Life and Death Theory

Part 2

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Important Biological Carriers

-energy and electron

$$\mathrm{ADP} + \mathrm{Pi} \longrightarrow \mathrm{ATP}$$
$$\mathrm{NAD^+} + 2\,\mathrm{e^-} \longrightarrow \mathrm{NADH}$$
$$\mathrm{NADP^+} + 2\,\mathrm{e^-} \longrightarrow \mathrm{NADPH}$$

Notes on How Constants are calculated

-thermodynamic helps

$$\Delta G = RT\ln(\frac{Q}{Q_{eq}}) = RT\ln(\frac{Q/Q^\circ}{Q_{eq}/Q^\circ})$$

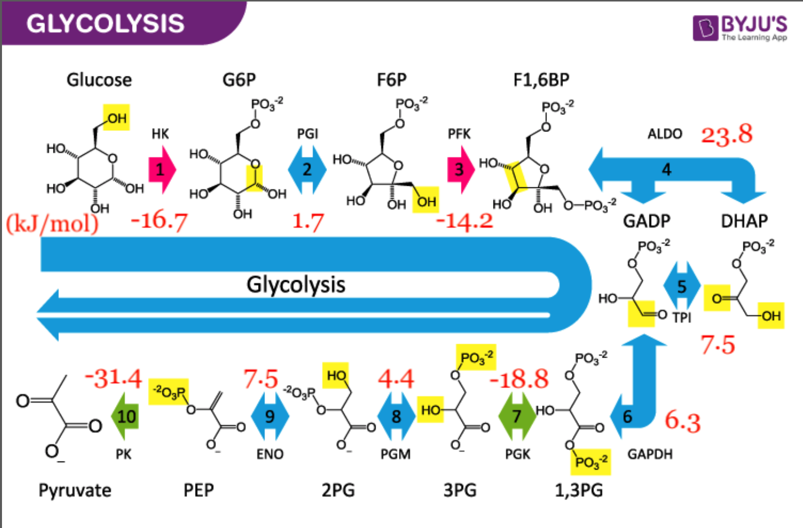
$$k_c = \frac{Q_{eq}}{Q^\circ}$$

$$\Delta G^\circ := -RT\ln(k_c)$$

$$\Rightarrow \Delta G = \Delta G^\circ + RT\ln(\frac{Q}{Q^\circ})$$

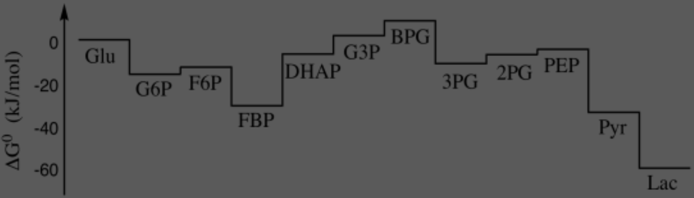
Glycolysis

$-\Delta G^{\circ}$



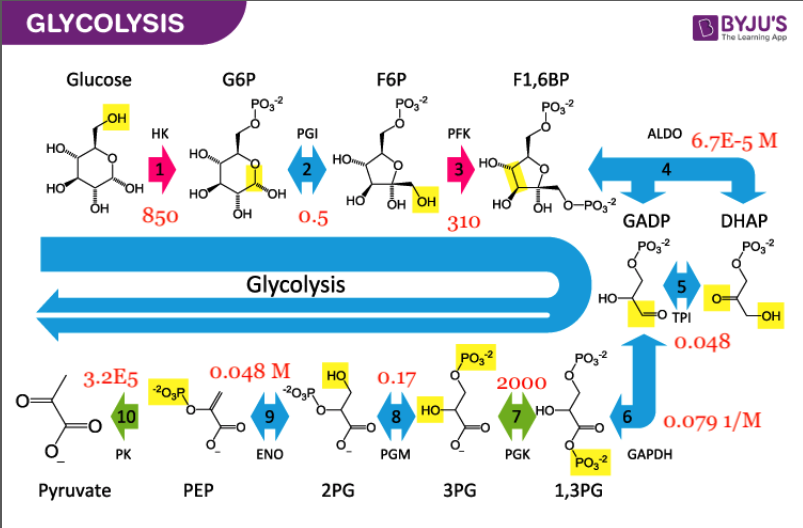
Glycolysis

-ΔG°



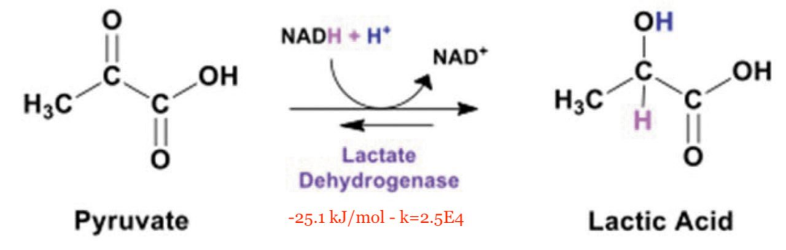
Glycolysis

-$k_{eq} := Q^{\circ} k_c = Q_{eq}$



Lactate Production

-completes fermentation



Glycolysis Reaction 1

-Glc $\rightarrow$ G6P

$$\cdots \rightleftharpoons \mathrm{Glc} \underset{k_{-1}}{\overset{\mathrm{ATP} \quad \mathrm{ADP}}{\overset{k_1}{\rightleftharpoons}}} \mathrm{G6P} \rightleftharpoons \cdots$$

$$v = k_1[Glc][\mathrm{ATP}] - k_{-1}[G6P][\mathrm{ADP}]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 850$$

