FYTN05/TEK267
Chemical forces and self assembly

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Chapters

- This part of the course includes chapter 8. 8.6.2 has been left for SW.

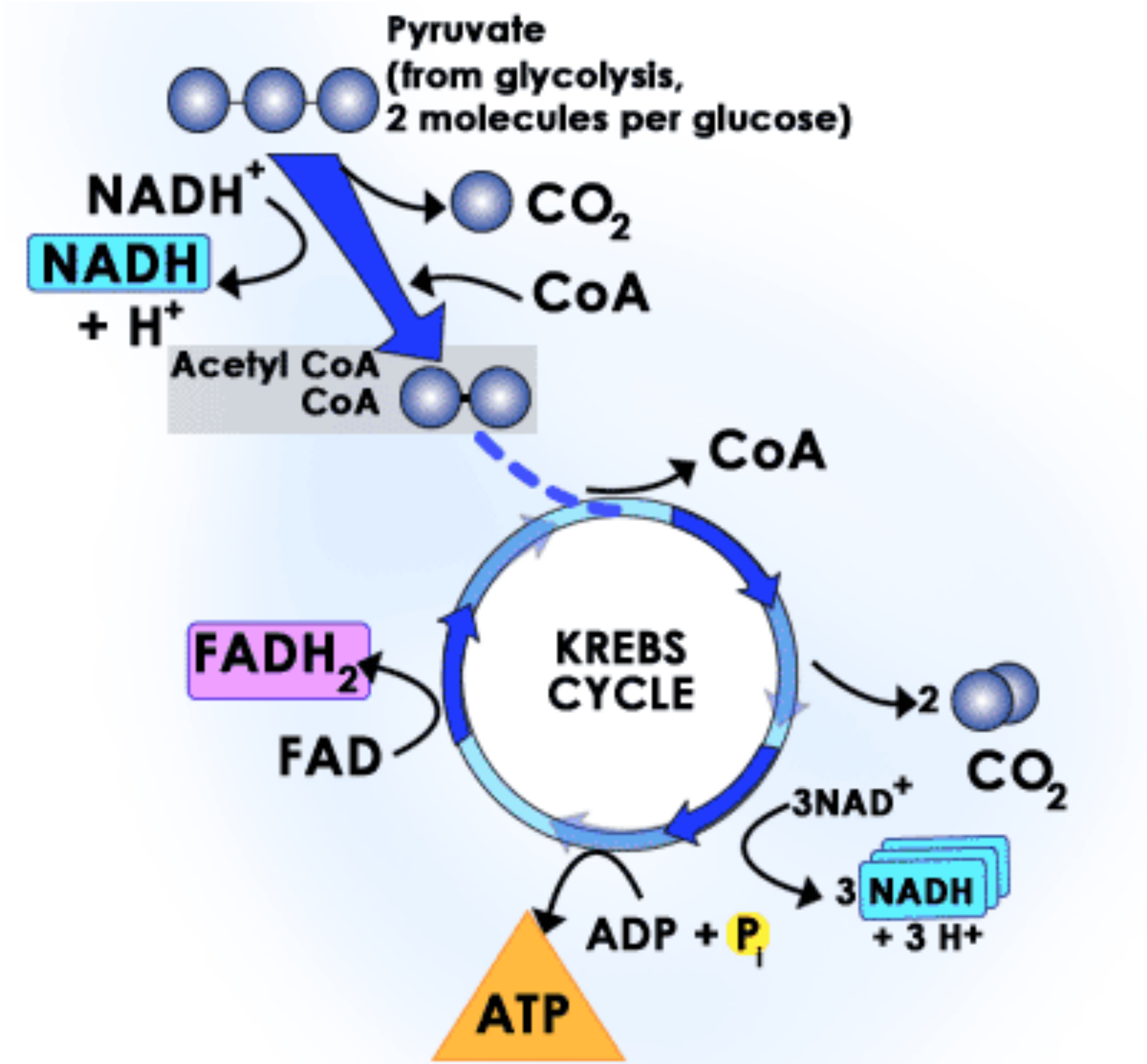
- In addition I have used information from other chapters, which not are compulsatory to read but which might be useful. For the discussion of reaction coordinates, transition states and their connction to rate constants I have included material that can be found in 3.2.4, 6.6.2, 10.3.2. For the discussion on enzymes and Michaelis-Menten I have included information that can be found in 10.3.3 and 10.4.1.

Exercises

- Exercises from Nelson: 8.2, 8.3, 8.5 and 8.6
- Other exercises in chapter 8 relate the chapter with findings in other chapters. These might also bee useful to do, although they depend on your knowledge from those chapters.
- The “Your turn” exercises can all be done, although 8C relies heavily on chapter 6. Some of these will be addressed during the lectures.
- A handout with additional exercises is handed out. These address how to write down ODEs for different reactions.

Energy is stored in molecules

The Krebs cycle (citric acid cycle)



Release of Energy

ATP -> ADP

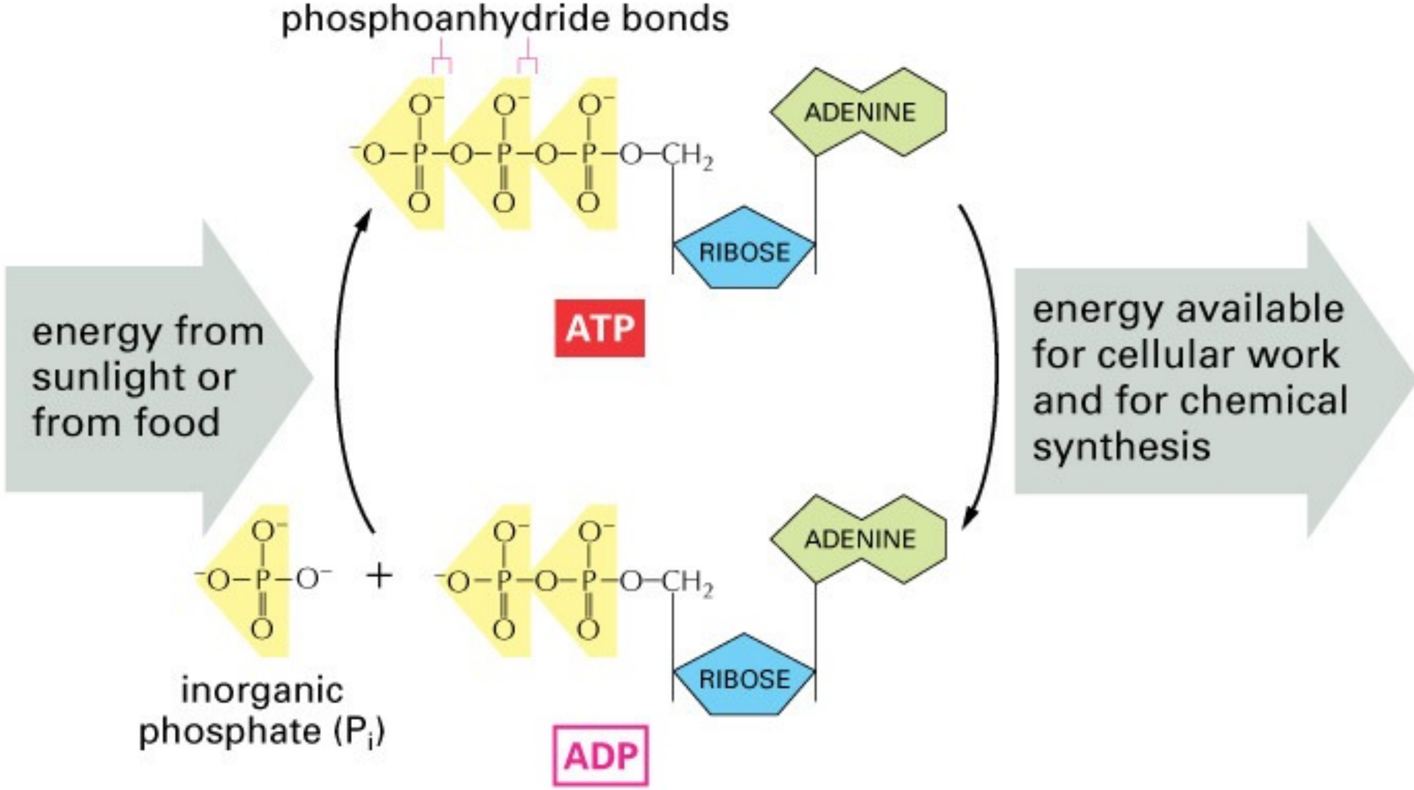
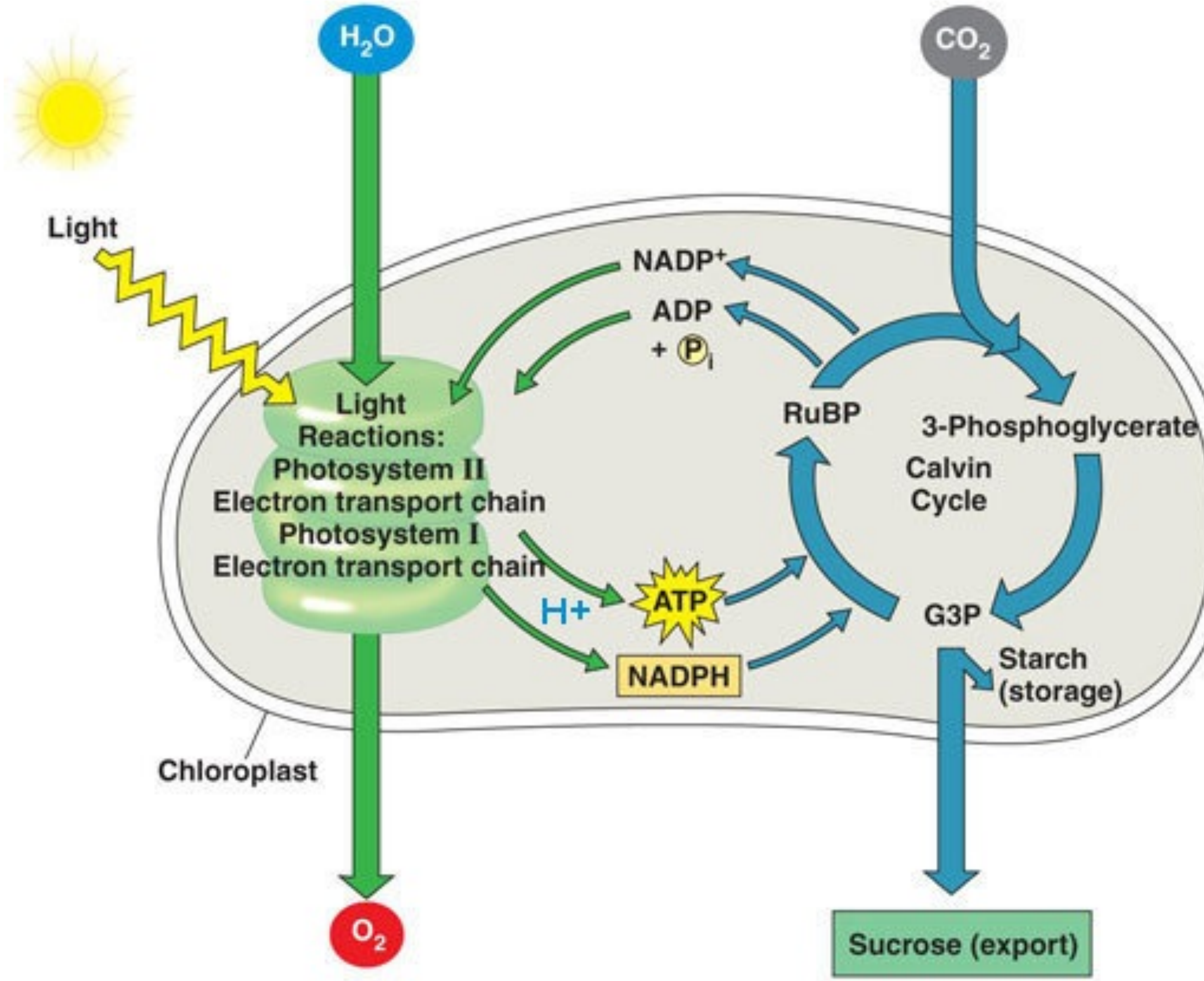


Figure 3-32 Essential Cell Biology, 2/e. (© 2004 Garland Science)

