

Multiscale modeling: A mathematical-based tool for bioprocess design, control and scale up/down

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Supplementary material

S1. Bioreactor modeling

A compartment model consists of decomposing the spatial zone of a bioreaction vessel into several units (compartments) of equal volume and assumed to be fully mixed [1]. The reactor depicted in figure S1 (left hand side) is broken down into 70 compartments (right hand side).

Hydrodynamics in the vessel is characterized by the different fluxes assumed to be generated by the action of a stirrer and/or the gassed pneumatic power following sound approaches [2-3]. Description of these fluxes are:

Circulation flux (CF): It is the flux caused by the stirrer mechanical power.

Exchange flux (EF): this flux accounts for the presence of eddies causing an axial turbulent flow throughout the vessel.

Induced flux (IF): This flux is only considered when there is pneumatic power caused by gas injection, frequently air. It is responsible for interconnecting zones delimited by several impellers when gas bubbles are present.

Power input by impellers: The power input is a critical aspect in compartment models. Here, the bottom impeller is assumed to be a single impeller in the vessel, and its power input is assumed to be the smaller among the other impellers because air is usually sparged below it.

Relative power input for the bottom impeller

$$\frac{Q_G N^{0.25}}{D^2} \leq 0.055: \quad 1 - \frac{P_G}{P} = 9.9 \left(\frac{Q_G N^{0.25}}{D^2} \right) \quad (\text{S1a})$$

$$\frac{Q_G N^{0.25}}{D^2} > 0.055: \quad 1 - \frac{P_G}{P} = 0.52 + 0.62 \left(\frac{Q_G N^{0.25}}{D^2} \right) \quad (S1b)$$

Here, the power input depends on Q_G , gas flowrate; N , agitation speed; and the impeller diameter, D . $\frac{P_G}{P}$ is relative power.

