Innotargets Modelling Workshop Pune 2024

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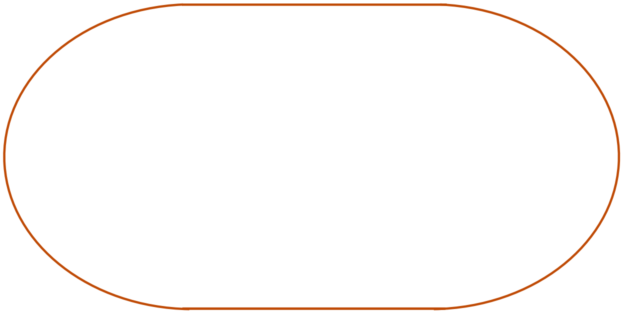
September 17, 2024

The Problem



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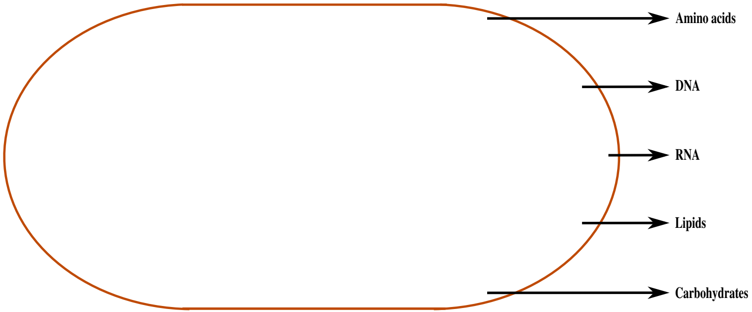

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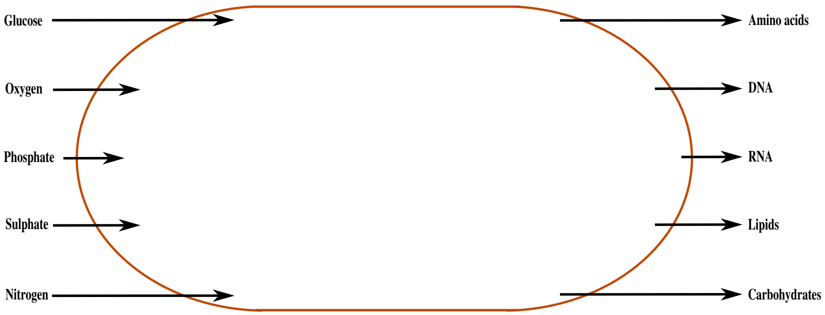
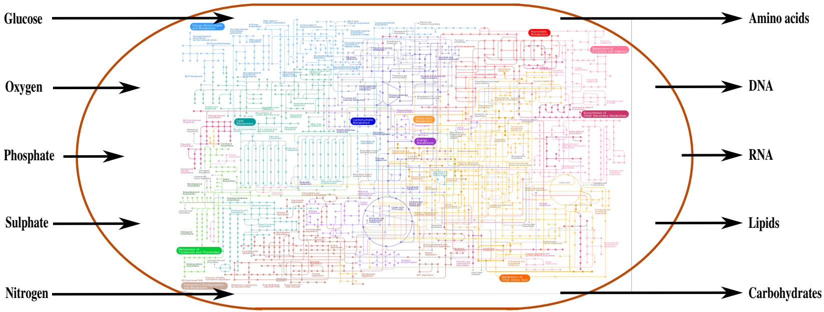
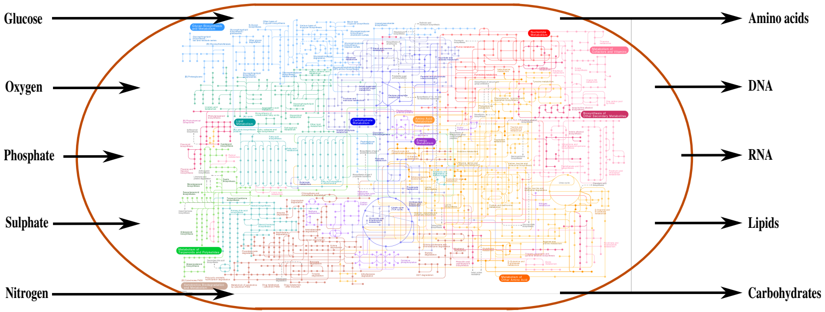

