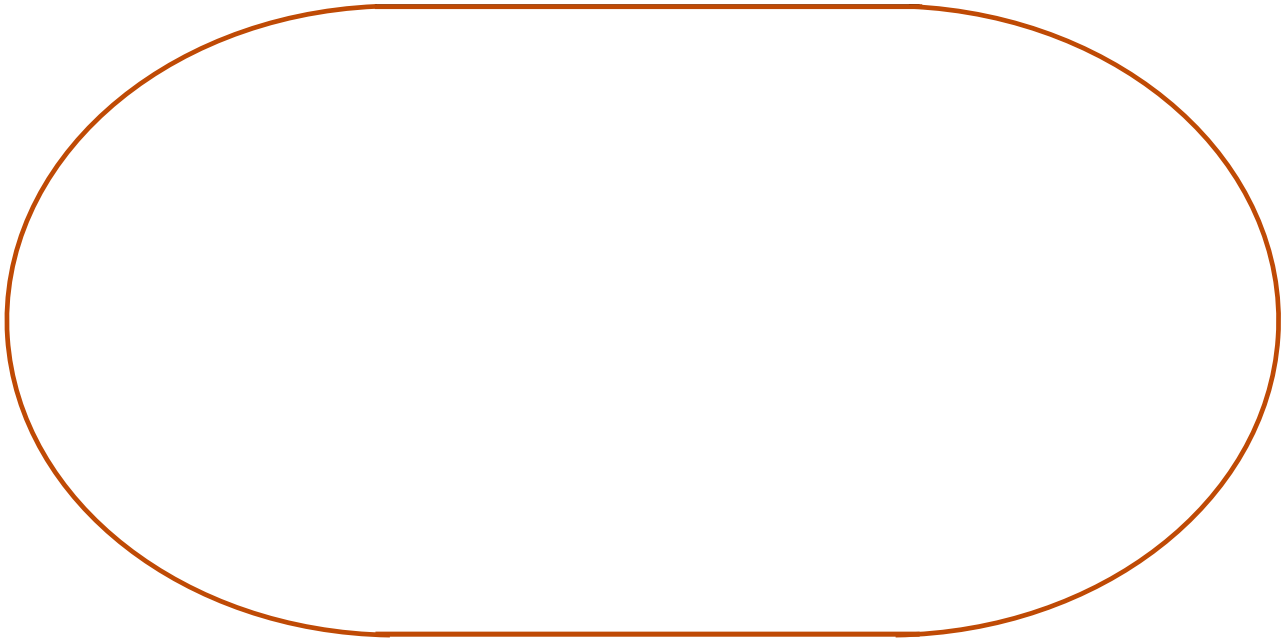
Null Space, Subsets, Elementary Modes and Conserved Cycles Nottingham 2022

Mark Poolman

May 18, 2023

Recap - The Problem



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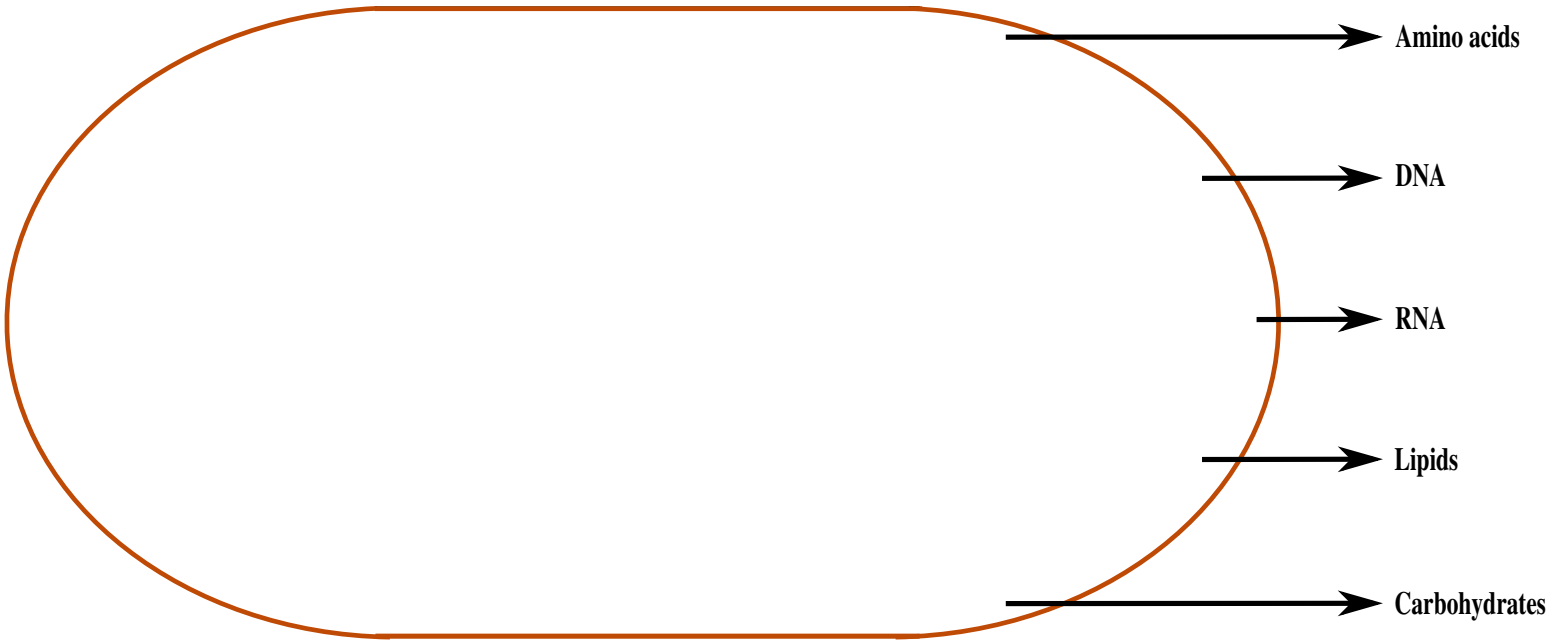

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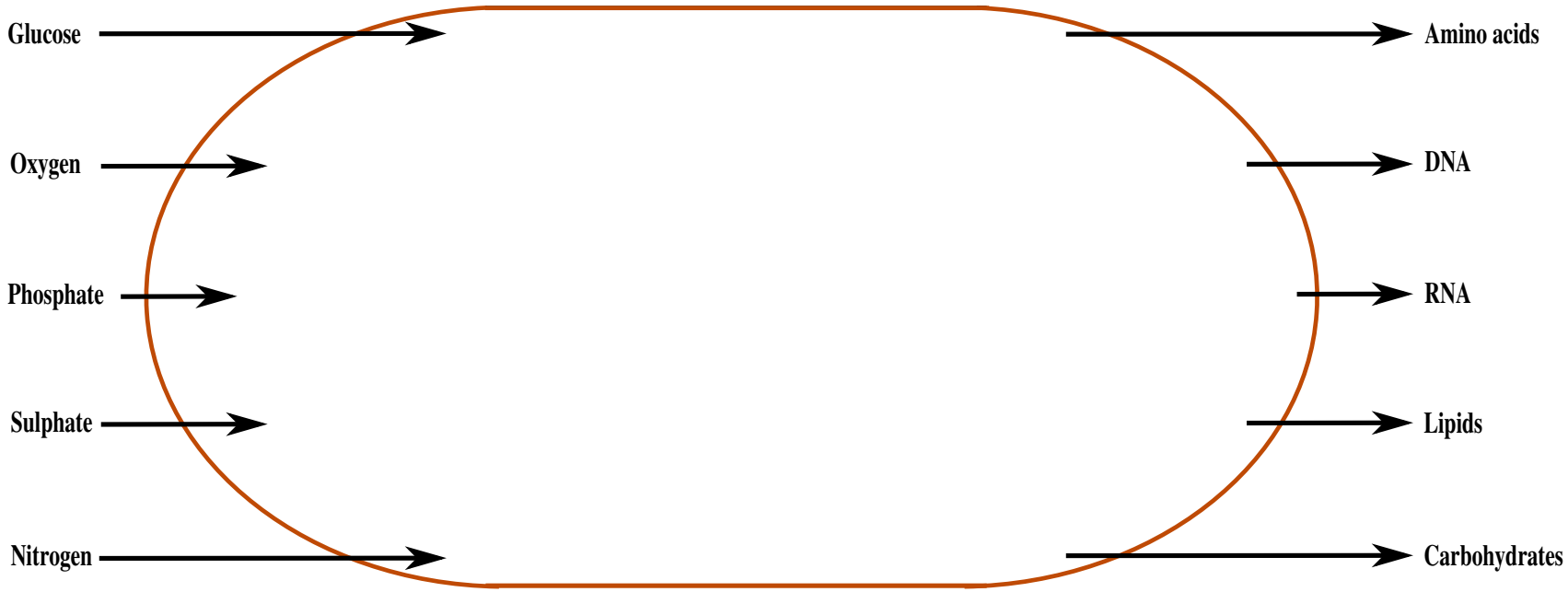

