Elementary Modes and Photosynthesis

Mark Poolman

October 15, 2012

Definition of a metabolic system

A list of reactions defined by:

- Stoichiometry.
- And possibly:
  1. Thermodynamics,
  2. Kinetics,
  3. Metabolite concentrations,
  4. Other experimental observations.
- External (boundary) metabolites.

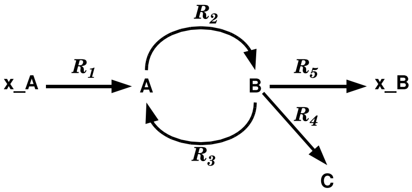
Structural analysis

- Assume steady state.
- Identify properties of all possible steady-states.
- Theory - based on LA manipulations of a matrix representation of the network.
- Can (potentially) be used on very large networks.
- Models can (potentially) built from publically available data-bases.

Modelling networks of reactions (1)

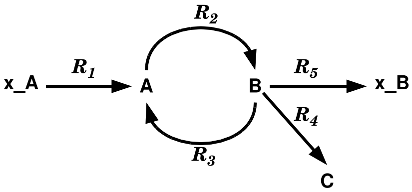
- Reactions interconvert substrates and products whilst conserving mass.
- Transporters are a special case of reaction. (Internal vs external metabolites)
- Reactions are not enzymes.
- Enzymes are not genes.
- Rate of change concentration is sum of reaction rates.
- This is assumed to tend to zero in the long term (steady state)

Modelling networks of reactions (2)

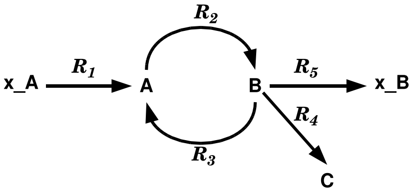


$$\frac{dA}{dt} = R_1 + R_3 - R_2$$
$$\frac{dB}{dt} = R_2 - R_3 - R_4 - R_5$$
$$\frac{dC}{dt} = R_4$$

Modelling networks of reactions (2)



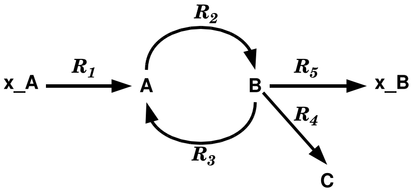
$$\frac{dA}{dt} = R_1 + R_3 - R_2$$
$$\frac{dB}{dt} = R_2 - R_3 - R_4 - R_5$$
$$\frac{dC}{dt} = R_4$$



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

Or more succinctly:

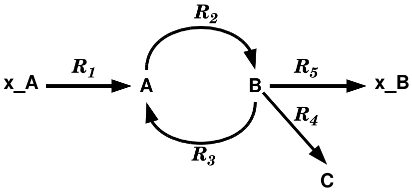
$$\mathbf{Nv} = \mathbf{0}$$



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

Or more succinctly:

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

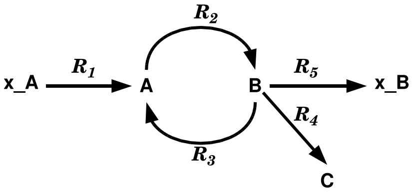


$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Or more succinctly:

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

Modelling networks of reactions (3)

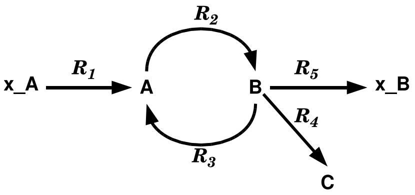


$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

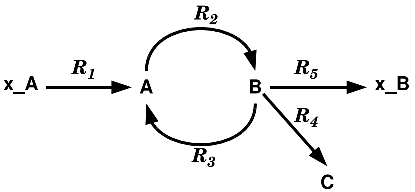
Or more succinctly:

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

Kernels

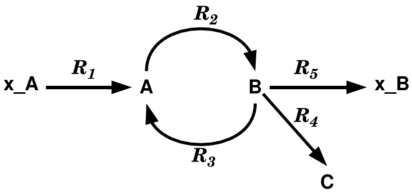


$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix}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