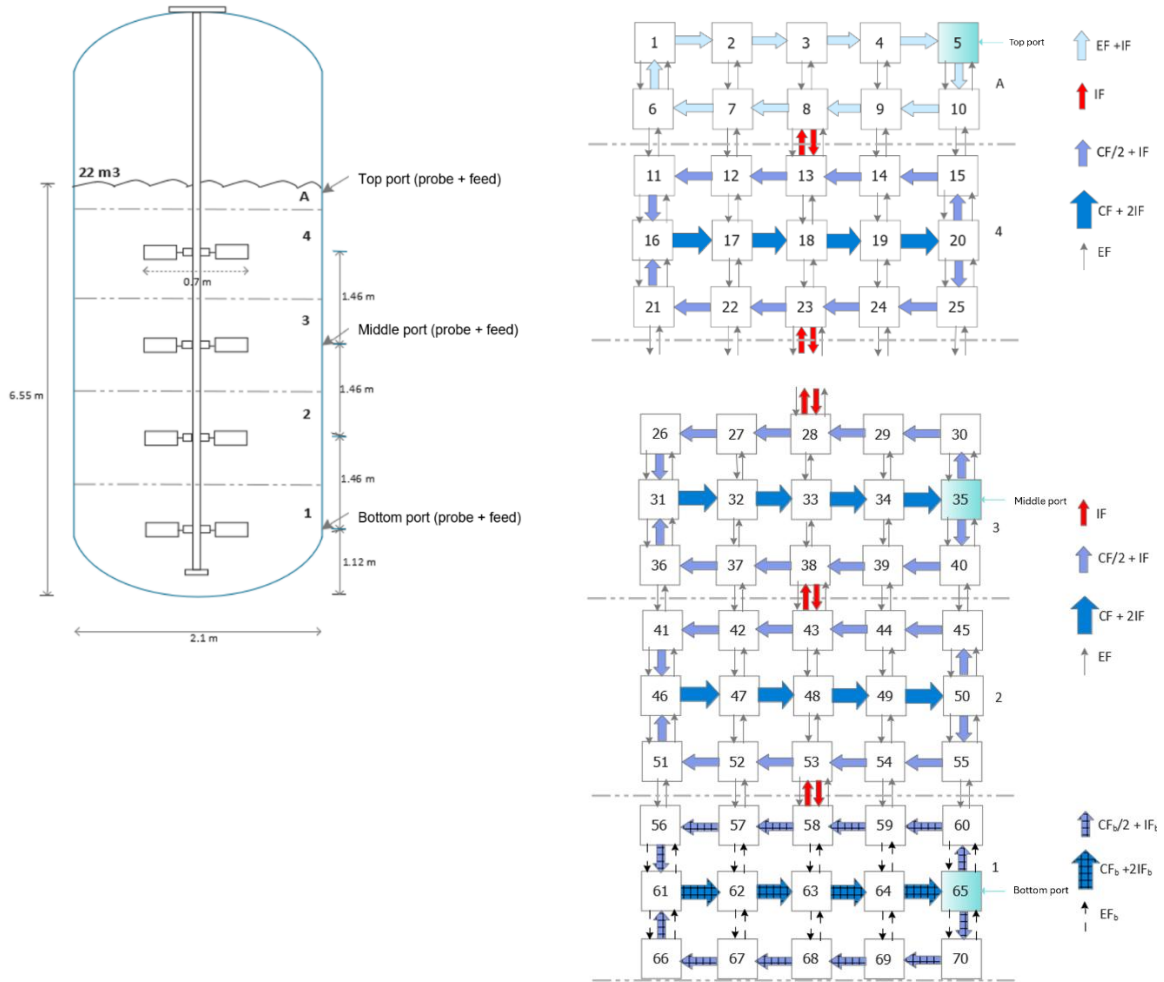


Figure S1. Bioreactor description

All the other impellers behave similarly since no air sparger is located beneath them; however, their power input is lower and can be described by equation S2 as follows, for instance for impeller 2:

$$P_{G_2} = 1.224 \left(\frac{P_{L_2}^2 N D^3}{Q_G^{0.56}} \right)^{0.432} \quad (S2)$$

Where P_{L_2} is the total power input by two Rushton turbines without gas, which can be derived from:

$$P_{L_n} = nP_{L_1} \quad (S3)$$

This equation states that, under no gassing conditions, the total power delivered by n impellers equals n times the power on one single impeller. To calculate the power on one single impeller without gas, the classical expression shown in equation S4 can be used.

$$P_{L_1} = P_0 \rho_l N^3 D^5 \quad (S4)$$

Based on the above considerations, it is possible to know the power input for the set of impellers, which imply two different values for CF, IF and EF, the one related to the bottom impeller and the other for the rest.

Vrabel's model [2] considers:

1. The compartment model is built for half of the bioreactor assuming an axial symmetry.
2. Each impeller produces two loops, one above and one below. Each loop is assumed to be an agitated vessel in series with the other linked by an axial exchange flux (EF).
3. Liquid streams linking two different impeller zones is the induced flux (IF).
4. CF and IF are real fluxes within the vessel in only one direction, while EF is an apparent flux that considers a turbulent exchange between compartments and is modeled as a two-direction flux

CF can be calculated from equation S5 depending on whether the impeller is under gassed conditions or not.

$$Q_{LG} = \left(\frac{P_G}{P}\right)^\beta \text{ or } Q_L = \left(\frac{P_G}{P}\right)^\beta K_P N D^3 \quad (S5)$$

Q_L : flowrate discharged by the impeller when there is not gas, subscript G stands for gassed conditions ; K_P : flow number; β : constant

N : stirrer speed; D : impeller diameter; P : power of the impeller

P_G : power input when under gassed conditions

Values for K_P and β depend on the impeller type. Here, for a radial Rushton turbine 0.75 and 0.34 are used, respectively. Thus:

$$CF = \left(\frac{P_G}{P}\right)^{0.34} K_c N D^3 \quad (S6a)$$

$$K_C = 2 * 0.8 * K_P \quad (S6b)$$

In equation S6a, K_p is altered by factors 2 and 0.8, which consider that CF is twice Q_{LG} to account for the flux dragged by momentum, but not all goes in the radial direction, hence an 80% of it is established.