Glycolysis Reaction 1

-Glc $\rightarrow$ G6P

$$v = k_1[Glc][\mathrm{ATP}] - k_{-1}[G6P][\mathrm{ADP}]$$

$$[G6P] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}.[Glc] - \frac{v}{k_{-1}}.\frac{1}{[\mathrm{ADP}]} = A[Glc] - B$$

$$A = 850.\frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}, \quad B = \frac{v}{k_{-1}}.\frac{1}{[\mathrm{ADP}]}$$

Glycolysis Reaction 2

-G6P $\rightarrow$ F6P

$$\cdots \rightleftharpoons \boxed{G6P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} F6P} \rightleftharpoons \cdots$$

$$v = k_1[Glc] - k_{-1}[G6P]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 0.5$$

Glycolysis Reaction 2

-G6P $\rightarrow$ F6P

$$v = k_1[Glc] - k_{-1}[G6P]$$

$$[F6P] = \frac{k_1}{k_{-1}}.[Glc] - \frac{v}{k_{-1}} = A[G6P] - B$$

$$A = 0.5, \quad B = \frac{v}{k_{-1}}$$

Glycolysis Reaction 3

-F6P $\rightarrow$ FBP

$$\cdots \rightleftharpoons \mathrm{F6P} \xrightleftharpoons[k_{-1}]{\overset{\mathrm{ATP}\quad\mathrm{ADP}}{k_1}} \mathrm{FBP} \rightleftharpoons \cdots$$

$$v = k_1[F6P][\mathrm{ATP}] - k_{-1}[FBP][\mathrm{ADP}]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 310$$

Glycolysis Reaction 3

-F6P $\rightarrow$ FBP

$$v = k_1[F6P][\mathrm{ATP}] - k_{-1}[FBP][\mathrm{ADP}]$$

$$[FBP] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}.[F6P] - \frac{v}{k_{-1}}.\frac{1}{[\mathrm{ADP}]} = A[F6P] - B$$

$$A = 310.\frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}, \quad B = \frac{v}{k_{-1}}.\frac{1}{[\mathrm{ADP}]}$$

Glycolysis Reaction 4

-FBP → DHAP + G3P

$$\cdots \rightleftharpoons \mathrm{FBP} \underset{k_{-1}}{\overset{\overset{\mathrm{DHAP}}{k_1}}{\rightleftharpoons}} \mathrm{G3P} \rightleftharpoons \cdots$$

$$v = k_1[FBP] - k_{-1}[G3P][DHAP]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 6.7 \times 10^{-5}\mathrm{M}$$

Glycolysis Reaction 4

-F6P $\rightarrow$ FBP

$$v = k_1[FBP] - k_{-1}[G3P][DHAP]$$

$$[G3P][DHAP] = \frac{k_1}{k_{-1}}.[FBP] - \frac{v}{k_{-1}} = A[FBP] - B$$

$$A = 6.7 \times 10^{-5}\mathrm{M}, \quad B = \frac{v}{k_{-1}}$$

Glycolysis Reaction 5

-DHAP $\rightarrow$ G3P

$$\cdots \rightleftharpoons \boxed{\mathrm{DHAP} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{G3P}} \rightleftharpoons \cdots$$

$$v = k_1[DHAP] - k_{-1}[G3P]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 0.048$$

Glycolysis Reaction 5

-DHAP $\rightarrow$ G3P

$$v = k_1[DHAP] - k_{-1}[G3P]$$

$$[G3P] = \frac{k_1}{k_{-1}}.[DHAP] - \frac{v}{k_{-1}} = A[DHAP] - B$$

$$A = 0.048, \quad B = \frac{v}{k_{-1}}$$

Glycolysis Reactions 4 and 5 Together

-simplifying the branch

$$[G3P][DHAP] = (6.7 \times 10^{-5})[FBP] - v.\frac{1}{k_{-1}^{(4)}}$$

$$[G3P] = 0.048[DHAP] - v.\frac{1}{k_{-1}^{(5)}}$$

$$\Rightarrow [G3P]([G3P] + v.\frac{1}{k_{-1}^{(5)}}) = 0.048 \times (6.7 \times 10^{-5})[FBP] - v.\frac{0.048}{k_{-1}^{(4)}}$$

Glycolysis Reactions 1 to 5 Altogether

-linear equations

$$\alpha_{\mathrm{ATP}} := \frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}$$

$$[G6P] = 850.\alpha_{\mathrm{ATP}}.[Glc] - v.\frac{1}{k_{-1}^{(1)}[\mathrm{ADP}]}$$

$$[F6P] = 0.5[G6P] - v.\frac{1}{k_{-1}^{(2)}}$$

$$[FBP] = 310.\alpha_{\mathrm{ATP}}.[F6P] - v.\frac{1}{k_{-1}^{(3)}[\mathrm{ADP}]}$$

$$[G3P]([G3P] + v.\frac{1}{k_{-1}^{(5)}}) = 0.048 \times (6.7 \times 10^{-5})[FBP] - v.\frac{0.048}{k_{-1}^{(4)}}$$

