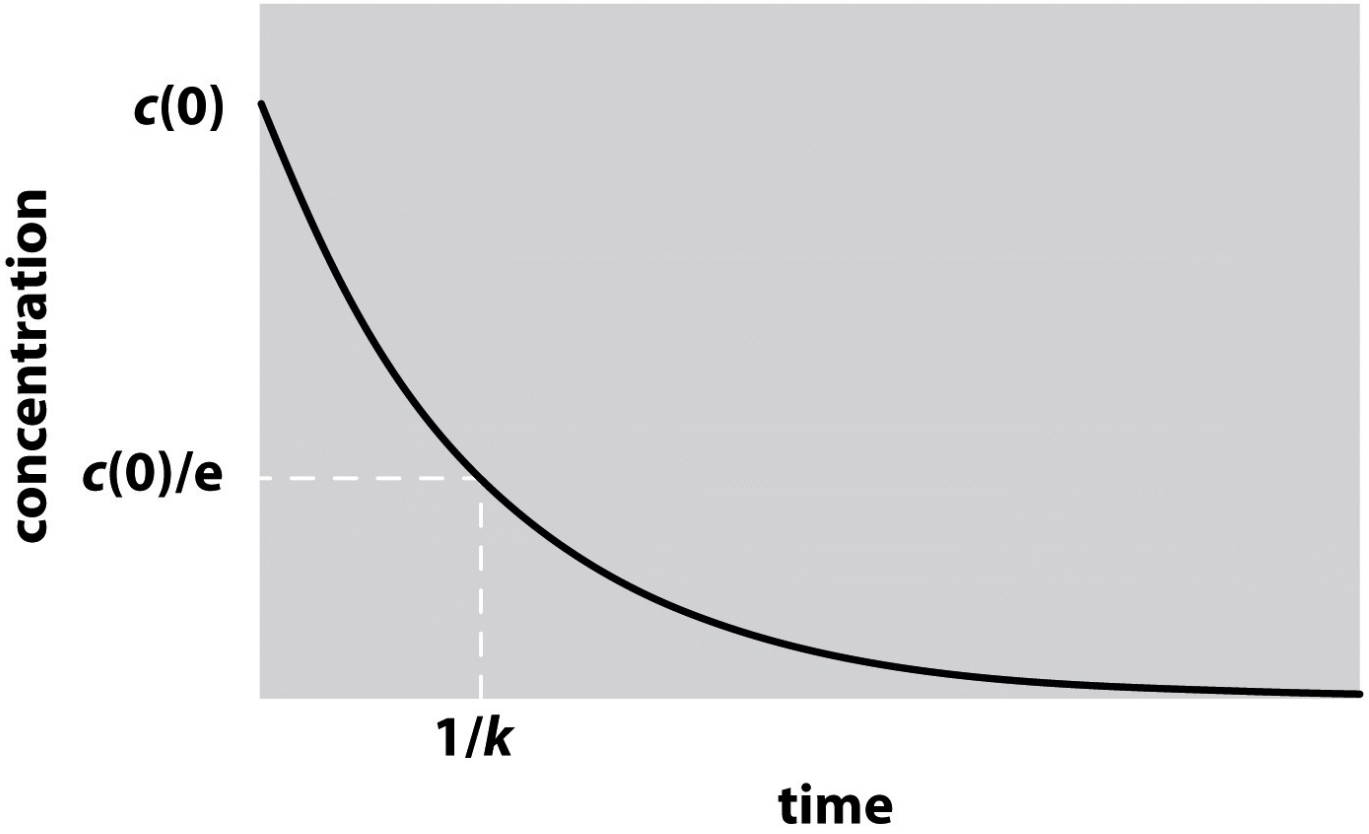


Figure 15.6 Physical Biology of the Cell (© Garland Science 2009)

$$c(t) = c_0 \times \exp(-kt)$$

However, the decay of one species corresponds to growth of another species:

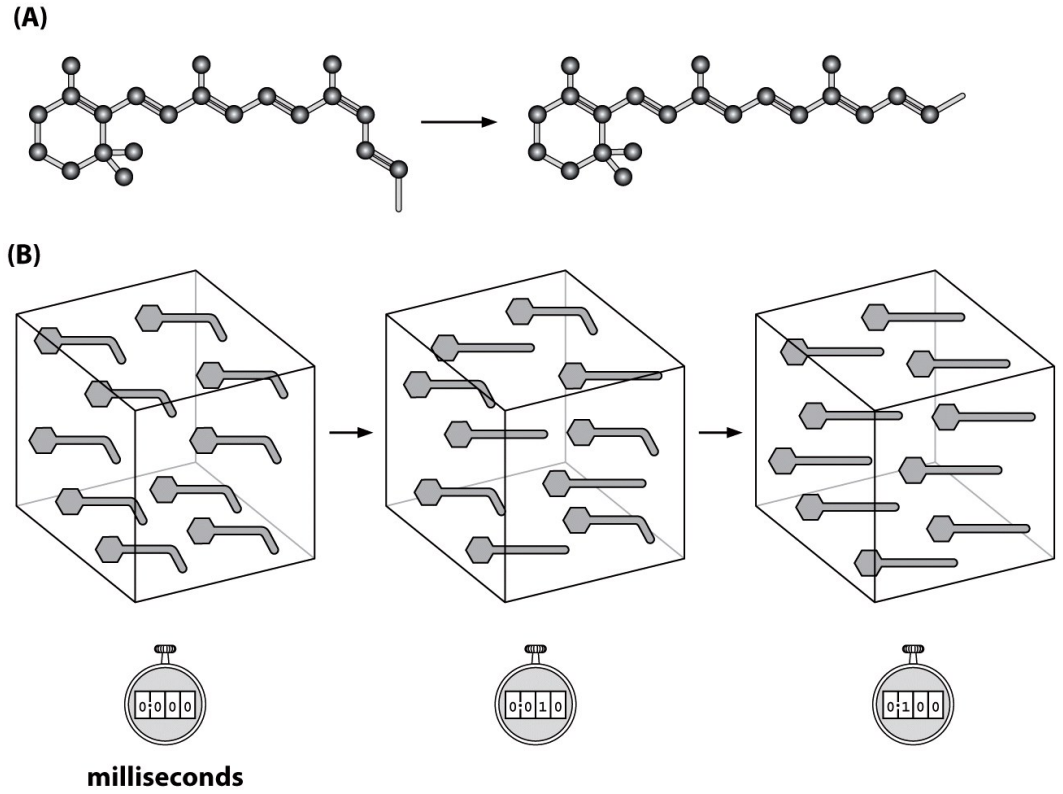


Figure 15.8 Physical Biology of the Cell (© Garland Science 2009)

$$c_A(t) = c_0 \times e^{-kt}$$

$$c_B(t) = c_0 \times (1 - e^{-kt})$$

But in a realistic case, there can be forward and backward reactions:

$$A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B \qquad \text{with} \quad c_A(t) + c_B(t) = c_0$$

But in a realistic case, there can be forward and backward reactions:

$$\mathrm{A} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{B} \qquad \text{with} \quad c_A(t) + c_B(t) = c_0$$

$$\frac{dc_A(t)}{dt} = -k_+ \times c_A(t) + k_- \times c_B(t)$$

$$\frac{dc_B(t)}{dt} = +k_+ \times c_A(t) - k_- \times c_B(t)$$

But in a realistic case, there can be forward and backward reactions:

$$\mathrm{A} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{B} \qquad \text{with} \quad c_A(t) + c_B(t) = c_0$$

$$\frac{dc_A(t)}{dt} = -k_+ \times c_A(t) + k_- \times c_B(t)$$

$$\frac{dc_B(t)}{dt} = +k_+ \times c_A(t) - k_- \times c_B(t)$$

With the solution:

$$c_A(t) = \frac{c_0 \times k_-}{k_+ + k_-} + \frac{c_0 \times k_+}{k_+ + k_-} \exp(-t(k_+ + k_-))$$