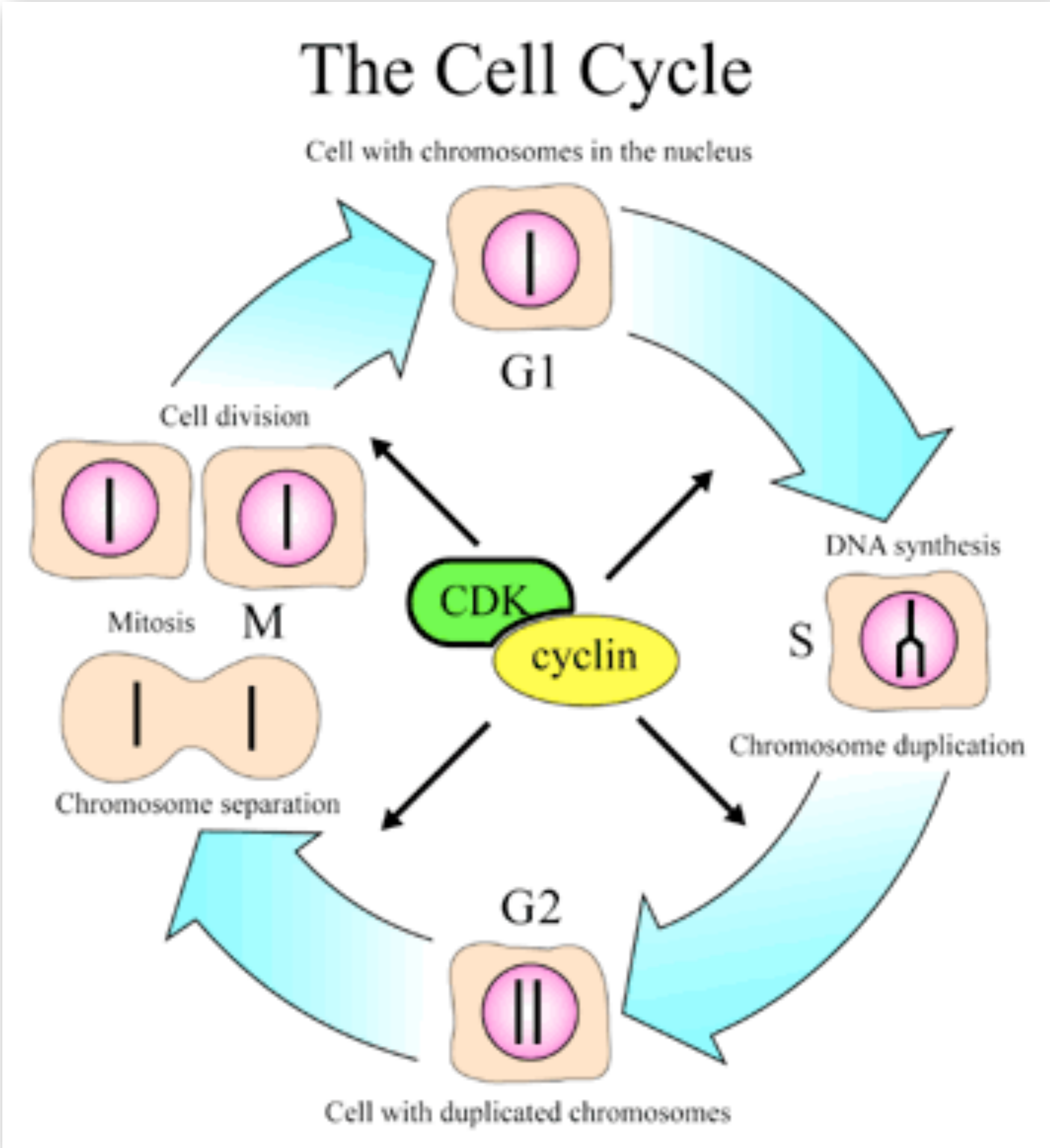
Converting solar Energy

Photosynthesis



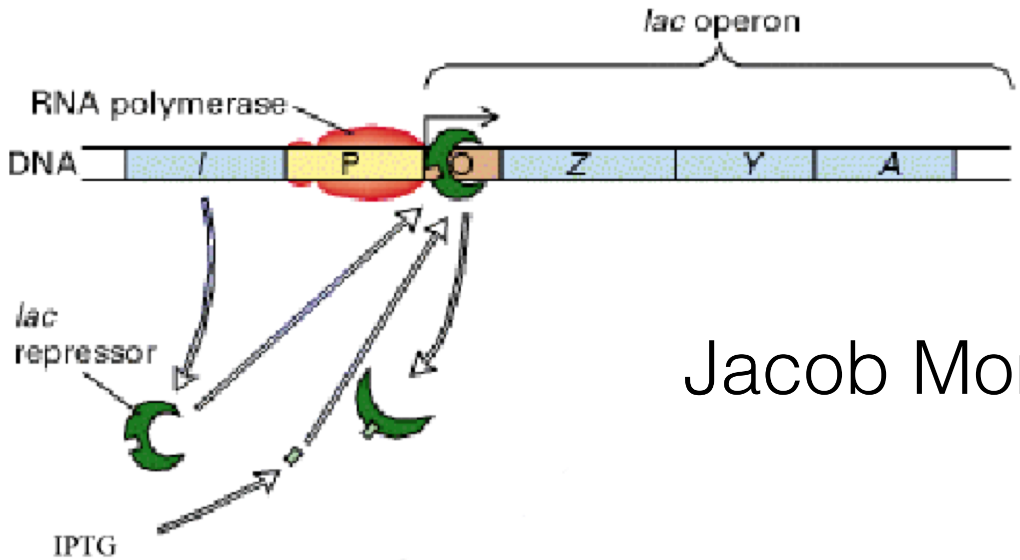
How does it work

Dynamics

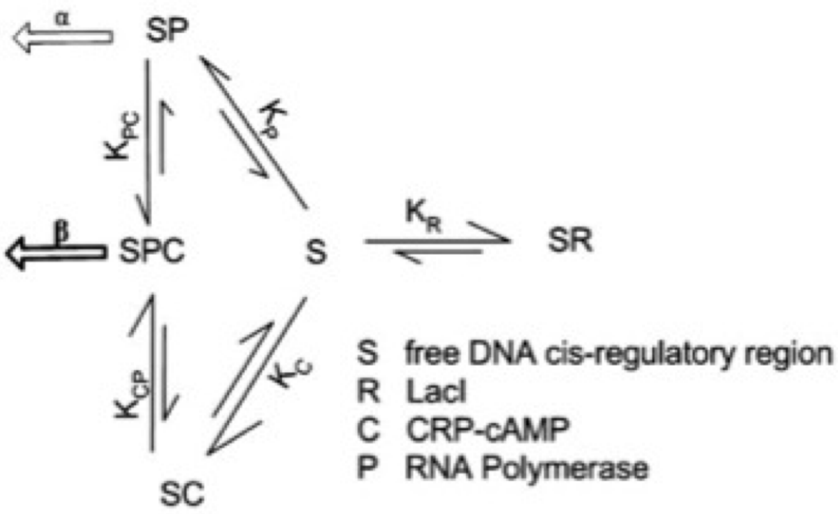


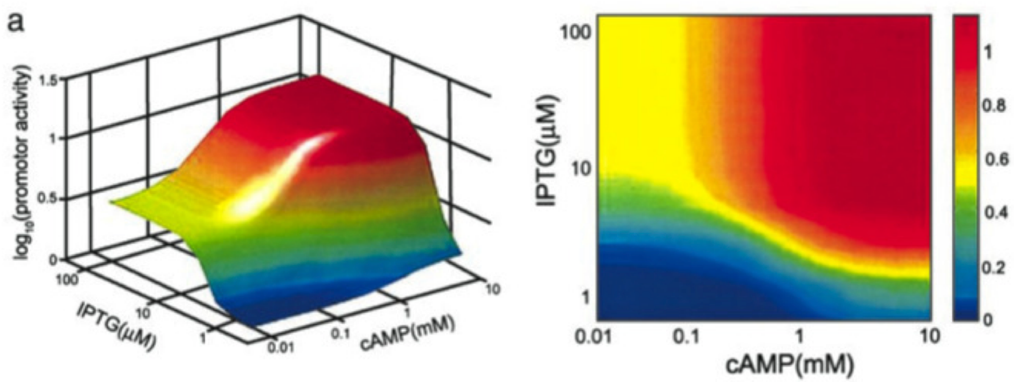
How does it work

Gene regulatory networks



Jacob Monod, 1960s

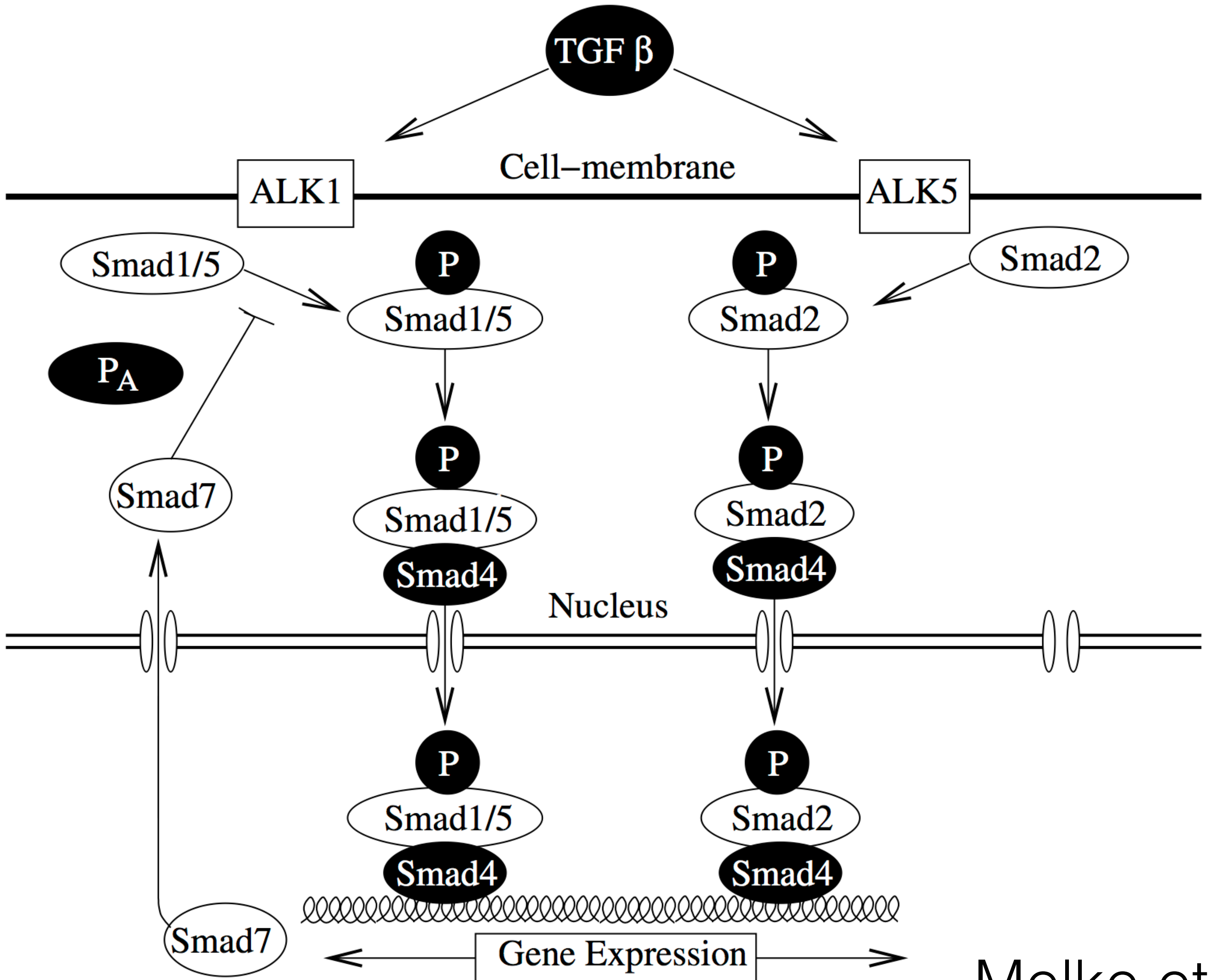




Uri Alon group, 2000s

How does it work

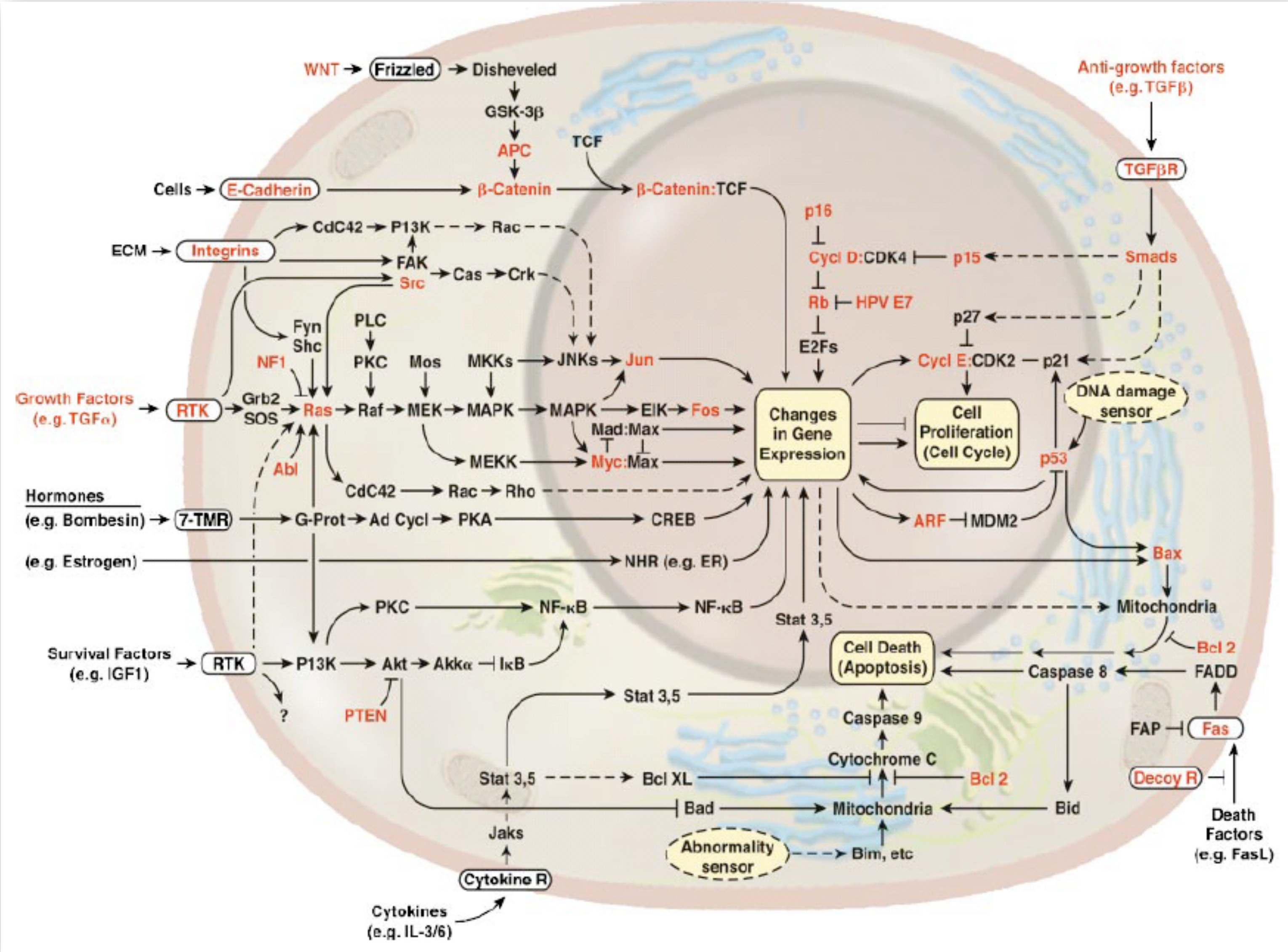
Signalling



Melke et al (2008)

