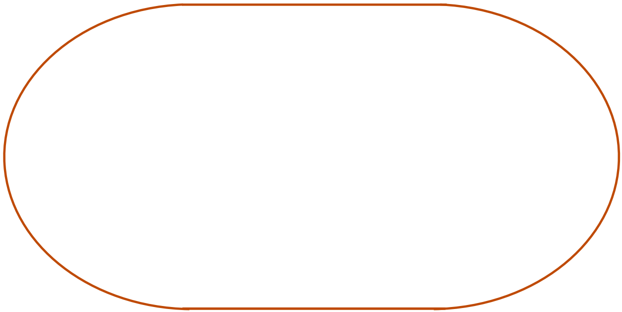
Innotargets Modelling Workshop June 2023

Mark Poolman

May 25, 2023

The Problem



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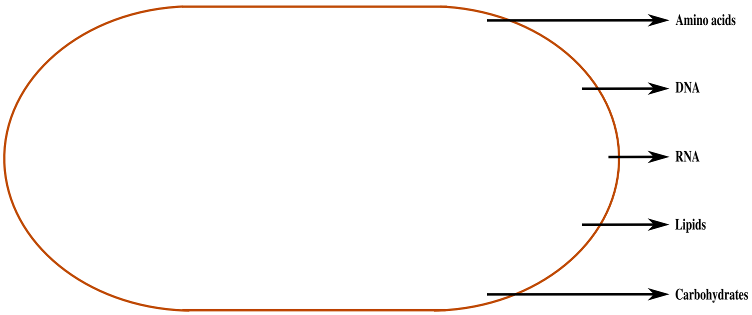

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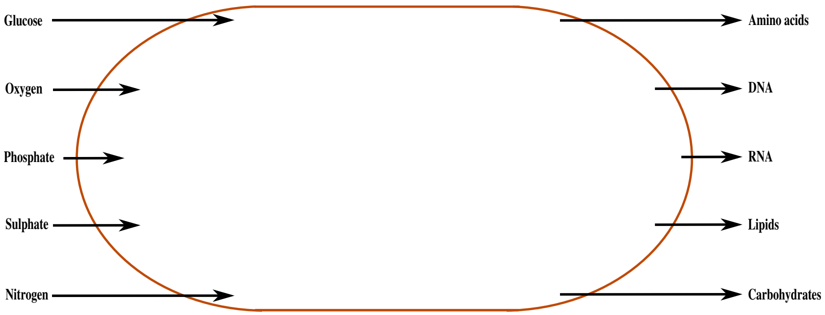
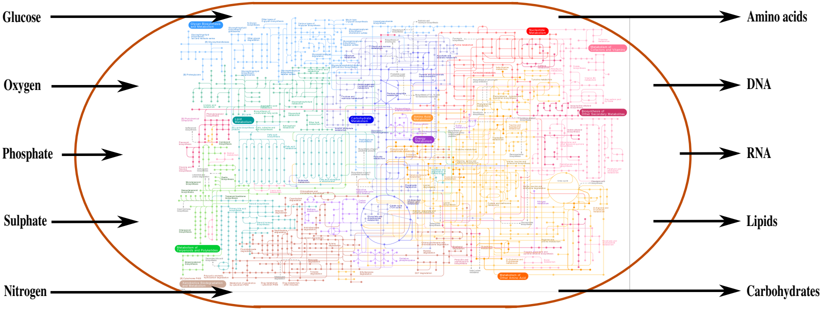

Glucose
Oxygen
Phosphate
Sulphate
Nitrogen
Amino acids
DNA
RNA
Lipids
Carbohydrates

The Problem



How to connect input(s) to output(s) ??

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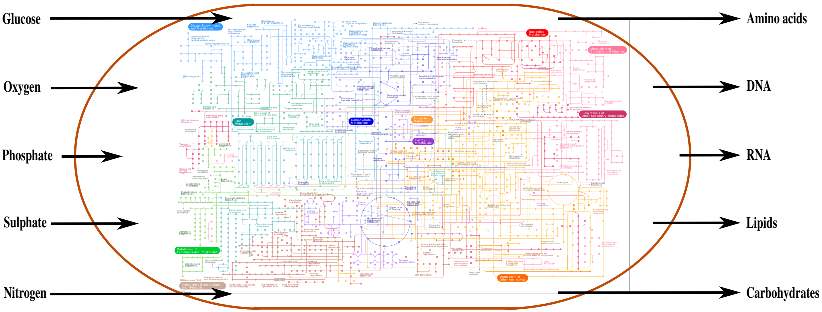