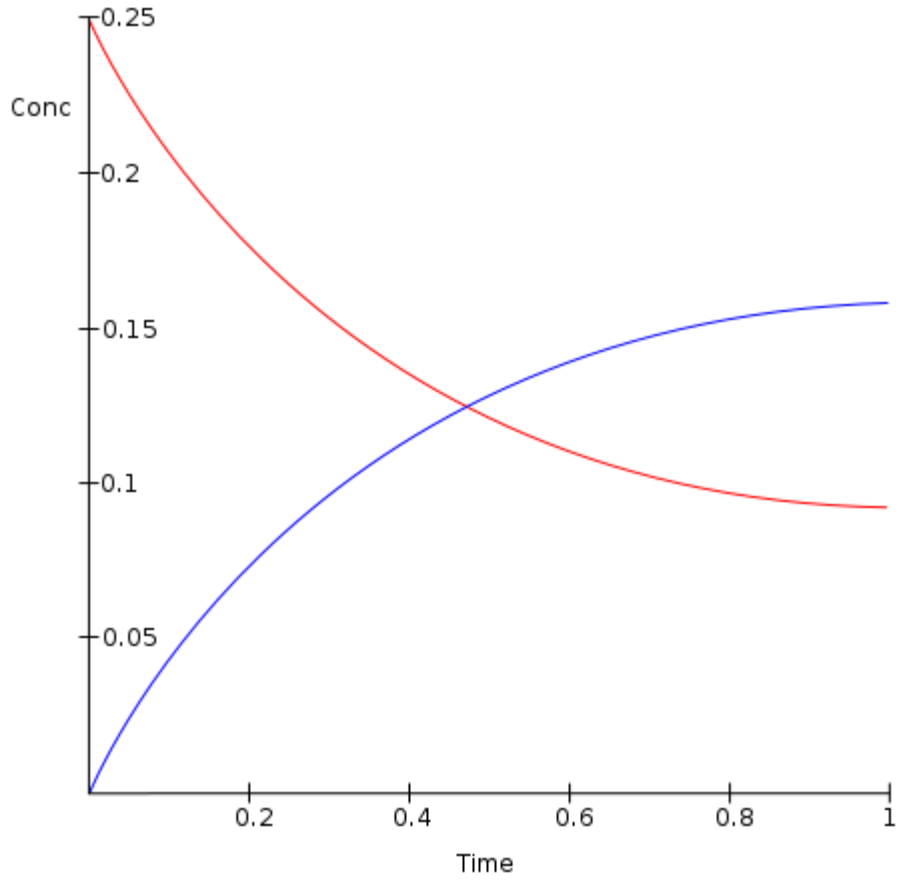
$$c_B(t) = \frac{c_0 \times k_+}{k_+ + k_-} - \frac{c_0 \times k_+}{k_+ + k_-} \exp(-t(k_+ + k_-))$$

But in a realistic case, there can be forward and backward reactions:

$$A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B \qquad \text{with} \quad c_A(t) + c_B(t) = c_0$$

$$c_A(t) = \frac{c_0 \times k_-}{k_+ + k_-} + \frac{c_0 \times k_+}{k_+ + k_-} \exp\big(-t(k_+ + k_-)\big)$$

$$c_B(t) = \frac{c_0 \times k_+}{k_+ + k_-} - \frac{c_0 \times k_+}{k_+ + k_-} \exp(-t(k_+ + k_-))$$



At time $t \longrightarrow \infty$:

$$\frac{c_A}{c_B} = \frac{k_-}{k_+}$$

Biomolecular reaction at the example of receptor-ligand interaction

$$L + R \rightleftharpoons LR$$

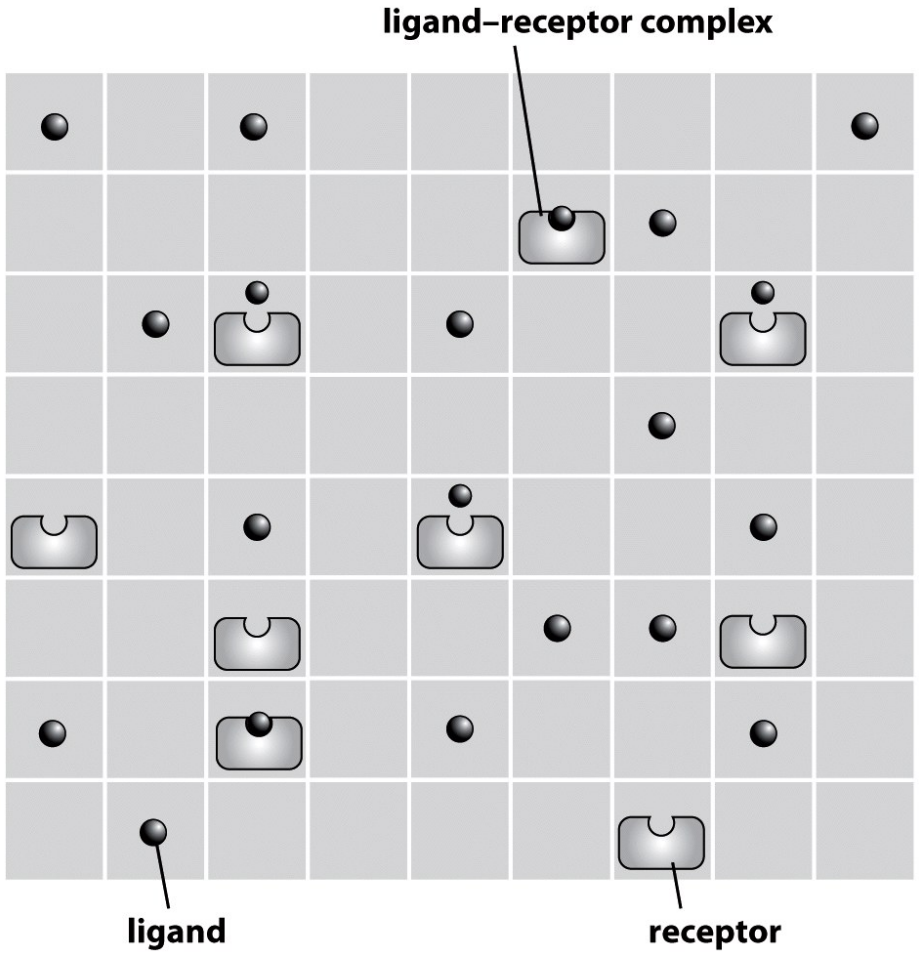


Figure 15.9 Physical Biology of the Cell (© Garland Science 2009)

Biomoelcular reaction at the example of receptor-ligand interaction

$$\mathrm{L} + R \rightleftharpoons LR$$

Box model allows to derive:

$$\frac{dc_{LR}(t)}{dt} = -k_{off} \times c_{LR}(t) + k_{on} \times c_R(t) \times c_L(t)$$

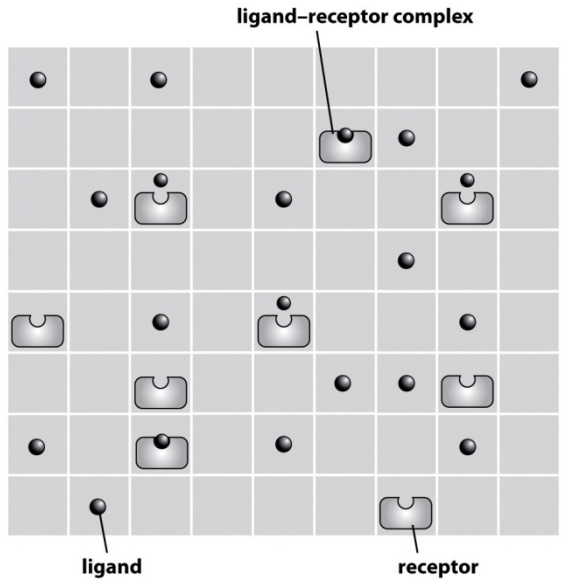


Figure 15.9 Physical Biology of the Cell (© Garland Science 2009)

Biomoelcular reaction at the example of receptor-ligand interaction

$$L + R \rightleftharpoons LR$$

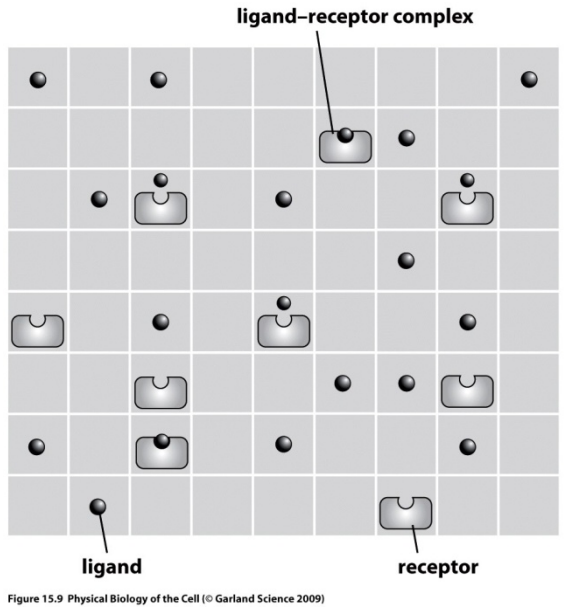


Figure 15.9 Physical Biology of the Cell (© Garland Science 2009)

Box model allows to derive:

$$\frac{dc_{LR}(t)}{dt} = -k_{off} \times c_{LR}(t) + k_{on} \times c_R(t) \times c_L(t)$$

At equilibrium we can then find the law of mass action and the dissociation constant:

$$\frac{dc_{LR}(t)}{dt} = 0$$

$$k_{off} \times c_{LR} = k_{on} \times c_R \times c_L$$

$$\frac{c_R \times c_L}{c_{LR}} = \frac{k_{off}}{k_{on}} = K_d$$

Rate equation give not only equilibrium state, but also the time evolution to reach the equilibrium

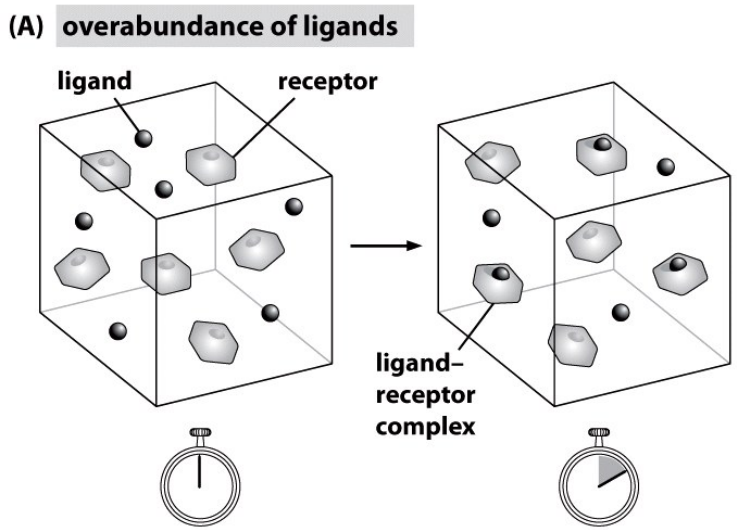


Figure 15.10 Physical Biology of the Cell (© Garland Science 2009)

Rapid equilibrium in a 3 element reaction

$$A \underset{k-}{\overset{k_+}{\rightleftarrows}} B \xrightarrow{r} C$$

We assume that the k's are much bigger than r. B-> C is irreversible.