To derive EF (Equation S7), expressions accounting for the presence of eddies are considered.

$$EF_G = 0.34\alpha T^2 D^{1/3} (1 - \varepsilon_G) \left(\frac{\left(\frac{P_G}{P}\right) P_0 N^3 D^5}{\frac{\pi}{4} T^2 H_i (1 - \varepsilon_G)} + g v_{Gs} \right)^{1/3} \quad (S7)$$

Where the expression for the mean quadratic velocity under gassed conditions is assumed (Equation S8)

$$u'_G = (e_G l_e)^{\frac{1}{3}} \quad (S8a)$$

$$l_e = 0.08D \quad (S8b)$$

$$e_G = \frac{\left(\frac{P_G}{P}\right) \rho_L P_0 N^3 D^5}{\rho_L \frac{\pi}{4} T^2 H_i (1 - \varepsilon_G)} + g v_{Gs} \quad (S8c)$$

ρ_L : liquid density; P_0 : Power number; v_{Gs} : superficial gas velocity
 ε_G : gas holdup; H_i : height of the impeller region; T : bioreactor diameter

l_e is a characteristic length of the eddies and is correlated to the impeller diameter. e_G is the power dissipated under gassed conditions.

The induced flux, IF is obtained from equation S9

$$IF = k_i \frac{Q_G}{Q_{LG}} = k_{AX} \frac{Q_G}{\left(\frac{P_G}{P}\right)^{0.34} N D^3} \quad (S9)$$

Here k_i is a proportionality constant and k_{AX} is a constant that depends on the dimensional configuration of the bioreactor. Equation S9 correlates the volumetric flowrate of the injected gas, Q_G , and the flowrate discharged by the impeller, Q_{LG} .

Finally, the model is completed with the mass balance for each compartment once the three fluxes characterizing hydrodynamics have been defined. Thus, equation S10 represents the mass balance for component i , and considers a reactive term, R_i , and a gas-liquid mass transfer term, T_i [1].

$$V_n \frac{\partial C_i^n}{\partial t} = R_i + T_i + \sum_{m=1}^N (M_{m,n}^f C_i^m) - C_i^n \sum_{m=1}^N (M_{n,m}^f) \quad (\text{S10a})$$

$$\frac{\partial C_i^n}{\partial t} = q_i^n X^n + k_l a(C_i^* - C_i^n) + \frac{1}{V_n} \sum_{m=1}^N (M_{m,n}^f C_i^m) - \frac{C_i^n}{V_n} \sum_{m=1}^N (M_{n,m}^f) \quad (\text{S10b})$$

S2. Modeling cellular metabolism

The modeling approach used here consists of a set of differential mass balances for the intracellular metabolites in which the different reaction fluxes are modeled with corresponding kinetic expressions. This approach allows us to capture the dynamic variation of metabolite concentrations and fluxes in time. The general representation of the model is described by equation S11.

$$\frac{dx}{dt} = S \cdot v \quad , \quad v(x, k, E) \quad (\text{S11})$$

x : vector of intracellular metabolite concentrations; E : enzyme concentration;

k : kinetic parameters

The glucose uptake is modeled by the traditional hyperbolic function (Equation S12)

$$q_s = \frac{q_{s,max} [Glc_{ex}]}{K_s + [Glc_{ex}]} \quad (4)$$

$q_{s,max}$: Maximal specific rate for glucose uptake; K_s : Affinity constant

$[Glc_{ex}]$: Extracellular glucose concentration.

The model considers a set of intracellular metabolic networks as shown in figure S2, which includes the glycolytic pathway, the pentose phosphate pathway and some pathways for the metabolism of reserve carbohydrates, such as glycogen and trehalose, following the study of Suarez-Mendez et al. [4].