How does it work

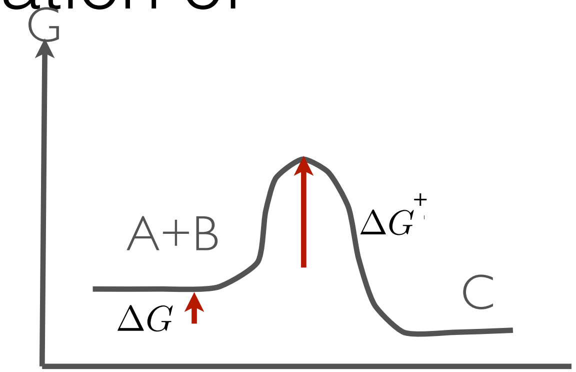
Signalling



Chemical reactions (8.2)

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$$

- The reaction rate is proportional to concentration of reactants (Law of Mass Action)



- reaction rates depend on activation barriers
- equilibrium concentrations depend on potential differences
- ‘formalised’ from statistical mechanics via chemical potentials and ‘forces’

Chemical reactions (8.2)

$A+B \rightleftharpoons C$

Deterministic description
(ordinary differential equations)

$$\frac{dC_A}{dt} = -k_f C_A C_B + k_b C_C$$

Stochastic description

$$P_f(t, t+dt) = k_f \frac{N_A}{V}\frac{N_B}{V} \longrightarrow (N_A \to N_A - 1, N_B \to N_B - 1, N_C \to N_C + 1)$$

$$P_b(t, t+dt) = k_b \frac{N_C}{V} \longrightarrow (N_A \to N_A + 1, N_B \to N_B + 1, N_C \to N_C - 1)$$

solved e.g. by Gillespie algorithm:

- select reaction randomly from probabilities
- step forward in time via random distribution

Chemical reactions (8.2)

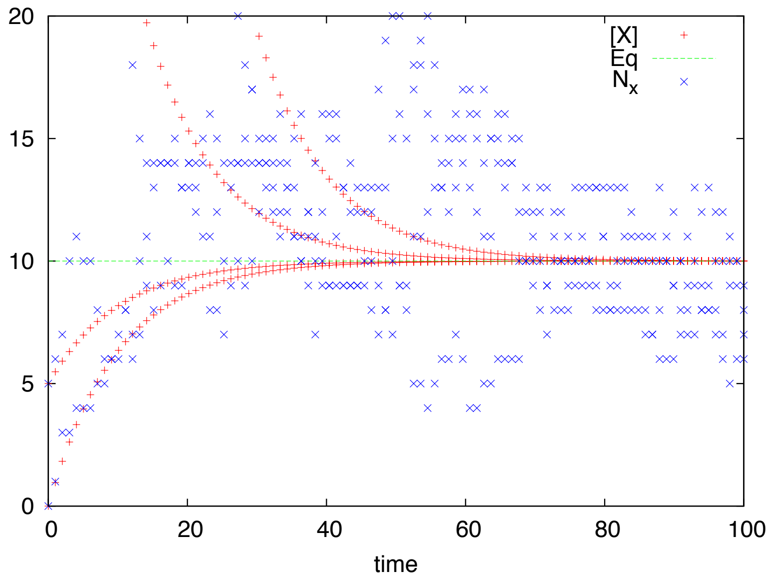
Statistical equilibrium: forward rate equals backward rate

A+B $\rightleftarrows$ C

$$\frac{dC_A}{dt} = 0 \longrightarrow \frac{C_C^*}{C_A^* C_B^*} = \frac{k_f}{k_b} = K_{eq}$$ (equilibrium constant)

$$C_A > C_A^* \longrightarrow C_A \searrow$$

$$C_A < C_A^* \longrightarrow C_A \nearrow$$

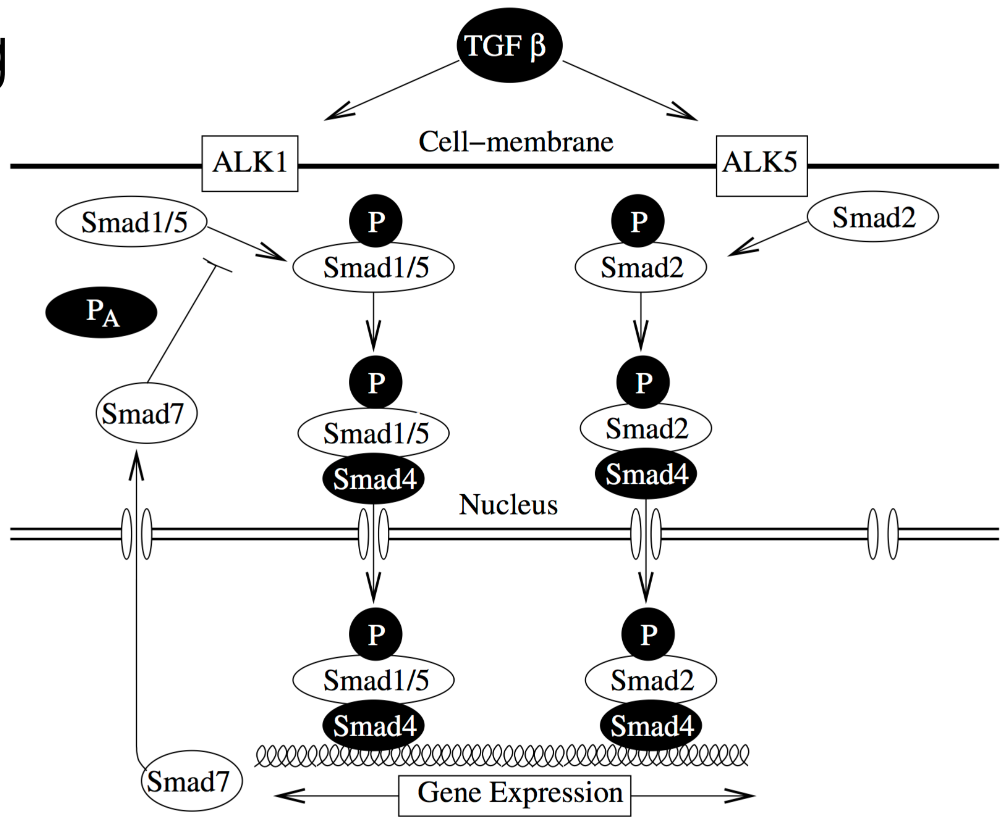


Equilibrium is a stable fixed-point

Chemical reactions (8.2)

Multiple reactions can provide complex dynamical behaviour

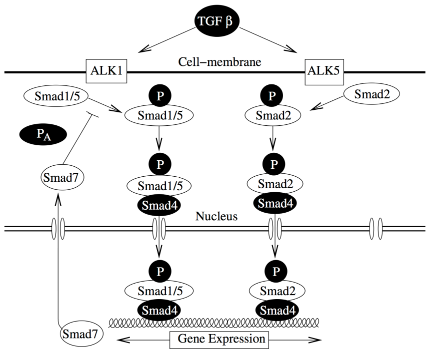
Example:
TGFb-signalling



Melke et al (2008)

Chemical reactions (8.2)

Example: TGFb-signalling



$$\emptyset \underset{p_0 p_1}{\overset{p_0}{\rightleftharpoons}} \mathrm{ALK1} \quad (1)$$

$$\emptyset \underset{p_4 p_5}{\overset{p_4}{\rightleftharpoons}} \mathrm{Smad4} \quad (2)$$

$$\emptyset \underset{p_8 p_9}{\overset{p_8}{\rightleftharpoons}} \mathrm{ALK5} \quad (3)$$

$$\mathrm{TGF}\beta + \mathrm{ALK1} \underset{p_{14}}{\overset{p_{13}}{\rightleftharpoons}} \mathrm{TA1} \quad (4)$$

$$\mathrm{PSmad1} + \mathrm{Smad4} \underset{p_{19}}{\overset{p_{18}}{\rightleftharpoons}} \mathrm{PS14} \quad (5)$$

$$\mathrm{TGF}\beta + \mathrm{ALK5} \underset{p_{21}}{\overset{p_{20}}{\rightleftharpoons}} \mathrm{TA5} \quad (6)$$

$$\mathrm{P_A} + \mathrm{TA1} \underset{p_{28}}{\overset{\mathrm{Smad7}\atop p_{27}}{\rightleftharpoons}} \mathrm{TA1P} \quad (7)$$

$$\mathrm{P_B} + \mathrm{TA5} \underset{p_{32}}{\overset{\mathrm{Smad7}\atop p_{31}}{\rightleftharpoons}} \mathrm{TA2P} \quad (8)$$

$$\emptyset \underset{p_2 p_3}{\overset{p_2}{\rightleftharpoons}} \mathrm{Smad1} \quad (9)$$

$$\emptyset \underset{p_6 p_7}{\overset{p_6}{\rightleftharpoons}} \mathrm{Smad2} \quad (10)$$

$$\emptyset \underset{p_{10}}{\overset{PS14N \atop (p_{11}, p_{12})}{\rightleftharpoons}} \mathrm{Smad7} \quad (11)$$

$$\mathrm{Smad1} \underset{p_{17}}{\overset{TA1 \atop (p_{15}, p_{16})}{\rightleftharpoons}} \mathrm{PSmad1} \quad (12)$$

$$\mathrm{Smad2} \underset{p_{24}}{\overset{TA5 \atop (p_{22}, p_{23})}{\rightleftharpoons}} \mathrm{PSmad2} \quad (13)$$

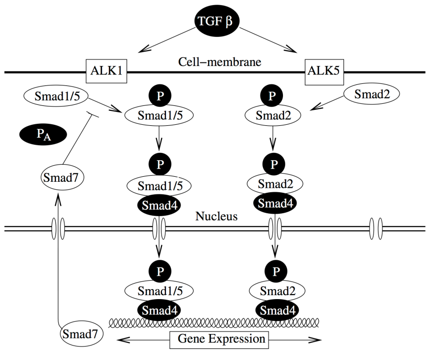
$$\mathrm{PSmad2} + \mathrm{Smad4} \underset{p_{26}}{\overset{p_{25}}{\rightleftharpoons}} \mathrm{PS24} \quad (14)$$

$$\mathrm{PS14} \underset{k_{30}}{\overset{p_{29}}{\rightleftharpoons}} \mathrm{PS14N} \quad (15)$$

Melke et al (2008)

Chemical reactions (8.2)

Example: TGFb-signalling



$$\frac{dA_1}{dt} = p_0(1 - p_1 A_1) - p_{13} T_\beta A_1 + p_{14} T_1$$

$$\frac{dS_1}{dt} = p_2(1 - p_3 S_1) - \frac{p_{15} T_1 S_1}{p_{16} + S_1} + p_{17} P_1$$

$$\frac{dS_4}{dt} = p_4(1 - p_5 S_4) - p_{18} P_1 S_4 + p_{19} P_{14} - p_{25} P_2 S_4 + p_{26} P_{24}$$

$$\frac{dS_2}{dt} = p_6(1 - p_7 S_2) - \frac{p_{22} T_1 S_2}{p_{23} + S_2} + p_{24} P_2$$

$$\frac{dA_5}{dt} = p_8(1 - p_9 A_5) - p_{20} T_\beta A_5 + p_{21} T_5$$

$$\frac{dS_7}{dt} = \frac{p_{11} P_{14}}{p_{12} + P_{14}} - p_{10} S_7$$

$$\frac{dP_1}{dt} = \frac{p_{15} T_1 S_1}{p_{16} + S_1} - p_{17} P_1 - p_{18} P_1 S_4 + p_{19} P_{14}$$

$$\frac{dP_{14}}{dt} = p_{18} P_1 S_4 - p_{19} P_{14} - p_{29} P_{14} + p_{30} P_{14N}$$

$$\frac{dP_{14N}}{dt} = p_{29} P_{14} - p_{30} P_{14N}$$

$$\frac{dP_2}{dt} = \frac{p_{22} T_1 S_2}{p_{23} + S_2} - p_{24} P_2 - p_{25} P_2 S_4 + k_{17} P_{26}$$

$$\frac{dP_{24}}{dt} = p_{25} P_2 S_4 - p_{26} P_{24}$$

$$\frac{dT_1}{dt} = p_{13} T_\beta A_1 - p_{14} T_1 - p_{27} S_7 P_{P1} T_1 + p_{28} T_{1P}$$

$$\frac{dT_5}{dt} = p_{20} T_\beta A_5 - p_{21} T_5 - p_{31} S_7 P_{P2} T_5 + p_{32} T_{5P}$$

$$\frac{dP_A}{dt} = -p_{27} S_7 P_A T_1 + p_{28} T_{1P}$$

$$\frac{dP_B}{dt} = -p_{31} S_7 P_B T_1 + p_{32} T_{1P}$$

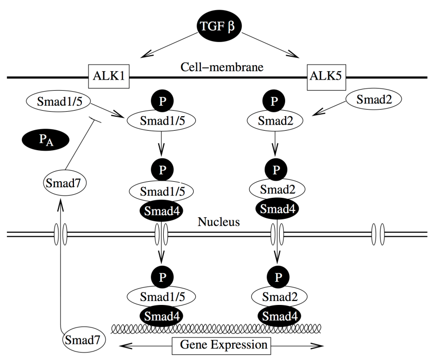
$$\frac{dT_{1P}}{dt} = p_{27} S_7 P_A T_1 - p_{28} T_{1P}$$