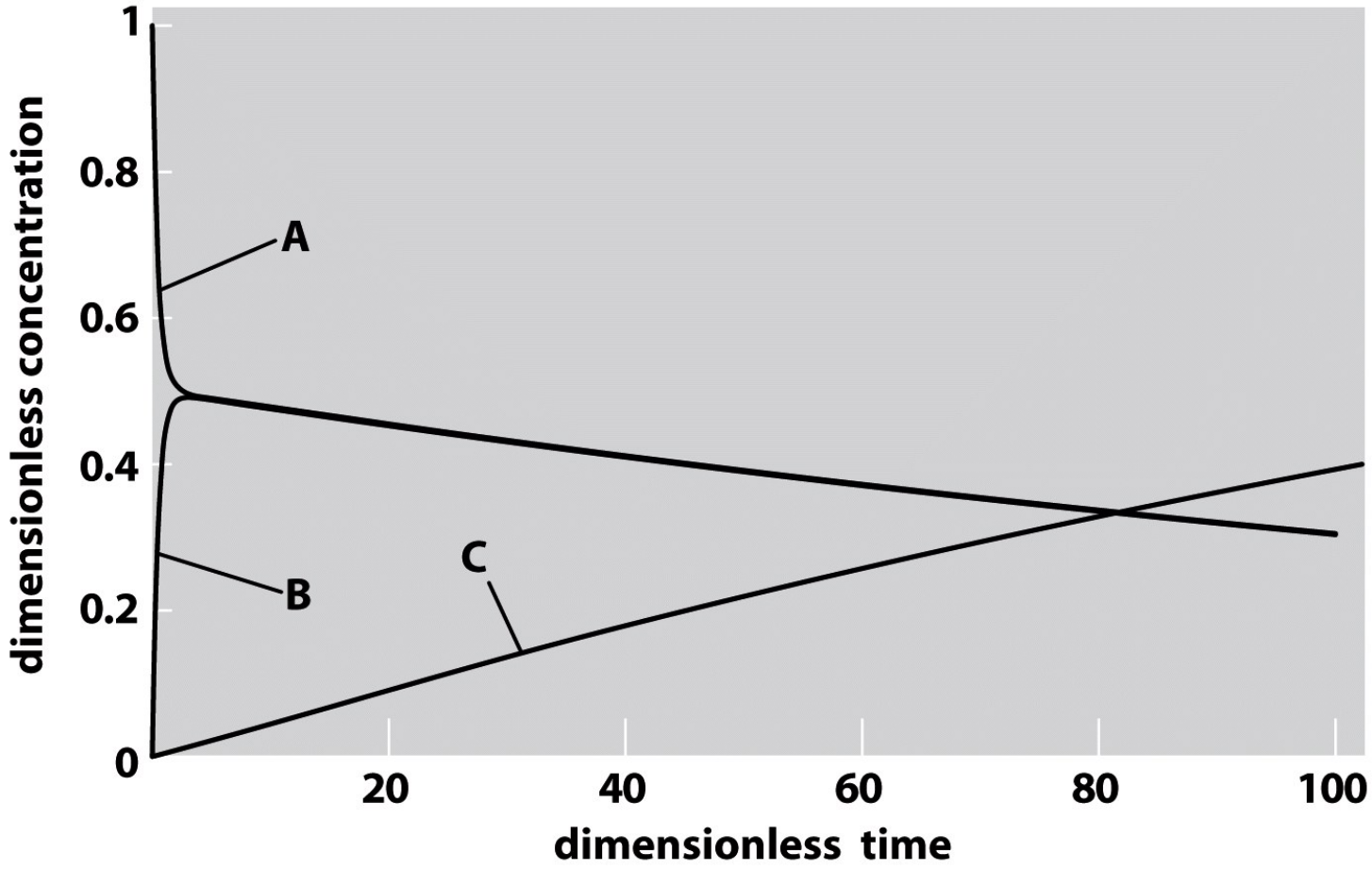


Figure 15.14 Physical Biology of the Cell (© Garland Science 2009)

Rapid equilibrium in a 3 element reaction

$$A \underset{k-}{\overset{k_+}{\rightleftarrows}} B \xrightarrow{r} C$$

We can set up a coupled set of rate equations.

$$\frac{d[A]}{dt} = -k_+[A] + k_-[B]$$

$$\frac{d[B]}{dt} = +k_+[A] - k_-[B] - r_-[B] = +k_+[A] - (k_- + r)[B]$$

$$\frac{d[C]}{dt} = r[B]$$

Rapid equilibrium in a 3 element reaction

$$A \underset{k-}{\overset{k_+}{\rightleftarrows}} B \xrightarrow{r} C$$

This can be solved analytically for the decoupled 2 first eq.:

$$[A] = 1/(k+1)\exp\left(-k\varepsilon/(k+1)\tau\right) + k/(k+1)\exp\left(-(k+1)\tau\right)$$

$$[B] = k/(k+1)\exp\left(-k\varepsilon/(k+1)\tau\right) - k/(k+1)\exp\left(-(k+1)\tau\right)$$

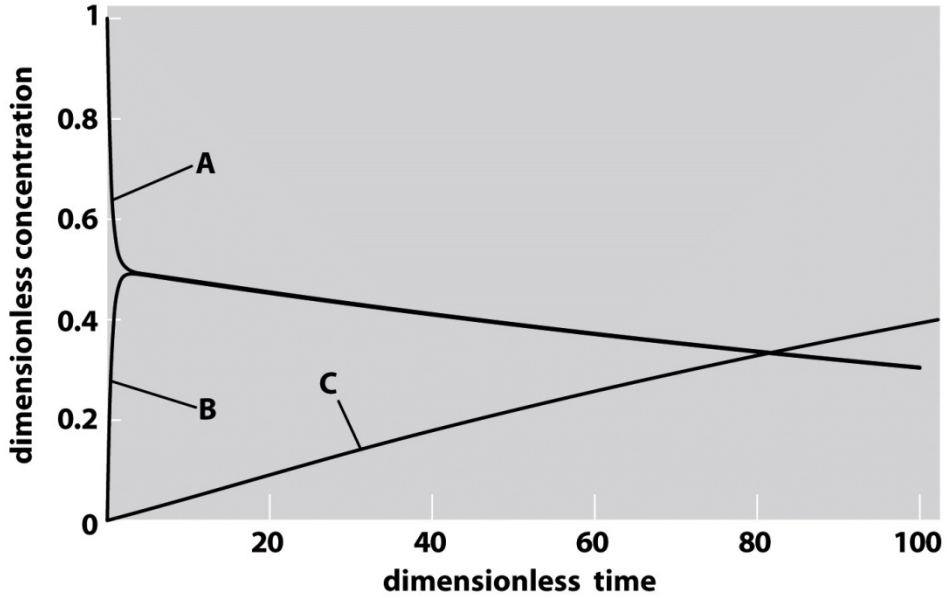


Figure 15.14 Physical Biology of the Cell (© Garland Science 2009)

Using dimensionless rates and time:

$$k = \frac{k_+}{k_-} \qquad \epsilon = \frac{r}{k_-}$$

$$\tau = tk_-$$

Michaelis Menten type of reaction

$$S + E \underset{k-}{\overset{k_+}{\rightleftarrows}} ES \xrightarrow{r} E + P$$