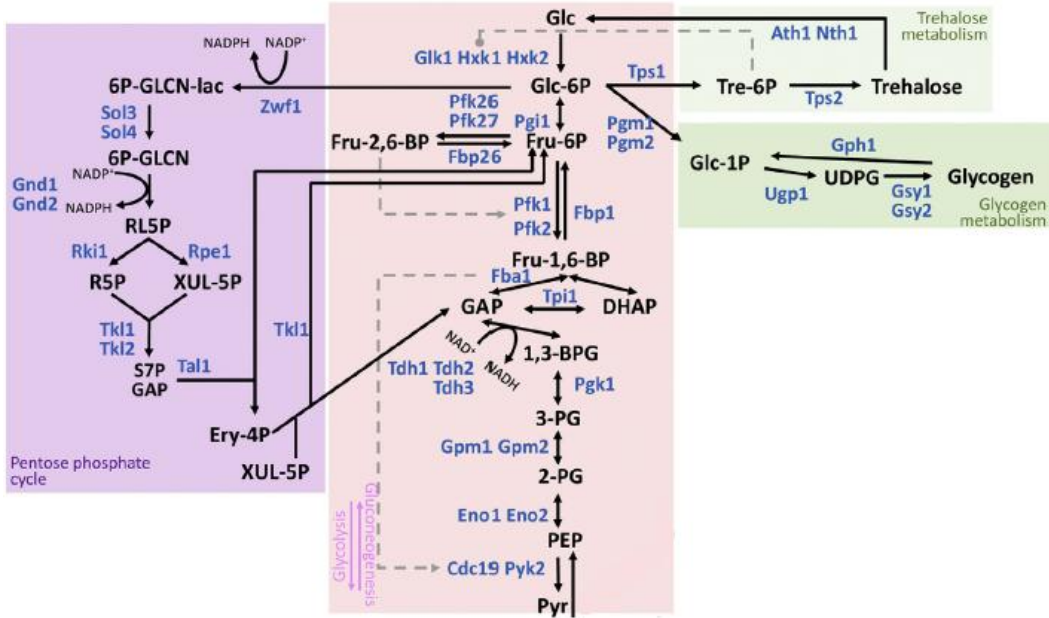


Figure S2. Main kinetic pathway considered in the metabolic model. Adapted from [5]

Mass balances (Differential equations)

The set of differential equations that describe the network mathematically is as follows:

$$\frac{d[Glc]}{dt} = v_{uptake} - v_1 + 2v_{20} + v_{34}$$

$$\frac{d[Glc6P]}{dt} = v_1 - v_2 - v_3 - v_{16} - v_{18} - v_{22}$$

$$\frac{d[Fru6P]}{dt} = v_3 - v_4 + v_{28} + v_{29}$$

$$\frac{d[FruBP]}{dt} = v_4 - v_5 - k_f[FruBP]$$

$$\frac{d[GAP]}{dt} = v_5 + v_9 - v_{10} + v_{27} - v_{28} + v_{29} - k_g[GAP]$$

$$\frac{d[DHAP]}{dt} = v_5 - v_9$$

$$\frac{d[BPG]}{dt} = v_{10} - v_{11}$$

$$\frac{d[3PG]}{dt} = v_{11} - v_{12}$$

$$\frac{d[2PG]}{dt} = v_{12} - v_{13}$$

$$\frac{d[PEP]}{dt} = v_{13} - v_{14}$$

$$\frac{d[Pyr]}{dt} = v_{14} - v_{15}$$

$$\frac{d[UTP]}{dt} = -v_{17} + v_{21}$$

$$\frac{d[UDP]}{dt} = v_{18} - v_{21} + v_{30} + v_{31}$$

$$\frac{d[UDPGlc]}{dt} = v_{17} - v_{18} - v_{30} - v_{31}$$

$$\frac{d[Glc1P]}{dt} = v_{16} - v_{17} + v_{33}$$

$$\frac{d[T6P]}{dt} = v_{18} - v_{19}$$

$$\frac{d[Treh]}{dt} = v_{19} - v_{20}$$

$$\frac{d[(\alpha_{1,4} \text{ glucosil})_n]}{dt} = v_{30} - v_{31}$$

$$\frac{d[(\alpha_{1,4} \text{ glucosil})_{n+1}]}{dt} = v_{31} - v_{32}$$

$$\frac{d[glyco]}{dt} = v_{32} - v_{33} - v_{34} - k_{gly}[glyco]$$

$$\frac{d[PGL6]}{dt} = v_{22} - v_{23}$$

$$\frac{d[PG6]}{dt} = v_{23} - v_{24}$$

$$\frac{d[Rul5P]}{dt} = v_{24} - v_{25} - v_{26}$$

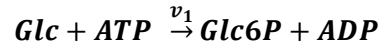
$$\begin{aligned}
\frac{d[Rib5P]}{dt} &= v_{25} - v_{27} \\
\frac{d[Xyl5P]}{dt} &= v_{26} - v_{27} - v_{29} \\
\frac{d[sed7P]}{dt} &= v_{27} - v_{28} \\
\frac{d[Ery4P]}{dt} &= v_{28} - v_{29} \\
\frac{d[ATP]}{dt} &= -v_1 - v_2 - v_4 + v_6 - v_7 - v_8 + v_{11} + v_{14} - v_{21} \\
\frac{d[ADP]}{dt} &= v_1 + v_2 + v_4 - v_6 + v_7 + 2v_8 - v_{11} - v_{14} + v_{21} \\
\frac{d[AMP]}{dt} &= -v_8
\end{aligned}$$

Where v_i is the metabolic flux of each enzymatic reaction and is represented by a kinetic expression.

Structure of the kinetic metabolic model

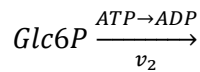
Kinetic expressions for intracellular reactions were adapted from literature, mainly those considered by Smallbone et al. [6] and Messiha et al. [7] due to its comprehensiveness including metabolic regulations and kinetic mechanisms for the different enzymatic reactions. Reactions for the intracellular cycling of reserve carbohydrates (i.e., glucose) were developed based on those following the reported in the study of Suarez-Mendez et al. [4].

Hexokinase



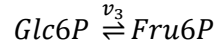
$$v_1 = \frac{v_{max}[Glc][ATP]}{K_{i,Glc} K_{ATP} \left(1 + \frac{[T6P]}{K_{T6P}}\right) + [Glc]K_{ATP} + [ATP]K_{Glc} \left(1 + \frac{[T6P]}{K_{T6P}}\right) + [Glc][ATP]}$$

Glc6P sink



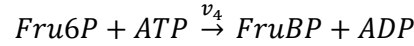
$$v_2 = k[Glc6P][ATP]$$

Glc6P isomerase



$$v_3 = [PGI] \frac{k_{cat} \left(\frac{[Glc6P]}{K_{Glc6P}} - \frac{[Fru6P]}{K_{Glc6P} K_{eq}} \right)}{1 + \frac{[Glc6P]}{K_{Glc6P}} + \frac{[Fru6P]}{K_{Fru6P}}}$$

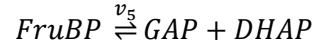
Phosphofructokinase



v_4

$$= \frac{[PFK] k_{cat} \frac{g_R [Fru6P]}{K_{Fru6P}} \frac{[ATP]}{K_{ATP}} \left(1 + \frac{[Fru6P]}{K_{Fru6P}} + \frac{[ATP]}{K_{ATP}} + \frac{g_R [Fru6P] [ATP]}{K_{Fru6P} K_{ATP}} \right)^3}{\left(1 + \frac{[Fru6P]}{K_{Fru6P}} + \frac{[ATP]}{K_{ATP}} + \frac{g_R [Fru6P] [ATP]}{K_{Fru6P} K_{ATP}} \right)^4 + L_0 \left(\frac{1 + \frac{c_{i,ATP} [ATP]}{K_{i,ATP}}}{1 + \frac{[ATP]}{K_{i,ATP}}} \right)^4 \left(\frac{1 + \frac{c_{i,AMP} [AMP]}{K_{i,AMP}}}{1 + \frac{[AMP]}{K_{i,AMP}}} \right)^4 \left(1 + \frac{c_{ATP} [ATP]}{K_{ATP}} \right)^4}$$

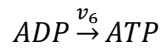
Fructose biphosphate aldolase



v_5

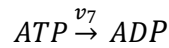
$$= \frac{V_1 V_2 \left([FruBP] - \frac{[GAP][DHAP]}{K_{eq}} \right)}{V_2 K_{FruBP} V_2 [FruBP] + \frac{V_1 K_{DHAP}}{K_{eq}} [GAP] + \frac{V_1 K_{GAP}}{K_{eq}} [DHAP] + \frac{V_2}{K_{i,GAP}} [FruBP][GAP] + \frac{V_1}{K_{eq}} [GAP][DHAP]}$$

ATP sintase



$$v_6 = k[ADP]$$

ATPase



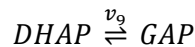
$$v_7 = \frac{\frac{v_{max}[ATP]}{K_{ATP}}}{1 + \frac{[ATP]}{K_{ATP}}}$$

