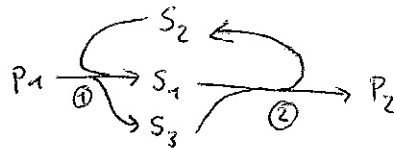


Exercise 1.1.



$$N = \begin{matrix} \text{tot} \\ S_1 \\ S_2 \\ S_3 \\ P_1 \\ P_2 \end{matrix} \begin{matrix} \textcircled{1} & \textcircled{2} \\ + & - \\ - & + \\ + & - \\ - & \\ + & \end{matrix} \Bigg\} N$$

$$NV = 0 \quad \Rightarrow \quad v_1 = -v_2$$

(stationarity)

$$\Rightarrow \quad v = \lambda \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \lambda \in \mathbb{R}$$

Conservation relations = $g^T N = 0$, Independent Solutions $g = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$

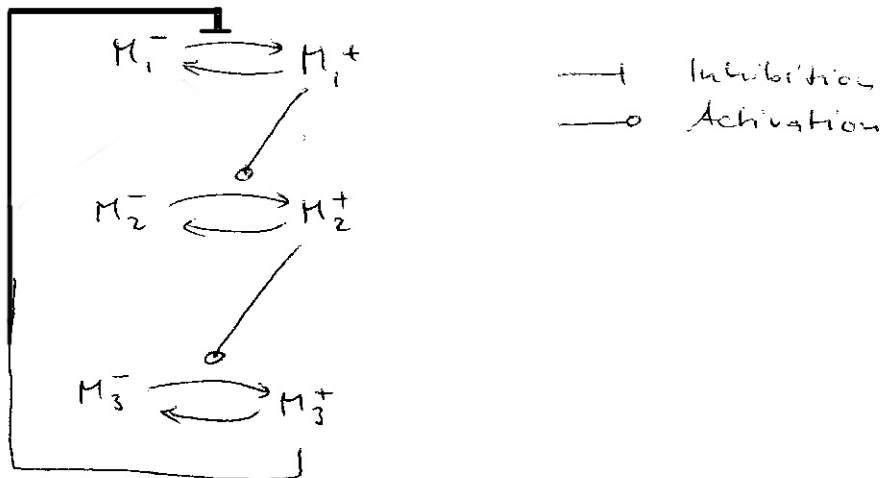
\Rightarrow General solution $g = \lambda_1 \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \lambda_2 \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$

Independent solutions can be interpreted as

$$S_1 + S_2 = \text{const.},$$

$$S_3 + S_2 = \text{const.}$$

Exercise 1.2



Exercise 1.3

a) $N = \begin{matrix} x_1 \\ x_2 \\ x_3 \end{matrix} \begin{matrix} v_{syn} & v_{deg} \\ \mathbf{I} & -\mathbf{I} \end{matrix}$

$$\dot{x}_1 = \frac{\beta}{1+x_3/k} - \alpha x_1$$

$$\dot{x}_2 = \frac{\beta}{1+x_1/k} - \alpha x_2$$

$$\dot{x}_3 = \frac{\beta}{1+x_2/k} - \alpha x_3$$

b) $\frac{\partial v_i^{syn}}{\partial x_{li}} = - \frac{\beta/k}{(1+x/k)^2}$

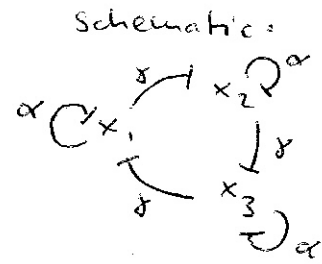
$\frac{\partial v_i^{deg}}{\partial x_i} = \alpha$

$$\bar{E} = \begin{matrix} v_{syn} & x_1 & x_2 & x_3 \\ \begin{matrix} \cdot & \cdot & -\alpha \\ -\alpha & \cdot & \cdot \\ \cdot & -\alpha & \cdot \\ \alpha & \cdot & \cdot \\ \cdot & \alpha & \cdot \\ \cdot & \cdot & \alpha \end{matrix} \end{matrix}$$

all other elasticities vanish

$$c) \quad M = N\bar{E} = \begin{matrix} x_1 \\ x_2 \\ x_3 \end{matrix} \begin{pmatrix} -\alpha & 0 & -\gamma \\ -\gamma & -\alpha & 0 \\ 0 & -\gamma & -\alpha \end{pmatrix}$$

Matrixzerlegung: $M = -\alpha \cdot I - Q$



d) Compute Eigenvalues of $Q = \begin{pmatrix} \cdot & \cdot & \gamma \\ \gamma & \cdot & \cdot \\ \cdot & \gamma & \cdot \end{pmatrix}$