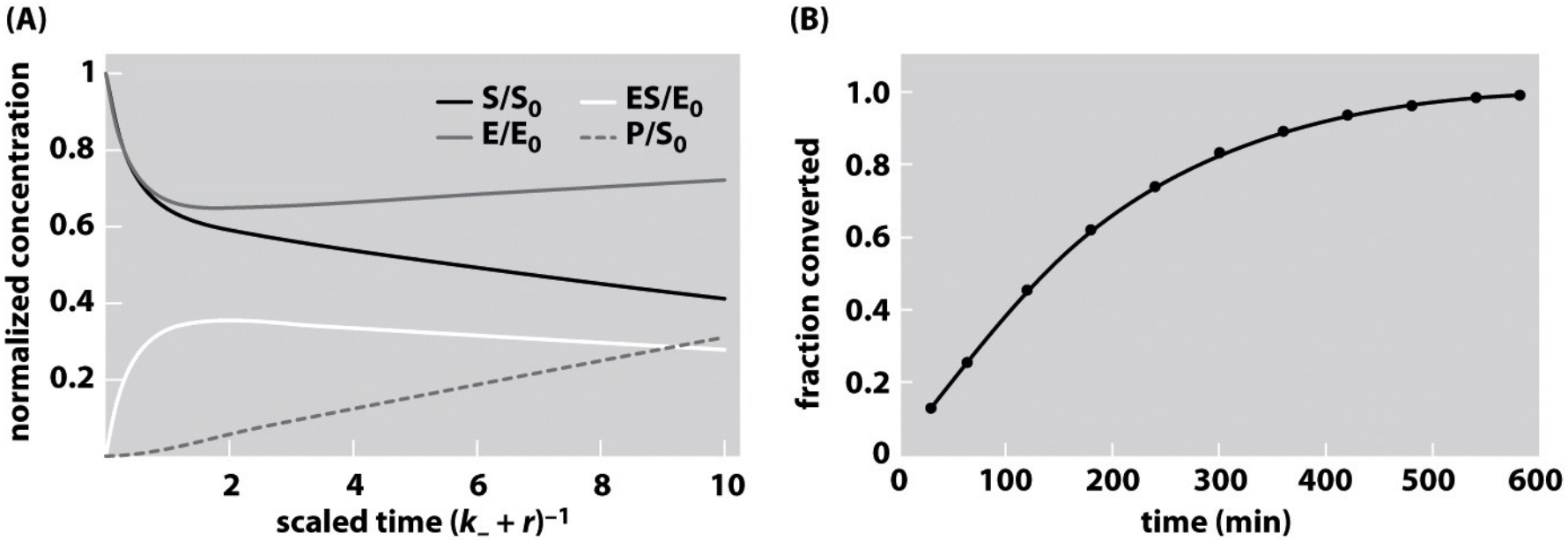


Figure 15.16 Physical Biology of the Cell (© Garland Science 2009)

Set up the rate equation.

Michaelis Menten type of reaction

$$S + E \underset{k-}{\overset{k_+}{\rightleftarrows}} ES \xrightarrow{r} E + P$$

Set up the rate equations.

$$\frac{d[E]}{dt} = -k_+[E][S] + k_-[ES] + r[ES]$$

$$\frac{d[S]}{dt} = -k_+[E][S] + k_-[ES]$$

$$\frac{d[ES]}{dt} = k_+[E][S] - (k_- + r)[ES]$$

$$\frac{d[P]}{dt} = r[ES]$$

Problem too complex to be solved analytically. This needs to be solved numerically.

Michaelis Menten type of reaction

$$S + E \underset{k-}{\overset{k_+}{\rightleftarrows}} ES \xrightarrow{r} E + P$$

To reach Michaelis Menten approximation we assume intermediate to be in steady state

$$\frac{d[ES]}{dt} = 0 \qquad \frac{d[ES]}{dt} = k_+[E][S] - (k_- + r)[ES]$$

Which then leads to:

$$\frac{[E][S]}{[ES]} = \frac{(k_- + r)}{k_+} = K_M$$

We are interested in:

$$\frac{d[P]}{dt} = r[ES] = r\frac{[E][S]}{K_M}$$

Michaelis Menten type of reaction

$$S + E \underset{k-}{\overset{k_+}{\rightleftarrows}} ES \xrightarrow{r} E + P$$

Now we introduce the maximal rate V_{Max}

$$V_{Max} = r\left[E_{tot}\right]$$

And put this in the production rate equation:

$$\frac{d\left[P\right]}{dt} = r\frac{\left[E\right]\left[S\right]}{K_M} = V_{Max}\frac{\left[E\right]\left[S\right]/K_M}{\left[E_{tot}\right]}$$

By definition E_{tot}=E+ES, and we had seen before that [ES]=[E][S]/K_M

$$\frac{d\left[P\right]}{dt} = V_{Max}\frac{\left[S\right]/K_M}{1+\left[S\right]/K_M}$$

Michaelis Menten numerical solution versus real data of ATP usage in myosin.

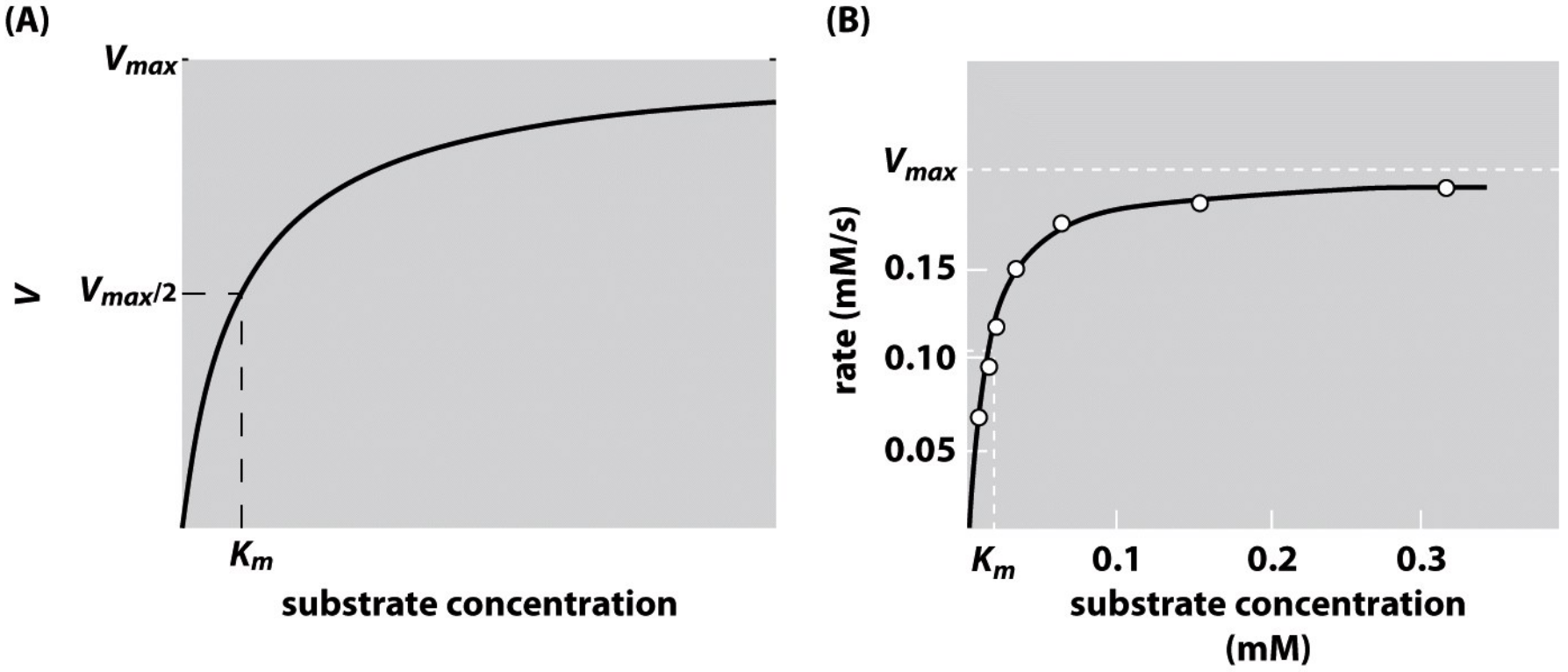
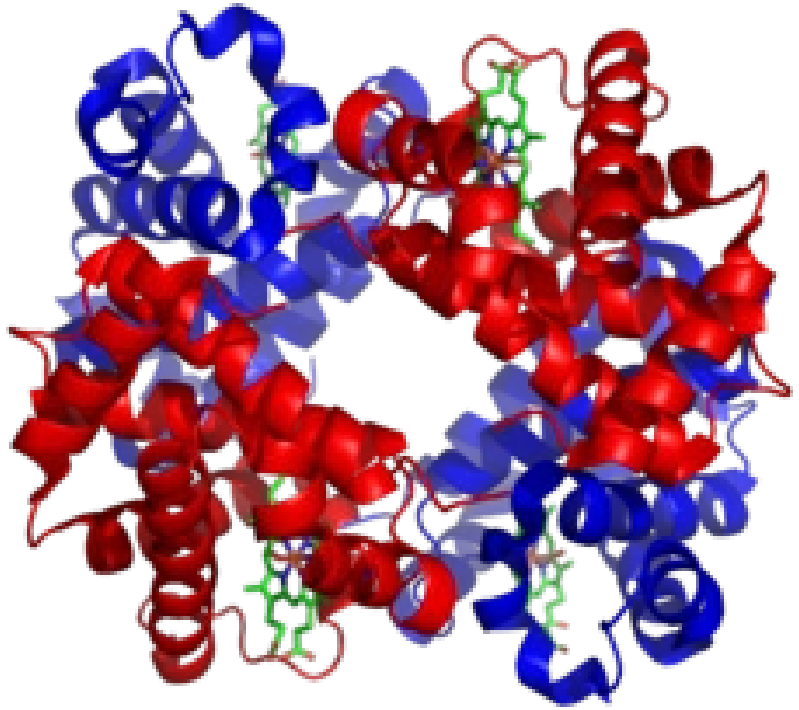


Figure 15.17 Physical Biology of the Cell (© Garland Science 2009)

Cooperativity and Hill-Equation



Hämoglobine (4 Binding sites for Oxygen and Carbondioxide)

$$\mathrm{H\ddot{a}} + 4\ \mathrm{O_2} \underset{\mathrm{k_d}}{\overset{k_a}{\rightleftarrows}} H\ddot{a}(O_2)_4$$