Glycolysis Reaction 6

-F6P $\rightarrow$ FBP

$$\cdots \rightleftharpoons \mathrm{G3P} \; \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \; \mathrm{BPG} \rightleftharpoons \cdots$$

$$\mathrm{NAD^+} + \mathrm{P}_i \qquad \mathrm{NADH} + \mathrm{H^+}$$

$$2v = k_1[G3P][\mathrm{NAD^+}][\mathrm{P}_i] - k_{-1}[BPG][\mathrm{NADH}]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 0.079\mathrm{M}^{-1}$$

$$([\mathrm{H}^+] = const. = 0.1\mu\mathrm{M})$$

Glycolysis Reaction 6

-F6P $\rightarrow$ FBP

$$2v = k_1[G3P][\mathrm{NAD}^+][\mathrm{P}_i] - k_{-1}[BPG][\mathrm{NADH}]$$

$$[BPG] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{NAD}^+][\mathrm{P}_i]}{[\mathrm{NADH}]}.[G3P] - \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{NADH}]} = A[G3P] - B$$

$$A = 0.079\frac{[\mathrm{NAD}^+][\mathrm{P}_i]}{[\mathrm{NADH}]}, \quad B = \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{NADH}]}$$

Glycolysis Reaction 7

-BPG $\rightarrow$ 3PG

$$\cdots \rightleftharpoons \mathrm{BPG} \underset{k_{-1}}{\overset{\mathrm{ADP} \quad \mathrm{ATP} \atop k_1}{\rightleftharpoons}} \mathrm{3PG} \rightleftharpoons \cdots$$

$$2v = k_1[BPG][\mathrm{ADP}] - k_{-1}[3PG][\mathrm{ATP}]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 2000$$

Glycolysis Reaction 7

-BPG $\rightarrow$ 3PG

$$2v = k_1[BPG][\mathrm{ADP}] - k_{-1}[3PG][\mathrm{ATP}]$$

$$[3PG] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{ADP}]}{[\mathrm{ATP}]}.[BPG] - \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{ATP}]} = A[BPG] - B$$

$$A = 2000.\frac{[\mathrm{ADP}]}{[\mathrm{ATP}]}, \quad B = \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{ATP}]}$$

Glycolysis Reaction 8

-3PG $\rightarrow$ 2PG

$$\cdots \rightleftharpoons \boxed{3PG \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2PG} \rightleftharpoons \cdots$$

$$2v = k_1[3PG] - k_{-1}[2PG]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 0.17$$

Glycolysis Reaction 8

-3PG $\rightarrow$ 2PG

$$2v = k_1[3PG] - k_{-1}[2PG]$$

$$[2PG] = \frac{k_1}{k_{-1}}.[3PG] - \frac{2v}{k_{-1}} = A[3PG] - B$$

$$A = 0.17, \quad B = \frac{2v}{k_{-1}}$$

Glycolysis Reaction 9

-2PG $\rightarrow$ PEP

$$\cdots \rightleftharpoons \mathrm{2PG} \underset{k_{-1}}{\overset{\overset{\mathrm{H_2O}}{k_1}}{\rightleftharpoons}} \mathrm{PEP} \rightleftharpoons \cdots$$

$$2v = k_1[2PG] - k_{-1}[PEP]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 0.048$$

$$([\mathrm{H_2O}] = const. = 1\mathrm{M}!)$$

Glycolysis Reaction 9

-2PG $\rightarrow$ PEP

$$2v = k_1[2PG] - k_{-1}[PEP]$$

$$[PEP] = \frac{k_1}{k_{-1}}.[2PG] - \frac{2v}{k_{-1}} = A[2PG] - B$$

$$A = 0.048, \quad B = \frac{2v}{k_{-1}}$$

Glycolysis Reaction 10

-PEP $\rightarrow$ Pyruvate

$$\cdots \rightleftharpoons \mathrm{PEP} \underset{k_{-1}}{\overset{\mathrm{ADP} \quad \mathrm{ATP} \atop k_1}{\rightleftharpoons}} \mathrm{PYR} \rightleftharpoons \cdots$$

$$2v = k_1[PEP][\mathrm{ADP}] - k_{-1}[PYR][\mathrm{ATP}]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 3.2 \times 10^5$$

Glycolysis Reaction 10

-PEP $\rightarrow$ Pyruvate

$$2v = k_1[PEP][\mathrm{ADP}] - k_{-1}[PYR][\mathrm{ATP}]$$

$$[PYR] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{ADP}]}{[\mathrm{ATP}]}.[PEP] - \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{ATP}]} = A[PEP] - B$$

$$A = (3.2 \times 10^5)\frac{[\mathrm{ADP}]}{[\mathrm{ATP}]}, \quad B = \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{ATP}]}$$

Glycolysis Reactions 6 to 10 Altogether

-linear equations

$$\alpha_{\mathrm{ATP}} := \frac{[\mathrm{ATP}]}{[\mathrm{ADP}]}, \quad \alpha_{\mathrm{NADH}} := \frac{[\mathrm{NAD}^+]}{[\mathrm{NADH}]} (\approx 240)$$

$$[BPG] = 0.079\alpha_{\mathrm{NADH}}.[\mathrm{P}_i][G3P] - 2v.\frac{1}{k_{-1}^{(6)}[\mathrm{NADH}]}$$

$$[3PG] = \frac{2000}{\alpha_{\mathrm{ATP}}}[BPG] - 2v.\frac{1}{k_{-1}^{(7)}[\mathrm{ATP}]}$$

$$[2PG] = 0.17[3PG] - 2v.\frac{1}{k_{-1}^{(8)}}$$

$$[PEP] = 0.048[2PG] - 2v.\frac{1}{k_{-1}^{(9)}}$$

$$[PYR] = \frac{(3.2 \times 10^5)}{\alpha_{\mathrm{ATP}}}[PEP] - 2v.\frac{1}{k_{-1}^{(10)}[\mathrm{ATP}]}$$