Glucose
Oxygen
Phosphate
Sulphate
Nitrogen
Amino acids
DNA
RNA
Lipids
Carbohydrates

The Problem



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

The Problem



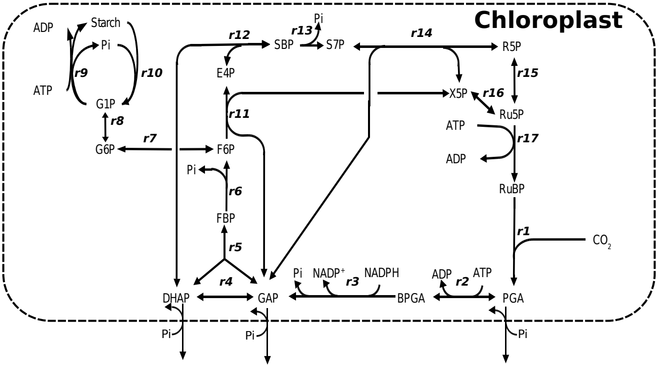
How to connect input(s) to output(s) ??

Motivation

What do we want to know - can we:

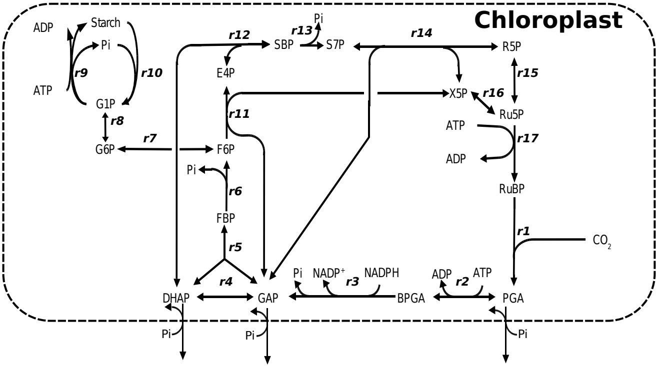
- Predict network behaviour (assign fluxes to reactions)?
- Predict the effect of network modification?
- Predict the modification needed to achieve a specific effect?

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?

The Problem



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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.

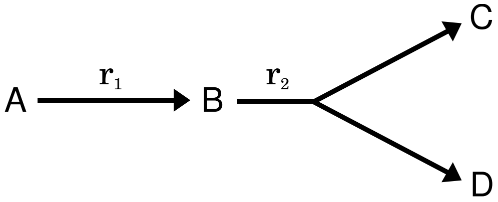
Fundamental assumptions

- 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)

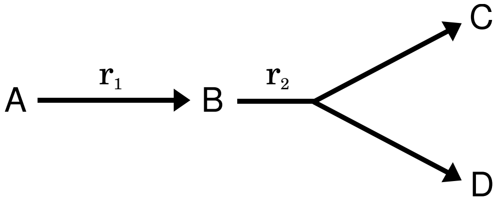
Note

- Reactions are not enzymes.
- Enzymes are not genes.

Modelling networks of reactions — Example One



Modelling networks of reactions — Example One



results in:

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

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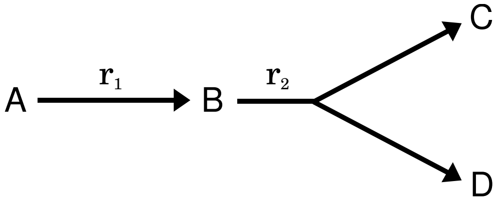

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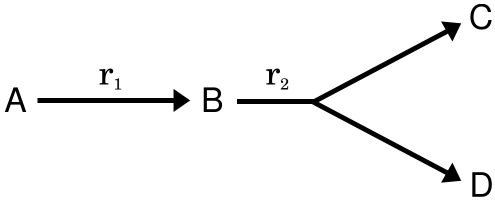
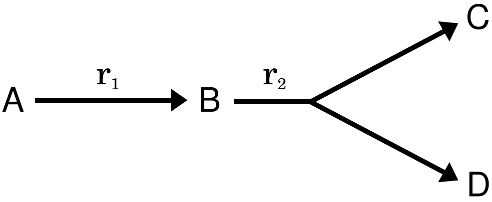


results in:

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

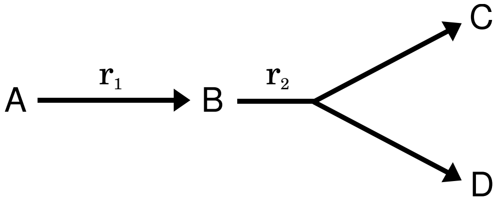


results in:

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

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

Modelling networks of reactions — Example One



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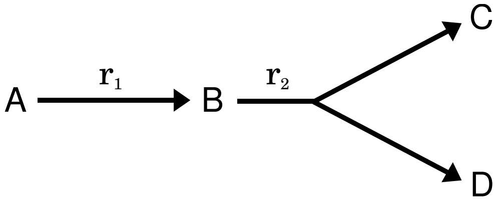

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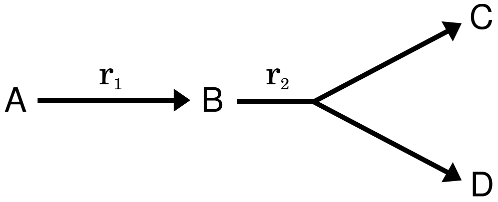

The steady-state assumption:

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

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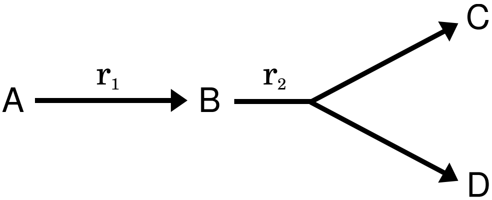

The steady-state assumption:

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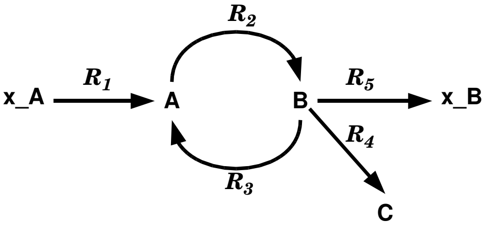
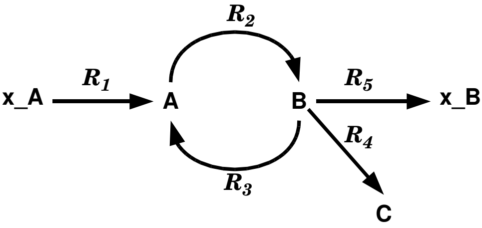
Modelling networks of reactions — Example Two



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

Modelling networks of reactions — Example Two



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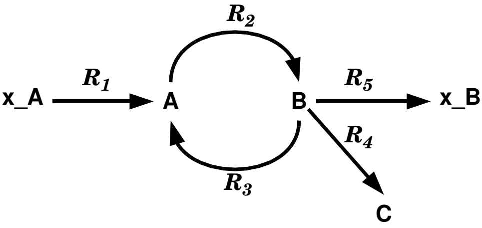

$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Or more succinctly:

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

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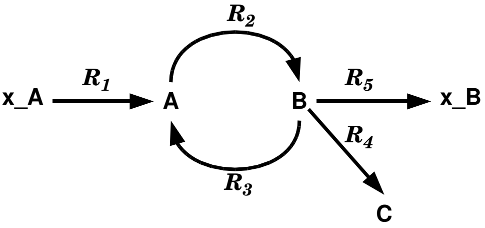

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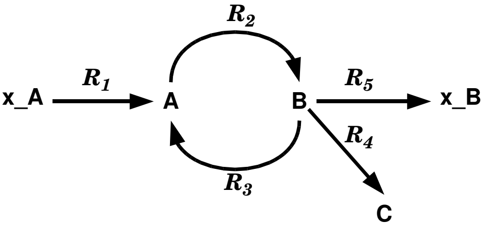

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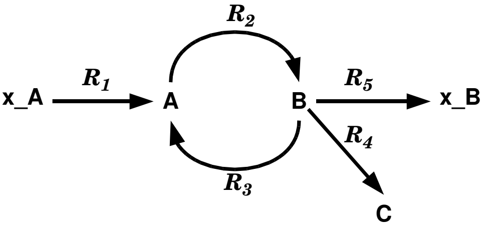