Cooperativity and Hill-Equation

General approach: $P + nL \rightarrow PL_n$

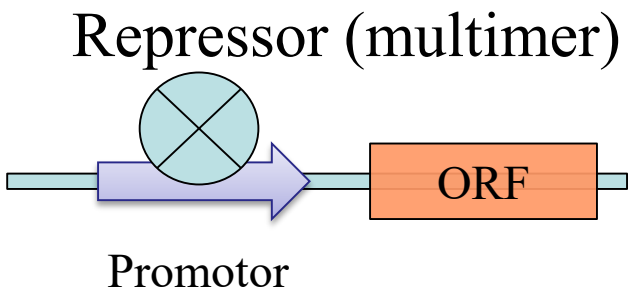
$$K_d = \frac{[P][L]^n}{[PL_n]} \Leftrightarrow [PL_n] = \frac{[P][L]^n}{K_d}$$

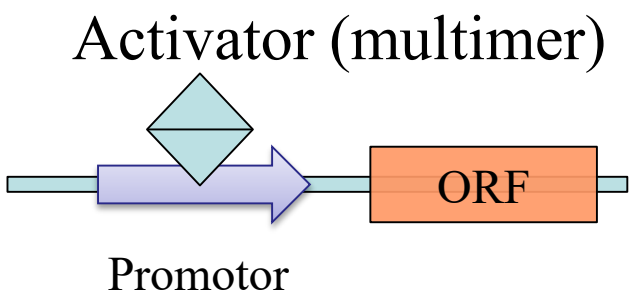
$$\Theta_B = \frac{protein\ bound}{protein\ total} = \frac{[PL_n]}{[P] + [PL_n]}$$

$$\Theta_B = \frac{[P][L]^n}{K_d} \frac{1}{[P] + [P][L]^n / K_d} = \frac{[L]^n}{K_d + [L]^n}$$

$$\Theta_u = 1 - \Theta_o = \frac{K_d}{K_d + [L]^n}$$

Genexpression as Hill-Equation depending on activator or repressor





Repressor:

$$\frac{dy}{dt} = k \times \Theta_u = k \frac{K_d}{K_d + [L]^n}$$

Activator:

$$\frac{dx}{dt} = k \times \Theta_B = k \frac{[L]^n}{K_d + [L]^n}$$

Including Diffusion:

$$change\ of\ particles = source\ - sink + Diffusion$$

$$\frac{dc}{dt} = k_+ - k\_c + D\ \Delta c$$

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 5051–5055, July 1988
Biochemistry

Molecular model for receptor-stimulated calcium spiking

(inositol phospholipid cascade/inositol trisphosphate/calcium channels/oscillations/frequency encoding)

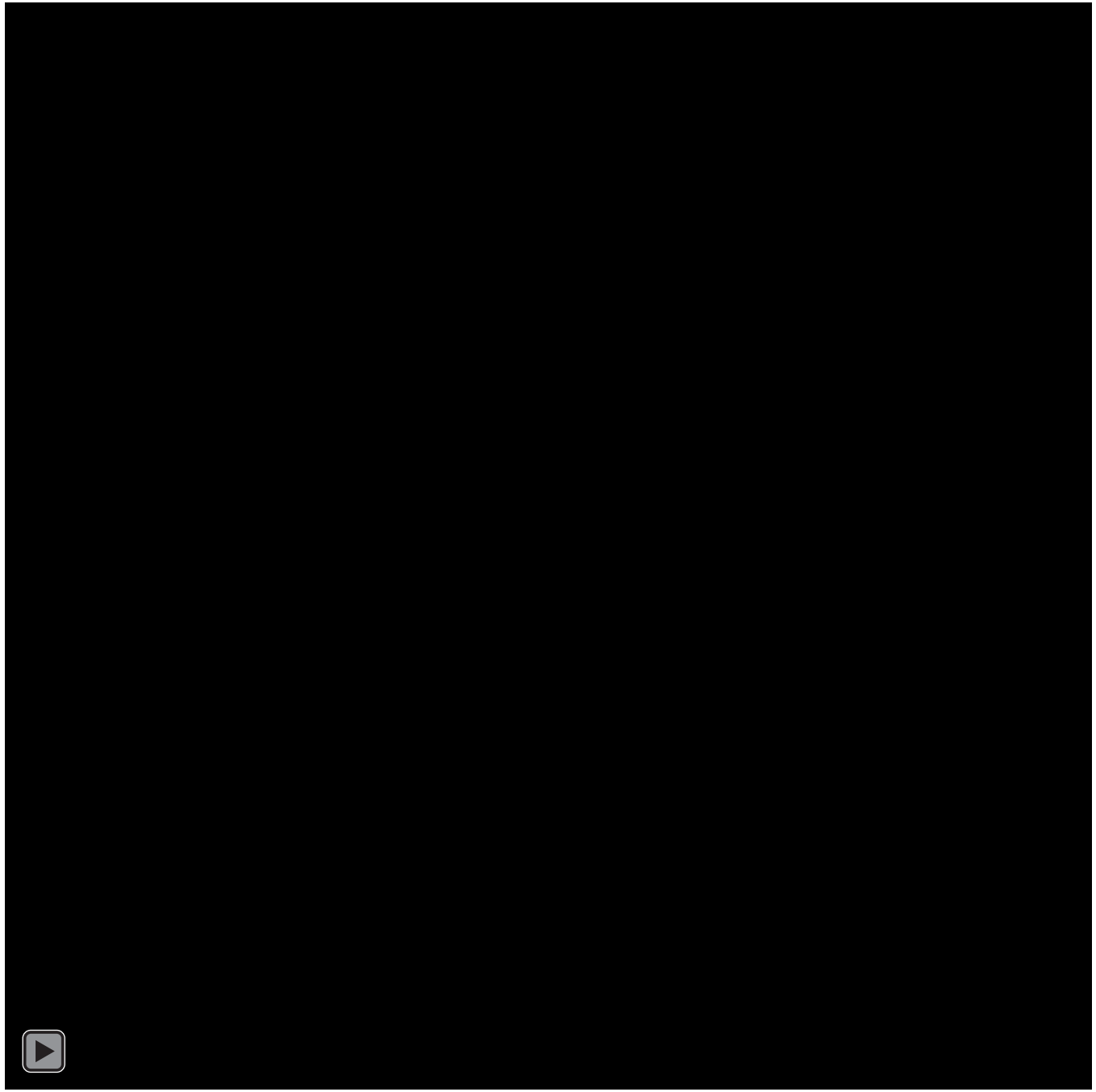
TOBIAS MEYER AND LUBERT STRYER

Department of Cell Biology, Sherman Fairchild Center, Stanford University School of Medicine, Stanford, CA 94305

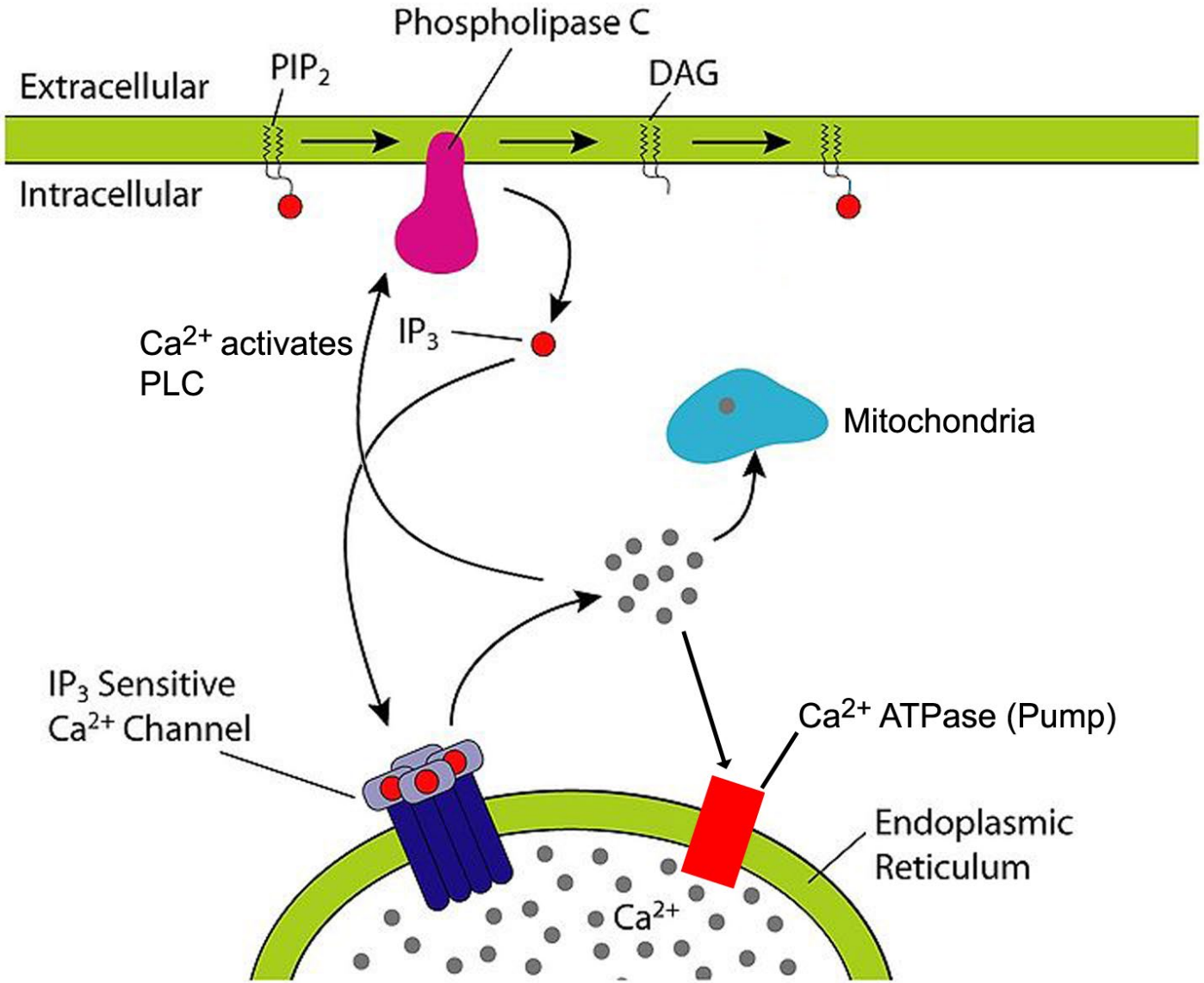
Contributed by Lubert Stryer, April 18, 1988