Lactate Reaction

-Pyruvate → Lactate

$$\mathrm{NADH} + \mathrm{H}^+$$

$$\cdots \rightleftharpoons \mathrm{PYR} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{LAC} \rightleftharpoons \cdots$$

$$\mathrm{NAD}^+$$

$$2v = k_1[PYR][\mathrm{NADH}] - k_{-1}[LAC][\mathrm{NAD}^+]$$

$$k_{eq} = \frac{k_1}{k_{-1}} = 25000$$

$$([\mathrm{H}^+] = const. = 0.1\mu\mathrm{M})$$

Lactate Reaction

-Pyruvate $\rightarrow$ Lactate

$$2v = k_1[PYR][\mathrm{NADH}] - k_{-1}[LAC][\mathrm{NAD}^+]$$

$$[LAC] = \frac{k_1}{k_{-1}}.\frac{[\mathrm{NADH}]}{[\mathrm{NAD}^+]}.[PYR] - \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{NAD}^+]} = A[PYR] - B$$

$$A = 25000\frac{[\mathrm{NADH}]}{[\mathrm{NAD}^+]}, \quad B = \frac{2v}{k_{-1}}.\frac{1}{[\mathrm{NAD}^+]}$$

$$\Rightarrow [LAC] = \frac{25000}{\alpha_{\mathrm{NADH}}}.[PYR] - 2v.\frac{1}{k_{-1}^{(11)}[\mathrm{NAD}^+]}$$

Overal

-steady-state condition

$$[X_i] = f_i([Glc], v, \alpha_{\mathrm{ATP}}, [\mathrm{P}_i])$$

Death Condition

-$v = 0$

$$
\begin{aligned}
&[G6P] = 850.\alpha_{\mathrm{ATP}}.[Glc], && [F6P] = 0.5[G6P] \\
&[FBP] = 310.\alpha_{\mathrm{ATP}}.[F6P] && \\
&[G3P]^2 = 0.048 \times (6.7 \times 10^{-5})[FBP] = 0.0018^2[FBP] && \\
&[BPG] = 0.079\alpha_{\mathrm{NADH}}.[\mathrm{P}_i][G3P], && [3PG] = \frac{2000}{\alpha_{\mathrm{ATP}}}[BPG] \\
&[2PG] = 0.17[3PG], && [PEP] = 0.048[2PG] \\
&[PYR] = \frac{(3.2 \times 10^5)}{\alpha_{\mathrm{ATP}}}[PEP], && [LAC] = \frac{25000}{\alpha_{\mathrm{NADH}}}.[PYR]
\end{aligned}
$$

Death Condition

-$v = 0$

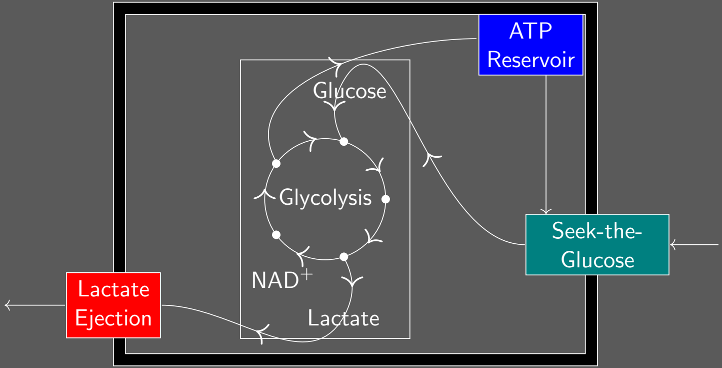
$$[G3P]^2 = 0.424.\alpha_{\mathrm{ATP}}^2[Glc]$$

$$\Rightarrow [G3P] = 0.65\alpha_{\mathrm{ATP}}\sqrt{[Glc]}$$

$$[LAC] = \frac{1.03 \times 10^{10}}{\alpha_{\mathrm{ATP}}^2}.[\mathrm{P}_i][G3P] = \frac{0.68 \times 10^{10}}{\alpha_{\mathrm{ATP}}}[\mathrm{P}_i]\sqrt{[Glc]}$$

Class 0 Modeling

-bio-modules



ATP Production

-not in steady-state

$$\begin{aligned}
\frac{d[\mathrm{ATP}]}{dt} =& k_1^{(10)}[PEP][\mathrm{ADP}] - k_{-1}^{(10)}[PYR][\mathrm{ATP}] \\
&+ k_1^{(7)}[BPG][\mathrm{ADP}] - k_{-1}^{(7)}[3PG][\mathrm{ATP}] \\
&- k_1^{(3)}[F6P][\mathrm{ATP}] + k_{-1}^{(3)}[FBP][\mathrm{ADP}] \\
&- k_1^{(1)}[Glc][\mathrm{ATP}] + k_{-1}^{(1)}[G6P][\mathrm{ADP}] \\
=& (k_1^{(10)}[PEP] + k_1^{(7)}[BPG] + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P])[\mathrm{ADP}] \\
&- (k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG] + k_1^{(3)}[F6P] + k_1^{(1)}[Glc])[\mathrm{ATP}]
\end{aligned}$$