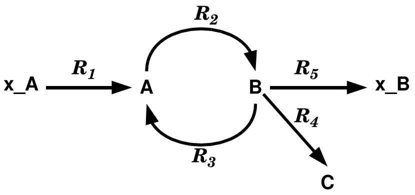
$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix}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

Kernels



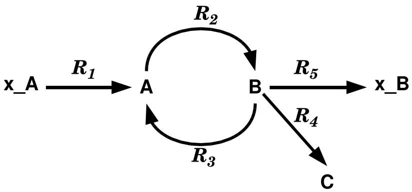
$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix}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

Kernels



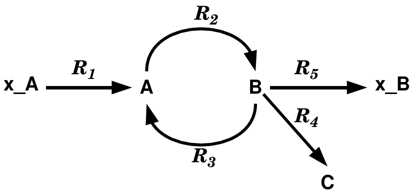
$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix}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

Kernels



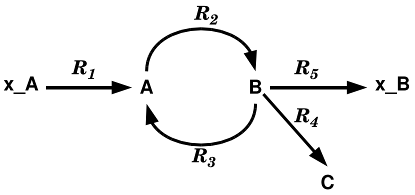
$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 0 & 0 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{bmatrix} = \begin{bmatrix} 1w_1 + 0w_2 \\ 1w_1 + 1w_2 \\ 0w_1 + 1w_2 \\ 0w_1 + 0w_2 \\ 1w_1 + 0w_2 \end{bmatrix} \begin{matrix}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

Kernels



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

Kernels are not unique



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

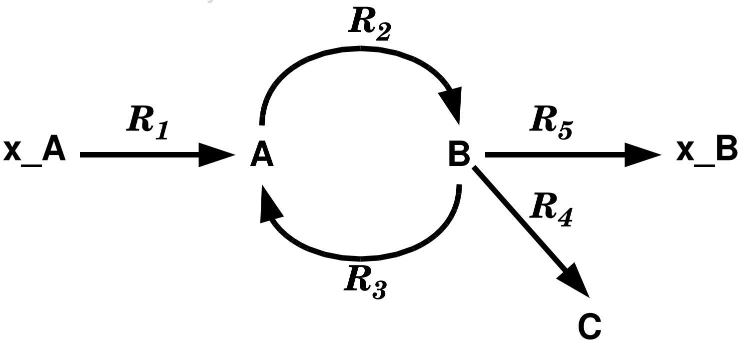
Elementary modes (1)

Definition:
A set of reactions in a system that:

- Balance all internal metabolites.
- Respect reversibility.
- Cannot be decomposed. (ie a *minimal* set of reactions)

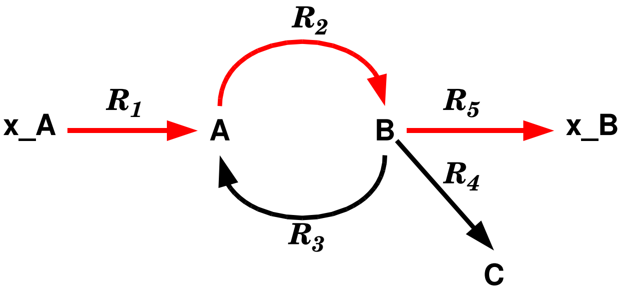
Elementary modes (2)

Non Elementary modes



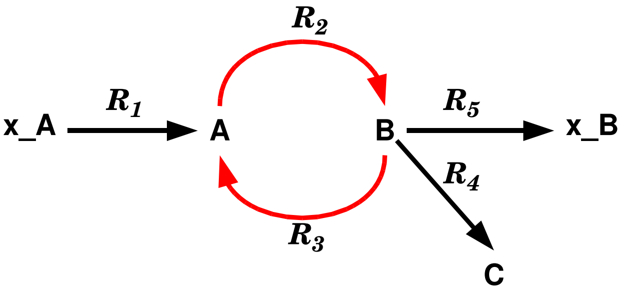
Elementary modes (2)