Eigenvalue equation $(Q - \lambda I) = 0$

$$\Rightarrow 0 = \left| \begin{pmatrix} -\lambda & \gamma \\ \gamma & -\lambda \\ \gamma & -\lambda \end{pmatrix} \right| = -\lambda^3 + \gamma^3 \Rightarrow \lambda^3 = \gamma^3$$

Solutions: $\lambda = \gamma$

Polynom 3. Grades \rightarrow 3 Eigenvalues

mit: $\exp(2i\pi) = 1$

folgt \rightarrow

$$\lambda = \gamma e^{\pm 2/3 i \pi} \stackrel{\text{(Eulerformel angewendet)}}{=} \gamma \left(-\frac{1}{2} \pm \frac{\sqrt{3}}{2} i \right) \leftarrow \text{Eulerformel: } \exp(ia) = \cos(a) + i\sin(a)$$

Eigenvalues of $M = -\alpha - \text{Eig}(Q)$

Largest Real value
(\rightarrow alle anderen Werte sind sowieso kleiner)

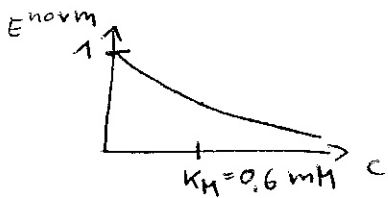
$$= -\alpha + \frac{\gamma}{2}$$

must be negative for stability

$$\Rightarrow \alpha > \frac{\gamma}{2}$$

Exercise 2.1

a) $\frac{\partial v}{\partial c} \cdot \frac{c}{v} = \frac{k_M}{k_M + c}$



b) $v = \frac{v_{\max}}{1 + I/k_I} \cdot \frac{c}{\frac{k_M}{1 + I/k_I} + c} = \frac{v'_{\max} c}{k'_M + c}$

\rightarrow same elasticity as in (a), but with $k'_M = k_M / (1 + I/k_I)$

Exercise 2.2

a) $N = (+ -)$,

$$\bar{E}_{x_1}^v = k_{+1}, \quad \bar{E}_y^v = -k_{-1}$$

$$\Rightarrow E_{x_1}^v = \frac{x_1 k_{+1}}{k_{+1} x_1 - k_{-1} y}, \quad E_y^v = \frac{-y k_{-1}}{k_{+1} x_1 - k_{-1} y}$$

$$b) \quad v_1 = v_2$$

$$\Rightarrow k_{+1} x_1 - k_{-1} y = k_{+2} y - k_{-2} x_2$$

$$\Rightarrow y^{st} = \frac{k_{+1} x_1 + k_{-2} x_2}{k_{-1} + k_{+2}}$$

Steady state: influx = efflux

$$j_1 = j_2 = v_1(x_1, y^{st}) = k_{+1} x_1 - k_{-1} \underbrace{[\dots]}_{y^{st}}$$

$$c) \quad \bar{R}_{x_1}^{v_1} = \frac{\partial j_1}{\partial x_1} = k_{+1} - k_{-1} \frac{\partial y^{st}}{\partial x_1}$$

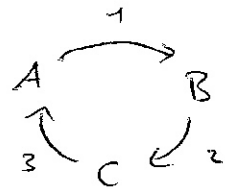
$$= k_{+1} \left[1 - \frac{k_{-1}}{k_{-1} + k_{+2}} \right]$$

$$= \frac{k_{+1} (k_{-1} + k_{+2})}{(k_{-1} + k_{+2})^2} = \frac{k_{+1}}{k_{-1} + k_{+2}}$$

In the response coefficient, the elasticity k_{+1} is multiplied by a factor smaller than 1. In steady state, an increase of x_1 leads to an increase of the product y , which then slows down the reaction.

Exercise 2.3

Stationarity requires that all fluxes have the same sign. Positive fluxes would require positive reaction affinities



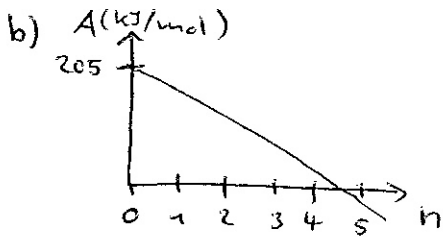
$$A_1 = \mu_A - \mu_B > 0, \quad A_2 = \mu_B - \mu_C > 0, \quad A_3 = \mu_C - \mu_A > 0$$

This leads to $\mu_A > \mu_B > \mu_C > \mu_A$, which is a contradiction. Negative fluxes can be excluded accordingly, so the only remaining possibility are zero fluxes

Exercise 2.4

a) Reaction affinity $A(n) = \overbrace{[205 - n \cdot 49]}^{= -\Delta \mu}$ kJ/mol $\stackrel{!}{>} 0$
 ($n = \# \text{ATP molecules}$)

$n=2 \Rightarrow A(n) = 107$ kJ/mol > 0 ✓



The reaction affinity becomes negative above $n=4$, so this is the maximal number.

