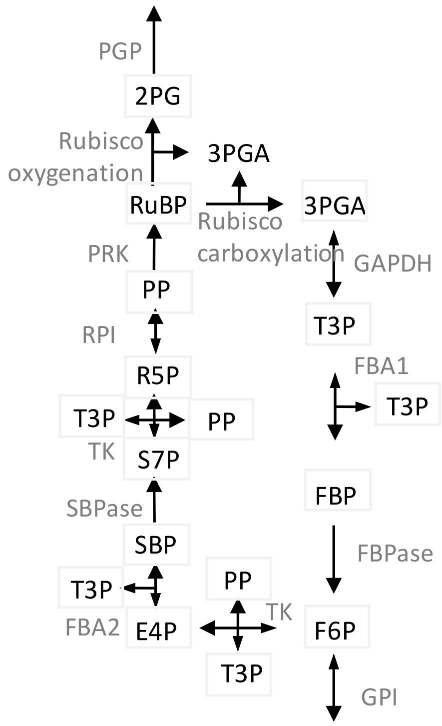
Constraint-based Modeling of Cellular Networks

Exercise 4 – Metabolic models

10. 11. 2022

Mathematical representation of metabolic network as system of ODEs

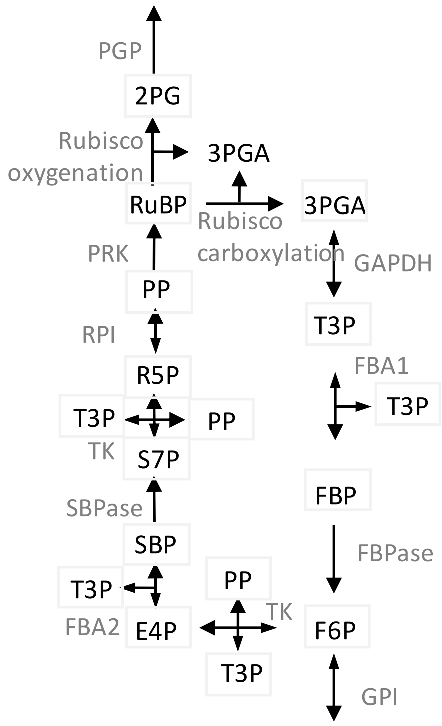


Let us buid the stoichiometric matrix ...

Q1: What is in the rows? What is in the columns?

Q2: What is the dimension of the stoichiometric matrix?

Mathematical representation of metabolic network as system of ODEs



Let us buid the stoichiometric matrix ...

Q1: What is in the rows? What is in the columns?

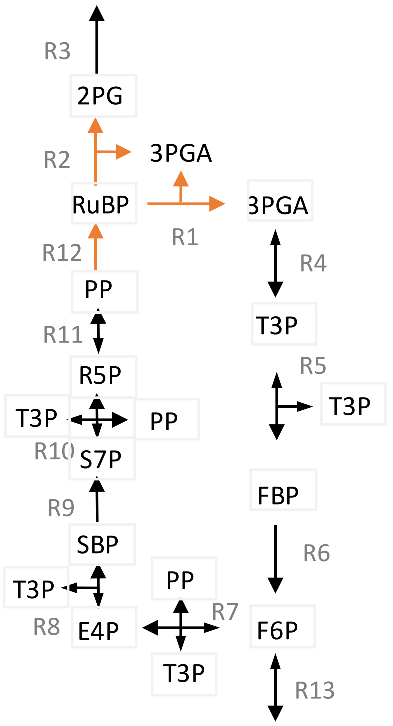
Q2: What is the dimension of the stoichiometric matrix?