Inspecting how feedback can lead to oscillations in the intracellular Calcium level.

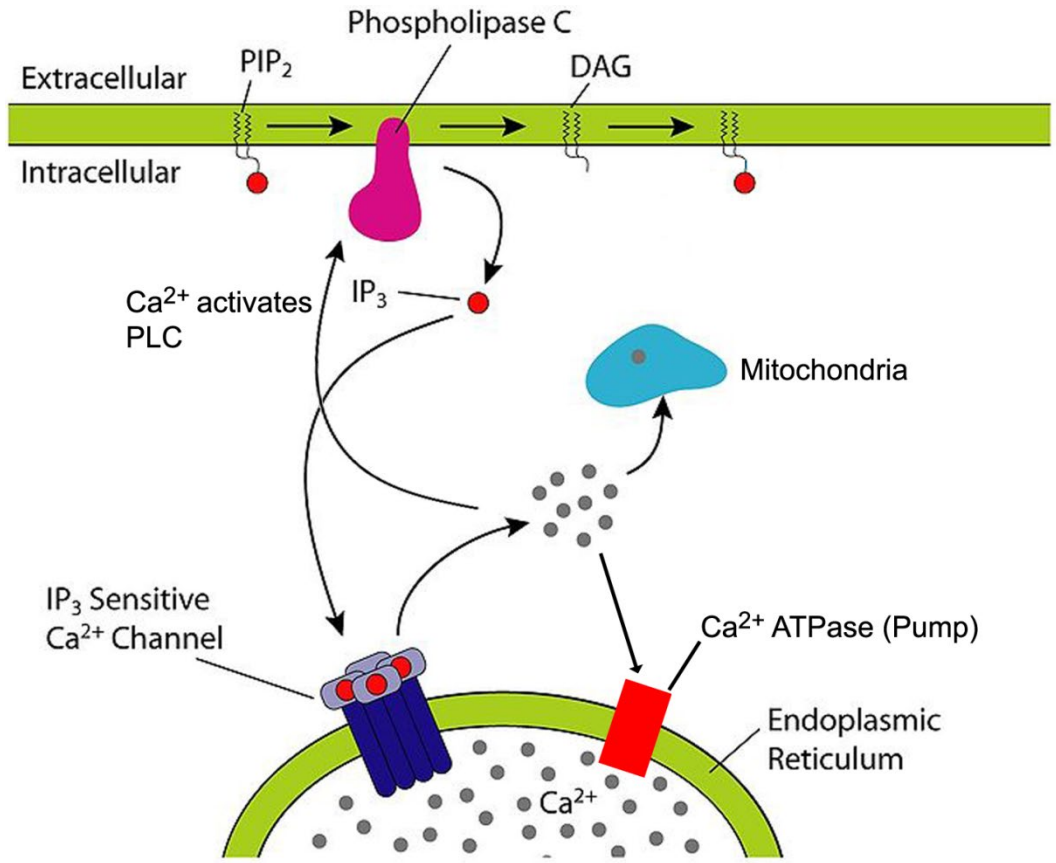
Challenge of the model: How can a hormone concentration control the Ca spike frequency



The system:


Phospholipase C
Extracellular
PIP2
DAG
Intracellular
Ca2+ activates
PLC
IP3
Mitochondria
IP3 Sensitive
Ca2+ Channel
Ca2+ ATPase (Pump)
Endoplasmic
Reticulum
Ca2+

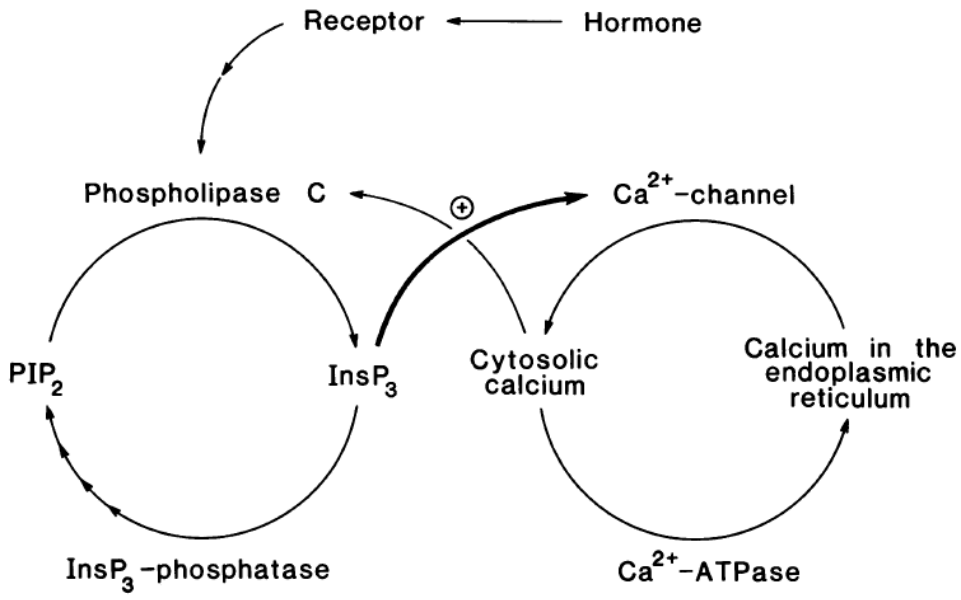
The system:



The individual processes:

1. Signal (e.g. hormone) activates PLC
2. PIP2 ⟶ IP3 + DAG
3. IP3 activates Calcium channel in ER
4. Increased calcium activates PLC ⟶ positive feedback
5. Calcium is taken up by Mitochondria, and pumped back in ER by ATPase
6. IP3 is degraded to PIP2

A scheme of the system:



The individual processes:

1. Signal (e.g. hormone) activates PLC
2. PIP2 ⟶ IP3 + DAG
3. IP3 activates Calcium channel in ER
4. Increased calcium activates PLC ⟶ positive feedback
5. Calcium is taken up by Mitochondria, and pumped back in ER by ATPase
6. IP3 is degraded to PIP2

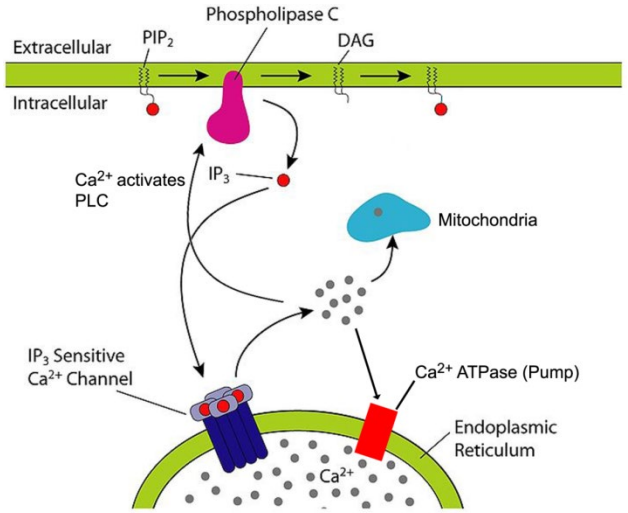
What will happen? Well, it depends how fast things happen…

To understand what will happen, we need to quantify the individual processes:

1. First we look at the Calcium flux from the opened ER channel. This shows cooperativity:

$$J_1 = c_1 f z$$

$$f = y^3 / (K_1 + y)^3$$



J_1 : IP3 induced calcium flux from the ER

c_1 : Flux rate of a single channel

f : Fraction of channels open

z : Calcium concentration in the ER

y : IP3 concentration

K_1 : IP3 dissociation constant on channels

To understand what will happen, we need to quantify the individual processes:

Then we check the how the Calcium is pumped back:

$$J_2 = \underbrace{c_2 x^2/(x+K_2)^2}_{\text{Pumps}} - \underbrace{c_3 z^2}_{\text{Leakage}}$$