Adenylate Kinase



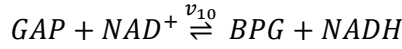
$$v_8 = k \left([AMP][ATP] - \frac{[ADP]^2}{K_{eq}} \right)$$

Triose phosphate isomerase



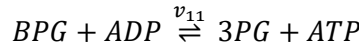
$$v_9 = \frac{\frac{[TPI]k_{cat}}{K_{DHAP}} \left([DHAP] - \frac{[GAP]}{K_{eq}} \right)}{1 + \frac{[DHAP]}{K_{DHAP}} + \frac{[GAP]}{K_{GAP}} \left(1 + \left(\frac{[GAP]}{K_{i,GAP}} \right)^4 \right)}$$

GAP dehydrogenase



$$v_{10} = \frac{[TDH]k_{cat} \left(\frac{[GAP][NAD]}{K_{GAP}K_{NAD}} - \frac{[BPG][NADH]}{K_{GAP}K_{NAD}K_{eq}} \right)}{\left(1 + \frac{[GAP]}{K_{GAP}} + \frac{[BPG]}{K_{BPG}} \right) \left(1 + \frac{[NAD]}{K_{NAD}} + \frac{[NADH]}{K_{NADH}} \right)}$$

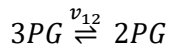
Phosphoglycerate kinase



$$v_{11} = \frac{V_1 V_2 \left([BPG][ADP] - \frac{[ATP][3PG]}{K_{eq}} \right)}{D}$$

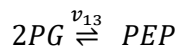
$$\begin{aligned} D = & K_{i,BPG}K_{ADP}V_2 + K_{ADP}V_2[BPG] + K_{BPG}V_2[ADP] + V_2[BPG][ADP] + \frac{K_{3PG}V_1[ATP]}{K_{eq}} + \frac{K_{ATP}V_1[3PG]}{K_{eq}} \\ & + \frac{V_1[ATP][3PG]}{K_{eq}} + \frac{K_{3PG}V_1[BPG][ATP]}{K_{i,BPG}K_{eq}} + \frac{K_{BPG}V_2[ADP][3PG]}{K_{i,3PG}} + \frac{V_2[BPG][ADP][ATP]}{K_{i,ATP}} \\ & + \frac{V_1[ADP][ATP][3PG]}{K_{i,ADP}k_{eq}} \end{aligned}$$

Phosphoglycerate mutase



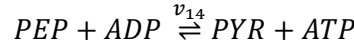
$$v_{12} = \frac{[GPM]k_{cat} \left(\frac{[3PG]}{K_{3PG}} - \frac{[2PG]}{K_{3PG}K_{eq}} \right)}{1 + \frac{[3PG]}{K_{3PG}} + \frac{[2PG]}{K_{2PG}}}$$

Enolase



$$v_{13} = \frac{[ENO]k_{cat} \left(\frac{[2PG]}{K_{2PG}} - \frac{[PEP]}{K_{2PG}K_{eq}} \right)}{1 + \frac{[2PG]}{K_{2PG}} + \frac{[PEP]}{K_{PEP}}}$$

Piruvate kinase



$$v_{14} = v_{max} \frac{g_R \alpha_1 \alpha_2 R^{n-1}}{R^n + LT^n}$$

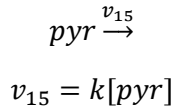
$$\alpha_1 = \frac{[PEP]}{K_{PEP}}, \alpha_2 = \frac{[ADP]}{K_{ADP}}$$

$$R = 1 + \alpha_1 + \alpha_2 + g_R \alpha_1 \alpha_2$$

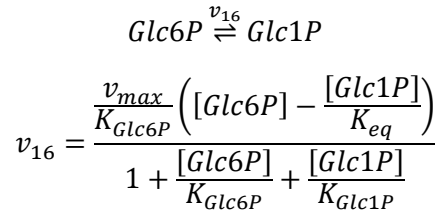
$$T = 1 + c_2 \alpha_2$$

$$L = L_0 \left(\frac{1 + \frac{c_{i,ATP}[ATP]}{K_{i,ATP}}}{1 + \frac{[ATP]}{K_{i,ATP}}} \right)^n \left(\frac{1 + \frac{c_{i,FruBP}[FruBP]}{K_{i,FruBP}}}{1 + \frac{[FruBP]}{K_{i,FruBP}}} \right)^n$$