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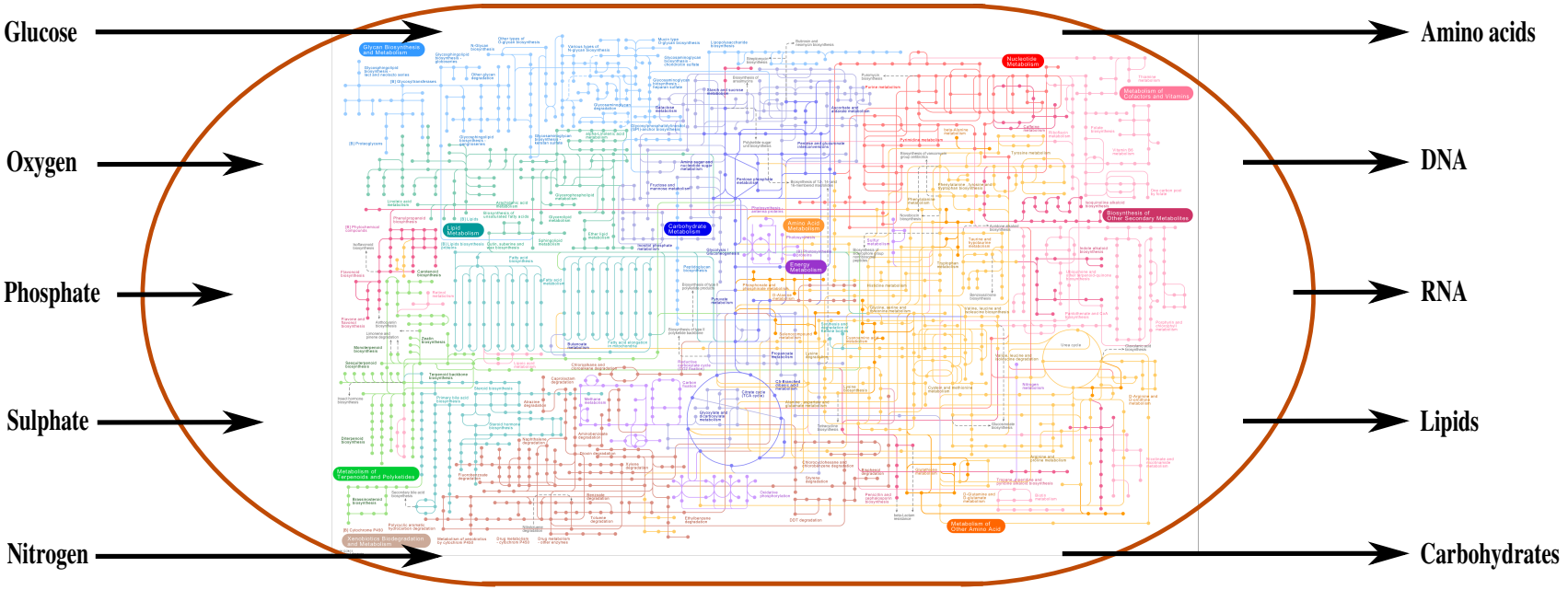

How to connect input(s) to output(s) ??

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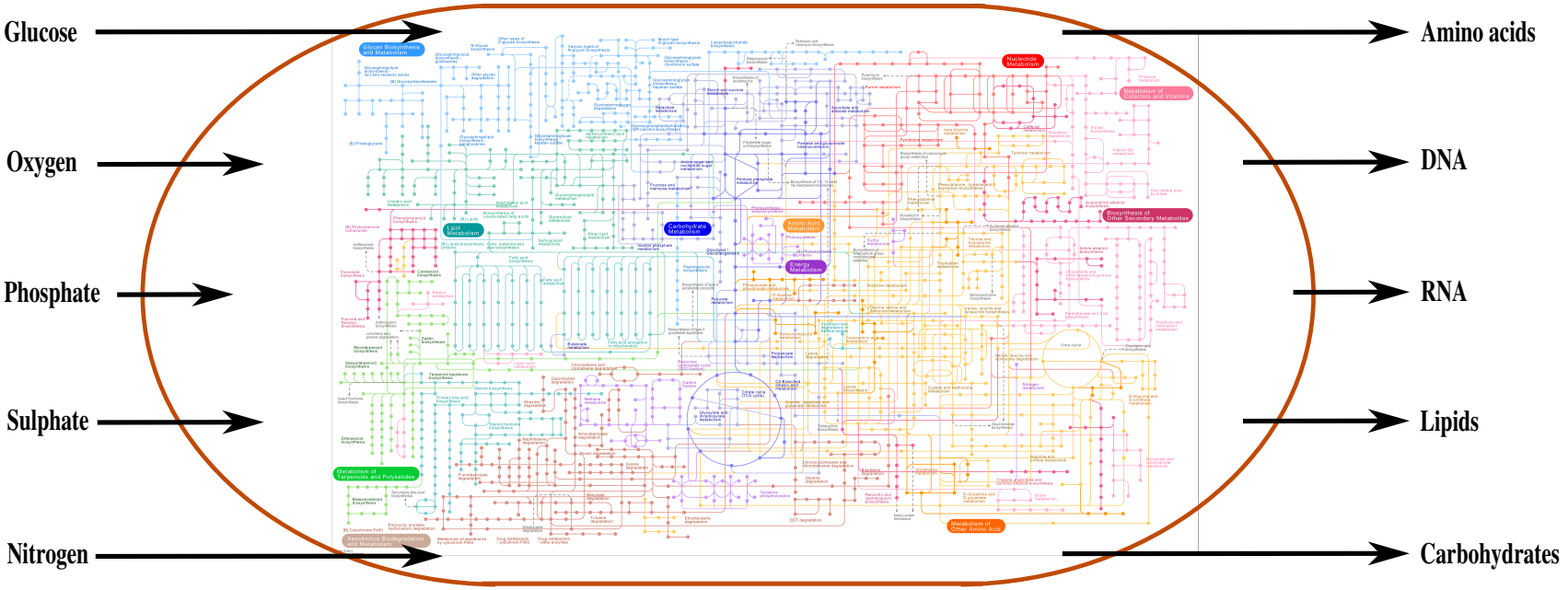


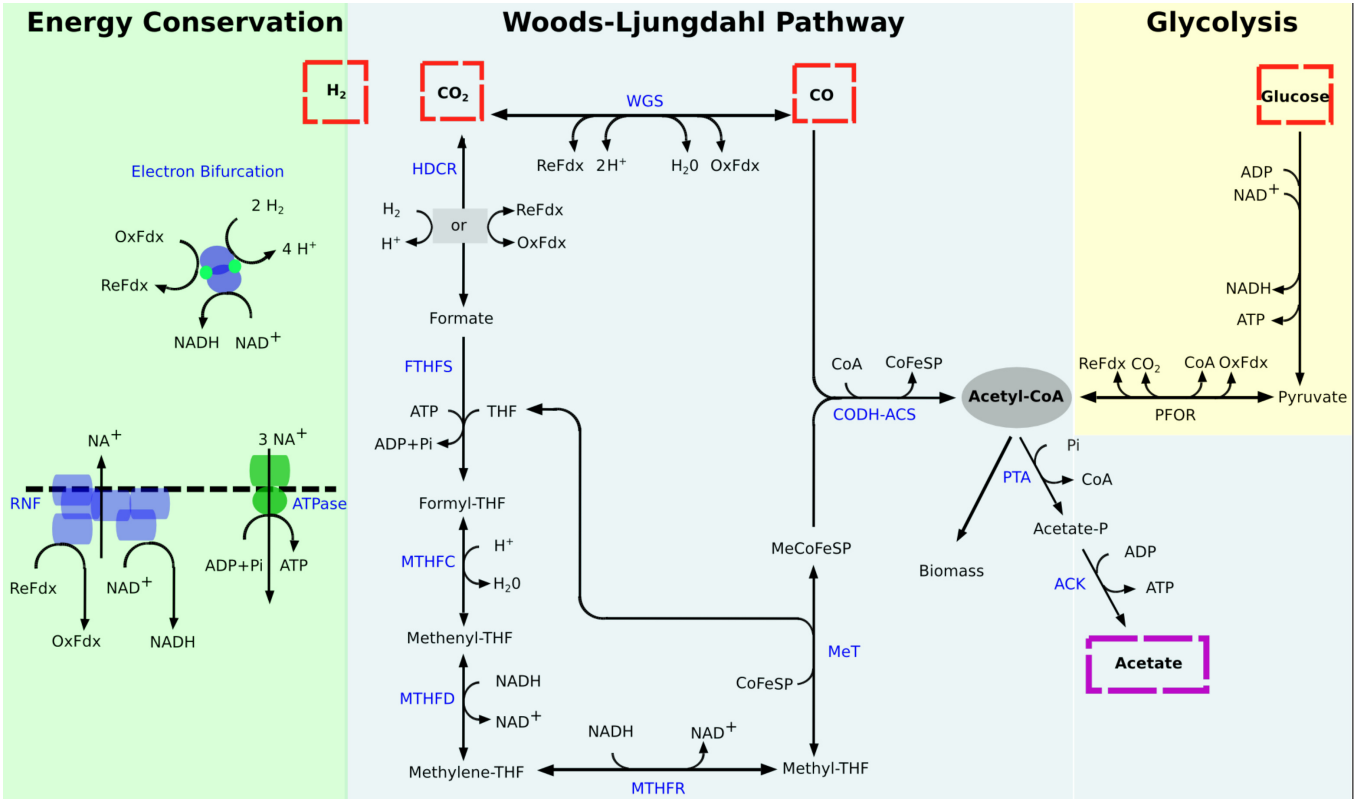
How to connect input(s) to output(s) ??