Number of rows = number of metabolites

Number of columns = number of reactions

-> 11 x 13 matrix

Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

$$
\begin{array}{cccccccccccccc}
R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 & R11 & R12 & R13 & \\
\end{array}
$$

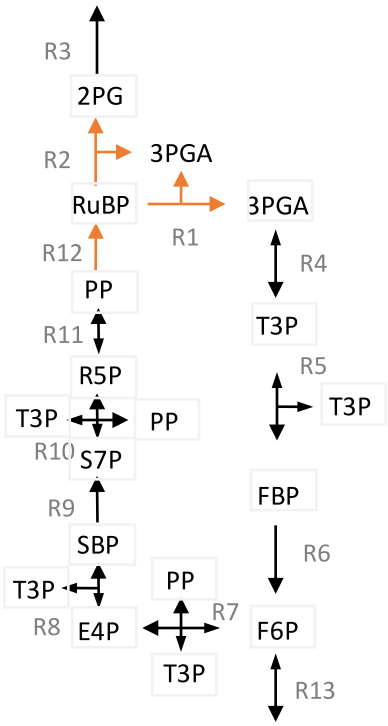
$$
S = \left[\begin{array}{ccccccccccccc}
 & & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 0 \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & & \\
 & & & & & & & & & & & &
\end{array}\right]
\begin{array}{c}
RuBP \\ 3PGA \\ 2PG \\ T3P \\ FBP \\ F6P \\ E4P \\ SBP \\ S7P \\ R5P \\ PP
\end{array}
$$

producing rxns - consuming rxns

$$
\frac{dRuBP}{dt} = R12 - R1 - R2
$$

Q: What are the coefficients we have to put in S?

Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

$$S = \begin{array}{c} \begin{matrix} R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 & R11 & R12 & R13 \end{matrix} \\ \begin{bmatrix} -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{bmatrix} \end{array} \begin{matrix} \\ RuBP \\ 3PGA \\ 2PG \\ T3P \\ FBP \\ F6P \\ E4P \\ SBP \\ S7P \\ R5P \\ PP \end{matrix}$$

producing rxns - consuming rxns

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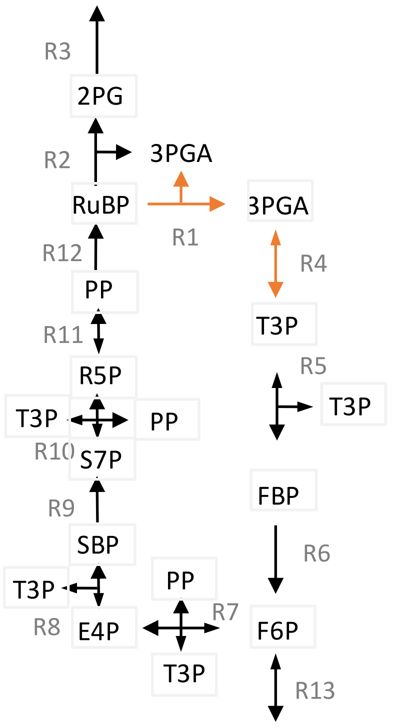
Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

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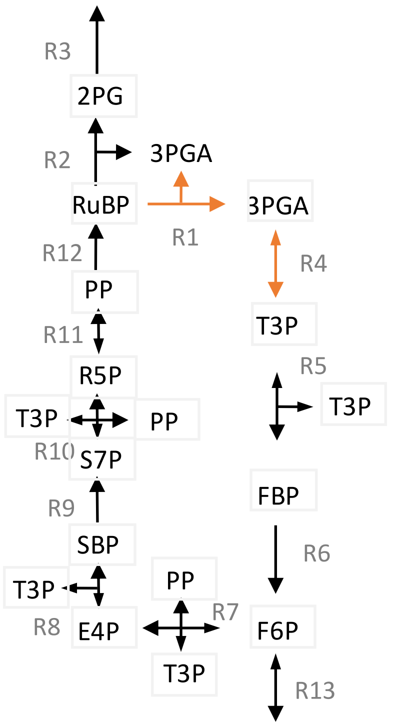
producing rxns - consuming rxns

$$\frac{dRuBP}{dt} = R12 - R1 - R2$$

$$\frac{d3PGA}{dt} = 2*R1 + R2 - R4$$

Q: What are the coefficients we have to put in S?

Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

$$
S = \begin{array}{c} \\ \\ \end{array}
\begin{array}{ccccccccccccc|l}
R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 & R11 & R12 & R13 & \\
\hline
-1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & RuBP \\
2 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 3PGA \\
 & & & & & & & & & & & & & 2PG \\
 & & & & & & & & & & & & & T3P \\
 & & & & & & & & & & & & & FBP \\
 & & & & & & & & & & & & & F6P \\
 & & & & & & & & & & & & & E4P \\
 & & & & & & & & & & & & & SBP \\
 & & & & & & & & & & & & & S7P \\
 & & & & & & & & & & & & & R5P \\
 & & & & & & & & & & & & & PP
\end{array}
$$

producing rxns - consuming rxns

$$\frac{dRuBP}{dt} = R12 - R1 - R2$$

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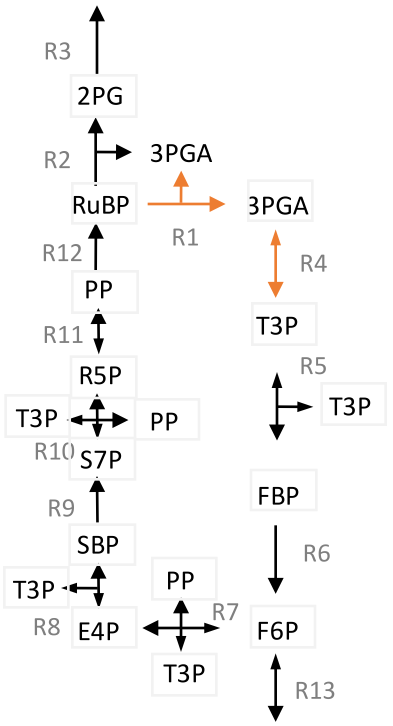
Mathematical representation of metabolic network as system of ODEs



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\left[\begin{array}{ccccccccccccc}
-1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
2 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -2 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & -1 & 0
\end{array}\right]
\end{array}
\begin{array}{l} \\ RuBP \\ 3PGA \\ 2PG \\ T3P \\ FBP \\ F6P \\ E4P \\ SBP \\ S7P \\ R5P \\ PP \end{array}
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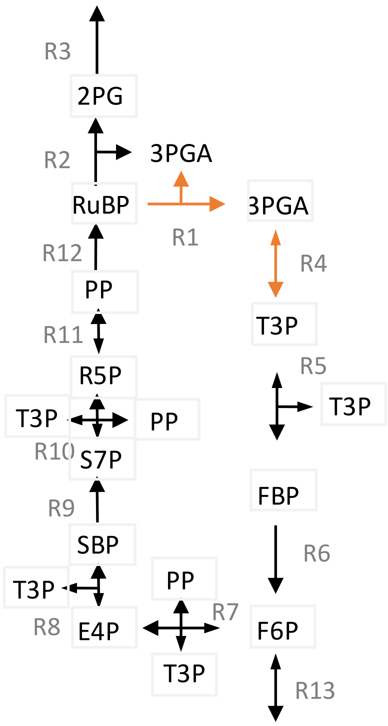
Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

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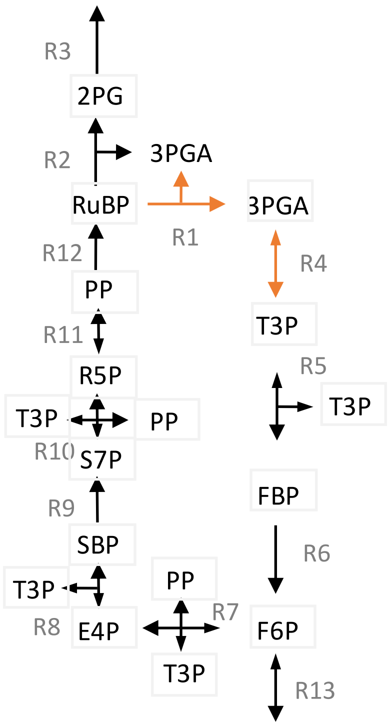
S = \begin{array}{c}
\begin{array}{ccccccccccccc} R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 & R11 & R12 & R13 \end{array} \\
\left[\begin{array}{ccccccccccccc}
-1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
2 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -2 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & -1 & 0
\end{array}\right]
\end{array}
\begin{array}{c} \\ RuBP \\ 3PGA \\ 2PG \\ T3P \\ FBP \\ F6P \\ E4P \\ SBP \\ S7P \\ R5P \\ PP \end{array}
$$