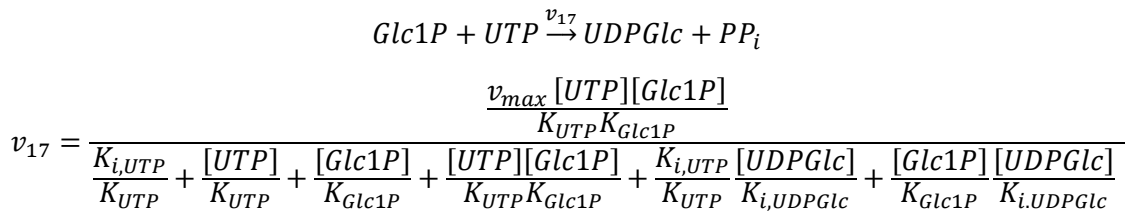
Piruvate sink



Phosphoglucomutase



UDPGlc phosphorilase



T6P syntase

$$UDPGlc + Glc6P \xrightarrow{v_{18}} T6P + UDP$$
$$v_{18} = \frac{v_{max}[UDPGlc][Glc6P]}{K_{i,UDPGlc}K_{Glc6P} + K_{Glc6P}[UDPGlc] + [UDPGlc][Glc6P]}$$

T6P phosphatase

$$T6P \xrightarrow{v_{19}} P_i + Treh$$
$$v_{19} = \frac{V_1V_2[T6P]}{K_{T6P}V_2 + V_2[T6P] + \frac{K_{P_i}V_1[Treh]}{K_{eq}}}$$

Trehalase

$$Treh \xrightarrow{v_{20}} 2 Glc$$
$$v_{20} = \frac{V_1V_2\left([Treh] - \frac{[Glc]^2}{K_{eq}}\right)}{K_{Treh}V_2 + V_2[Treh] + 2\frac{K_{Glc}V_1[Glc]}{K_{eq}} + \frac{V_1[Glc]^2}{K_{eq}} + \frac{V_2[Treh][Glc]}{K_{i,Glc}}}$$

Diphosphate kinase

$$UDP + ATP \xrightarrow{v_{21}} UTP + ADP$$
$$v_{21} = k[UDP][ATP]$$

Glc6P dehydrogenase

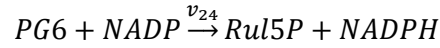
$$Glc6P + NADP \xrightarrow{v_{22}} PGL6 + NADPH$$
$$v_{22} = \frac{[ZWF]k_{cat}[Glc6P][NADP]}{K_{Glc6P}K_{NADP}\left(1 + \frac{[Glc6P]}{K_{Glc6P}} + \frac{[PGL6]}{K_{PGL6}}\right)\left(1 + \frac{[NADP]}{K_{NADP}} + \frac{[NADPH]}{K_{NADPH}}\right)}$$

6-phosphogluconolactonase

$$PGL6 \xrightarrow{v_{23}} PG6$$

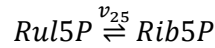
$$v_{23} = \frac{[SOL]k_{cat}[PGL6]}{K_{PGL6} \left(1 + \frac{[PGL6]}{K_{PGL6}} + \frac{[PG6]}{K_{PG6}} \right)}$$

PG6 dehydrogenase



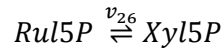
$$v_{24} = \frac{[GND]k_{cat}[PG6][NADP]}{K_{PG6}K_{NADP} \left(1 + \frac{[PG6]}{K_{PG6}} + \frac{[Rul5P]}{K_{Rul5P}} \right) \left(1 + \frac{[NADP]}{K_{NADP}} + \frac{[NADPH]}{K_{NADPH}} \right)}$$