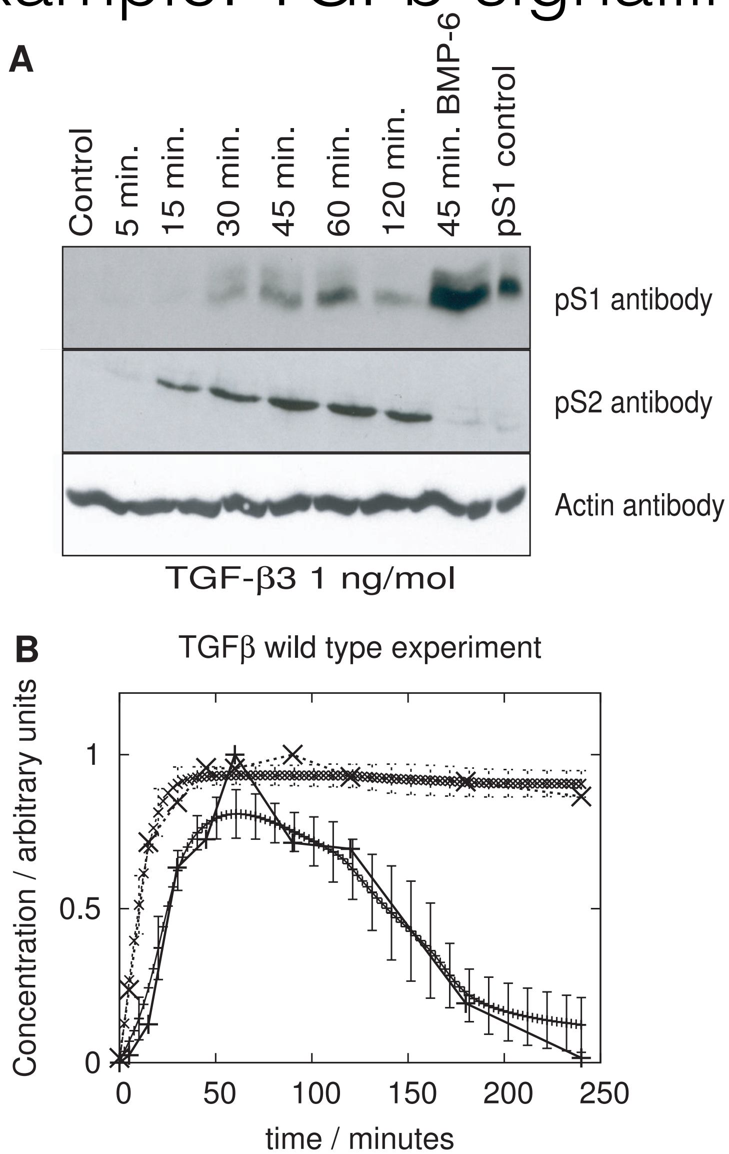
$$\frac{dT_{5P}}{dt} = p_{31} S_7 P_B T_5 - p_{32} T_{5P}$$

Melke et al (2008)

Chemical reactions (8.2)

Example: TGFb-signalling





Melke et al (2008)

Dissociation (8.3)

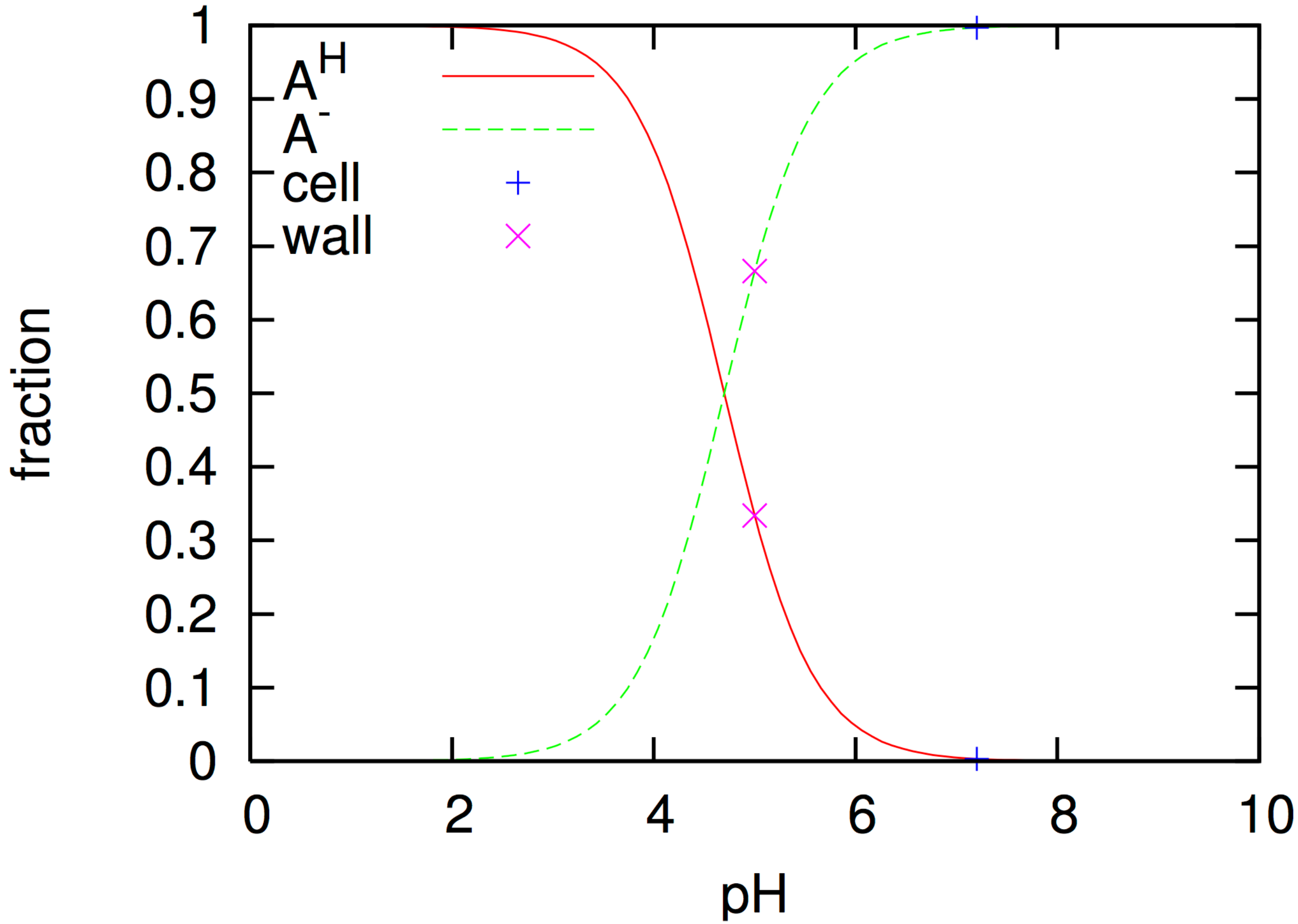
$$AH \rightleftharpoons A^{-} + H^{+}$$

- (de)protenated forms of ions
- rates and equilibrium depends on pH
- can be used to determine protein composition

Dissociation (8.3)

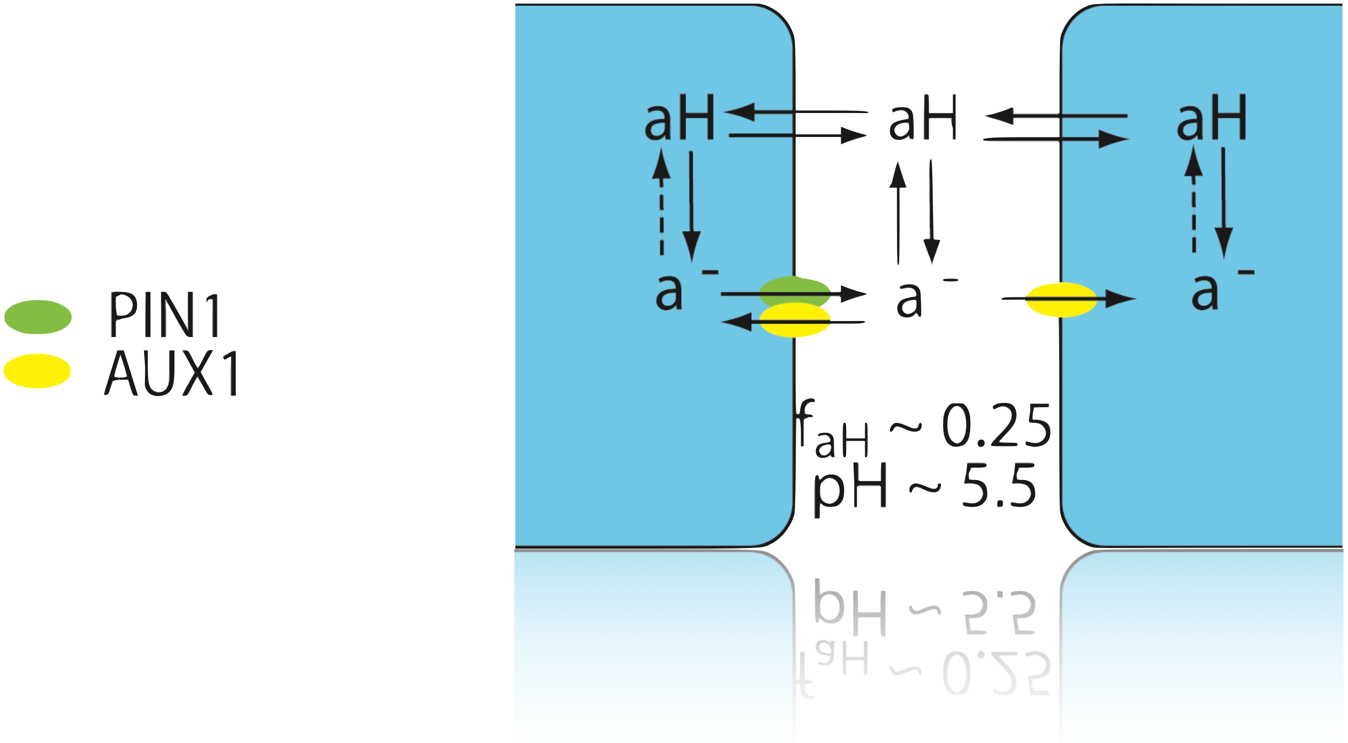
Example: auxin
(hormone important for plant development)

$$AH \rightleftharpoons A^- + H^+$$



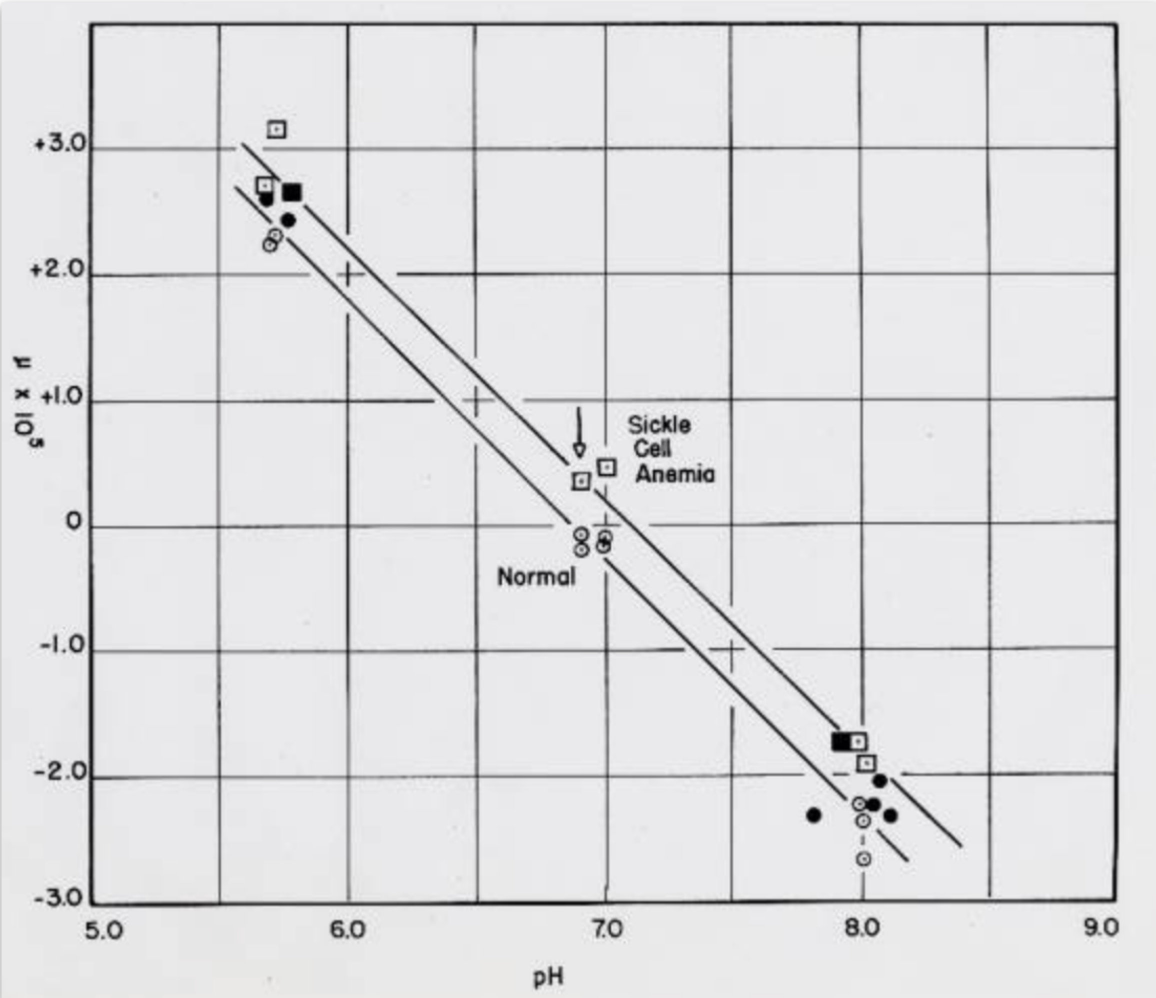
Dissociation (8.3)

Example: auxin
(hormone important for plant development)



Dissociation (8.3)