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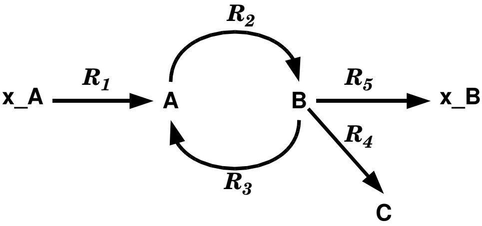
Null-space



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

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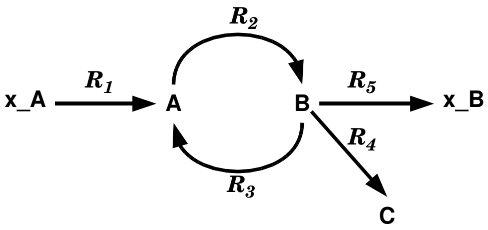

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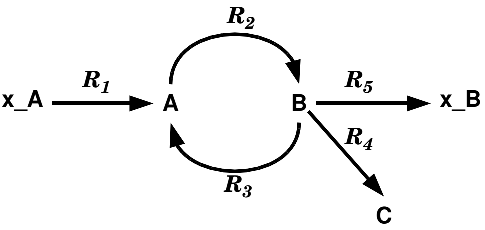

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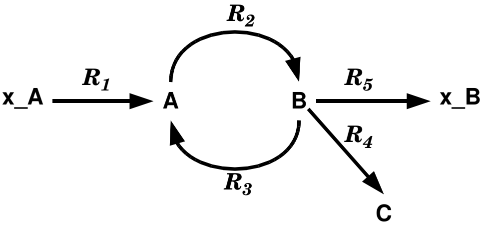

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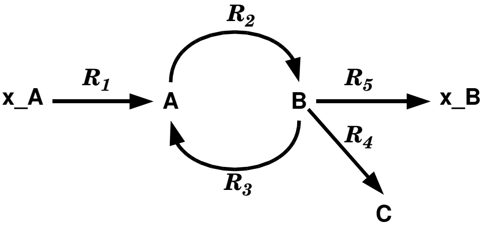

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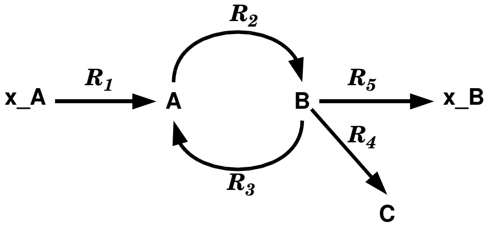

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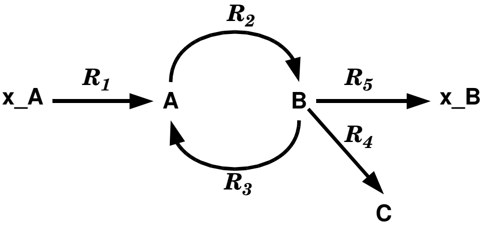
Significance of the null-space

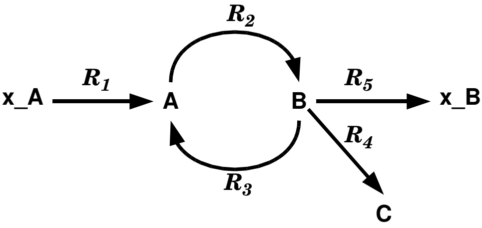
- The null-space captures steady-state invariants of a network that are independent of environment, metabolite levels etc.
- A dead reaction will *always* be dead regardless of kinetic parameters.
- Reactions in subsets carry steady-state flux in fixed ratio regardless of kinetic parameters.



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

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

Kernels are not unique



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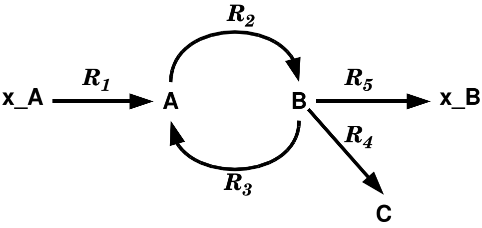

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So Now ...

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