Motivation

What do we want to know - can we:

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

Example - The Woods-Ljungdahl Pathway



TO DECIDE: We need a suitable, realistic, small model to illustrate and to then use as a basis for the following practical. Do we stick with WLP (a bit exotic) or use something else?

Questions:

- Which reactions are essential?

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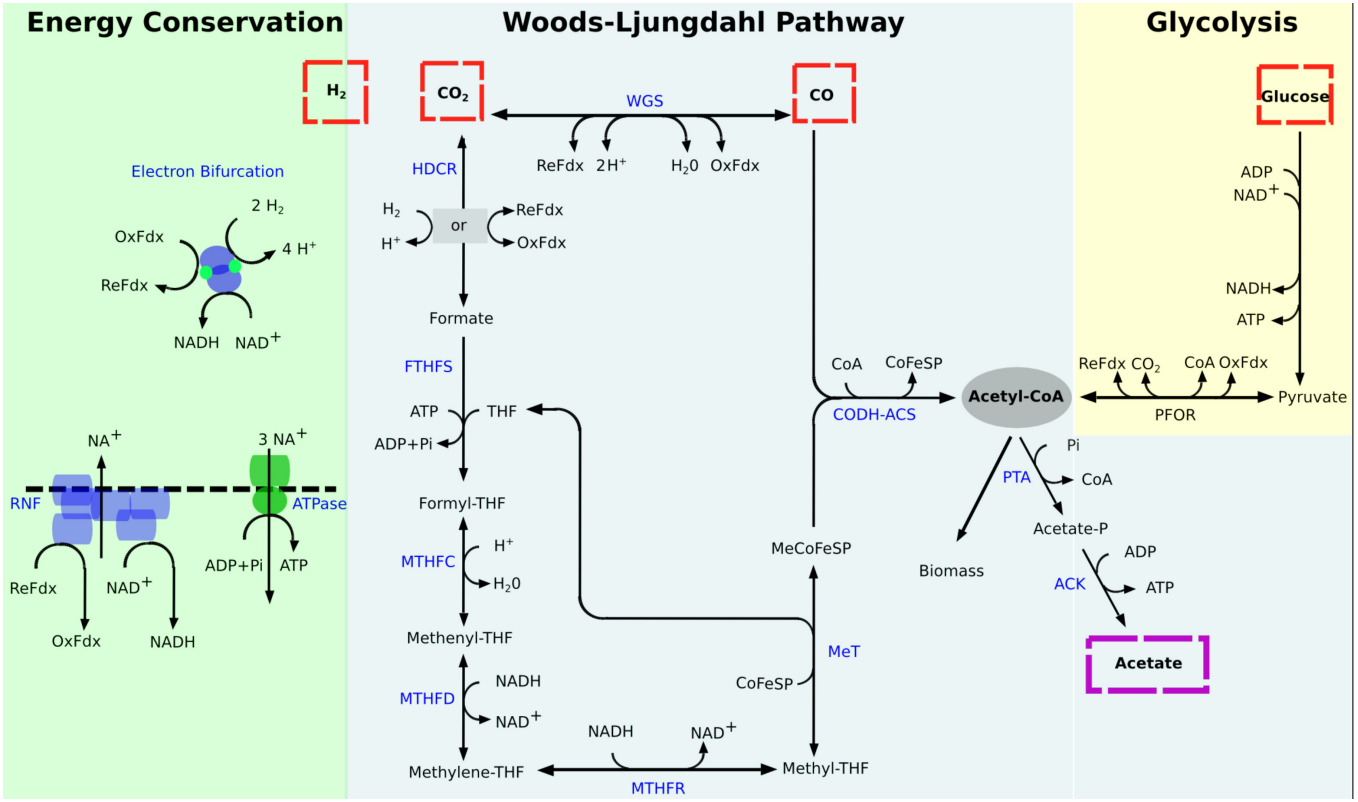

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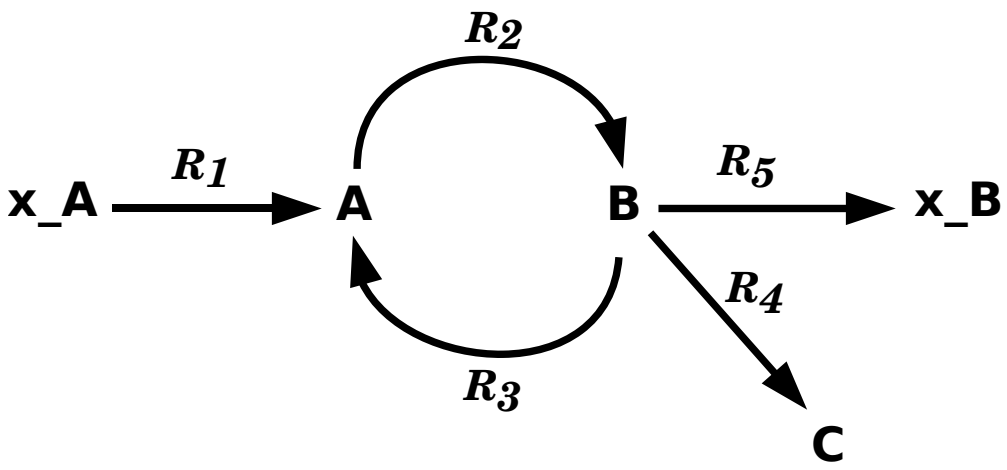
!! Remove before use !!

The first few slides here replicate trhe L1 material for pedagogic correctness.

Remove/edit as you think best

Modelling networks of reactions

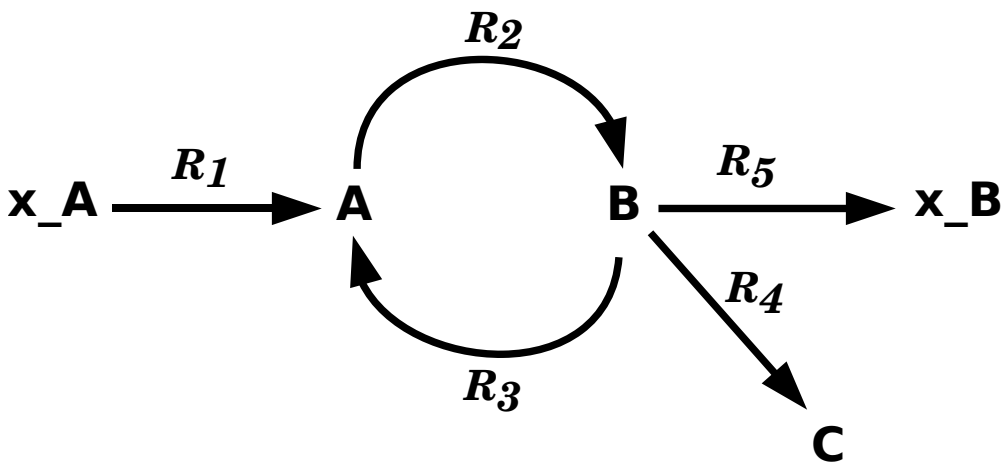


$$\mathbf{Nv} = \mathbf{0}$$

So What ?!

v is not unique

Modelling networks of reactions



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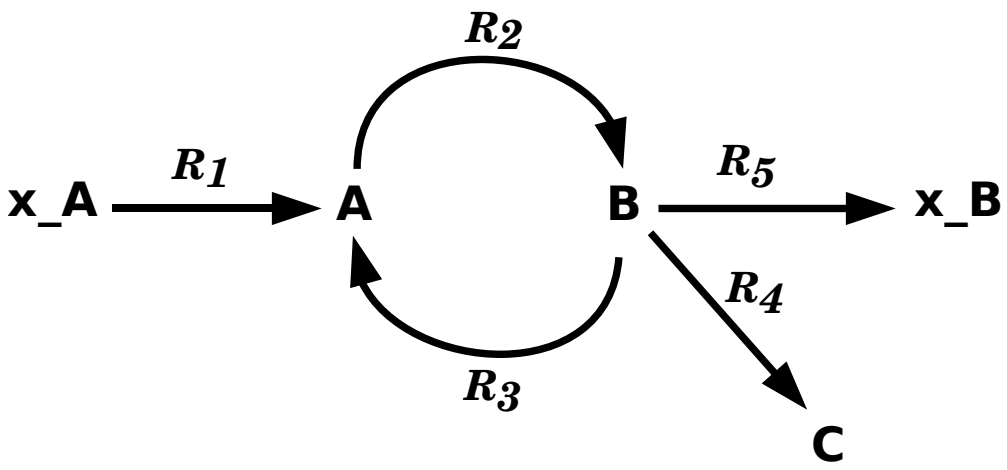