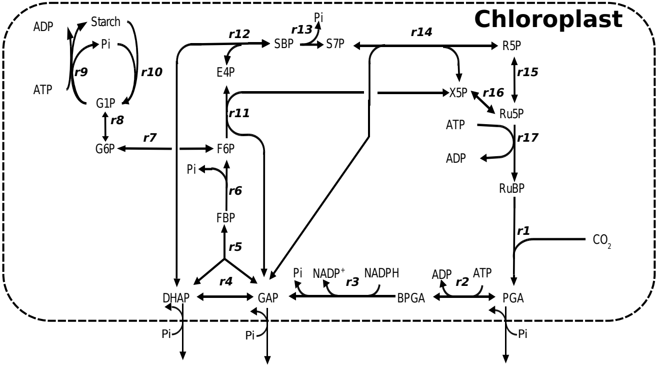
How to connect input(s) to output(s) ??

Motivation

What do we want to know - can we:

- Predict network behaviour (assign fluxes to reactions)?
- Predict the effect of network modification?
- Predict the modification needed to achieve a specific effect?

The Problem



- Which reactions are essential?
- What does knowledge of flux in one reaction tell us about flux in another?
- What does knowledge of one metabolite concentration tell us about the concentration of another?
- What are the routes from Starch to PGA?

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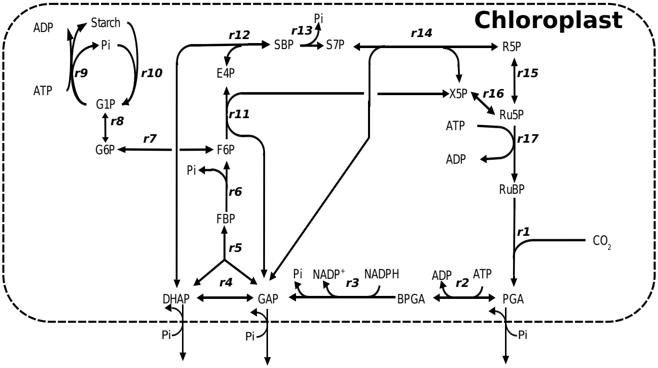

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Definition of a metabolic model

1. A set of *External* metabolites - inputs and outputs.
2. A set of *Internal* metabolites - no net production or consumption.
3. A set of reactions that inter-convert them defined by:
   - Stoichiometry.
   - Directionality.
   - Reversibility.

Fundamental assumptions

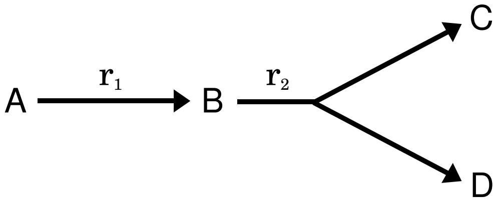
- Reactions interconvert substrates and products whilst conserving mass.
- Transporters are a special case of reaction (interconvert internal with external metabolites)
- Rate of change concentration is sum of reaction rates.
- This is assumed to tend to zero in the long term (steady state)

Note

- Reactions are not enzymes.

- Enzymes are not genes.

Modelling networks of reactions — Example One



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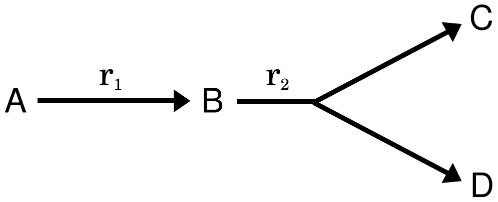

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$$\frac{\mathrm{d}A}{\mathrm{d}t} = -r_1$$

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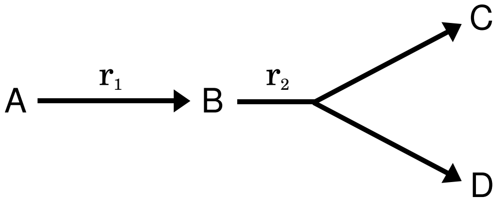

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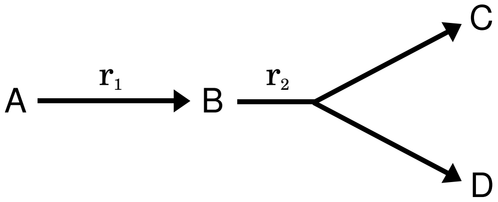


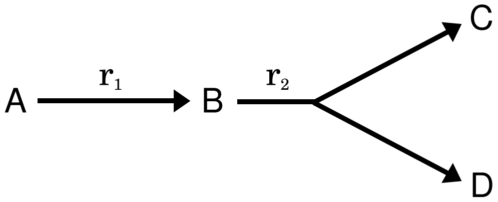
results in:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = -r_1$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = r_1 - r_2$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = r_2$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = r_2$$