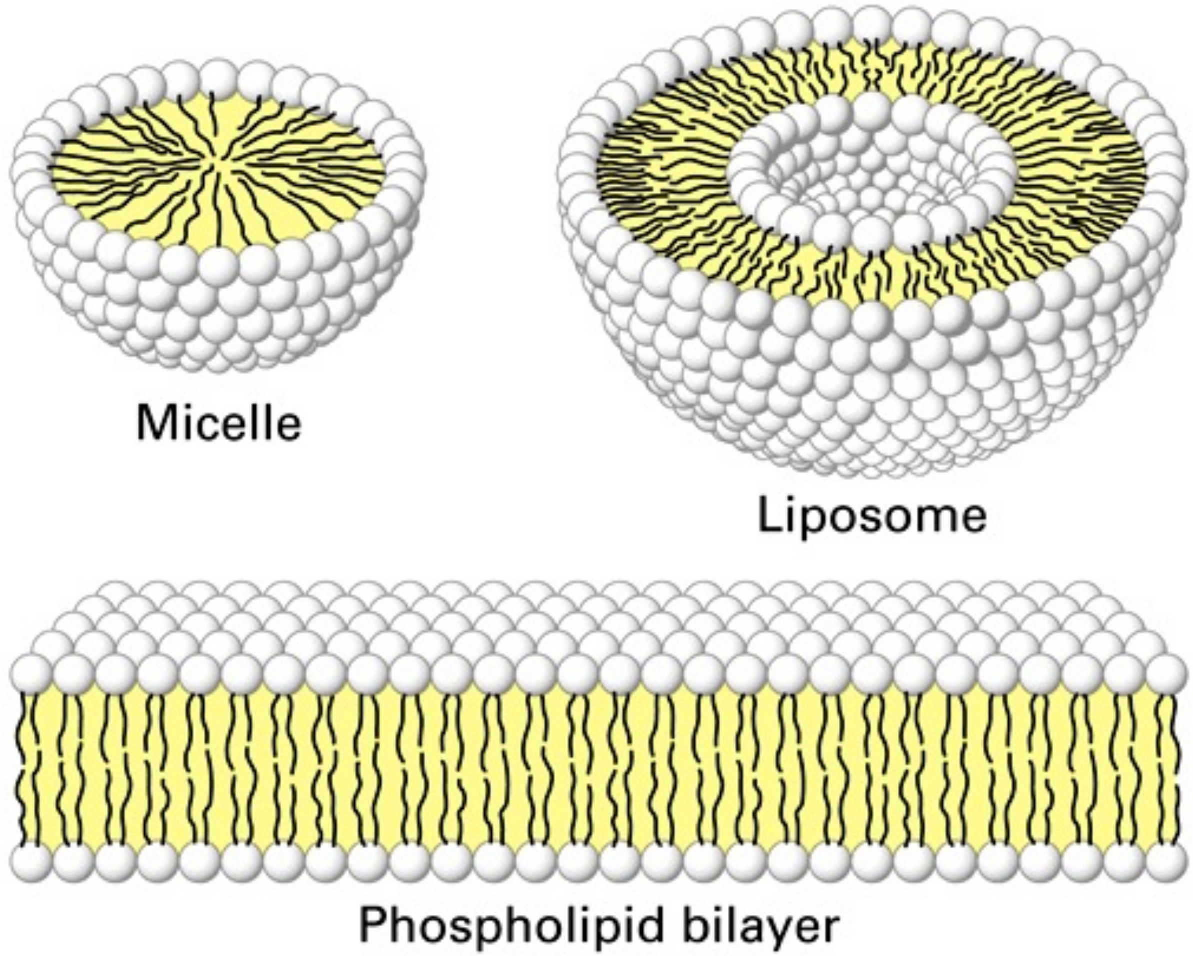
Example: Linus Pauling's sickle-cell experiment
(finding one amino acid difference in hemoglobin)



Itano (1950)

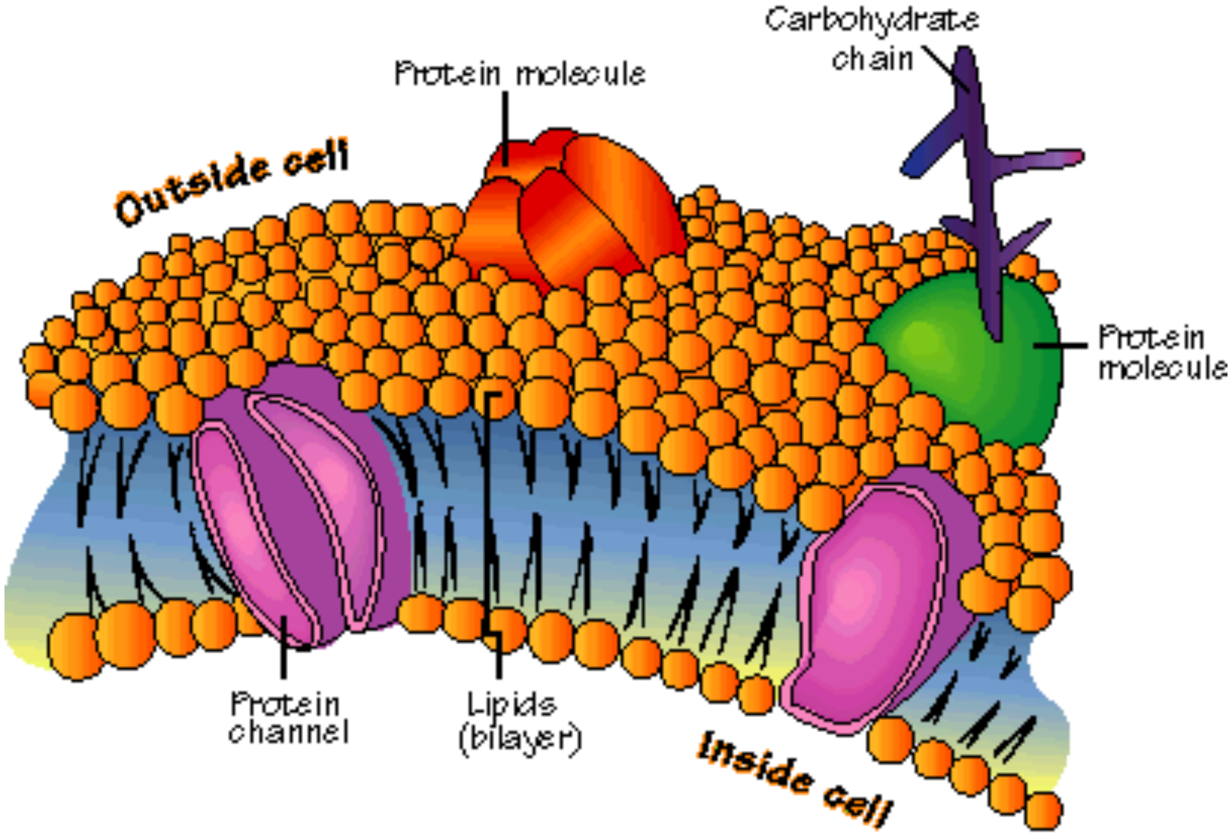
Self assembly (8.4,8.6)

- hydrophobicity (/polarity) can drive formation of organised structures (decreasing Free Energy)



Self assembly (8.4,8.6)

- important for cell membrane formation



Michaelis-Menten (10.3,10.4)

- Many reactions will not occur spontaneously
- Enzymes catalyse reactions

$$“ \; R+E \xrightarrow{k_1} P+E \; “$$

- The enzymes are not used up
- Formalism can be used in many contexts, e.g. gene regulation and active transport

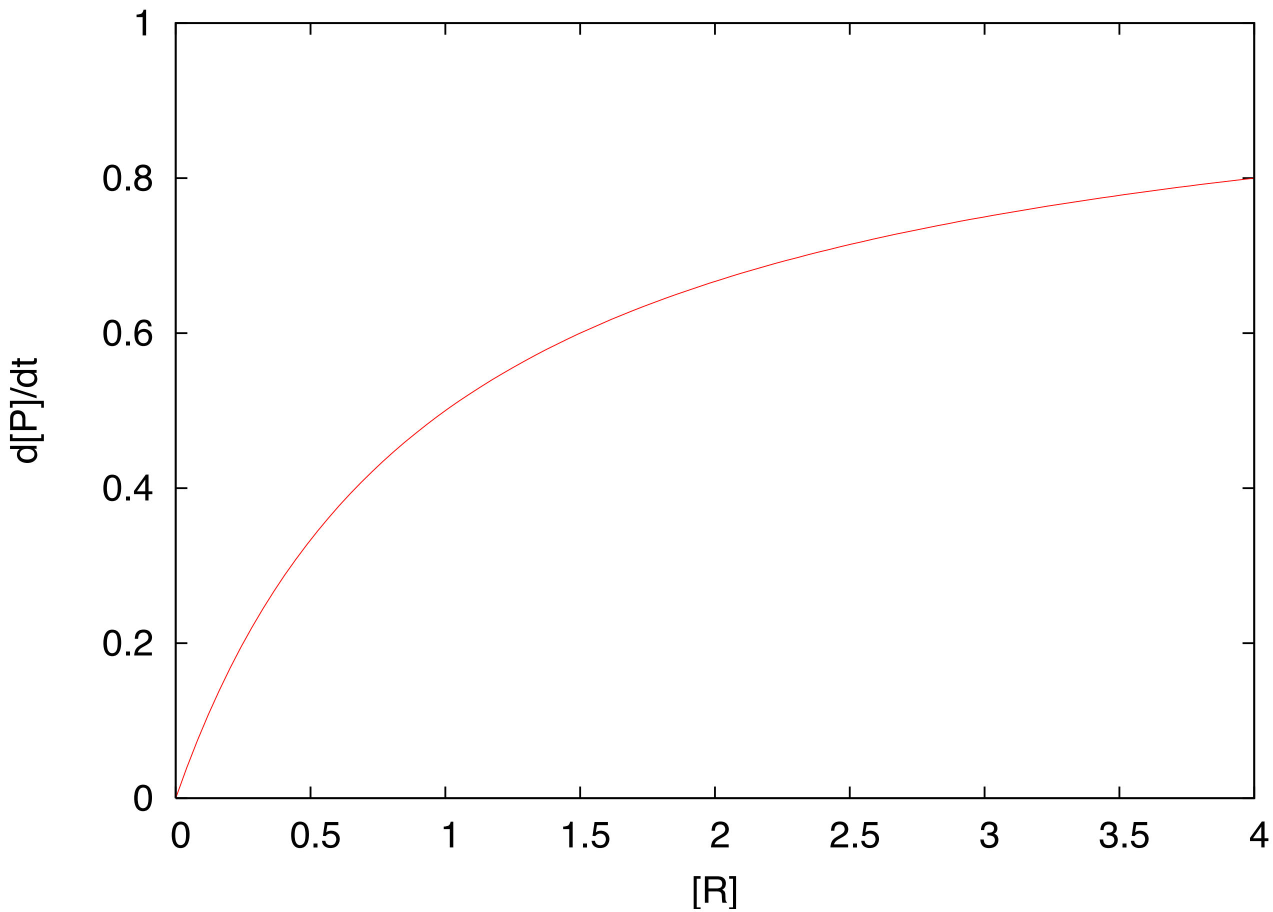
Michaelis-Menten (10.3,10.4)

$$\mathrm{R+E} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RE} \xrightarrow{k_3} \mathrm{P+E}$$

$$\begin{aligned}
\frac{d[R]}{dt} &= -k_1[R][E] + k_2[RE] \\
\frac{d[P]}{dt} &= k_3[RE] \\
\frac{d[RE]}{dt} &= -\frac{d[E]}{dt} = k_1[R][E] - (k_2 + k_3)[RE]
\end{aligned}$$

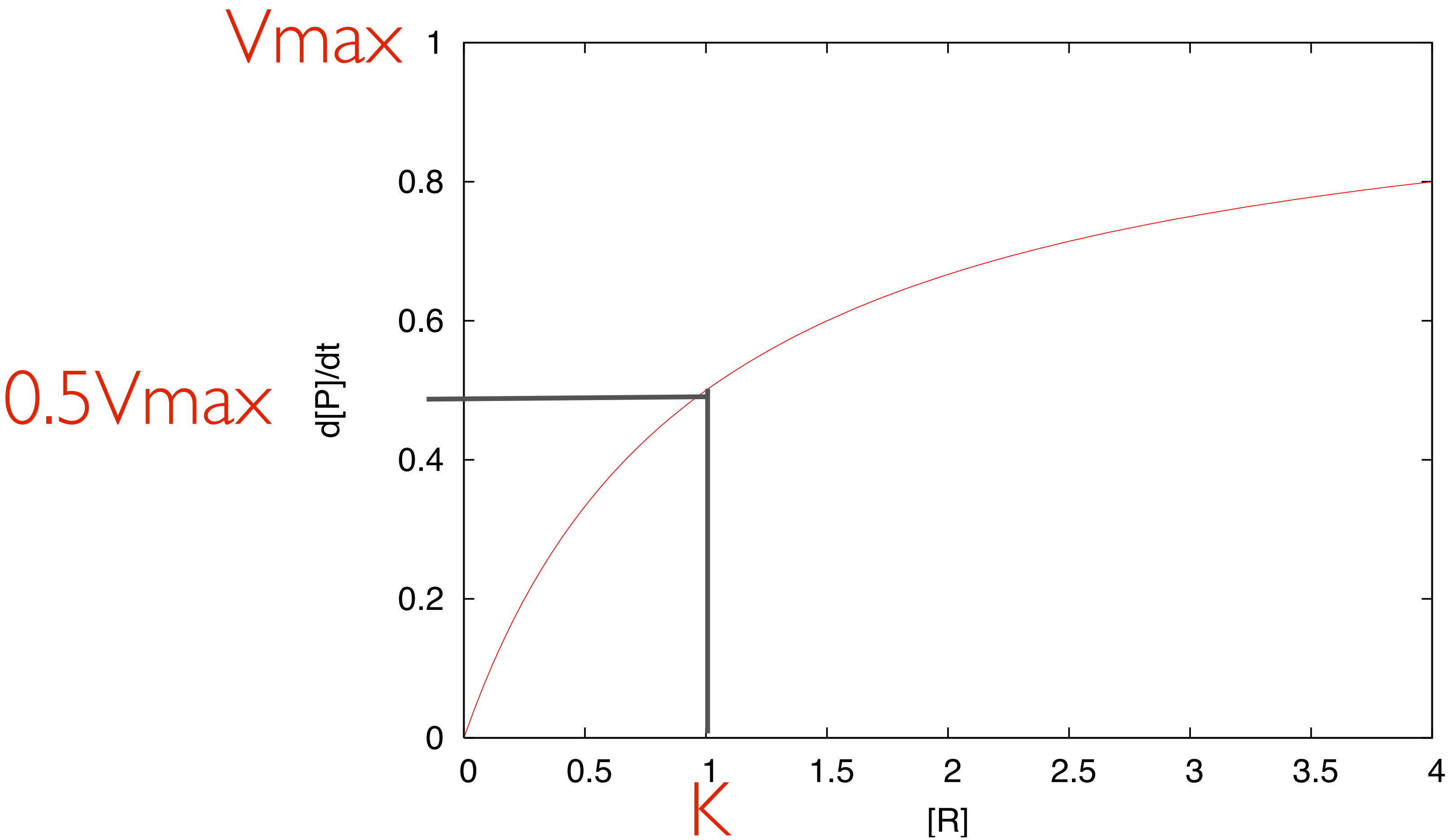
Michaelis-Menten (10.3,10.4)