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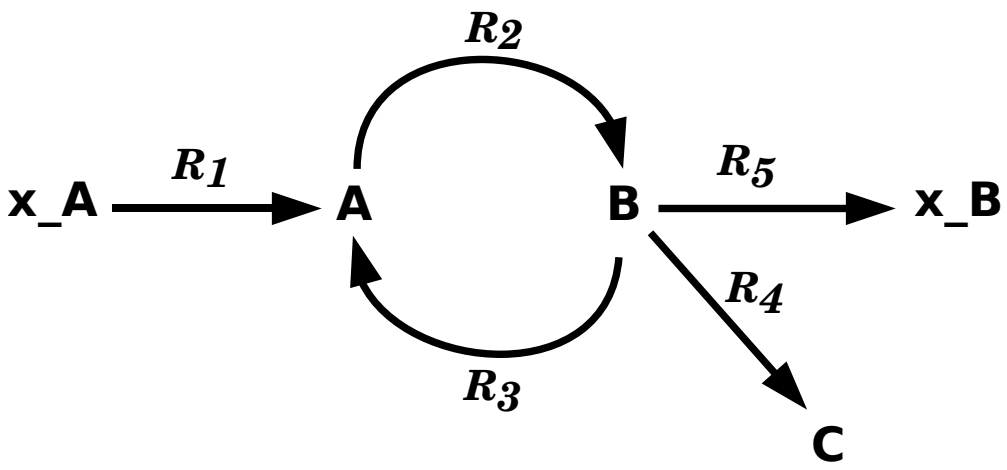
Kernels



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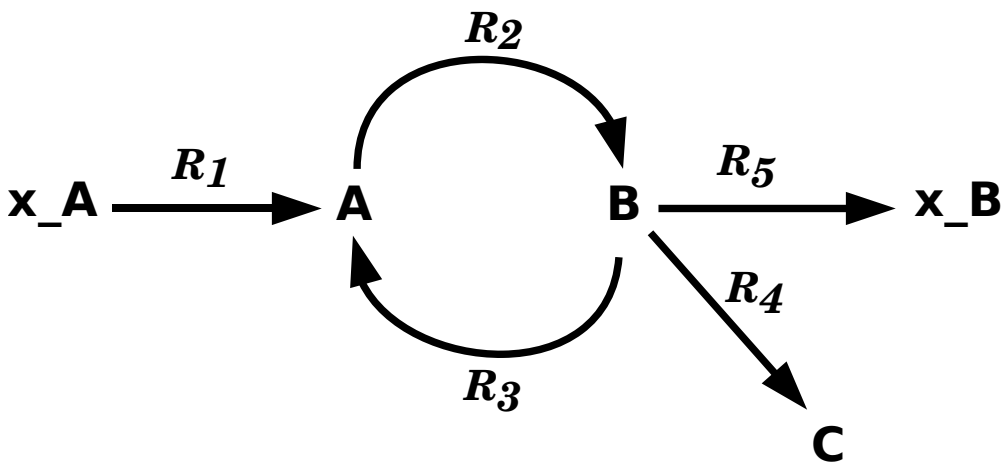

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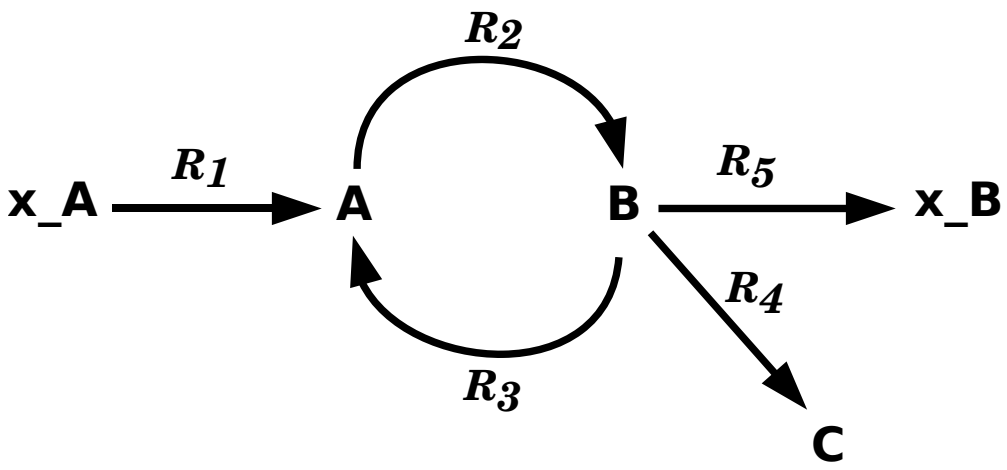

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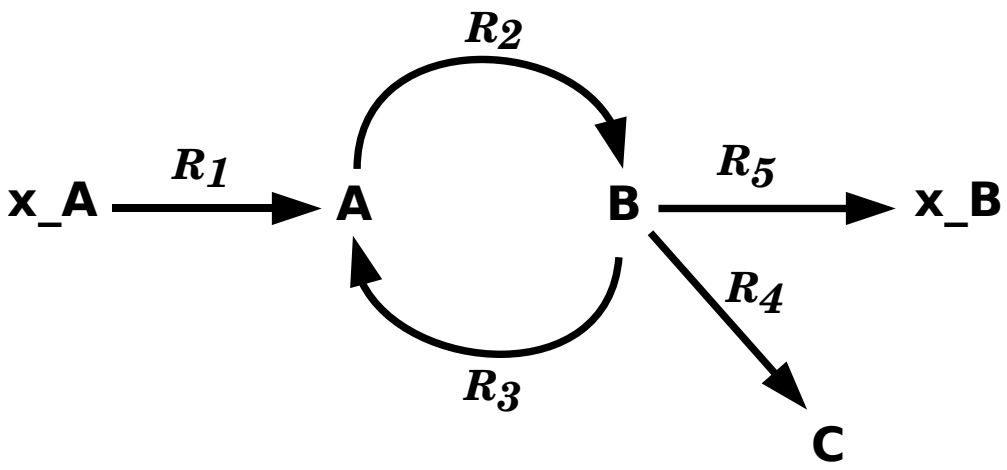

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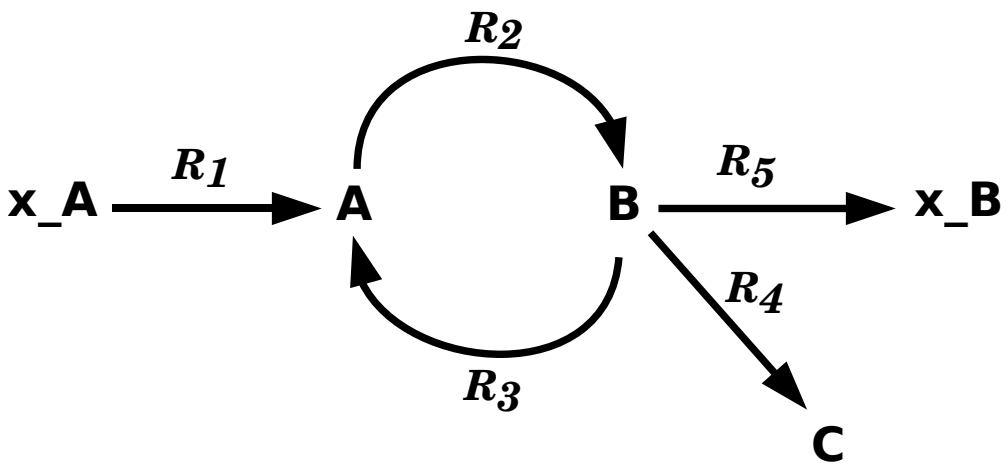

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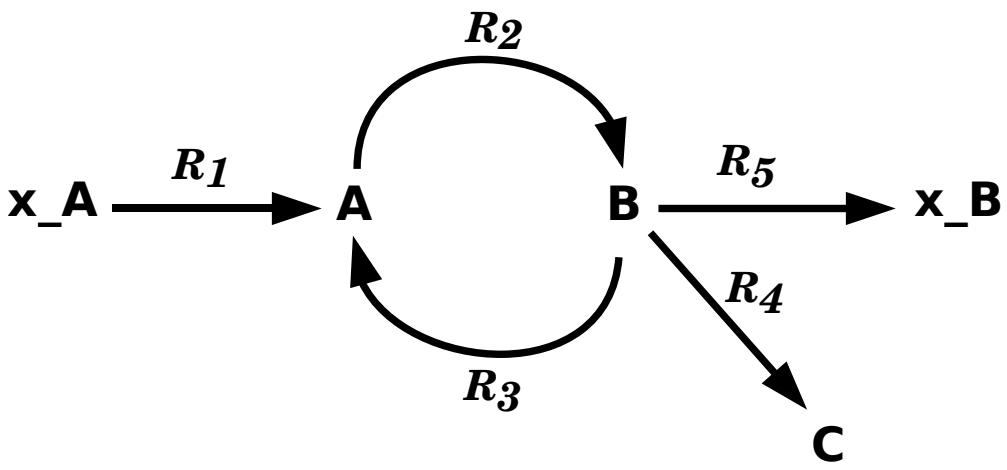