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$$\frac{dA}{dt} = -r_1$$
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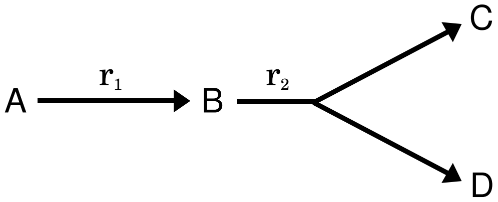
$$\frac{dD}{dt} = r_2$$

$$\begin{pmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \\ \frac{dD}{dt} \end{pmatrix} = \underbrace{\begin{pmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix}}_{\textit{stoichiometry matrix}} \begin{pmatrix} r_1 \\ r_2 \end{pmatrix}$$



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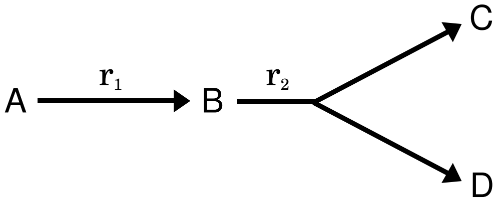

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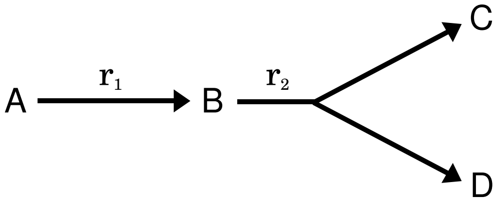
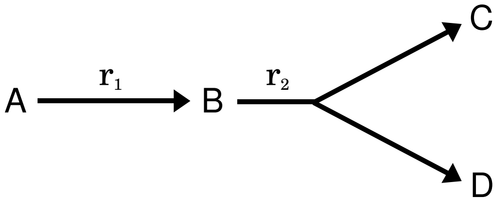


The steady-state assumption:

$$\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} r_1 \\ r_2 \end{pmatrix}$$



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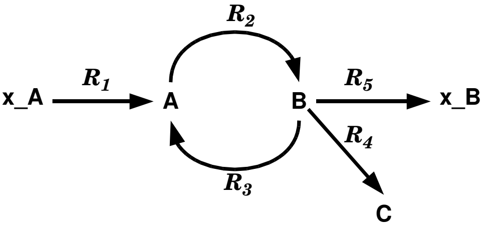
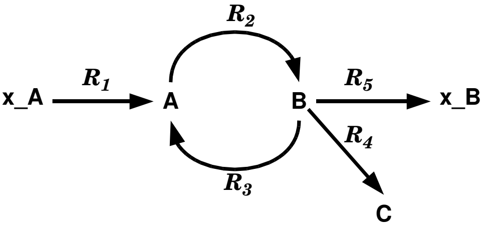


$$\frac{dA}{dt} = R_1 + R_3 - R_2$$
$$\frac{dB}{dt} = R_2 - R_3 - R_4 - R_5$$
$$\frac{dC}{dt} = R_4$$

Modelling networks of reactions — Example Two



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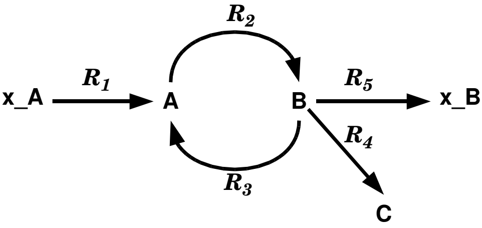
Modelling networks of reactions

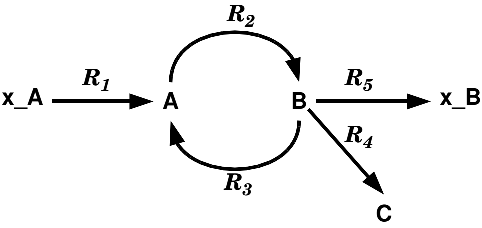


$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Or more succinctly:

$$\mathbf{Nv} = \mathbf{0}$$

Modelling networks of reactions



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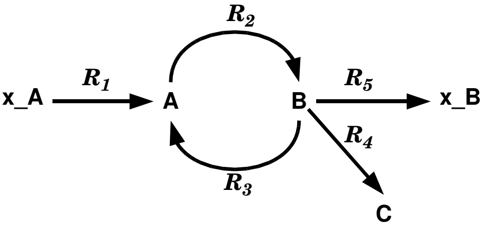

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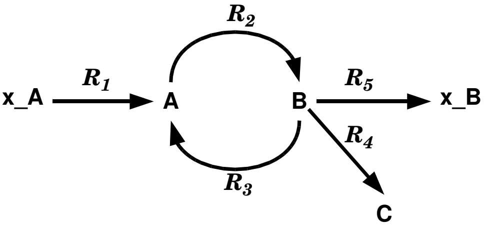

