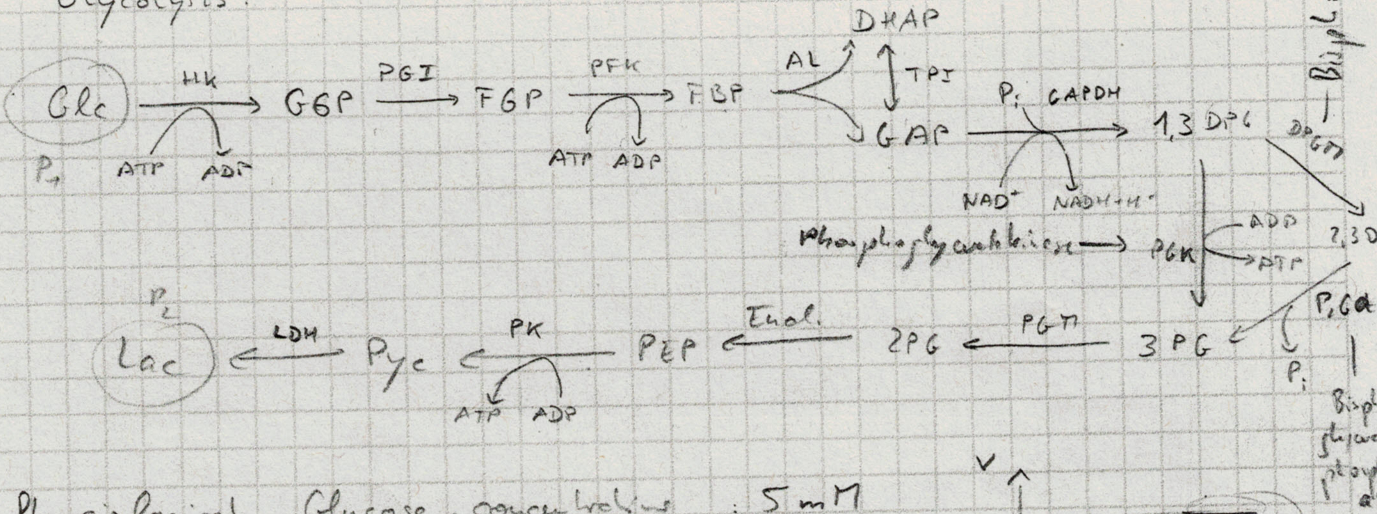
8-12-2006

Wiederholung
- st. Matrix N , $\frac{dS}{dt} = N \cdot v(S)$
- Stat. Flüsse, kernel $Nv = 0$
- conservation rules, left-sided kernel

ker-n+c

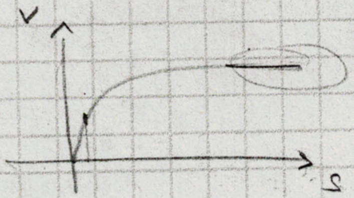
Example

Glycolysis:



Physiological Glucose concentration : 5 mM

K_m-value of HK : 40 μM



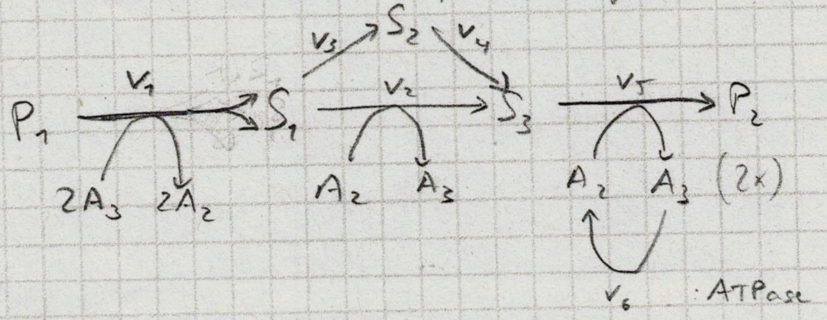
We can assume that conc. of glucose is approx. constant

13 Reactions, 11 metabolites + ATP, ADP, P_i, NAD^+, NADH, H^+

We consider a simplified system:

$A_2 \triangleq ADP$

$A_3 \triangleq ATP$



Differential equations:

$$\frac{dS_1}{dt} = 2v_1 - v_2 - v_3$$

$$\frac{dS_2}{dt} = v_3 - v_4$$

$$\frac{dS_3}{dt} = v_2 + v_4 - v_5$$

$$\left.\begin{aligned} \frac{dA_2}{dt} &= 2v_1 - v_2 - v_5 + v_6 \\ \frac{dA_3}{dt} &= -2v_1 + v_2 + v_5 - v_6 \end{aligned}\right\} \quad \frac{d(A_2 + A_3)}{dt} = 0 \Rightarrow A_2 + A_3 = A = \text{const.}$$

$$\Rightarrow A_2 = A - A_3$$

replace

$$N = \begin{array}{c} \begin{array}{cccccc} R_1 & R_2 & R_3 & R_4 & R_5 & R_6 \end{array} & \\ \begin{bmatrix} 2 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 & 0 \\ 2 & -1 & 0 & 0 & -1 & 1 \\ -2 & 1 & 0 & 0 & 1 & -1 \end{bmatrix} & \begin{array}{c} S_1 \\ S_2 \\ S_3 \\ A_2 \\ A_3 \end{array} \end{array}$$

$$(0, 0, 0, 1, 1) \cdot N = 0$$

left-sided kernel

1 conservation rule: $A_2 + A_3 = \text{const.}$

Dim. of the kernel: $k = r - n + c = 6 - 5 + 1 = \underline{2}$

We can "reduce" N by omitting the row for A_2:

$$N_R = \begin{bmatrix} 2 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 & 0 \\ -2 & 1 & 0 & 0 & 1 & -1 \end{bmatrix} \begin{array}{c} S_1 \\ S_2 \\ S_3 \\ A_3 \end{array}$$

8.12.06

<u>kinetic analysis</u>

simplest description, based on linear / bilinear ~~rate~~ laws:

$v_1 = k_1 \cdot P_1 \cdot A_3$ $\quad v_4 = k_4 \cdot S_2$ (neglection of

$v_2 = k_2 \cdot S_1 \cdot A_2$ $\quad v_5 = k_5 \cdot S_3 \cdot A_2$ saturating effects)

$v_3 = k_3 \cdot S_1$ $\quad v_6 = k_6 \cdot A_3$

Insert these in diff. equations, calculate steady state

I $\quad 0 = \frac{dS_1}{dt} = 2v_1 - v_2 - v_3 = 2k_1 P_1 A_3 - k_2 S_1 A_2 - k_3 S_1$

II $\quad 0 = \frac{dS_2}{dt} = v_3 - v_4 = k_3 S_1 - k_4 S_2$

III $\quad 0 = \frac{dS_3}{dt} = v_2 + v_4 - v_5 = k_2 S_1 A_2 + k_4 S_2 - k_5 S_3 A_2$

IV $\quad 0 = \frac{dA_3}{dt} = -2v_1 + v_2 + v_5 - v_6$

$= -2k_1 P_1 A_3 + k_2 S_1 A_2 + k_5 S_3 A_2 - k_6 A_3$

4 eqns, 4 unknown quantities S_1, S_2, S_3, A_3 ($A_2 = A - A_3$)

I + II + III + IV: $\quad v_2 - v_6 = 0 \Leftrightarrow k_2 S_1 A_2 - k_6 A_3 = 0$

$\Leftrightarrow \boxed{S_1 = \frac{k_6 A_3}{k_2 A_2}}$

in I $\quad 2k_1 P_1 A_3 - \cancel{k_2} \cancel{A_2} \frac{k_6 A_3}{\cancel{k_2} \cancel{A_2}} - k_3 \frac{k_6 A_3}{k_2 A_2} = 0$ $\quad$ only variable left: A_3:

$\Leftrightarrow A_3 \left(2k_1 P_1 - k_6 - \frac{k_3 k_6}{k_2 A_2} \right) = 0$

← contains A_3!

Solutions: 1) $A_3 = 0 \rightarrow$ physiologically irrelevant, but mathematically important

2) $0 = 2k_1 P_1 - k_6 - \frac{k_3 k_6}{k_2 A_2} \Leftrightarrow A_2 = \frac{k_3 k_6}{k_2(2k_1 P_1 - k_6)} = A - A_3$