ATP Production
-steady-state

$$\frac{d[\mathrm{ATP}]}{dt} = 0 \text{ iff}$$

$$\alpha_{\mathrm{ATP}} = \frac{[\mathrm{ATP}]}{[\mathrm{ADP}]} = \frac{k_1^{(10)}[PEP] + k_1^{(7)}[BPG] + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P]}{k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG] + k_1^{(3)}[F6P] + k_1^{(1)}[Glc]}$$

ATP Production

-not in steady-state

Assumption: $[\mathrm{ATP}] + [\mathrm{ADP}] = const. := s$

$$\Rightarrow [\mathrm{ATP}] = \frac{\alpha_{\mathrm{ATP}}.s}{1 + \alpha_{\mathrm{ATP}}}$$
$$\Rightarrow [\mathrm{ADP}] = \frac{s}{1 + \alpha_{\mathrm{ATP}}}$$

ATP Production

-not in steady-state

Consider α_{ATP} is regulated in a constant value $\alpha^{\circ}_{\mathrm{ATP}}$ in cell;
And all ...

Glucose Transport
-feeding module

$$\cdots \rightleftharpoons \text{Glc in} \underset{\beta_{-1}\ \swarrow\ \mathrm{ADP}+\mathrm{P}_i}{\overset{\beta_1\ \nearrow\ \mathrm{ATP}}{\rightleftharpoons}} \text{Glc out}$$

Assumption (about Seek-the-Glucose module):

$$\begin{aligned} v_{[Glc]} &= \beta_1[\mathrm{ATP}] - \beta_{-1}[\mathrm{ADP}][\mathrm{P}_i] \\ &= (\beta_1\alpha_{\mathrm{ATP}} - \beta_{-1}[\mathrm{P}_i])[\mathrm{ADP}] \\ &= s.\frac{(\beta_1\alpha_{\mathrm{ATP}} - \beta_{-1}[\mathrm{P}_i])}{1+\alpha_{\mathrm{ATP}}} \end{aligned}$$

ATP Production

-road to death

$$p := (k_1^{(10)}[PEP] + k_1^{(7)}[BPG] + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P])$$

$$q := (k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG] + k_1^{(3)}[F6P] + k_1^{(1)}[Glc])$$

$$\frac{d[\mathrm{ATP}]}{dt} = p[\mathrm{ADP}] - q[\mathrm{ATP}]$$

Road to death:

$$\frac{d[\mathrm{ATP}]}{dt}(t+dt) < \frac{d[\mathrm{ATP}]}{dt}(t)$$

$$\begin{aligned}
\Rightarrow & p(t+dt)\{[\mathrm{ADP}] - p(t)[\mathrm{ADP}]dt + q(t)[\mathrm{ATP}]dt\} \\
& -q(t+dt)\{[\mathrm{ATP}] + p(t)[\mathrm{ADP}]dt - q(t)[\mathrm{ATP}]dt\} \\
& < p(t)[\mathrm{ADP}] - q(t)[\mathrm{ATP}]
\end{aligned}$$

ATP Production

-road to death

$$
\begin{aligned}
\Rightarrow & \frac{dp}{dt}[\mathrm{ADP}] - p^2[\mathrm{ADP}] + pq[\mathrm{ATP}] \\
& < \frac{dq}{dt}[\mathrm{ATP}] + pq[\mathrm{ADP}] - q^2[\mathrm{ATP}] \\
\Rightarrow & (q(p+q) - \dot{q})\alpha_{\mathrm{ATP}} < p(p+q) - \dot{p} \\
\Rightarrow & p - q\alpha_{\mathrm{ATP}} > \frac{\dot{p} - \dot{q}\alpha_{\mathrm{ATP}}}{p+q}
\end{aligned}
$$

ATP Production

-road to death

$$\eta := \frac{p}{q}, \quad \delta := \eta - \alpha_{\mathrm{ATP}}, \quad \dot{\eta} = \frac{\dot{p} - \eta\dot{q}}{q}$$

$$\begin{aligned}
p - q\alpha_{\mathrm{ATP}} &> \frac{\dot{p} - \dot{q}\alpha_{\mathrm{ATP}}}{p+q} \\
\Rightarrow \eta - \alpha_{\mathrm{ATP}} &> \frac{1}{p+q}\left(\frac{\dot{p} - \dot{q}\alpha_{\mathrm{ATP}}}{q}\right) \\
&= \frac{1}{p+q}\left(\dot{\eta} + (\eta - \alpha_{\mathrm{ATP}})\frac{\dot{q}}{q}\right) \\
\Rightarrow \delta &> \frac{1}{p+q}\left(\dot{\eta} + \delta\frac{\dot{q}}{q}\right)
\end{aligned}$$

ATP Production

-road to death

$$p := (k_1^{(10)}[PEP] + k_1^{(7)}[BPG] + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P])$$
$$q := (k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG] + k_1^{(3)}[F6P] + k_1^{(1)}[Glc])$$

$$\frac{d[\mathrm{ATP}]}{dt} < 0 \Leftrightarrow \alpha_{\mathrm{ATP}} > \frac{p}{q}$$

$$\frac{d^2[\mathrm{ATP}]}{dt^2} < 0 \Leftrightarrow (q(p+q) - \dot{q})\alpha_{\mathrm{ATP}} < p(p+q) - \dot{p}$$