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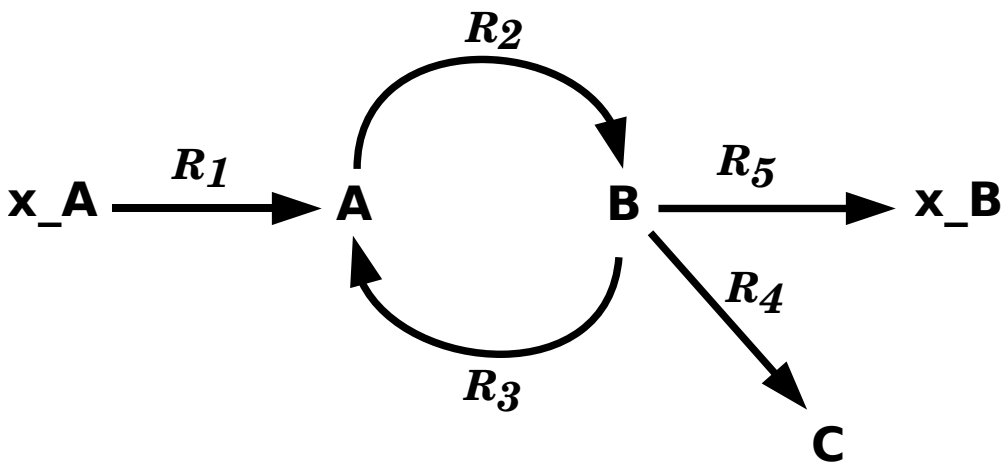
Significance of the kernel

- The kernel captures steady-state invariants of a network that are independent of environment, metabolite levels etc.
- Any and all steady state flux distributions can be represented as a linear combination of columns of the null space.
- 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.
- Unexpected behaviour in other results can often be explained by consideration of the kernel.

Kernels are not unique



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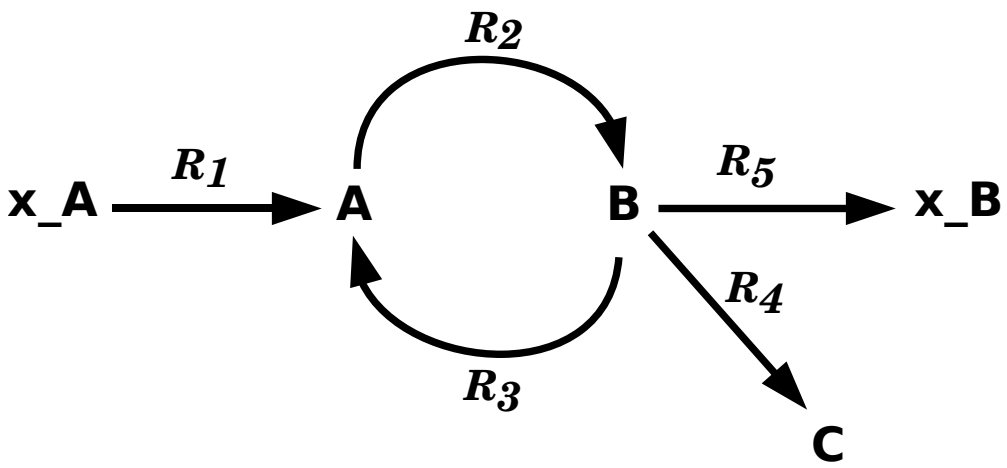

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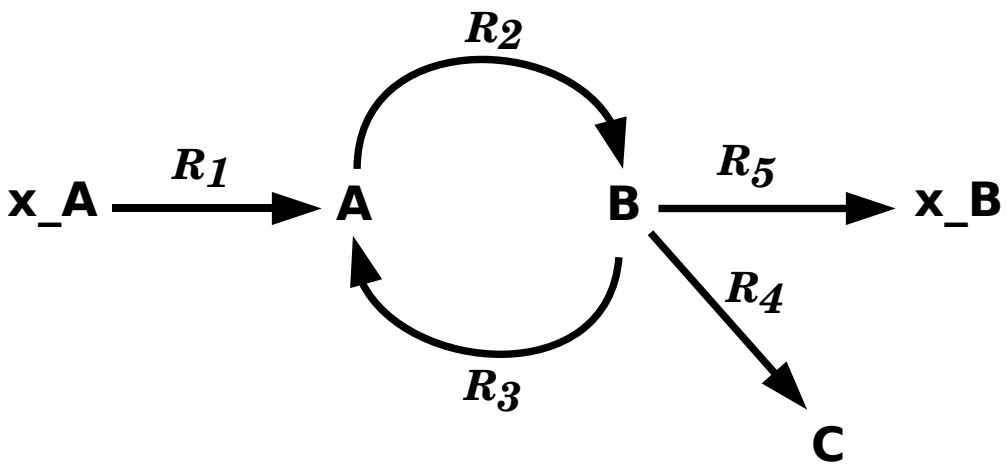

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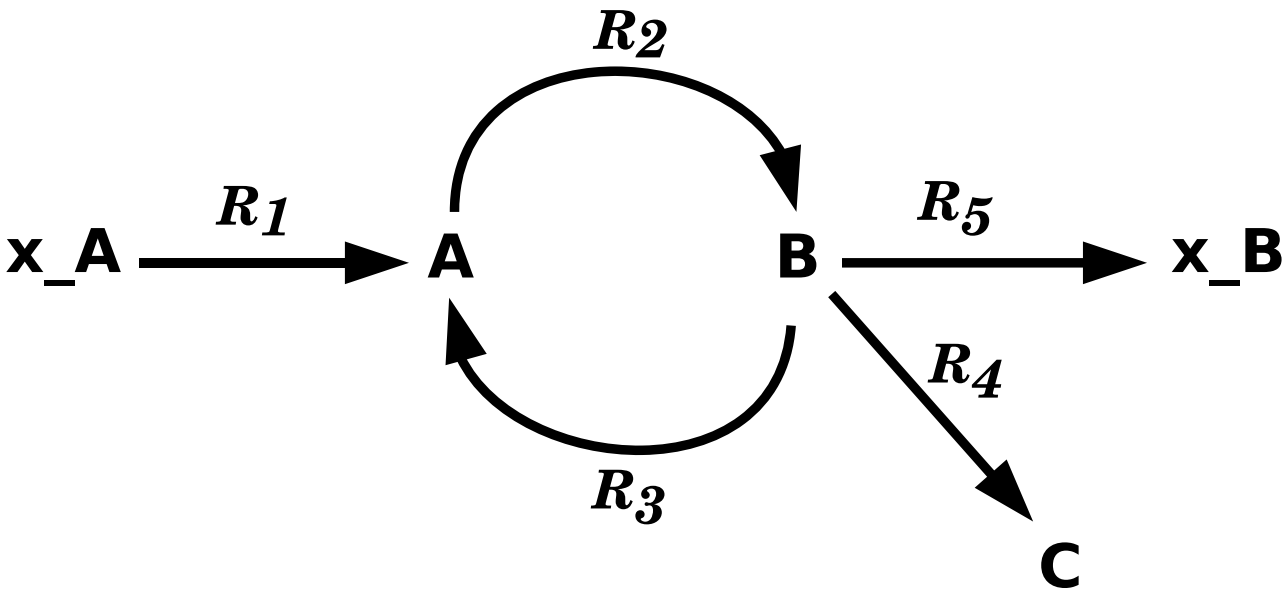
Elementary modes (1)

Definition:
A set of reactions in a system that:

- Balance all internal metabolites.
- Respect reversibility.
- Cannot be decomposed. (ie a *minimal* set of reactions)
- Are associated with a single net stoichiometry involving only external metabolites (or none).

Elementary modes (2)

Non Elementary modes



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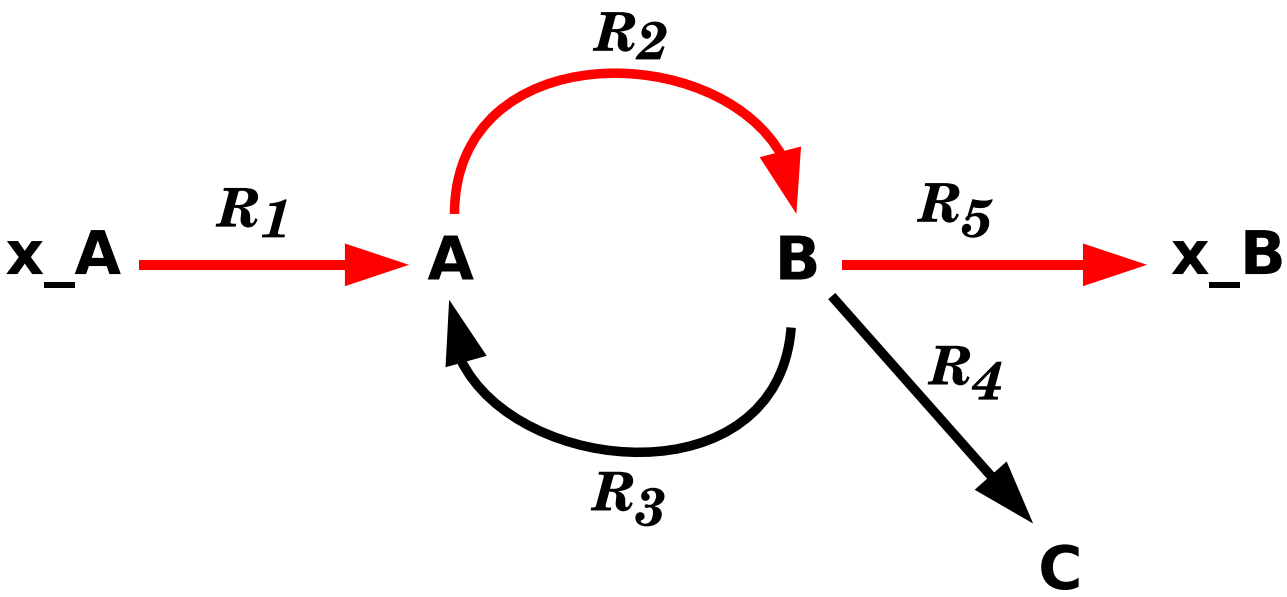