Thermodynamically, there is no lower limit for n , but $n < 0$ would imply consumption of ATP.

c) $J = \alpha \cdot A$, $\alpha > 0$

ATP Production rate $J_{\text{ATP}} = n \cdot J = n \cdot \alpha \cdot (205 - n \cdot 49)$

Optimum? Assume $n \in \mathbb{R}$ and find $\text{argmax}_n J_{\text{ATP}}$!

$0 = \frac{dJ_{\text{ATP}}}{dn} = \alpha [205 - 2 \cdot 49 \cdot n] \Rightarrow n \approx 2$

Exercise 3.1

Steady state: $\bar{c}_x = 1$, $\bar{c}_y = 1$

$\Delta c_x = c_x - \bar{c}_x \Rightarrow \Delta \dot{c}_x = \dot{c}_x = 1 - c_x = -\Delta c_x$

$\Rightarrow \Delta c_x = \frac{\Delta c_x(0) \cdot e^{-t}}{(c_x(0) - 1)} \Rightarrow c_x = 1 + (c_x^* - 1) e^{-t}$

$\Delta c_y = c_y - \bar{c}_y \Rightarrow$

Ansatz:

$\Delta c_y = (\alpha + \beta t) e^{-\beta t}$

$\Delta \dot{c}_y = \dot{c}_y \stackrel{(1)}{=} 1 + (c_x^* - 1) e^{-t} - (1 + \Delta c_y)$

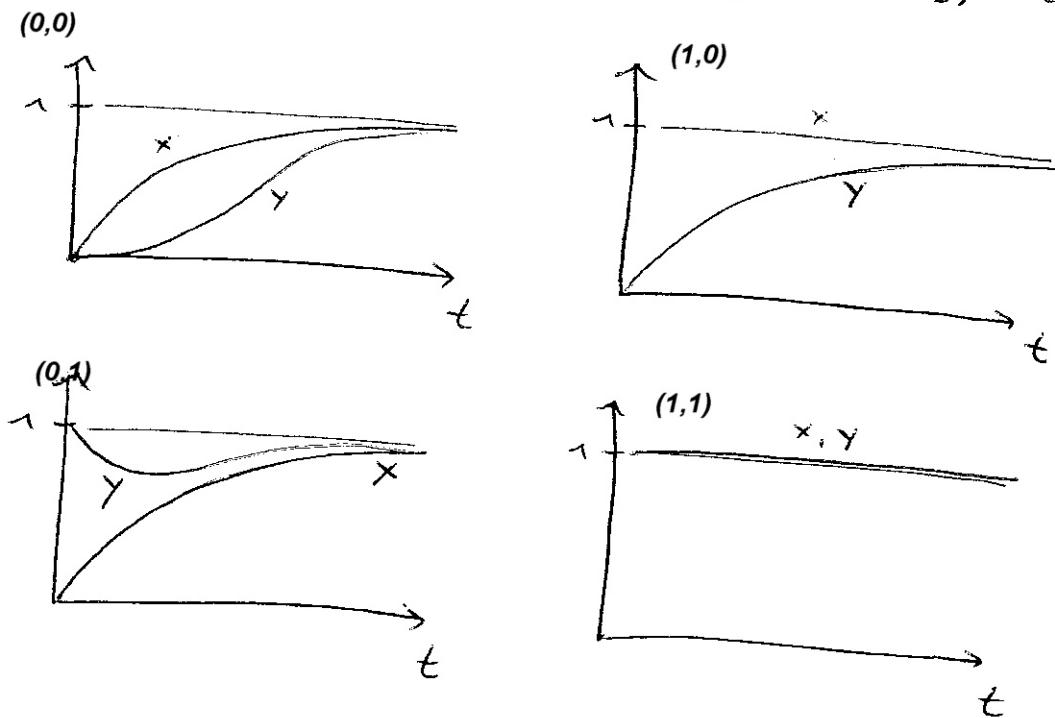
$\beta e^{-t} - (\alpha + \beta t) e^{-t} = (c_x^* - 1) e^{-t} - (\alpha + \beta t) e^{-t}$

$\Rightarrow (\beta - \alpha - \beta t) e^{-t} = [c_x^* - 1 - \alpha - \beta t] e^{-t}$