ATP Production

-road to death

$$\frac{d[\mathrm{ATP}]}{dt} < 0 \Leftrightarrow \eta - \alpha_{\mathrm{ATP}} < 0$$

$$\frac{d^2[\mathrm{ATP}]}{dt^2} < 0 \Leftrightarrow \eta - \alpha_{\mathrm{ATP}} > \frac{1}{p+q}\left(\frac{\dot{p} - \dot{q}\alpha_{\mathrm{ATP}}}{q}\right)$$

$$\Rightarrow \text{ most have } \dot{p} < \dot{q}\alpha_{\mathrm{ATP}}$$

ATP Production

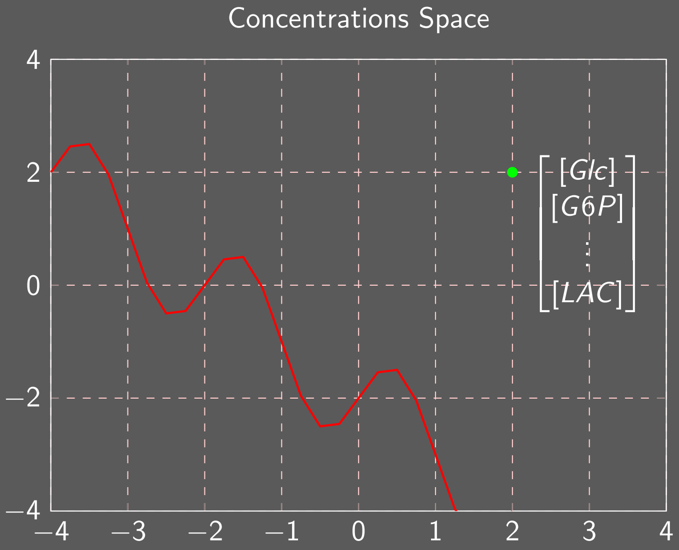
-death sink point

$$\frac{d[\mathrm{ATP}]}{dt} < 0 \text{ and } \frac{d^2[\mathrm{ATP}]}{dt^2} = 0$$

$$0 > \eta - \alpha_{\mathrm{ATP}} = \frac{1}{p+q}\left(\frac{\dot{p} - \dot{q}\alpha_{\mathrm{ATP}}}{q}\right)$$

Intuition

-boundary of death



Simplified Death Condition

-still general case enough

Assumption: Internal Enzymes are much faster than Port Enzyme; (i.e. $\beta \ll k^{(i)}$), therefore Glycolysis would be in steady-state:

$$v = v_{[Glc]}$$

$$\Rightarrow [X_i] = f_i([Glc], v_{[Glc]}, \alpha_{\mathrm{ATP}}, [\mathrm{P}_i])$$

Simplified Death Condition

-ATP

$$[X_i] = f_i([Glc], v_{[Glc]}, \alpha_{\mathrm{ATP}}, [\mathrm{P}_i])$$

$$\Rightarrow p = p([Glc], v_{[Glc]}, \alpha_{\mathrm{ATP}}, [\mathrm{P}_i]) \text{ and}$$
$$q = q([Glc], v_{[Glc]}, \alpha_{\mathrm{ATP}}, [\mathrm{P}_i])$$

$$\frac{d\alpha_{\mathrm{ATP}}}{dt} = (1 + \alpha_{\mathrm{ATP}})(p - q\alpha_{\mathrm{ATP}})$$

$$v_{[Glc]} = s.\frac{(\beta_1\alpha_{\mathrm{ATP}} - \beta_{-1}[\mathrm{P}_i])}{1 + \alpha_{\mathrm{ATP}}}$$

Simplified Death Condition

-road to living or death?

$$\frac{\partial v_{[Glc]}}{\partial \alpha_{\mathrm{ATP}}} > 0$$

$$\frac{d\alpha_{\mathrm{ATP}}}{dt} > 0 \text{ and } \frac{d^2\alpha_{\mathrm{ATP}}}{dt^2} > 0 \rightarrow \text{ positive loop into Life}$$
$$\frac{d\alpha_{\mathrm{ATP}}}{dt} < 0 \text{ and } \frac{d^2\alpha_{\mathrm{ATP}}}{dt^2} < 0 \rightarrow \text{ negative loop into Death}$$
$$\frac{d\alpha_{\mathrm{ATP}}}{dt} = 0 \text{ and } \frac{d^2\alpha_{\mathrm{ATP}}}{dt^2} = 0 \rightarrow \text{ steady-state}$$

Other two cases: depend on $sign(\frac{d^2\alpha_{\mathrm{ATP}}}{dt^2})$ where $\frac{d\alpha_{\mathrm{ATP}}}{dt} = 0$.