J_2 : Calcium flux into the ER by pumps

c_2 : Pumping rate (2 Calcium per cycle)

x : Calcium concentration in the cytosole

c_3 : Calcium leakage through the ER without channel

Change of Calcium concentration in cytosol:

Outflux from ER due to channels - Influx in ER due to the pumps

$$\frac{dx}{dt} = J_1 - J_2 = c_1 y^3/(K_1+y)^3 z - c_2 x^2/(x+K_2)^2 + c_3 z^2$$

To understand what will happen, we need to quantify the individual processes:

Then we investigate the IP3 changes:

First the creation of IP3 by PLC

$$k_+ = c_4 R g$$

k_+ : PIP2 to IP3 conversion rate

c_4 : PIP2 to IP3 conversion rate per PLC

R : Degree of receptor dependent activation

$$\underbrace{g = x/(x + K_3)}$$

Calcium induced activation in PLC

K_3 : Calcium to PLC binding constant

To understand what will happen, we need to quantify the individual processes:

Then we investigate the IP3 changes:

Then the decay of IP3

$$k_- = c_5 y$$

k_+ : IP3 to PIP2 conversion rate

c_5 : Conversion constant

y : Concentration of IP3

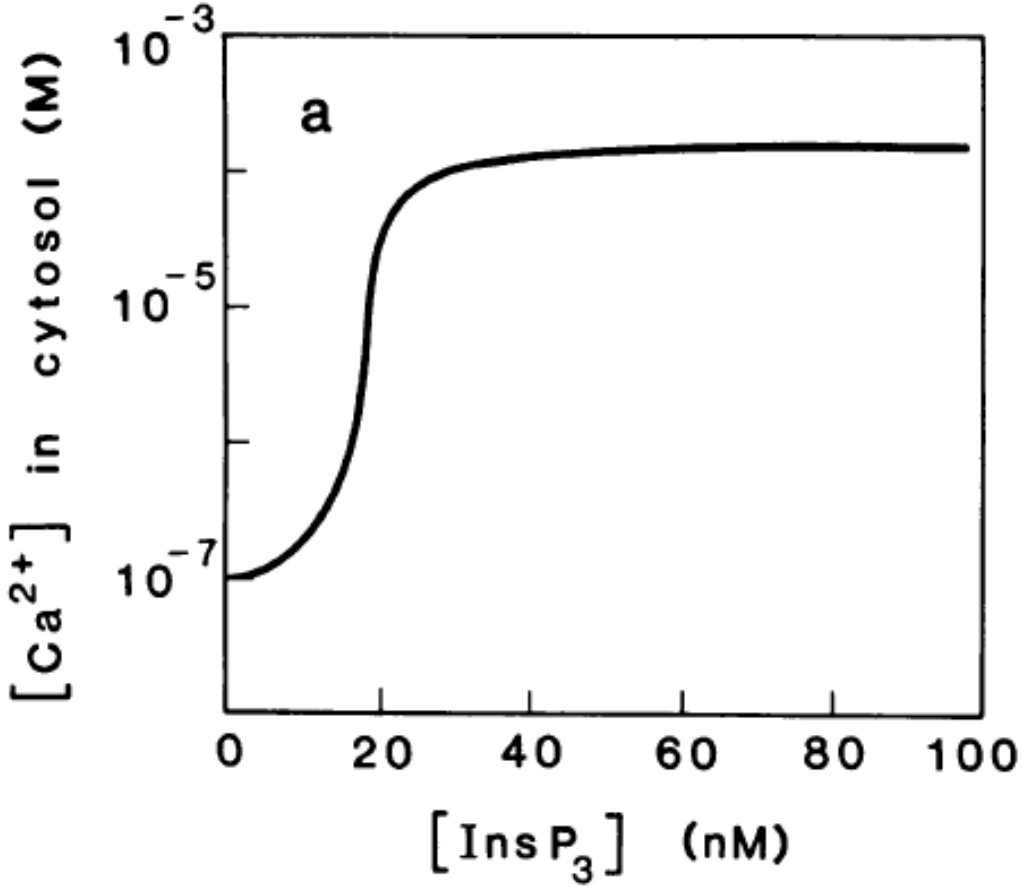
Change of IP3 concentration in cytosol:

Creation by PLC - decay over time (Remark, there was no square in the calcium dependence)

$$\frac{dy}{dt} = k_+ - k_- = c_4 R[x/(x + K_3)] - c_5 y$$

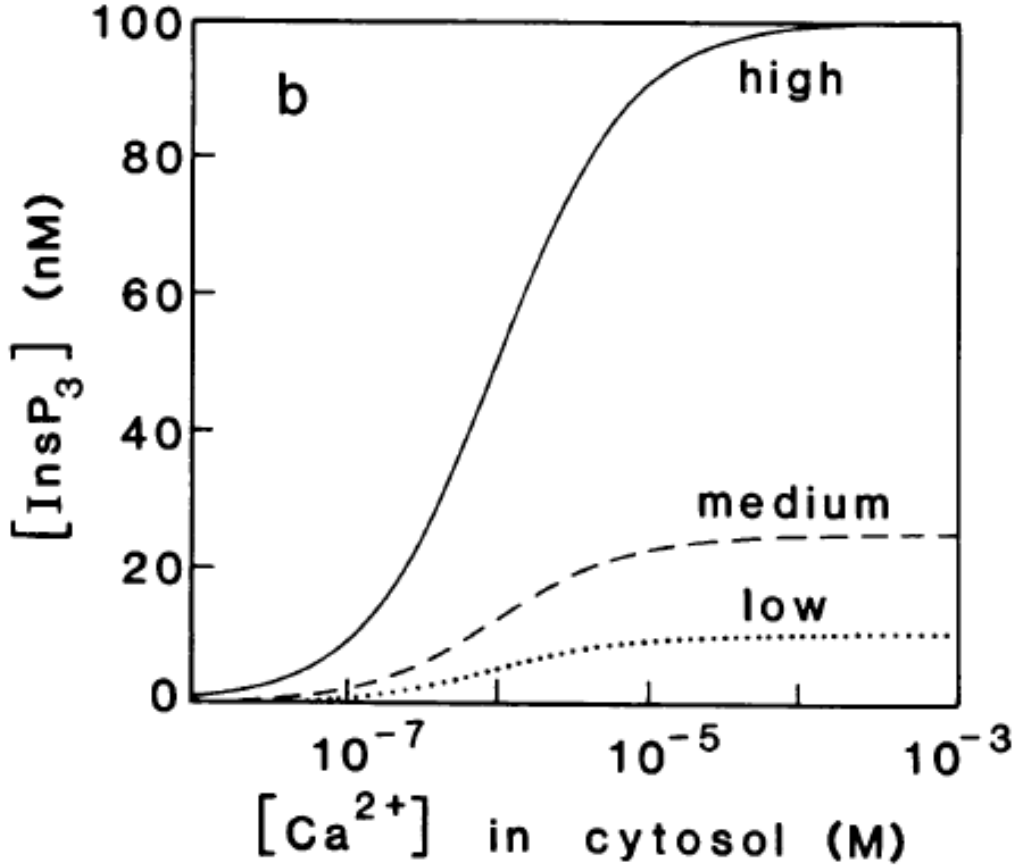
Find steady state (dx/dt=0) of Calcium (x) if IP3 concentration (y) is given

$$\frac{dx}{dt} = J_1 - J_2 = c_1 y^3 /(K_1 + y)^3 z - c_2 x^2 /(x + K_2)^2 + c_3 z^2$$

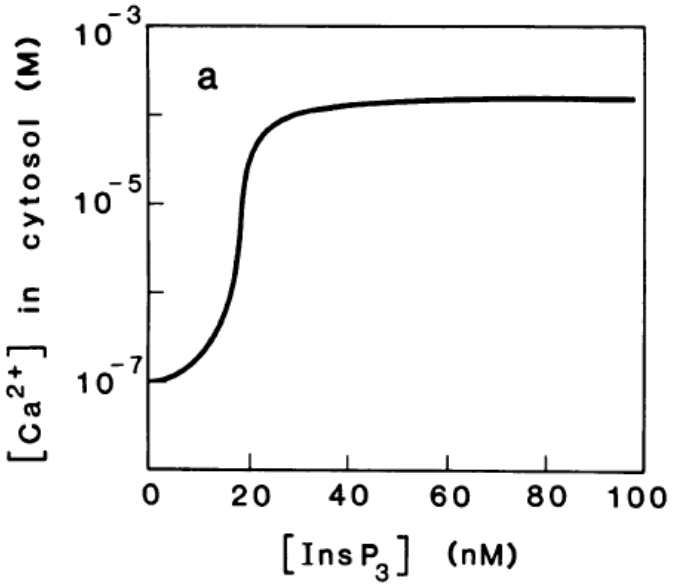


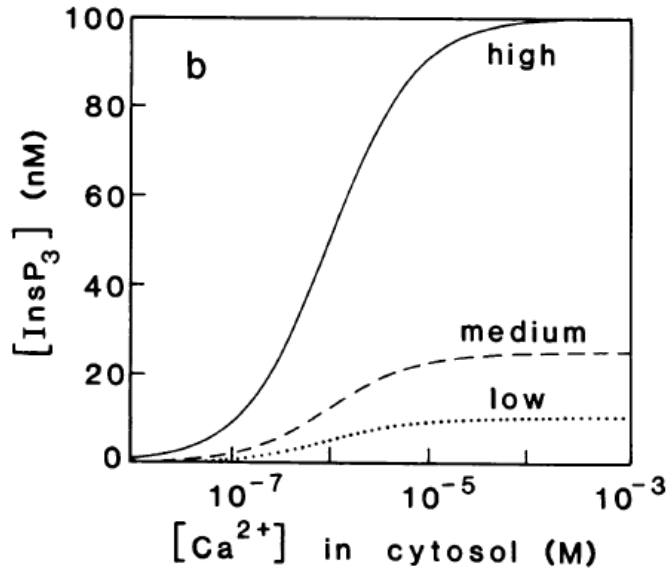
Find steady state (dy/dt=0) of IP3 (y) if Calcium concentration (x) is given