$\Rightarrow \beta = c_x^* - 1$

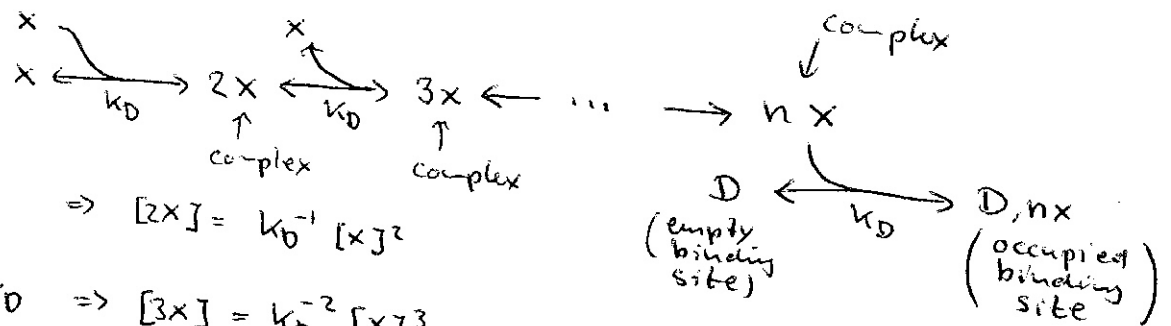
Initial condition:

$$\Delta c_Y(t=0) = c_Y^* - 1 \quad \text{Ansatz } \alpha \Rightarrow \alpha = c_Y^* - 1$$



Exercise 3.2

Scheme



$$\frac{[x]^2}{[2x]} = k_D \Rightarrow [2x] = k_D^{-1} [x]^2$$

$$\frac{[2x][x]}{[3x]} = k_D \Rightarrow [3x] = k_D^{-2} [x]^3$$

$$\dots \Rightarrow [nx] = k_D^{-n+1} [x]^n$$

Binding formula

$$D_{\text{occ}} = \frac{D_{\text{tot}}}{1 + \frac{x'}{k_D}} = \frac{D_{\text{tot}}}{1 + \left(\frac{[x]}{k_D}\right)^n}$$

(x' = free conc of active TF. = [nx])

Note that independent binding to n distinguishable binding sites would lead to another formula,

$$\frac{D_{\text{tot}}}{\left(1 + \frac{[x]}{k_D}\right)^n}$$

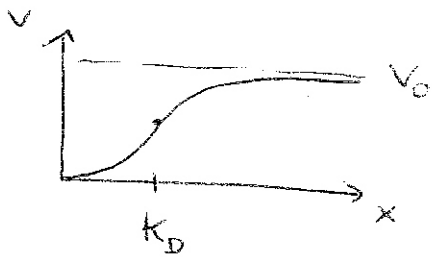
Exercise 3.3

Binding probability for a single site = $p_1 = \frac{x}{K_D + x}$

Binding probabilities for two independent, identical

sites = $P_{11} = p_1 \cdot p_1 = \frac{x^2}{(K_D + x)^2}$

Set $v(x) = v_0 \cdot P_{11}$



Exercise 3.4

AND = (i) x and y can only bind together
(single binding thermodynamically unfavorable)

(ii) Polymerase binding / transcription start
requires both transcription factors

Could be realised by a TF complex with
obligate presence of both TFs.

OR =

(i) x and y share the same binding site

(ii) One of them is sufficient for transcription
start

(iii) They can replace each other in a binding complex.

Exercise 4.1

- # Metabolites = several thousands
 - # Reactions = "
 - # Genes = "
 - # Compartments = 1-10 types, possibly many vesicles etc.
 - # molecules/mM (in small bacterial cell) ≈ 1000000
 - \Rightarrow Signalling proteins, order of magnitude 10000 / species
 - Metabolites " 10⁶ / species
- (Guess model sizes yourself!)

Exercise 4.2

Steady state for B = $0 = k_1 a - k_2 b^{st}$

$$\Rightarrow b^{st} = \frac{k_1 a}{k_2}$$

Exercise 4.3

Differential equation for $b+c$: $\frac{d}{dt}(b+c) = k_1 a - k_3 c$

Equilibrium ratio $\frac{c}{b} = k^{eq} = \frac{k_{+2}}{k_{-2}}$

\Rightarrow

$$\frac{c}{b+c} = \left(\frac{b+c}{c}\right)^{-1} = \left(\frac{b}{c} + 1\right)^{-1} = \left(\frac{k_{-2}}{k_{+2}} + 1\right)^{-1}$$

insert \Rightarrow $\frac{d}{dt}(b+c) = k_1 a - k_3 \left(\frac{k_{-2}}{k_{+2}} + 1\right)^{-1} (b+c)$

Exercise 4.4

Definitely true. Think of the weather forecast. (By the way, the 'all' statement cannot be proven by examples. But, if a model, by definition, differs from the thing described, it has to be wrong in some sense. This holds a priori. The 'some' statement can be proven by examples.)

Exercise 4.5

There is no single, fixed criterion to choose between models. In principle, a model with a better fit is usually preferred, but overfitting (which would imply poor predictions) has to be avoided. Possible methods to correct for overfitting in a comparison are crossvalidation, likelihood ratio test, and selection criteria (e.g. Akaike criterion). The best possible test would be to obtain more data and use them for scoring the model predictions.