Excess of ATP

-Bears hibernation

$\alpha_{\mathrm{ATP}} > \alpha_{\mathrm{ATP}}^{max}$:

Death Condition

-$v = 0$

$$[G6P] = 850.\alpha_{\mathrm{ATP}}.[Glc], \qquad [F6P] = 425.\alpha_{\mathrm{ATP}}.[Glc]$$

$$[FBP] = 1.318 \times 10^5.\alpha_{\mathrm{ATP}}^2.[Glc], \qquad [G3P] = 0.65\alpha_{\mathrm{ATP}}\sqrt{[Glc]}$$

$$[BPG] = 5.14 \times 10^{-2}\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}.[\mathrm{P}_i]\sqrt{[Glc]}$$

$$[3PG] = 102.7\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]}, \qquad [2PG] = 17.46\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]}$$

$$[PEP] = 0.838\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]}$$

$$[PYR] = 2.7 \times 10^5\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}}.[\mathrm{P}_i]\sqrt{[Glc]}$$

Death Condition

-$v = 0$

$$
\begin{aligned}
p =& (k_1^{(10)}[PEP] + k_1^{(7)}[BPG] + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P]) \\
=& (0.838.k_1^{(10)}\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]} \\
& +5.14 \times 10^{-2} k_1^{(7)}.\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}.[\mathrm{P}_i]\sqrt{[Glc]} \\
& +1.318 \times 10^5.k_{-1}^{(3)}.\alpha_{\mathrm{ATP}}^2.[Glc] + 850.k_{-1}^{(1)}.\alpha_{\mathrm{ATP}}.[Glc]) \\
q =& (k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG] + k_1^{(3)}[F6P] + k_1^{(1)}[Glc]) \\
=& (2.7 \times 10^5.k_{-1}^{(10)}.\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}}.[\mathrm{P}_i]\sqrt{[Glc]} \\
& +102.7.k_{-1}^{(7)}.\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]} \\
& +425.k_1^{(3)}.\alpha_{\mathrm{ATP}}.[Glc] + k_1^{(1)}[Glc])
\end{aligned}
$$

Death Condition

-$v = 0$

$$
\begin{aligned}
& p - \alpha_{\mathrm{ATP}}.q = 0 \\
& \Rightarrow (1.318 \times 10^5.k_{-1}^{(3)} - 425.k_1^{(3)})\sqrt{[Glc]}\alpha_{\mathrm{ATP}}^2 \\
& \quad + ((5.14 \times 10^{-2}.k_1^{(7)} - 102.7.k_{-1}^{(7)})\alpha_{\mathrm{NADH}}.[\mathrm{P}_i] \\
& \qquad + (850.k_{-1}^{(1)} - k_1^{(1)})\sqrt{[Glc]})\alpha_{\mathrm{ATP}} \\
& \quad + (0.838.k_1^{(10)} - 2.7 \times 10^5.k_{-1}^{(10)})\alpha_{\mathrm{NADH}}[\mathrm{P}_i] = 0 \\
& \Rightarrow \alpha_{\mathrm{ATP}}^{death} = g([Glc], [P_i])
\end{aligned}
$$

Death Condition

-$v = 0$

$$v_{[Glc]} = s.\frac{(\beta_1 \alpha_{\mathrm{ATP}} - \beta_{-1}[\mathrm{P}_i])}{1 + \alpha_{\mathrm{ATP}}} = 0$$

$$\Rightarrow \alpha_{\mathrm{ATP}} = \frac{\beta_{-1}}{\beta_1}[\mathrm{P}_i]$$

$$\Rightarrow [Glc],\ \alpha_{\mathrm{ATP}}^{death} \checkmark$$

Return from Death!

-until modules get depreciated

Steadily entrance of glucose (cycle) should start up

Return from Death!
-until modules get depreciated

Small disturbance in concentrations (e.g. adding some glucose)
$\frac{\partial v_{[Glc]}}{\partial \alpha_{\mathrm{ATP}}} > 0 \Rightarrow \alpha_{\mathrm{ATP}}$ should steadily increase.
Almost sufficient to have:

$$\frac{d\alpha_{\mathrm{ATP}}}{dt} > 0 \text{ and } \frac{d^2\alpha_{\mathrm{ATP}}}{dt^2} > 0$$

Return from Death!

-p and q stability in equilibrium

$$
\begin{aligned}
p =&(0.838.k_1^{(10)}\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]} \\
&+5.14\times 10^{-2}k_1^{(7)}.\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}.[\mathrm{P}_i]\sqrt{[Glc]} \\
&+1.318\times 10^{5}.k_{-1}^{(3)}.\alpha_{\mathrm{ATP}}^2.[Glc]+850.k_{-1}^{(1)}.\alpha_{\mathrm{ATP}}.[Glc]) \\
q =&(2.7\times 10^{5}.k_{-1}^{(10)}.\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}}.[\mathrm{P}_i]\sqrt{[Glc]} \\
&+102.7.k_{-1}^{(7)}.\alpha_{\mathrm{NADH}}[\mathrm{P}_i]\sqrt{[Glc]} \\
&+425.k_1^{(3)}.\alpha_{\mathrm{ATP}}.[Glc]+k_1^{(1)}[Glc])
\end{aligned}
$$

$$\frac{\partial}{\partial[Glc]}(\frac{p}{q}) \propto q\frac{\partial p}{\partial[Glc]} - p\frac{\partial q}{\partial[Glc]}$$

Return from Death!