Non Elementary modes



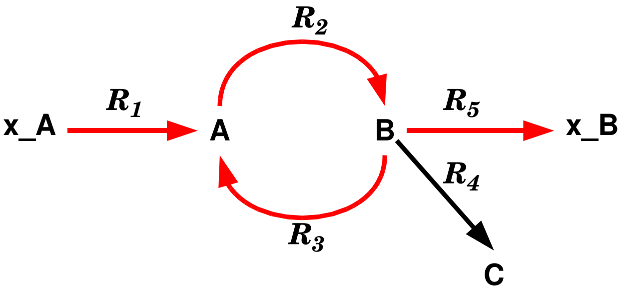
Elementary modes (2)

Non Elementary modes



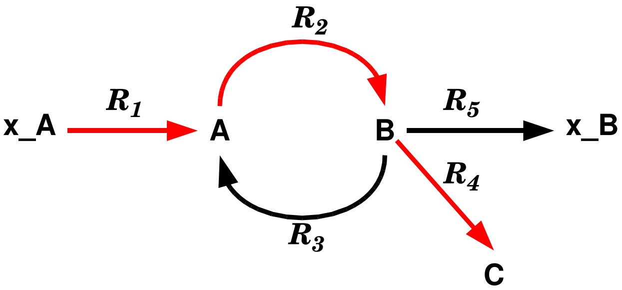
Elementary modes (2)

Non Elementary modes



Elementary modes (2)

Non Elementary modes



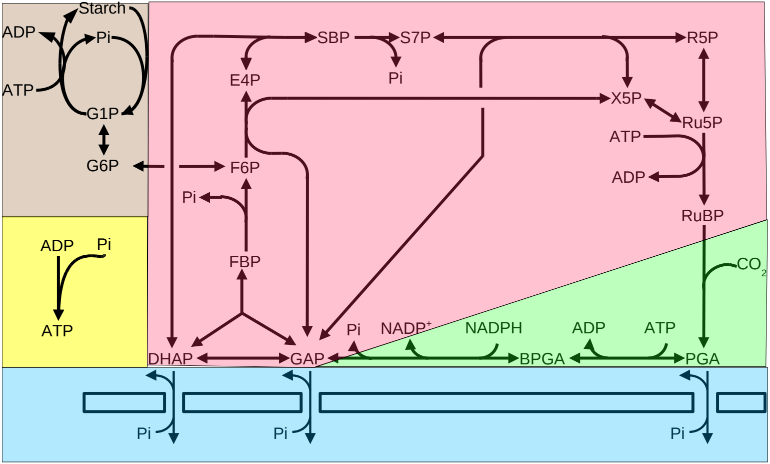
Significance of the null-space

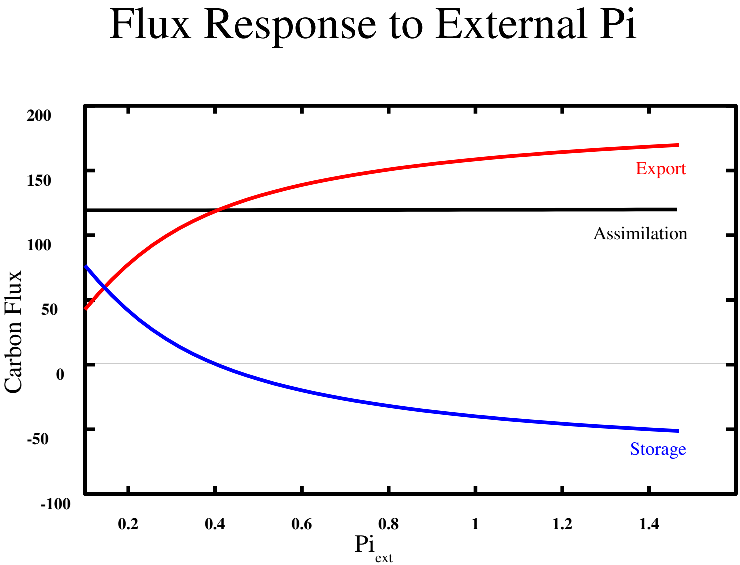
- Encapsulates *all* possible steady state behaviour.
- Allows identification of relationships between fluxes.
- Forms the starting point for most (if not all) structural analysis of metabolic networks.
- Can also be used to establish similar relationships between concentrations.