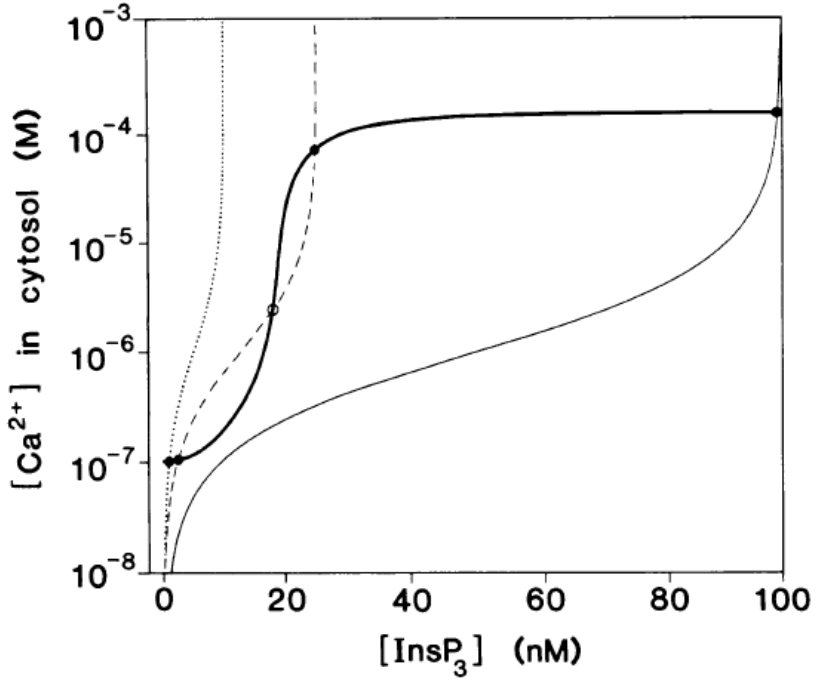
$$\frac{dy}{dt} = k_+ - k_- = c_4 R[x/(x + K_3)] - c_5 y$$



Overlaying the two gives for the medium activation 3 crossovers (these points are possible steady state for both Calcium and IP3

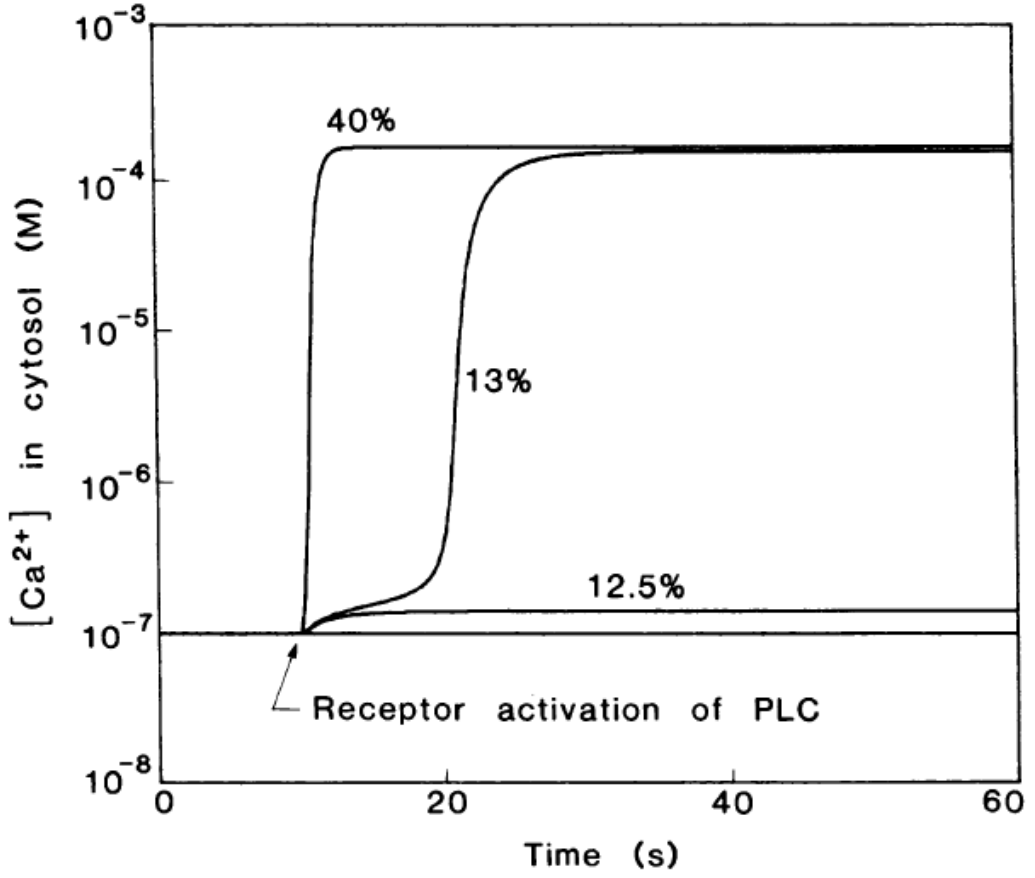






One steady state is instable (a small change will let the system flow in one of the other points). The other points are stable.

How to bring it to oscillate?



For this we need something that takes out Calcium ions if they are at a high concentration! This is done by the mitochondria, where the Calcium absorbance depends on the $[Ca]^{3.3}$

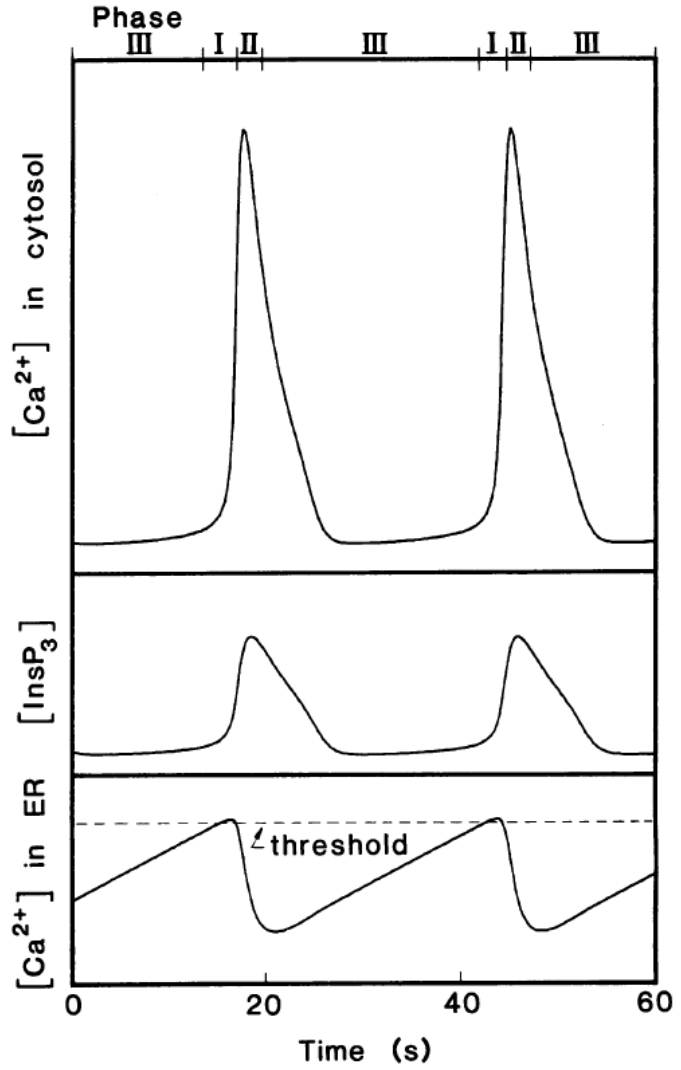
Now we put everything together:

A coupled nonlinear system

Change in Calcium: $$\frac{dx}{dt} = J_1 - J_2 - \underbrace{c_6(x/c_7)^{3.3} + c_6}_{\text{Uptake of Mitochondria}}$$

Change in IP3: $$\frac{dy}{dt} = k_+ - k_- = c_4 R[x/(x + K_3)] - c_5 y$$

Now we have suddenly a very strong reduction of Calcium, once we are at a high Calcium level.



Phase I:

Fast Calcium increase because of the feedback (IP3 activate Calcium, which increases IP3 concentration…)

Phase II:

The ER Calcium is used up, at the same time the mitochondria take up a lot of Ca. This goes back to the basal Calcium level

Phase III:

The Mitochondria slowly release the Calcium, which is restored in the ER.