-p and q stability in equilibrium

$$\frac{\frac{\partial p}{\partial [Glc]}}{\frac{\partial q}{\partial [Glc]}} = \{(0.838.k_1^{(10)}\alpha_{\mathrm{NADH}}\frac{[\mathrm{P}_i]}{2\sqrt{[Glc]}}$$

$$+5.14 \times 10^{-2} k_1^{(7)}.\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}\frac{[\mathrm{P}_i]}{2\sqrt{[Glc]}}$$

$$+1.318 \times 10^5.k_{-1}^{(3)}.\alpha_{\mathrm{ATP}}^2 + 850.k_{-1}^{(1)}.\alpha_{\mathrm{ATP}})\}\div$$

$$\{(2.7 \times 10^5.k_{-1}^{(10)}.\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}}\frac{[\mathrm{P}_i]}{2\sqrt{[Glc]}}$$

$$+102.7.k_{-1}^{(7)}.\alpha_{\mathrm{NADH}}\frac{[\mathrm{P}_i]}{2\sqrt{[Glc]}}$$

$$+425.k_1^{(3)}.\alpha_{\mathrm{ATP}} + k_1^{(1)})\}$$

Return from Death!

-p and q stability in equilibrium

$$\frac{\frac{\partial p}{\partial [Glc]}}{\frac{\partial q}{\partial [Glc]}} = \frac{0.5(k_1^{(10)}[PEP] + k_1^{(7)}[BPG]) + k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P]}{0.5(k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG]) + k_1^{(3)}[F6P] + k_1^{(1)}[Glc]}$$

Will enter Life if $> \frac{p}{q}$

Return from Death!

-p and q stability in equilibrium

$$\Rightarrow \frac{d\alpha_{\mathrm{ATP}}}{dt} > 0 \text{ iff } \frac{\partial}{\partial[Glc]}(\frac{p}{q}) \text{ iff}$$

$$(k_1^{(10)}[PEP] + k_1^{(7)}[BPG])(k_1^{(3)}[F6P] + k_1^{(1)}[Glc]) <$$

$$(k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P])(k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG])$$

Return from Death!

-p and q stability in equilibrium

$$(k_1^{(10)}[PEP] + k_1^{(7)}[BPG])(k_1^{(3)}[F6P] + k_1^{(1)}[Glc]) <$$
$$(k_{-1}^{(3)}[FBP] + k_{-1}^{(1)}[G6P])(k_{-1}^{(10)}[PYR] + k_{-1}^{(7)}[3PG])$$

iff:

$$(0.838.k_1^{(10)}\alpha_{\mathrm{NADH}} + 5.14 \times 10^{-2}k_1^{(7)}.\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}).$$
$$(425.k_1^{(3)}.\alpha_{\mathrm{ATP}} + k_1^{(1)}) <$$
$$(2.7 \times 10^5.k_{-1}^{(10)}.\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}} + 102.7.k_{-1}^{(7)}.\alpha_{\mathrm{NADH}}).$$
$$(1.318 \times 10^5.k_{-1}^{(3)}.\alpha_{\mathrm{ATP}}^2 + 850.k_{-1}^{(1)}.\alpha_{\mathrm{ATP}})$$

Return from Death!

-why practically impossible

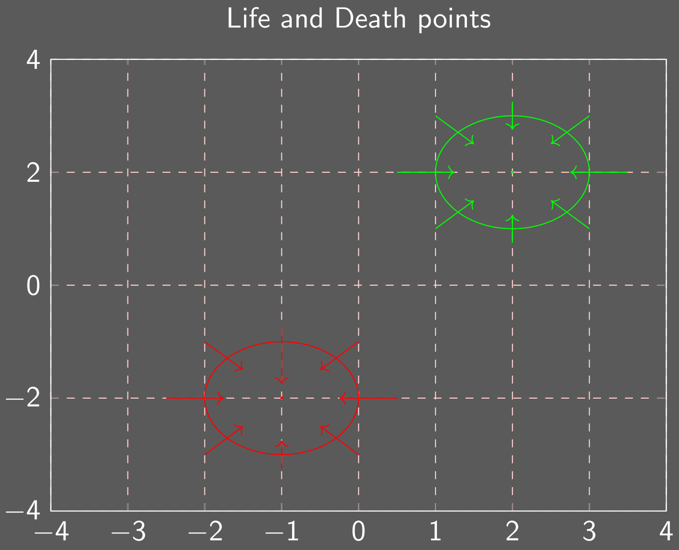
Conjecture! :

$$(0.838.k_1^{(10)}\alpha_{\mathrm{NADH}} + 5.14 \times 10^{-2} k_1^{(7)}.\alpha_{\mathrm{NADH}}.\alpha_{\mathrm{ATP}}^{death}).$$
$$(425.k_1^{(3)}.\alpha_{\mathrm{ATP}}^{death} + k_1^{(1)}) >$$
$$(2.7 \times 10^5.k_{-1}^{(10)}.\frac{\alpha_{\mathrm{NADH}}}{\alpha_{\mathrm{ATP}}^{death}} + 102.7.k_{-1}^{(7)}.\alpha_{\mathrm{NADH}}).$$
$$(1.318 \times 10^5.k_{-1}^{(3)}.(\alpha_{\mathrm{ATP}}^{death})^2 + 850.k_{-1}^{(1)}.\alpha_{\mathrm{ATP}}^{death})$$

(No phosphate and glucose!)

Life and Death

-sink areas



References

-for k_{eq} values

- Thermodynamic aspects of glycolysis; Athel Cornish-Bowden; University of Birmingham

Comparison Approaches

-Classics vs. Constraint based

Classics:

- $+$ Thorough! (quote: science is ended after finding out differential equations)
- $-$ Huge analytic difficulties

Constraint Based:

- $+$ Simple and practical
- $-$ Limited ability (e.g. only finds sufficient conditions)

Next Session
-part 3

- Entering other modules

Thanks :))