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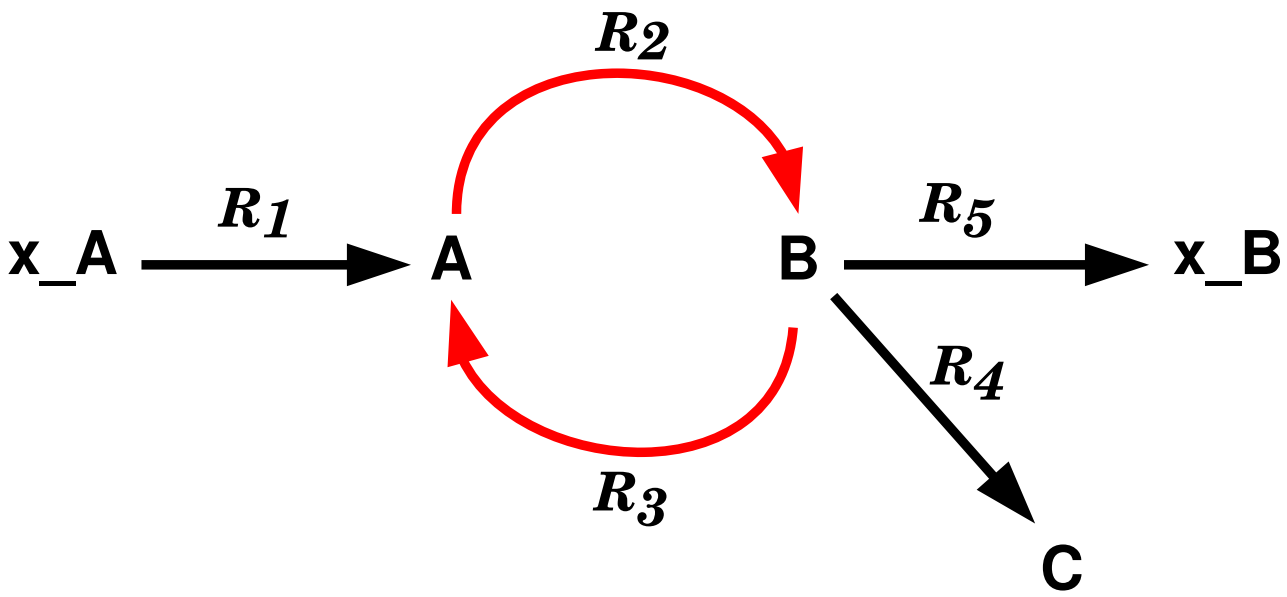

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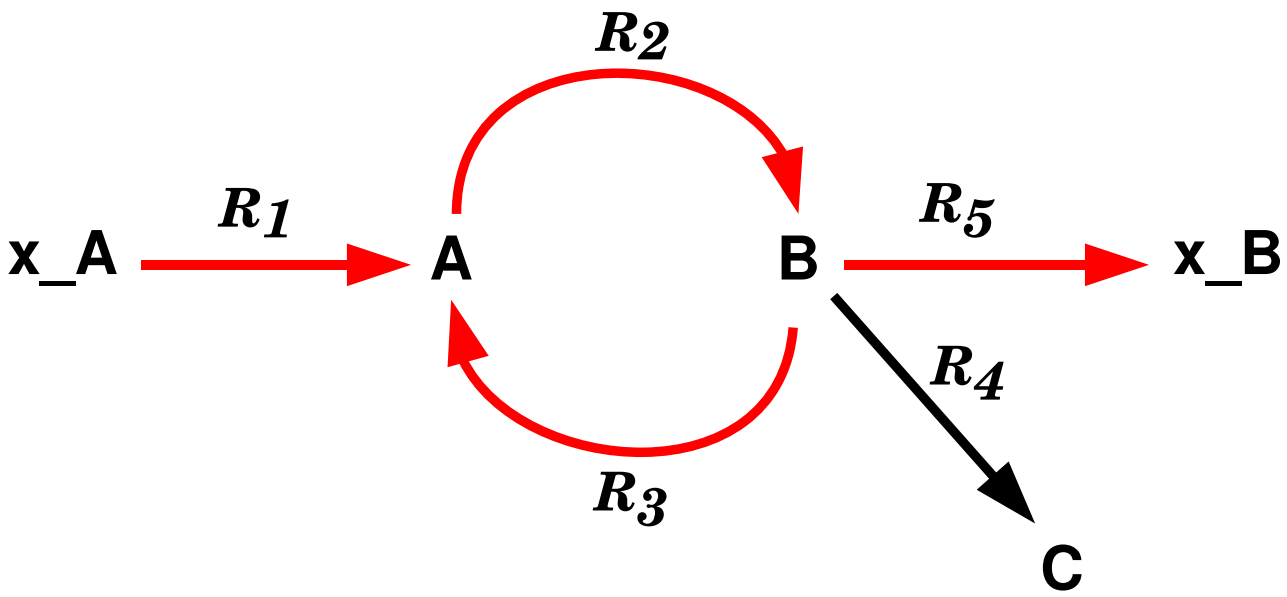

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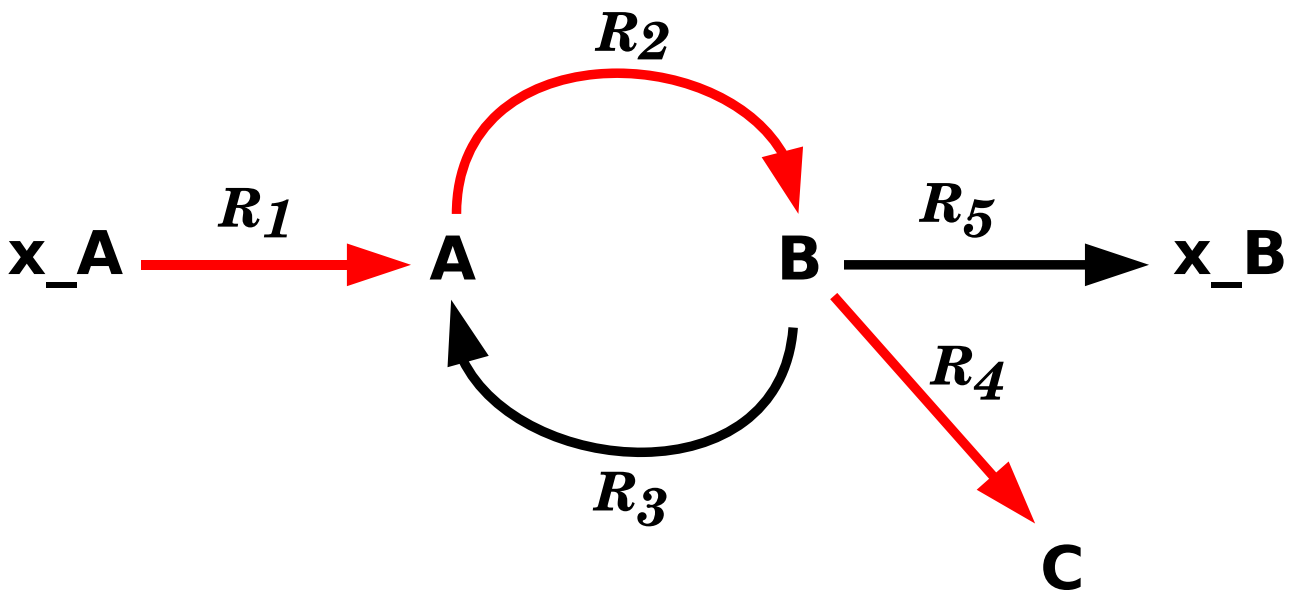


Elementary modes - Summary

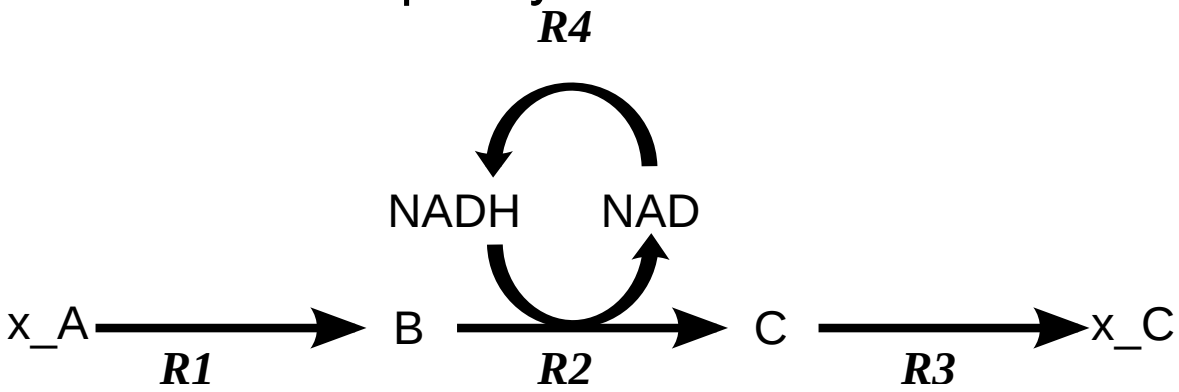
- Elementary modes represent independent paths in a system.
- They provide an *objective* definition of pathways.
- The set of reactions in an EM is unique.
- Every EM is associated with a net stoichiometry which may or may not be unique.
- The net metabolic behaviour of a system can always be expressed as a linear combination of its EMs.