Looking at a row we know the molarity with which a metabolite is produced (positive value) or consumed (negative value) by each reaction in the system

Mathematical representation of metabolic network as system of ODEs



Number of rows = number of metabolites, Number of columns = number of reactions, 11 x 13 matrix

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S = \begin{array}{c}
\begin{array}{ccccccccccccc} R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 & R11 & R12 & R13 \end{array} \\
\begin{bmatrix}
-1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
2 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & -2 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\
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0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\
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0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & -1 & 0
\end{bmatrix}
\end{array}
\begin{array}{l} \\ RuBP \\ 3PGA \\ 2PG \\ T3P \\ FBP \\ F6P \\ E4P \\ SBP \\ S7P \\ R5P \\ PP \end{array}
$$

- Looking at a column we directly see the substrates (negative values) and products (positive values) of a reaction

- And molarity with which a metabolite enters the reaction

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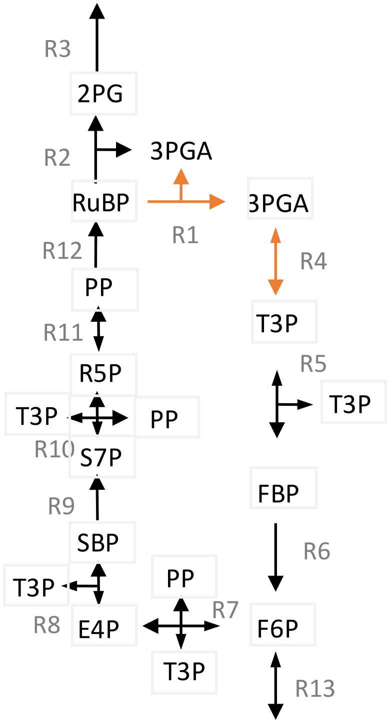

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Reactions that only consume or only produce metabolites are called **exchange reactions**

- Import reaction if it produces a metabolite
- Export reaction if it consumes a metabolite

Reaction reversibility

Irreversible

upper bound > 0 and lower bound = 0

lower bound < 0 and upper bound = 0

$$A \xrightarrow{r_1} B$$

Reversible

Reactions with upper bound > 0 and lower bound < 0

$$A \xleftrightarrow{r_1} B$$

Reaction reversibility

Irreversible

upper bound > 0 and lower bound = 0

lower bound < 0 and upper bound = 0

$$A \xrightarrow{r_1} B \qquad N = \begin{array}{cc} r_1 & \\ \begin{bmatrix} -1 \\ 1 \end{bmatrix} & \begin{array}{c} A \\ B \end{array} \end{array}$$

Reversible

Reactions with upper bound > 0 and lower bound < 0

$$A \xleftrightarrow{r_1} B \qquad N = \begin{array}{cc} r_1 & \\ \begin{bmatrix} -1 \\ 1 \end{bmatrix} & \begin{array}{c} A \\ B \end{array} \end{array}$$

No difference in stoichiometry!

Reversibility is defined over lower and upper bound values.

Q: Given a reversible reaction. How can we write it as two irreversible reactions?

Reaction reversibility

Irreversible

upper bound > 0 and lower bound = 0

lower bound < 0 and upper bound = 0

$$A \xrightarrow{r_1} B \qquad N = \begin{array}{cc} r_1 & \\ \begin{bmatrix} -1 \\ 1 \end{bmatrix} & \begin{matrix} A \\ B \end{matrix} \end{array}$$

Reversible

Reactions with upper bound > 0 and lower bound < 0

$$A \xleftrightarrow{r_1} B \qquad N = \begin{array}{cc} r_1 & \\ \begin{bmatrix} -1 \\ 1 \end{bmatrix} & \begin{matrix} A \\ B \end{matrix} \end{array}$$

No difference in stoichiometry!

Reversibility is defined over lower and upper bound values.

Q: Given a reversible reaction. How can we write it as two irreversible reactions?

$$r_1 = r_{1f} - r_{1b}$$

→ Add a new reaction with opposite signs to the stoichiometric matrix

$$A \xrightarrow{r_{1f}} B \qquad B \xrightarrow{r_{1b}} A$$