$\Leftrightarrow \boxed{A_3 = A - \frac{k_3 k_6}{k_2 (2k_1 P_1 - k_6)}}$

If A_3 is known: $$S_1 = \frac{k_6 A_3}{k_2 A_2}$$

$$S_2 = \frac{k_3 S_1}{k_4}$$

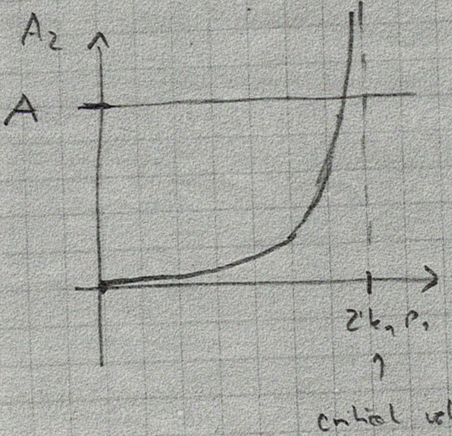
$$S_3 = \frac{k_2 S_1 A_2 + k_4 S_2}{k_5 A_2}$$

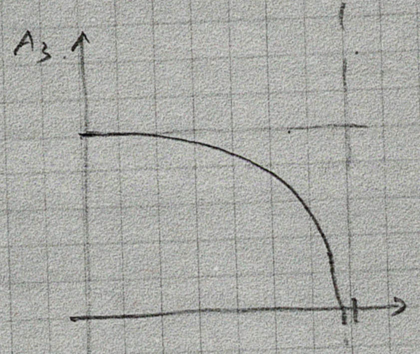
steady state ATP concentration depends on many k's: k_1, k_2, k_3, k_6 (not k_4, k_5)

Of particular interest:

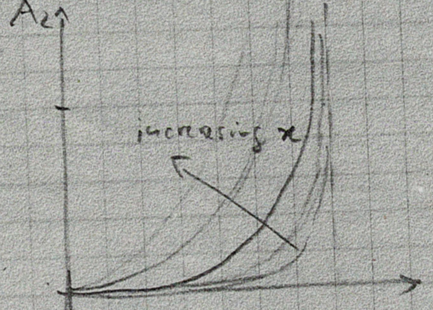
How does the steady-state concentr. of ATP depend on the ATP consumption rate?

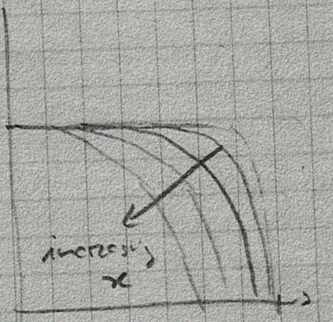
$$A_2 = \frac{k_3 k_6}{k_2 (2 k_1 P_1 - k_6)}$$





The shape of the curve depends on the ratio $x = \frac{k_3}{k_2}$



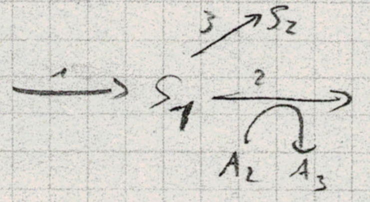


For small values of x, the ATP concentration is unsensitive to within a large range of consumption rates

→ ATP homeostasis

how can this be understood?

branching point:



(competition of reactions 2 and 3 for substrate S_1)

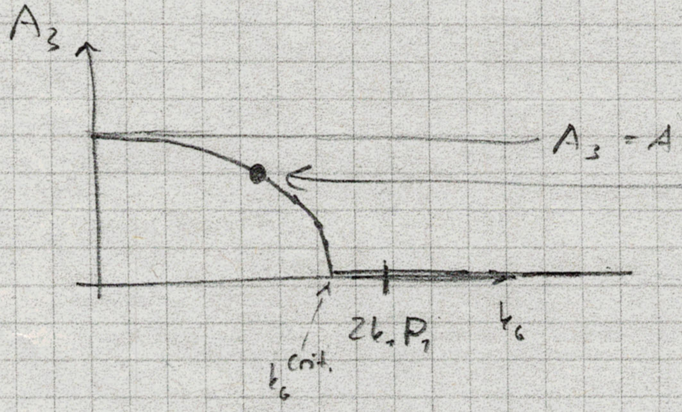
If k_6 is increased (demand of A_3), A_3 is reduced
$\Rightarrow$ A_2 is increased, v_2 is increased (over v_3) and more A_3 is produced.

The system reacts to a higher ATP demand by switching off the "ATP wasting" processes (2,3-DPG pathway).

There is a critical value of k_6 ($A_3 = 0$):

$$A = \frac{k_3 k_6}{k_2 (2 k_1 P_1 - k_6)} \qquad 2 k_1 k_2 P_1 A = k_6 (k_2 A + k_3)$$

$$\Leftrightarrow \quad k_6^{crit} = \frac{2 k_1 k_2 P_1 A}{k_3 + k_2 A} \le 2 k_1 P_1$$



In vivo : $A_3 \simeq 0.75 A$