So far we have considered relationships between steady-state reaction fluxes.

Can we say anything about metabolite concentrations?

Conserved cycles

Consider a simple cycle:



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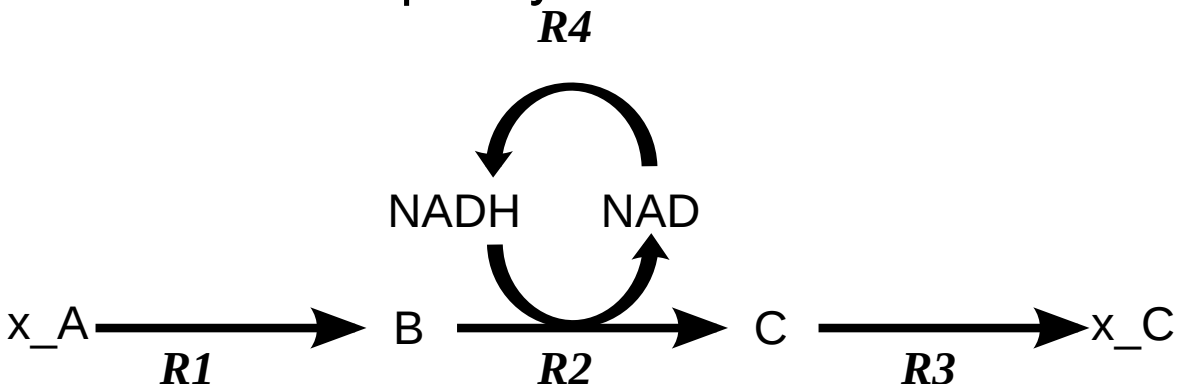

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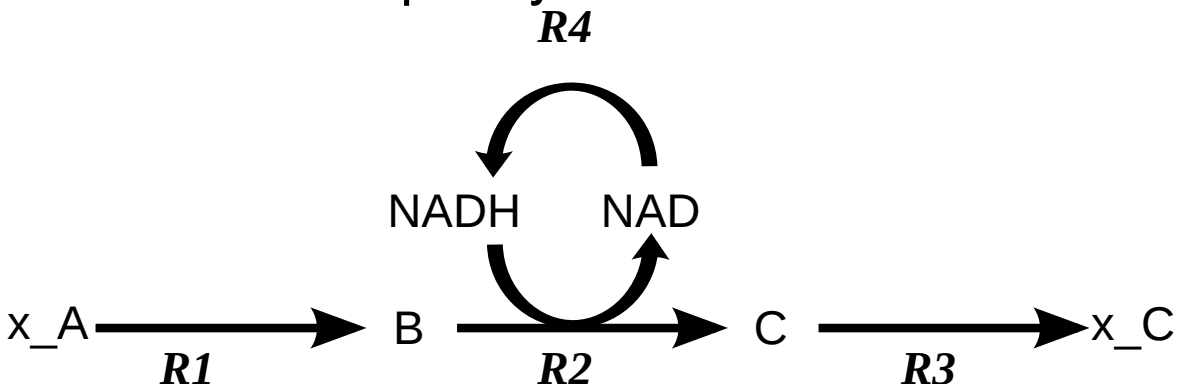

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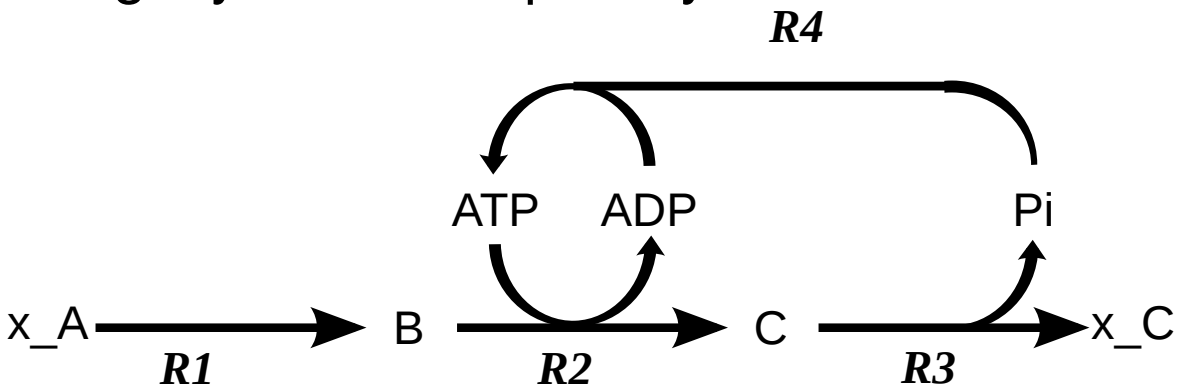

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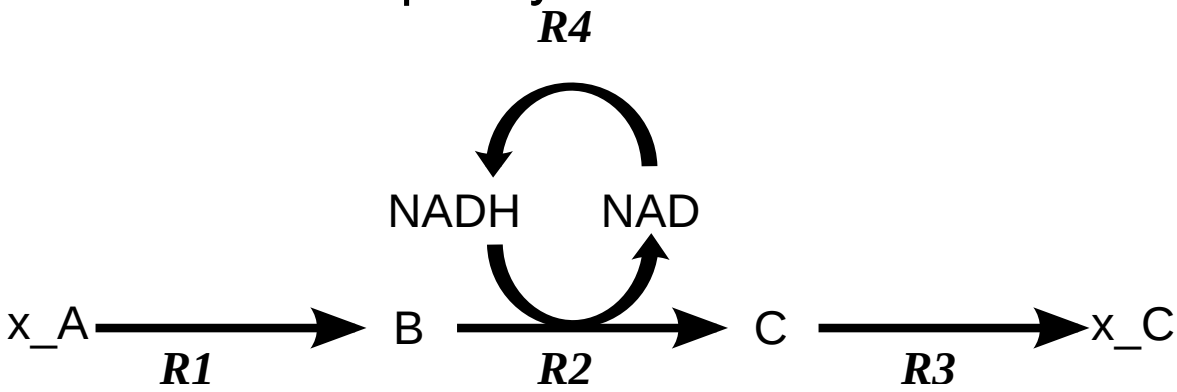

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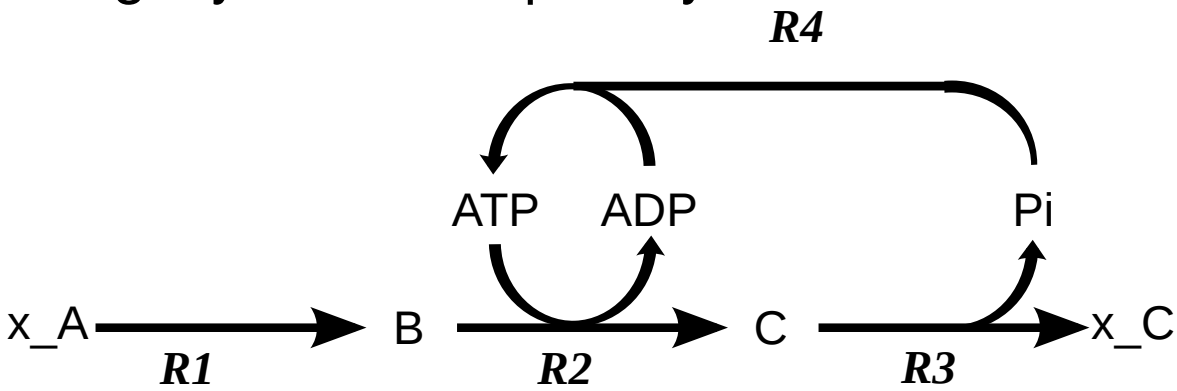

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Conserved cycles

These relationships are called

Moiety Conservation relationships.

They can be determined by analysis of the stoichiometry matrix.

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dB/dt = R1 - R2
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dNADH/dt = R4 - R2

$$dNAD/dt = -dNADH/dt$$

Integrating:

$$NAD = -NADH + k$$

$$NAD + NADH = k$$

k is the conserved total.