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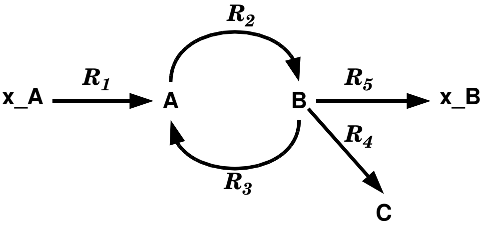
Null-space



$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix} \longleftarrow \text{subset} \\ \\ \\ \longleftarrow \text{dead} \\ \longleftarrow \text{subset} \end{matrix}$$

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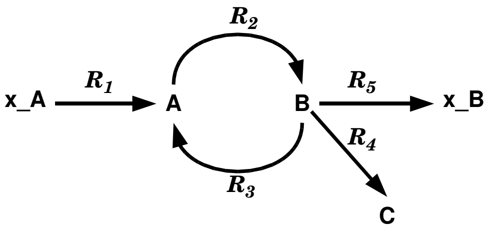

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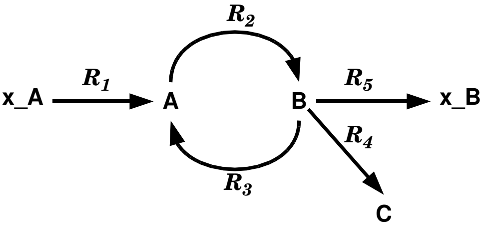

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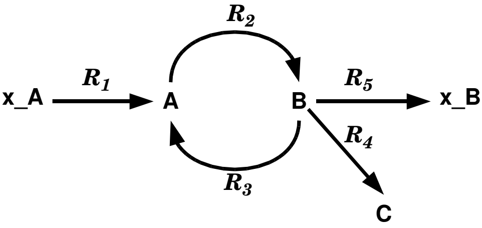

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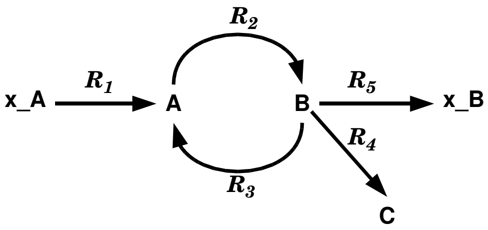

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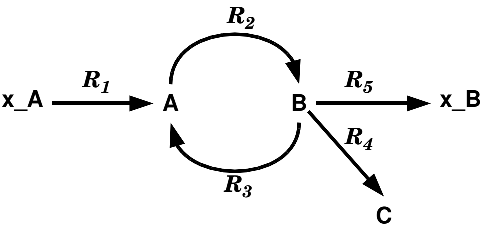

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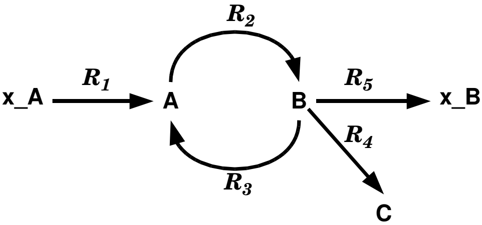
Significance of the null-space

- The null-space captures steady-state invariants of a network that are independent of environment, metabolite levels etc.
- A dead reaction will *always* be dead regardless of kinetic parameters.
- Reactions in subsets carry steady-state flux in fixed ratio regardless of kinetic parameters.

Kernels are not unique



$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \quad OR \quad \mathbf{K} = \begin{bmatrix} 1 & 1 \\ 1 & 0 \\ 0 & -1 \\ 0 & 0 \\ 1 & 1 \end{bmatrix}$$

$$\mathbf{E} = \begin{bmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & -1 & 1 \\ 0 & 0 & 0 \\ 1 & 1 & 0 \end{bmatrix}$$

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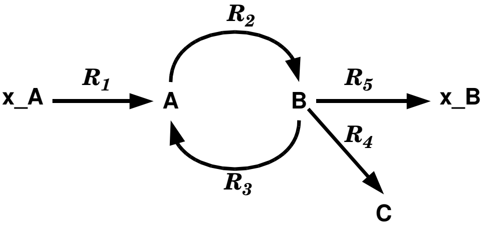

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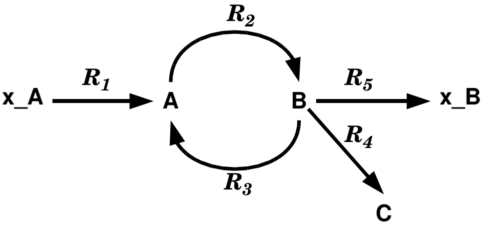

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So Now ...

We have an understanding of how metabolic behaviour can be mathematically described.