Rib5P isomerase



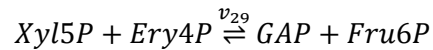
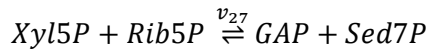
$$v_{25} = \frac{[RKI]k_{cat} \left([Rul5P] - \frac{[Rib5P]}{K_{eq}} \right)}{K_{Rul5P} \left(1 + \frac{[Rul5P]}{K_{Rul5P}} + \frac{[Rib5P]}{K_{Rib5P}} \right)}$$

Rul5P epimerase



$$v_{26} = \frac{[RPE]k_{cat} \left([Rul5P] - \frac{[Xyl5P]}{K_{eq}} \right)}{K_{Rul5P} \left(1 + \frac{[Rul5P]}{K_{Rul5P}} + \frac{[Xyl5P]}{K_{Xyl5P}} \right)}$$

Transketolase



$$v_{27} = \frac{[TKL]k_{cat} \left([Xyl5P][Rib5P] - \frac{[GAP][Sed7P]}{K_{eq}} \right)}{K_{Xyl5P}K_{Rib5P} \left(1 + \frac{[Xyl5P]}{K_{Xyl5P}} + \frac{[GAP]}{K_{GAP}} \right) \left(1 + \frac{[Ery4P]}{K_{Ery4P}} + \frac{[Fru6P]}{K_{Fru6P}} + \frac{[Rib5P]}{K_{Rib5P}} + \frac{[Sed7P]}{K_{Sed7P}} \right)}$$

$$v_{29} = \frac{[TKL]k_{cat} \left([Xyl5P][Ery4P] - \frac{[GAP][Fru6P]}{K_{eq}} \right)}{K_{Xyl5P}K_{Ery4P} \left(1 + \frac{[Xyl5P]}{K_{Xyl5P}} + \frac{[GAP]}{K_{GAP}} \right) \left(1 + \frac{[Ery4P]}{K_{Ery4P}} + \frac{[Fru6P]}{K_{Fru6P}} + \frac{[Rib5P]}{K_{Rib5P}} + \frac{[Sed7P]}{K_{Sed7P}} \right)}$$

Transaldolase

$$GAP + Sed7P \xrightleftharpoons{v_{28}} Fru6p + Ery4P$$

$$v_{28} = \frac{[TAL]k_{cat} \left([GAP][Sed7P] - \frac{[Fru6P][Ery4P]}{K_{eq}} \right)}{K_{GAP}K_{Sed7P} \left(1 + \frac{[GAP]}{K_{GAP}} + \frac{[Fru6P]}{K_{Fru6P}} \right) \left(1 + \frac{[Sed7P]}{K_{Sed7P}} + \frac{[Ery4P]}{K_{Ery4P}} \right)}$$

Glycogenin

$$glg + UDPGlc \xrightleftharpoons{v_{30}} (\alpha_{1,4} glucosil)_n + UDP$$

$$v_{30} = k[UDPGlc][Glg]$$

Glycogen synthase

$$(\alpha_{1,4} glucosil)_n + UDPGlc \xrightleftharpoons{v_{31}} (\alpha_{1,4} glucosil)_{n+1} + UDP$$

$$v_{31} = \frac{v_{max}}{\frac{L}{(1+\gamma)^4} + (1+\alpha)^4}; \alpha = \frac{[UDPGlc]}{K_{UDPGlc}}, \gamma = \frac{[Glc6P]}{K_{Glc6P}}$$

Branching enzyme

$$n(\alpha_{1,4} glucosil)_7 + (\alpha_{1,4} glucosil)_{n+1} \xrightleftharpoons{v_{32}} glyco_n$$

$$v_{32} = k[(\alpha_{1,4} glucosil)_{n+1}]$$

Glycogen phosphorylase

$$glyco_n(\alpha_{1,4}) + P_i \xrightleftharpoons{v_{33}} Glc1P + glyco_{n-1}$$

$$v_{33} = v_{max} \frac{\alpha(1+\alpha)}{L(1+\beta)^2 + (1+\alpha)^2}; \alpha = \frac{[Glyco]}{K_{Glyco}}, \beta = \frac{[Glc6P]}{K_{Glc6P}}$$

Debranching enzyme

$$glyco_n(\alpha_{1,6}) \xrightleftharpoons{v_{34}} glyco_{n-1} + Glc$$

$$v_{34} = k[glyco]$$

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