$$\frac{d[P]}{dt} = \frac{V_{max}[R]}{K + [R]}$$



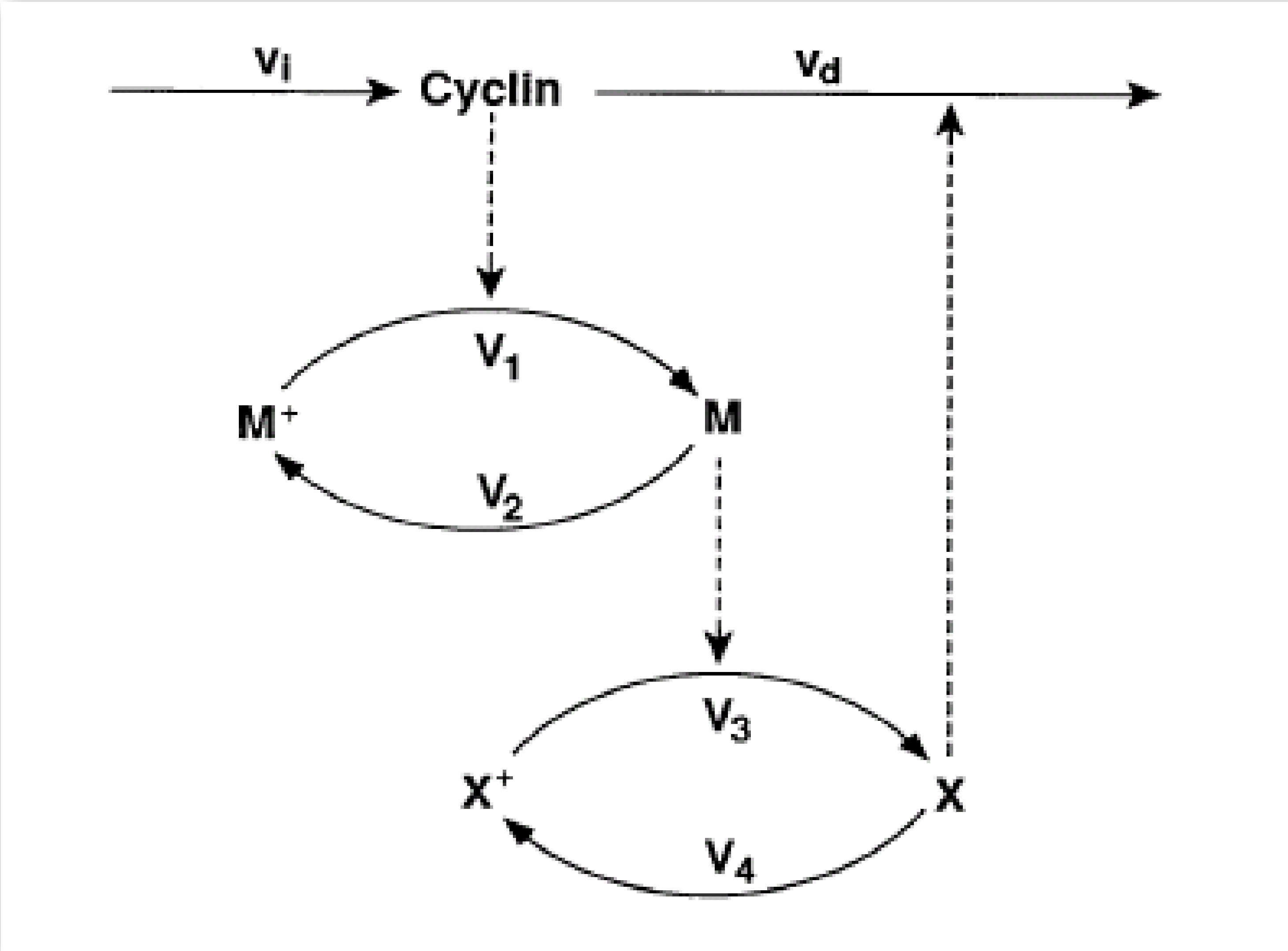
Michaelis-Menten (10.3,10.4)

$$\frac{d[P]}{dt} = \frac{V_{max}[R]}{K + [R]}$$



Michaelis-Menten (10.3,10.4)

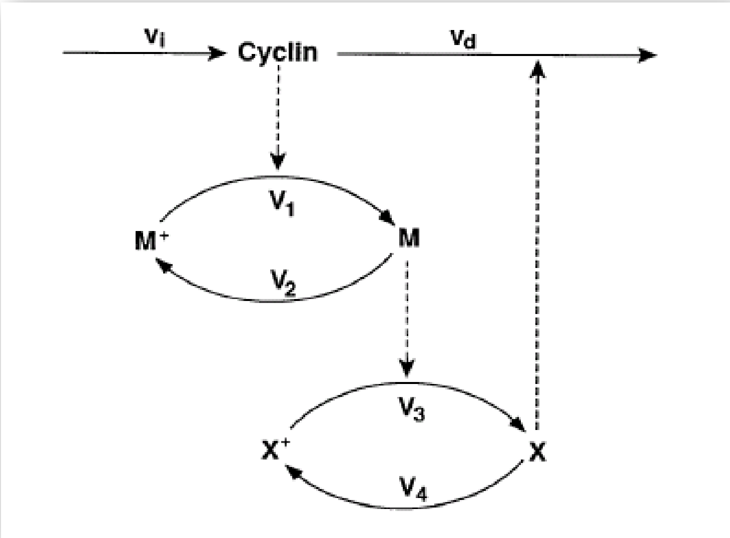
Example: cell-cycle model



Goldbeter (1991)

Michaelis-Menten (10.3,10.4)

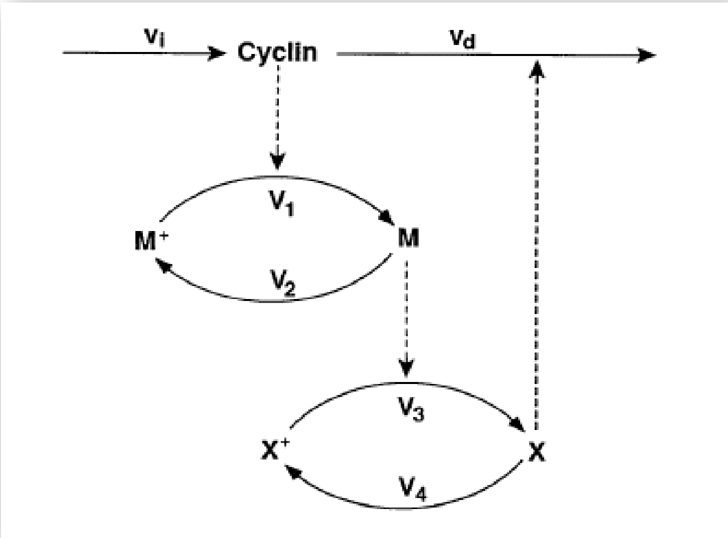
Example: cell-cycle model



Goldbeter (1991)

Michaelis-Menten (10.3,10.4)

Example: cell-cycle model



$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C$$

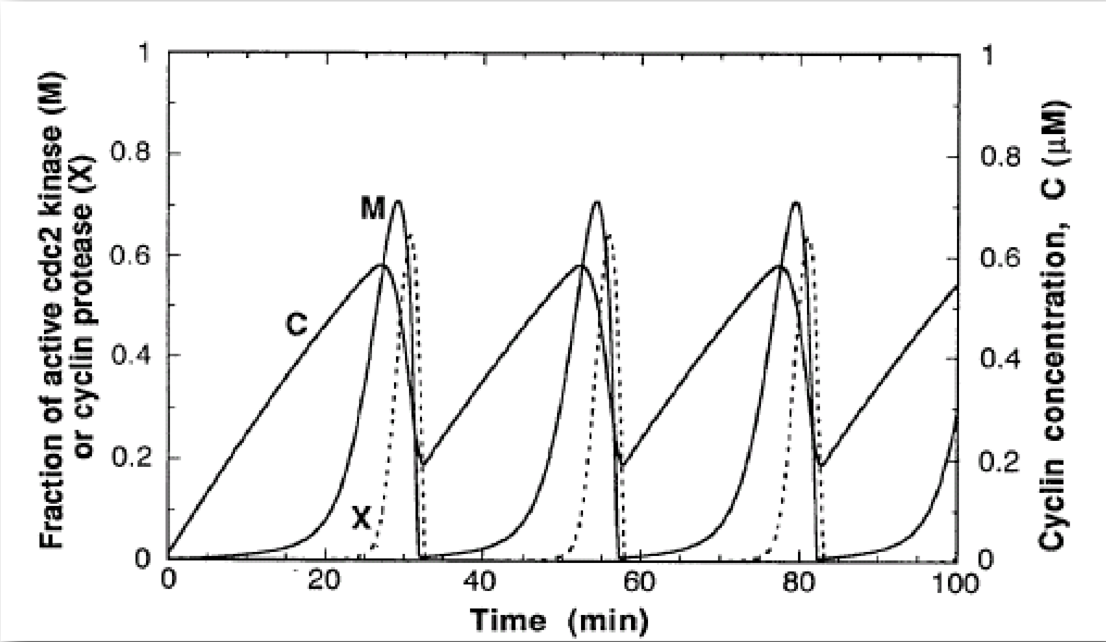
$$\frac{dM}{dt} = V_1 C \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M}$$

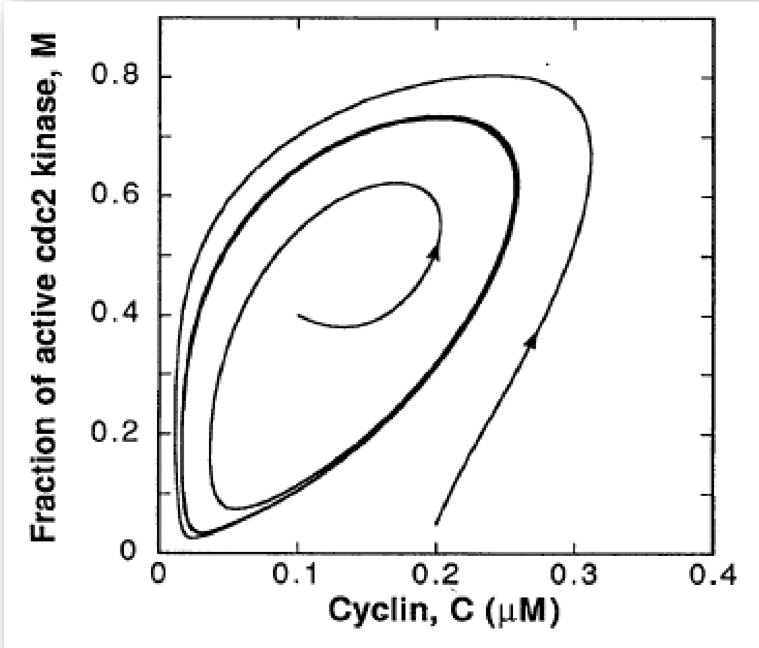
$$\frac{dX}{dt} = V_3 M \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

Goldbeter (1991)

Michaelis-Menten (10.3,10.4)

Example: cell-cycle model





Goldbeter (1991)

Michaelis-Menten (10.3,10.4)

Example: gene regulation

$$TF + DNA \rightleftarrows DNA\_b \longrightarrow X + DNA\_b$$

Michaelis-Menten (10.3,10.4)

Example: gene regulation

$$TF + DNA \rightleftarrows DNA\_b \longrightarrow X + DNA\_b$$

$$\text{Prob(TF bound)} = \quad P_1 \quad = \quad \frac{TF}{K + TF}$$

$$\text{Prob(TF not bound)} = \quad P_2 \quad = \quad \frac{K}{K + TF}$$

Michaelis-Menten (10.3,10.4)

Example: gene regulation

$$\text{TF+DNA} \rightleftarrows \text{DNA\_b} \longrightarrow \text{X+DNA\_b}$$

$$\text{Prob(TF bound)} = \quad P_1 = \frac{TF}{K + TF}$$

$$\text{Prob(TF not bound)} = \quad P_2 = \frac{K}{K + TF}$$

Activator: transcription if TF bound

$$\frac{d[X]}{dt} = VP_1 = \frac{V[TF]}{K + [TF]}$$

Michaelis-Menten (10.3,10.4)

Example: gene regulation

$$TF+DNA \rightleftarrows DNA\_b \longrightarrow X+DNA\_b$$

$$\text{Prob(TF bound)} = P_1 = \frac{TF}{K+TF}$$

$$\text{Prob(TF not bound)} = P_2 = \frac{K}{K+TF}$$

Activator: transcription if TF bound

$$\frac{d[X]}{dt} = VP_1 = \frac{V[TF]}{K+[TF]}$$

Repressor: transcription if TF not bound

$$\frac{d[X]}{dt} = VP_2 = \frac{VK}{K+[TF]}$$

Michaelis-Menten (10.3,10.4)