Significance of elementary modes

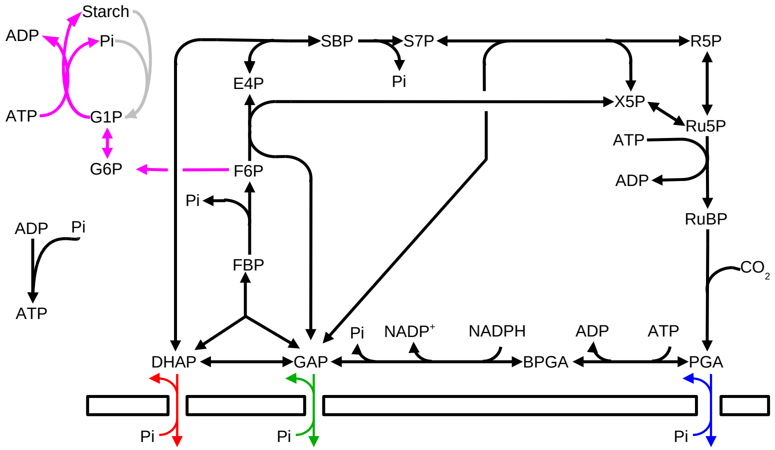
- Define all possible pathways (and hence net stoichiometries) through a network.
- Represent minimal subsystems in a network.
- Flux assignment to EMs gives a picture of how the system is utilising resources and allows an estimate as to how close an observed system is to steady-state.
- A fundamental concept in the structural analysis of metabolic networks.

The Calvin Cycle

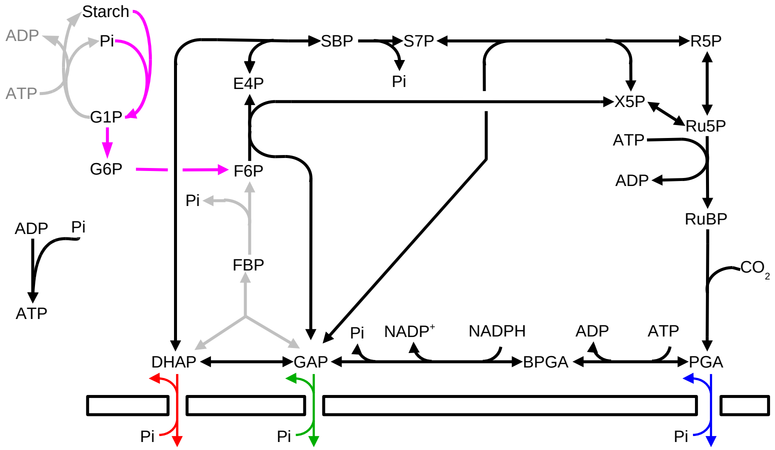



Flux Response to External Pi
Carbon Flux
200
150
100
50
0
-50
-100
0.2
0.4
0.6
0.8
1
1.2
1.4
Pi ext
Export
Assimilation
Storage