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$$\mathbf{N} = \begin{array}{r|cccc} & \text{R1} & \text{R2} & \text{R3} & \text{R4} \\ \text{B} & 1 & -1 & 0 & 0 \\ \text{C} & 0 & 1 & -1 & 0 \\ \text{NAD} & 0 & 1 & 0 & -1 \\ \text{NADH} & 0 & -1 & 0 & 1 \end{array} \quad \begin{array}{r} \\ \text{dB/dt = R1 - R2} \\ \text{dC/dt = R2 - R3} \\ \text{dNAD/dt = R2 - R4} \\ \text{dNADH/dt = R4 - R2} \end{array}$$

$$dNAD/dt = -dNADH/dt$$

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Structural analysis - The left Null-space

Such relationships can be identified from the *left* null space $\mathbf{K_l}$ which has the property:

$$\mathbf{K_l N} = \mathbf{0}$$

the dimension of which is equal to the number of conservation relationships in the system:

for the first example

$$\mathbf{K_l} = \begin{matrix} \text{B} & \text{C} & \text{NAD} & \text{NADH} \\ 0 & 0 & 1 & 1 \end{matrix} \quad \text{(one conservation relationship)}$$

and for the second example

$$\mathbf{K_l} = \begin{matrix} \text{B} & \text{C} & \text{ADP} & \text{ATP} & \text{Pi} \\ 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 & 1 \end{matrix} \quad \text{two conservation relationships}$$

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Notes:

- $\mathbf{K_l}$ is not always unique - there may not be a single way to represent the conservation relationships in a system.
- Negative elements in $\mathbf{K_l}$ do not imply negative concentrations.
- It is not possible to guarantee that an all positive $\mathbf{K_l}$ can be found.

Significance of $\mathbf{K_I}$

- Very important consideration in design of kinetic modelling software.
- Introduces “hidden” parameters in kinetic models.
- Changing concentrations in a model can lead to unexpected results.
- Need to identify the *dependent* metabolite in each relationship.
- The left null-space has received relatively scant attention and represents a potentially fruitful area for further theoretical research.

Conclusions

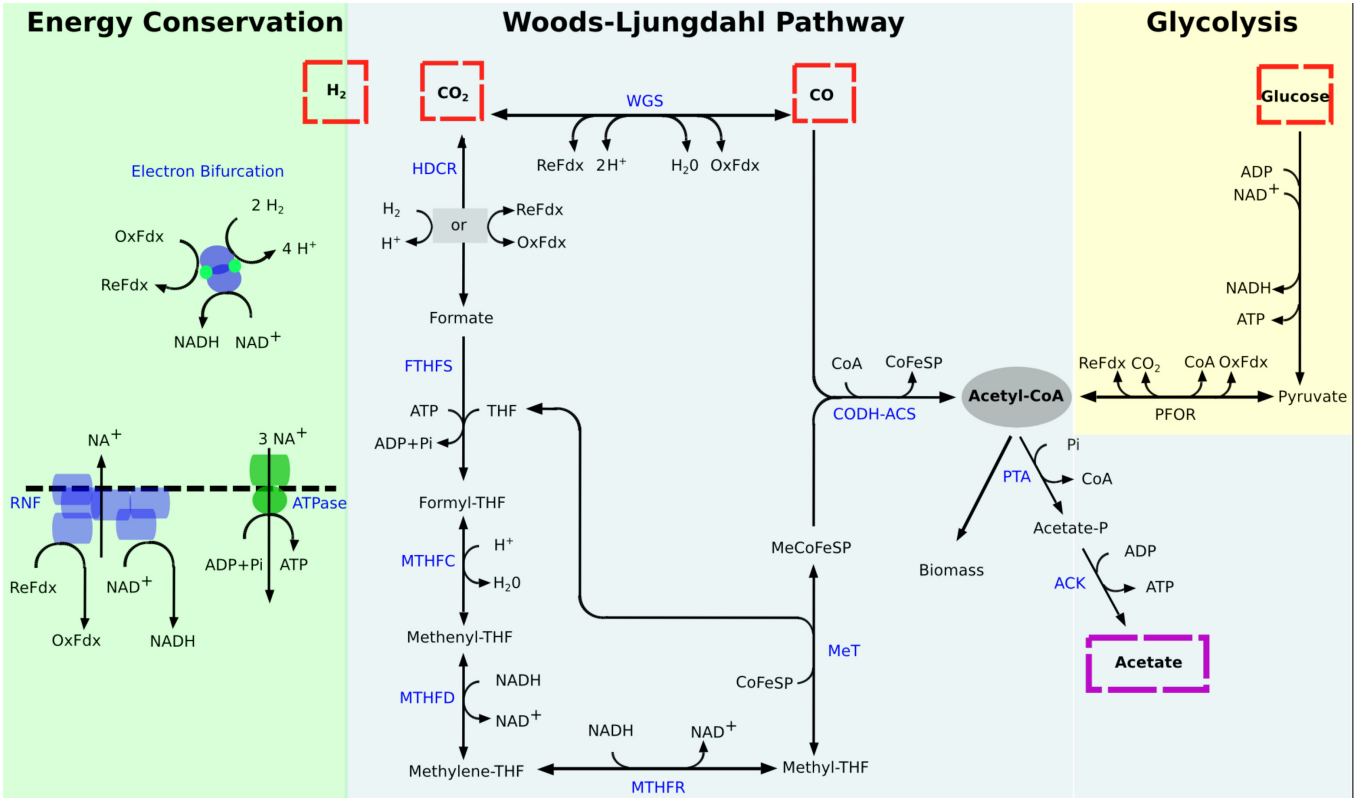
From consideration of the stoichiometry matrix, along with assumptions about reaction reversibility, we can:

- Identify independent routes through metabolic networks.
- Identify sets of reactions that carry flux in fixed ratios.
- Identify groups of metabolites with interdependent concentration values.

So Now ...

We have the *theoretical* tools to answer the questions posed earlier .

Example - WLP (Practical 4)



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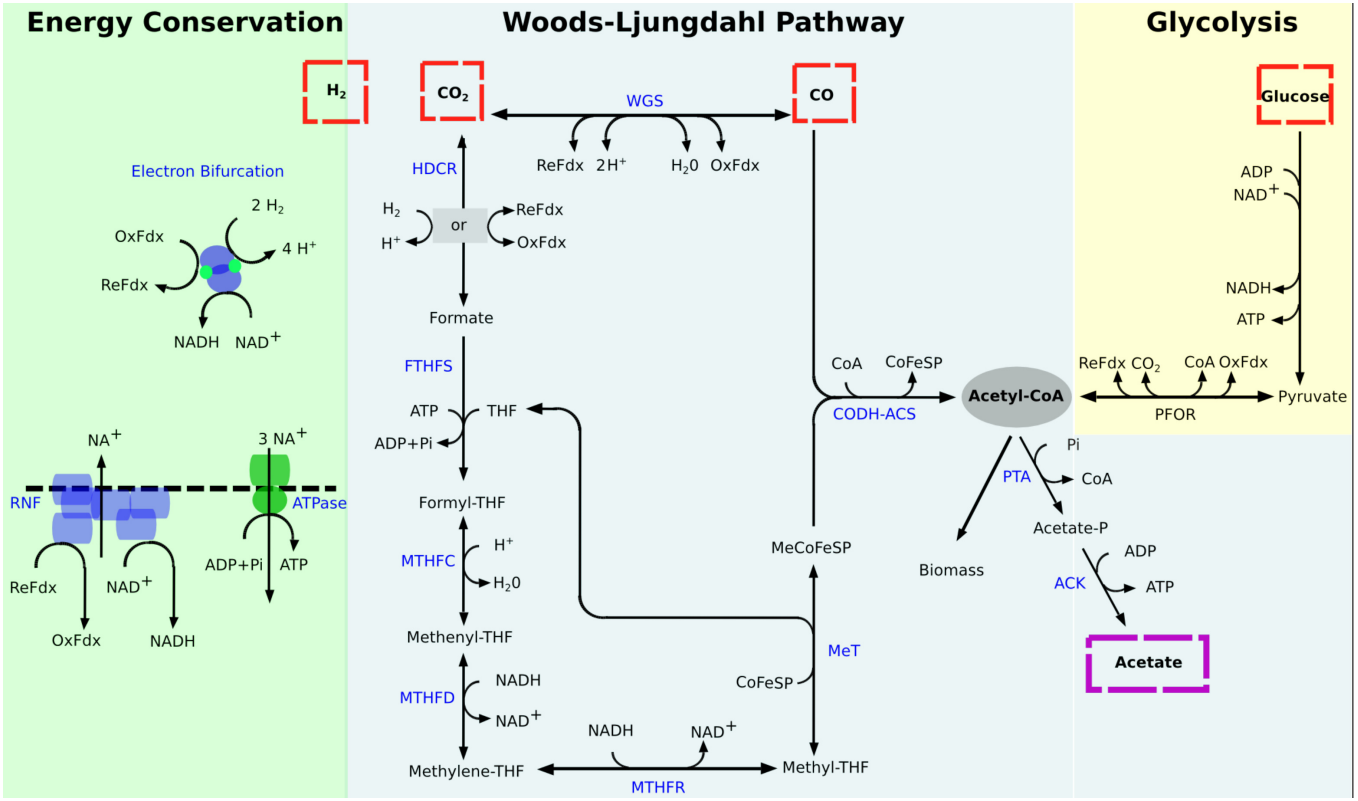

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