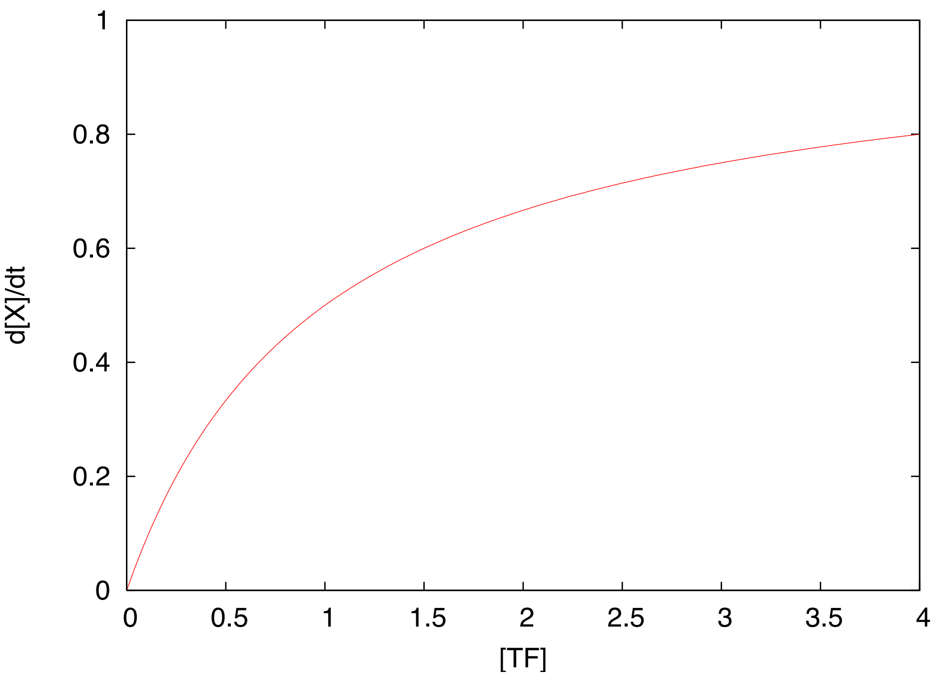
Example: gene regulation

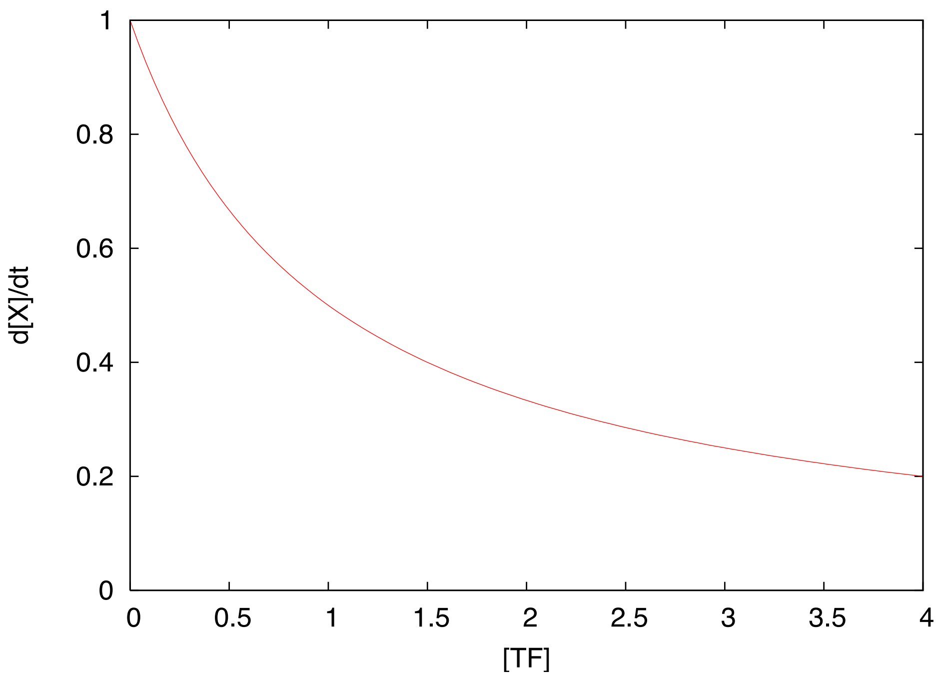
Activator: transcription if TF bound

$$\frac{d[X]}{dt} = VP_1 = \frac{V[TF]}{K+[TF]}$$

Repressor: transcription if TF not bound

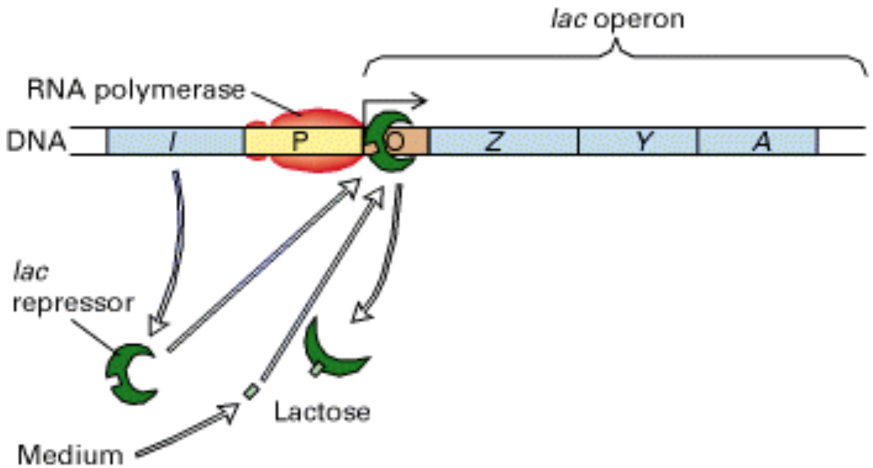
$$\frac{d[X]}{dt} = VP_2 = \frac{VK}{K+[TF]}$$

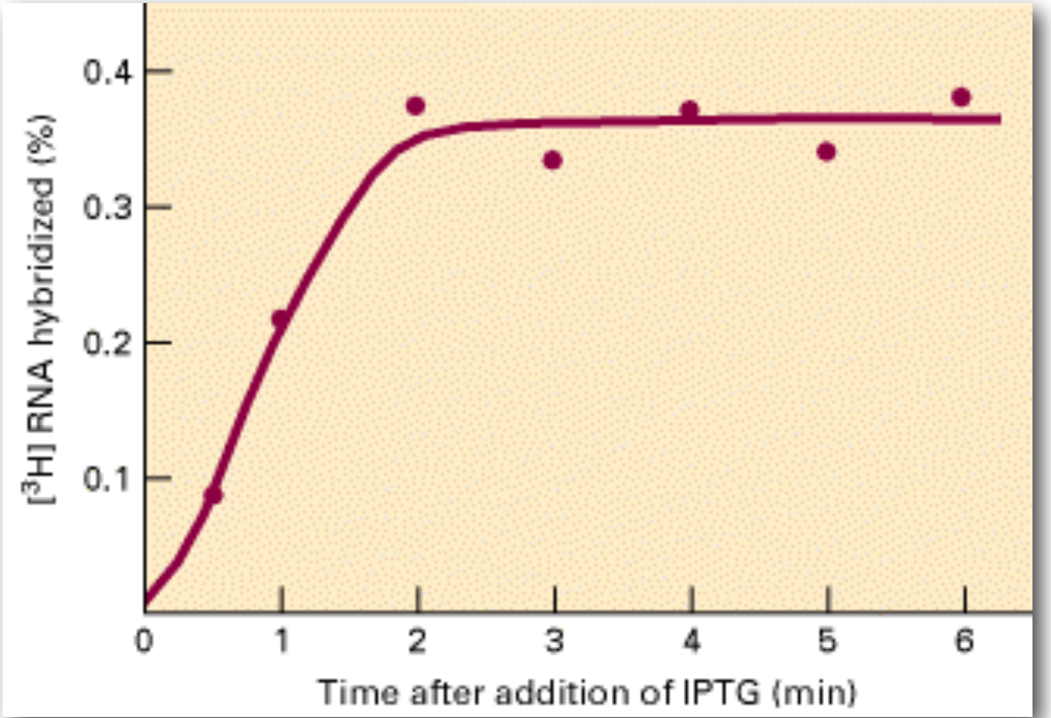




Michaelis-Menten (10.3,10.4)

Example: lac-operon

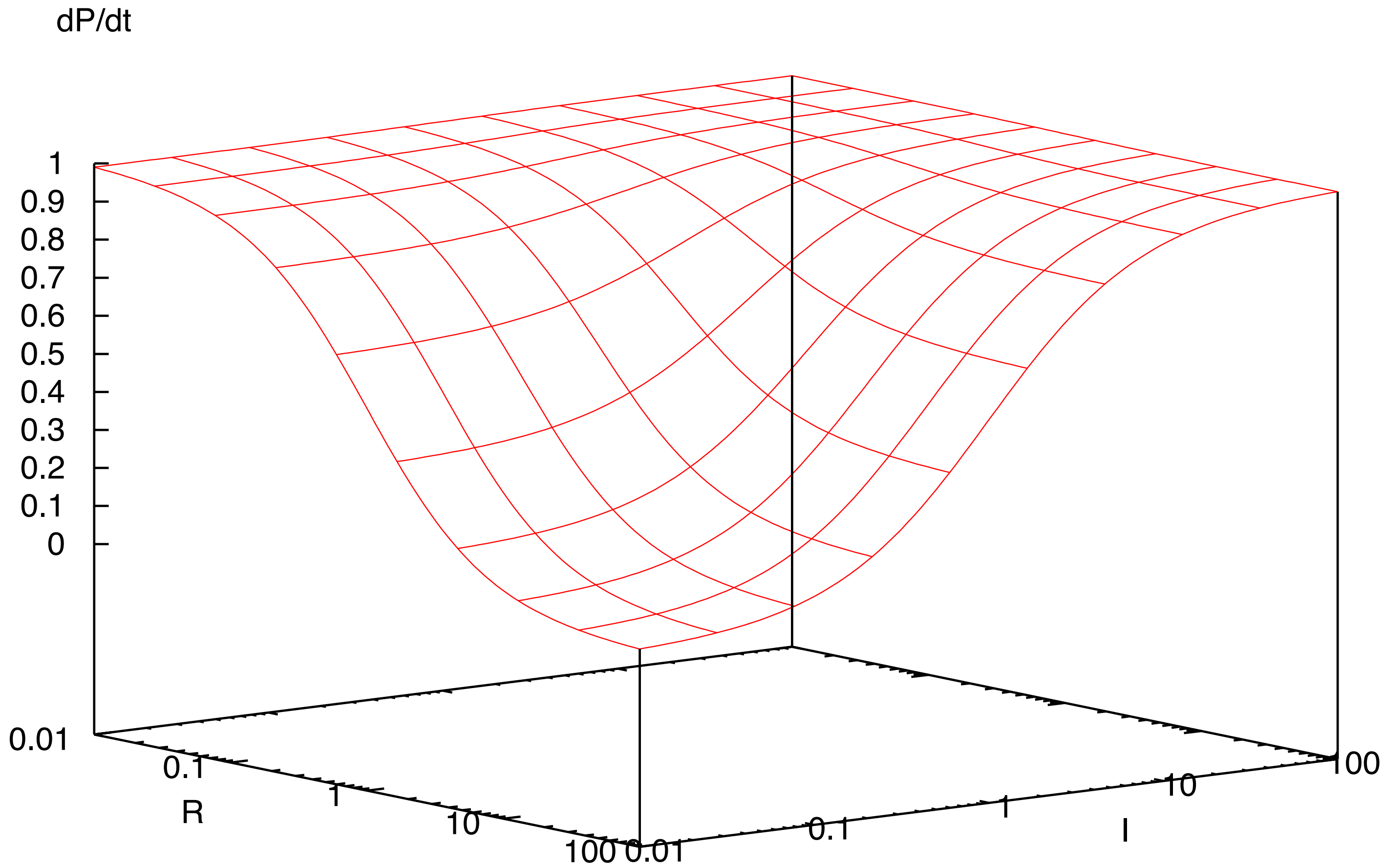




Jacob Monod, Nobel prize 1965

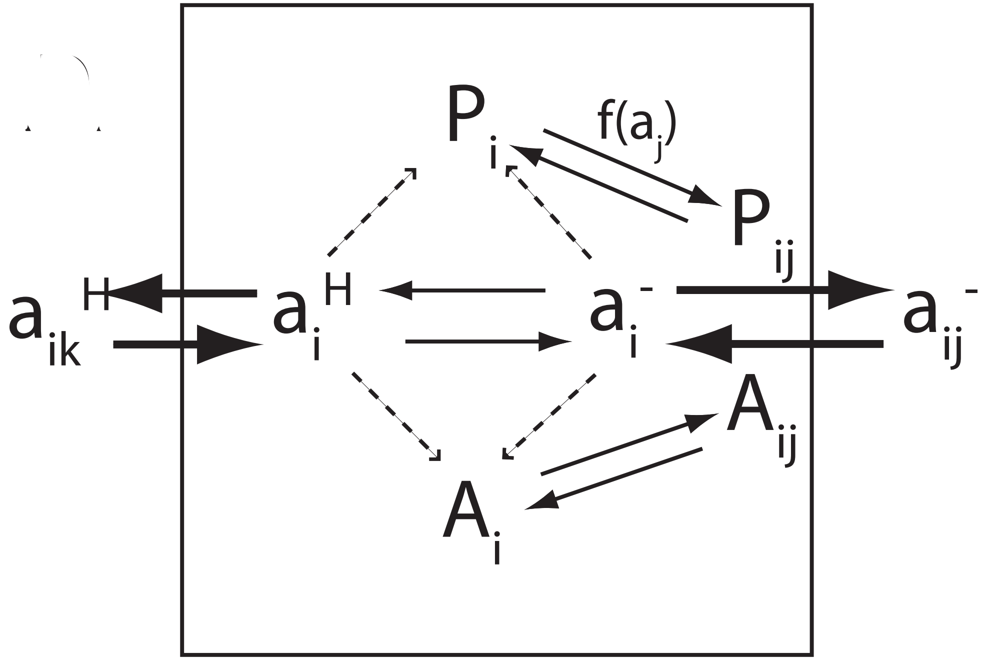
Michaelis-Menten (10.3,10.4)

Example: lac-operon



Michaelis-Menten (10.3,10.4)