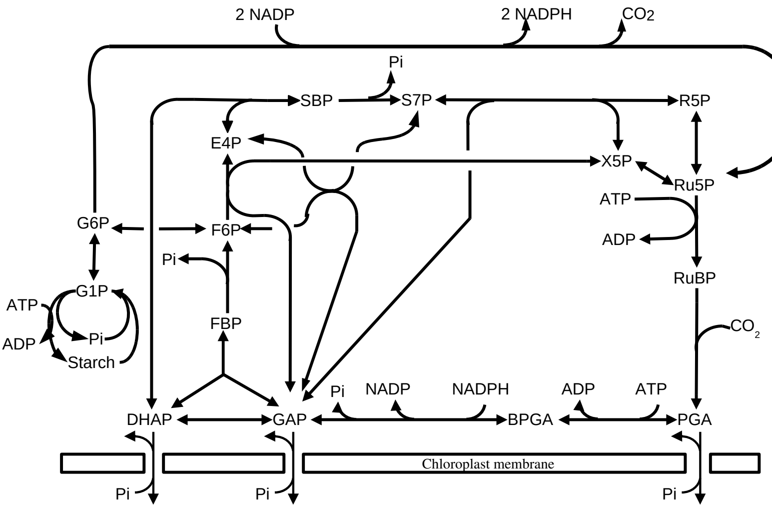
CO_2 consuming elementary modes



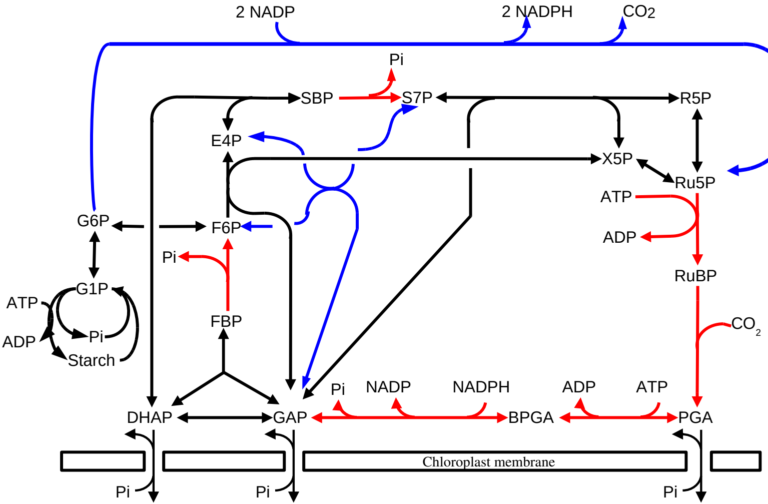
Starch consuming elementary modes



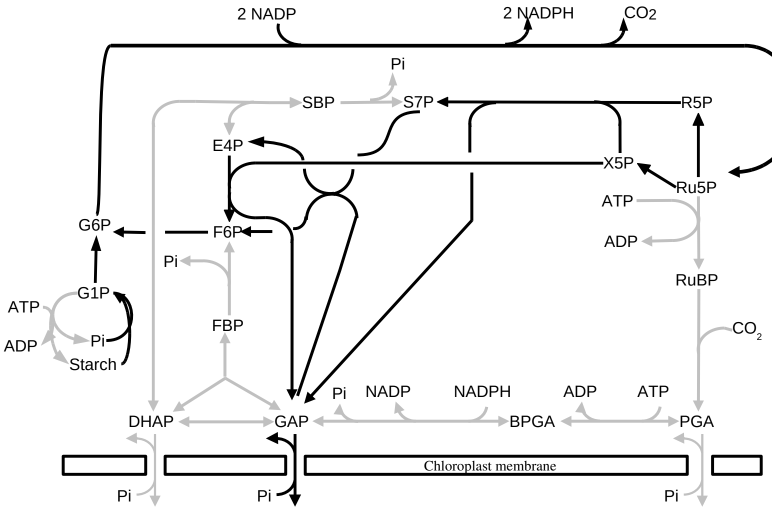
Calvin cycle + OPPP



Calvin cycle + OPPP + Thioredoxin system



Application of Elementary Modes to Photosynthesis



Further Reading

Schuster, Fell and Dandekar (2000) *Nature Biotechnology* 18, 326-232

Poolman, Fell and Raines (2003) *European Journal of Biochmistry* 270, 430-439

`http://mudshark.brookes.ac.uk`

`http://sysbio.brookes.ac.uk`

`http://mpa.brookes.ac.uk`