Example: active transport



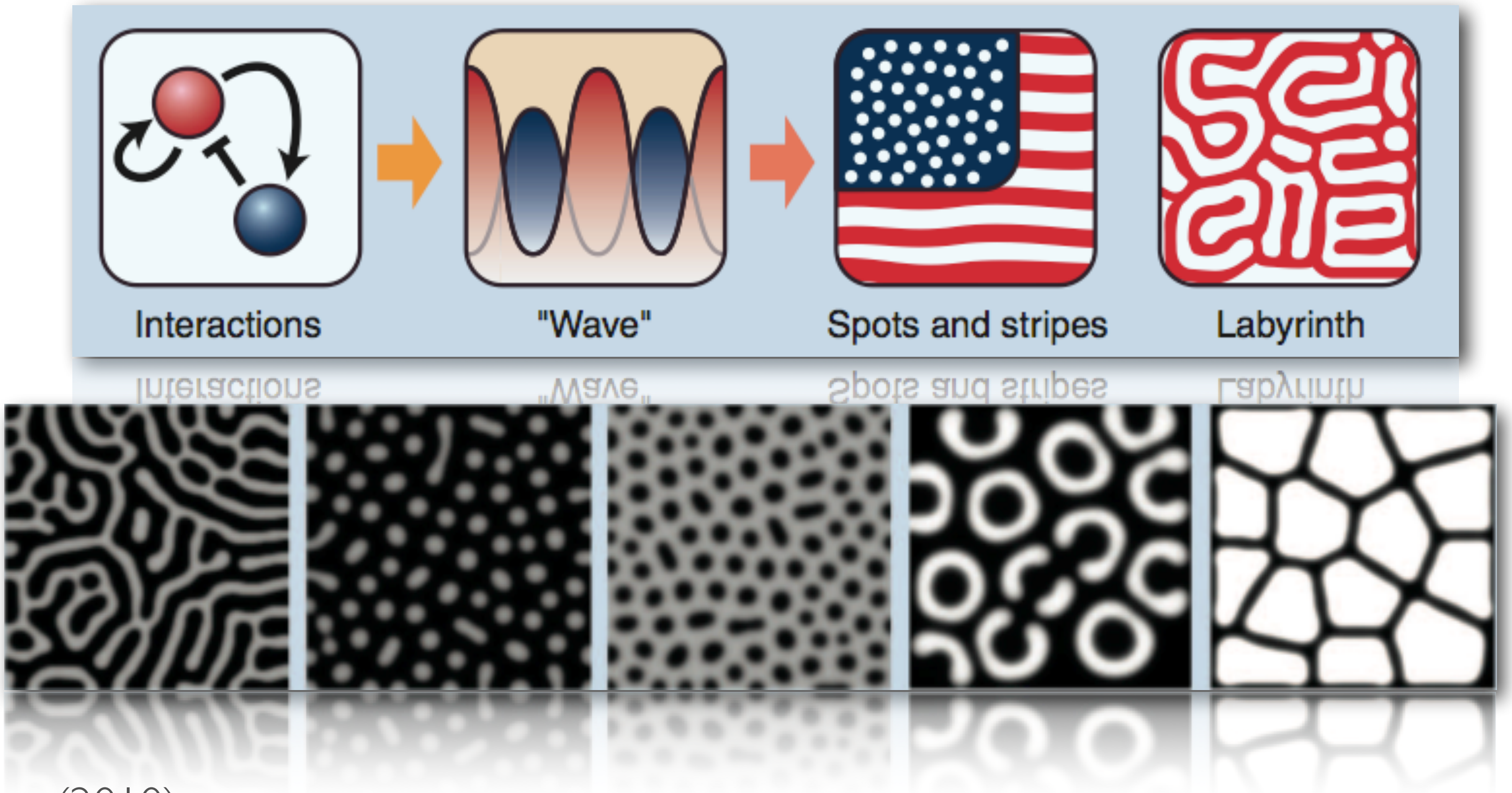
$$J_{a(cell \to wall)} = p_a^H(a_i^H - a_{ij}^H) + p_P P_{ij} \frac{a_i^-}{K_P + a_i^-} - p_A A_{ij} \frac{a_{ij}^-}{K_A + a_{ij}^-}$$

Jönsson et al (2006)

Reaction-Diffusion

(computer exercise)

- Chemical reactions combined with diffusion can create spatial concentration patterns



Kondo Miura (2010)

Reaction-Diffusion

computer exercise, Brusselator

$$A \rightarrow X$$

$$2X + Y \rightarrow 3X$$

$$B + X \rightarrow Y + C$$

$$X \rightarrow D.$$

X and Y can diffuse

Reaction-Diffusion

computer exercise, Brusselator

$$\frac{dX}{dt} = k_1 A + k_2 X^2 Y - k_3 B X - k_4 X + D_X \frac{d^2 X}{dx^2}$$

$$\frac{dY}{dt} = -k_2 X^2 Y + k_3 B X + D_Y \frac{d^2 Y}{dx^2}$$

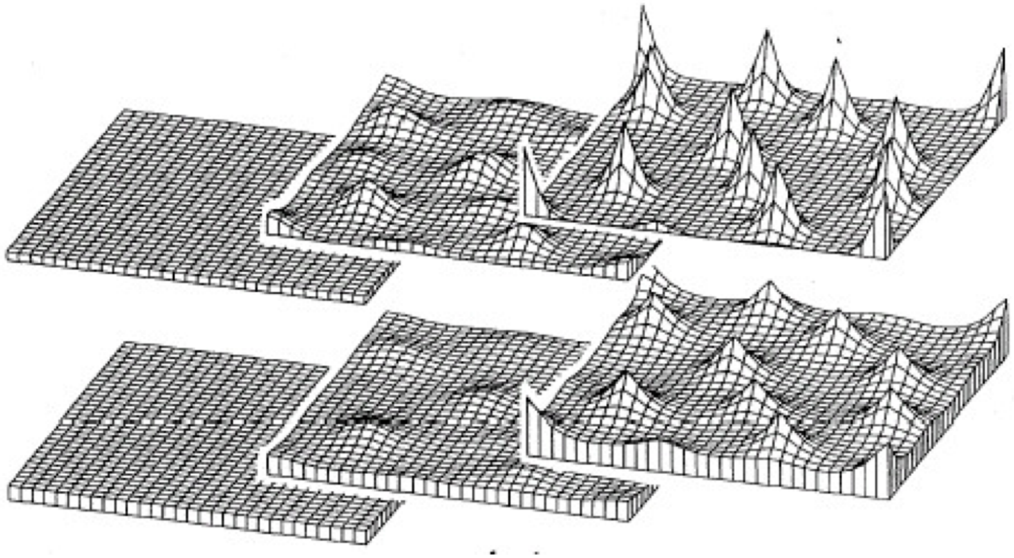
$$\frac{dB}{dt} = -k_3 B X$$

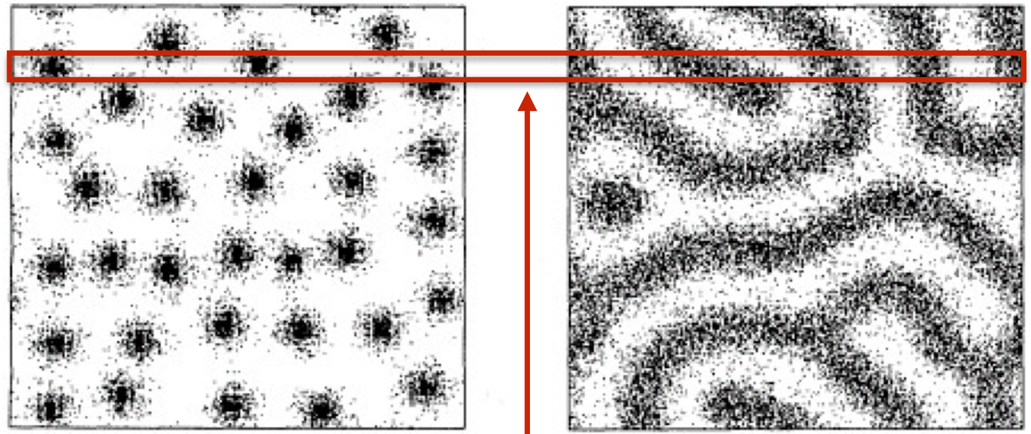
$$\frac{dC}{dt} = k_3 B X$$

$$\frac{dD}{dt} = k_4 X.$$

Reaction-Diffusion

computer exercise, Brusselator



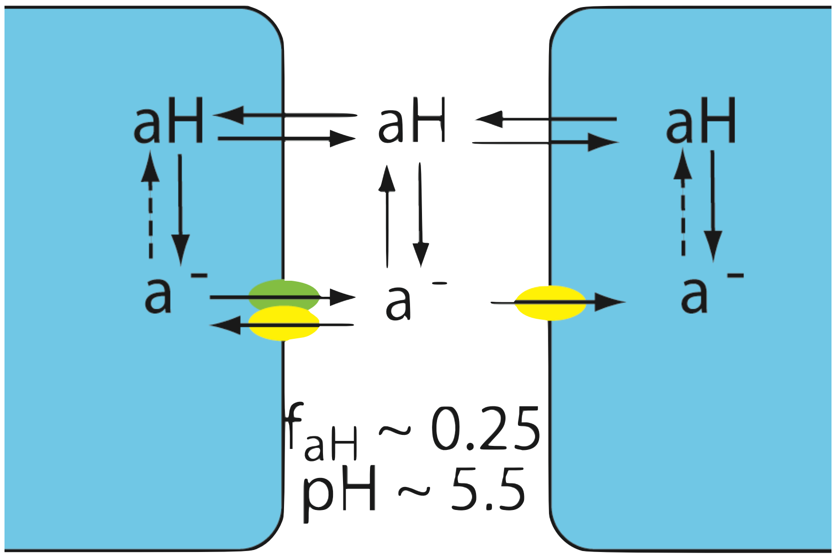


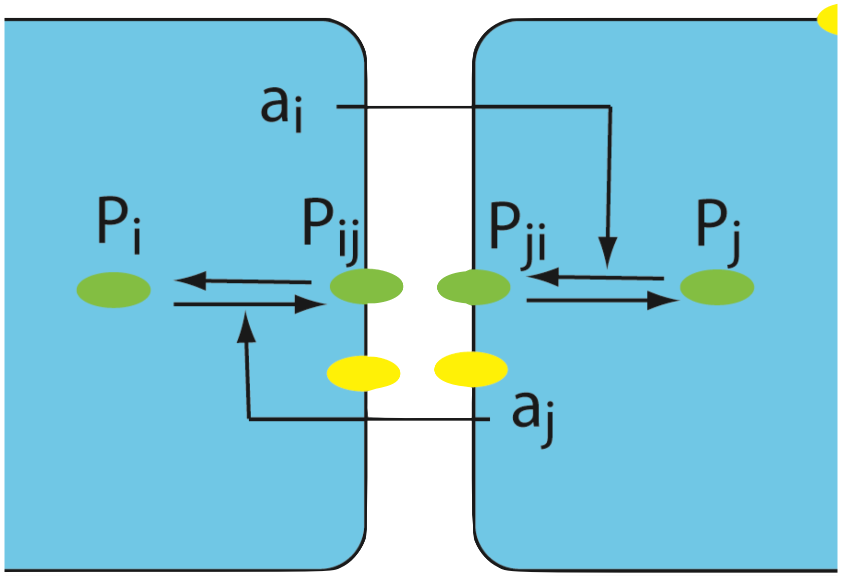
(b) (c)

computer exercise -> 1D

Reaction-Diffusion

Active transport can add to dynamics



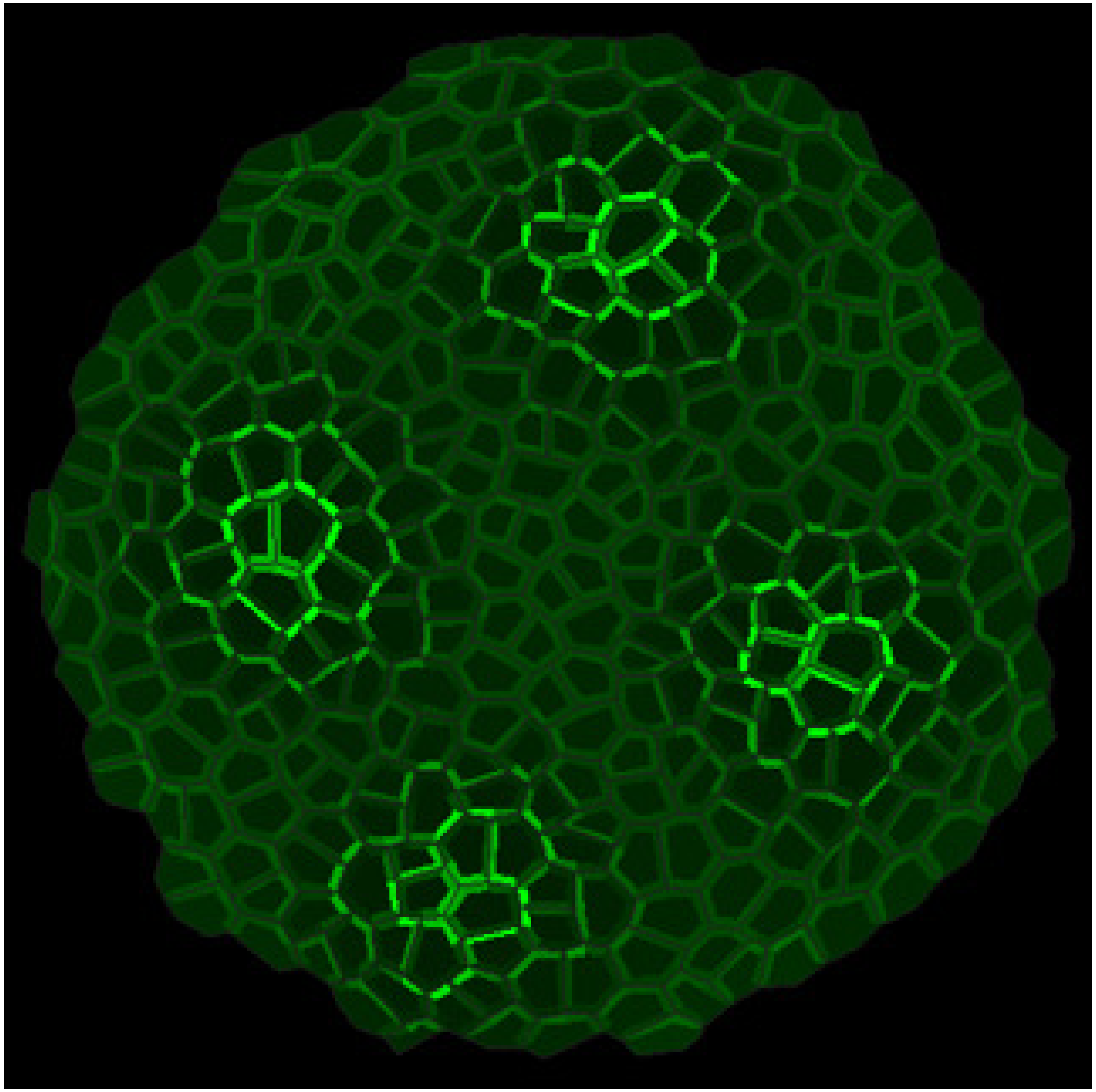


$$\frac{da_i}{dt} = D\left(\sum_j^{N_i} a_j - N_i a_i\right) + T\sum_j^{N_i}\left(P_{ji}\frac{a_j}{a_j+K} - P_{ij}\frac{a_i}{a_i+K}\right)$$

Jönsson et al (2006)

Reaction-Diffusion

Active transport can add to dynamics



Jönsson et al (2006)

A historic point

M.W.
Would you show this reprint to Hamer & ask him to order for library & myself.
E.T.G.

Hollymeade
Adlington Rd
Wilmslow,

Dear Woodger,

You might like to have this reprint. I am also enclosing some stuff about reverberation in delay lines that I think Newman was interested in. I would like this back some time.

Our new machine is to start arriving on Monday. I am hoping as one of the first jobs to do something about 'chemical embryology'. In particular I think one can account for the appearance of Fibonacci numbers in connection with fir-cones.

Yours,

A. M. Turing

6

A historic point

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