

Energy Metabolism in a Genome Scale Model of Rice

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Why analyse networks ?

Predicting network behaviour is hard but useful:

- How to predict the effects of addition or removal of reactions ?
- How to predict additions or removals of reaction to produce a desired effect ?
- What is basic principles that underlie such questions ?

Why analyse networks ?

- Can we extract simple subsystems from very large reaction networks ?
- How do the 'standard' biochemical pathways function in very large networks ?
- How will this help our practical understanding of biochemical networks ?

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.

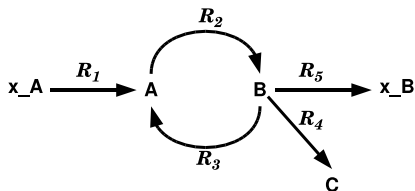
Structural analysis

- 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) be built from publically available data-bases.

Modelling networks of reactions (1)

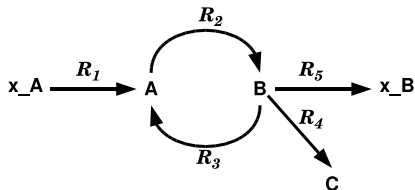
- Reactions interconvert substrates and products whilst conserving mass.
- Transporters are a special case of reaction. (Internal vs external metabolites)
- Reactions are not enzymes.
- Enzymes are not genes.
- Rate of change concentration is sum of reaction rates.
- This is assumed to tend to zero in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

Modelling networks of reactions (2)



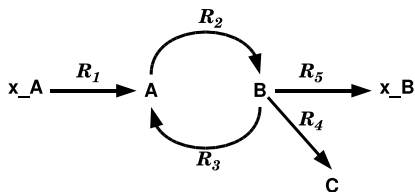
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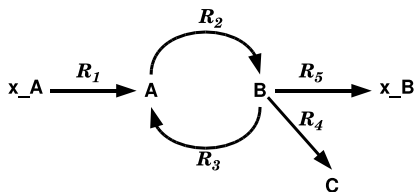


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Or more succinctly:

$$Nv = 0$$

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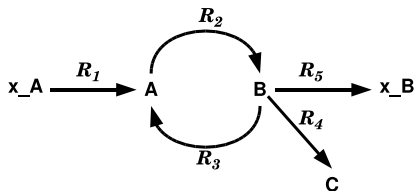


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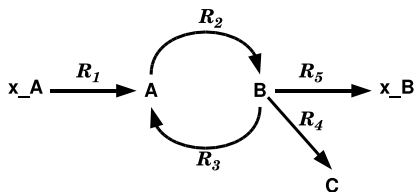


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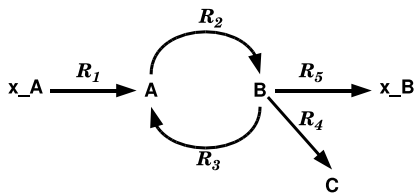
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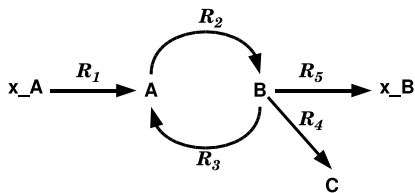
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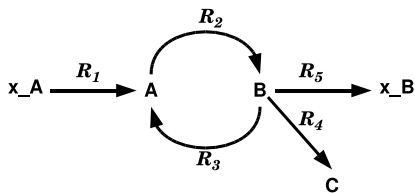
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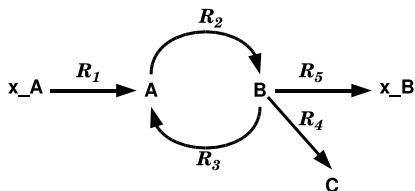
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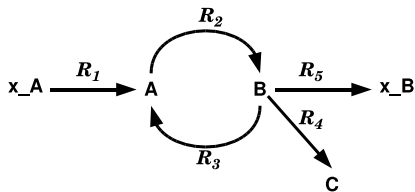
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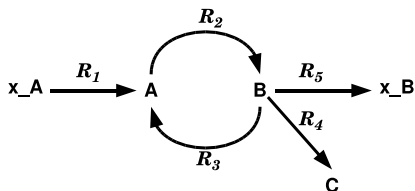
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Significance of the Null Space

- Encapsulates *all* possible steady state behaviour.
- Identifies *invariant properties* of the network.
- Allows identification of relationships between fluxes.
- Forms the starting point for most (if not all) structural analysis of metabolic networks.

Limitations of Null Space Analysis

- Provides an “unfocussed” view of the system.
- Difficult to formulate specific questions.
- Not always informative for *genome-scale* models.

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

Determine instances of \mathbf{v} with specific properties.

- Optimise (ie minimise or maximise) certain fluxes.
- Constrain (fix or limit) other fluxes.
- Constrain flux relationships to satisfy $\mathbf{Nv} = \mathbf{0}$

Application of LP to metabolic networks

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Application of LP to metabolic networks

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Note:

- Failure to find a solution is still useful.
- Once a solution has been found, it is easy to change flux constraints and quickly re-solve.
- This allows rapid exploration of the optimal space.

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Scanning LP constraints

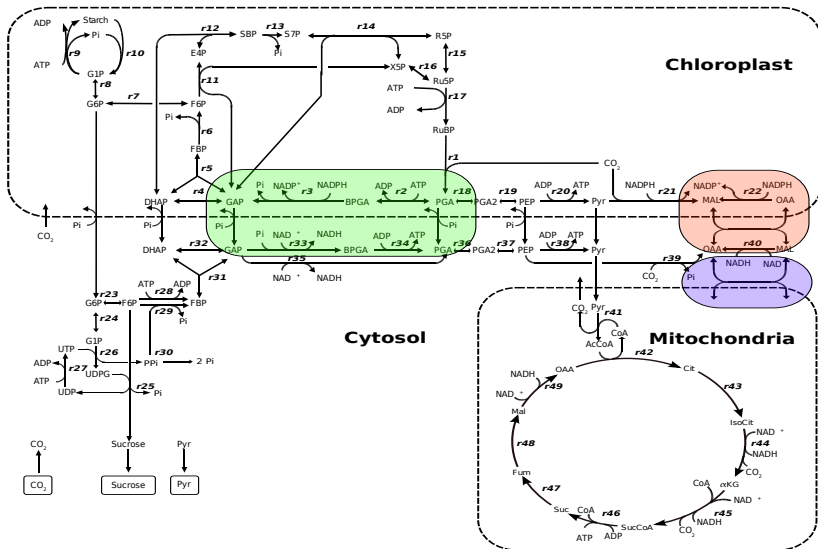
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```
for x in range(x_min,x_max):  
    lp.SetConstraint(x)  
    lp.Solve()  
    solution = lp.GetSolution()  
    results.AddData(solution)  
Analyse(results)
```

A Genome-scale Model of Rice

- Built from the 'Ricecyc' database <http://pathway.gamene.org/gamene/ricecyc.shtml>
- Extensive curation - ensure stoichiometric and thermodynamic consistency.
- **Inputs:** CO_2 , NH_3 , NO_3^- , SO_4^{2-} , P_i
- **Outputs:** O_2 , Amino acids, polysaccharides, DNA, RNA, lignin.
- 1400 metabolites, 1700 reactions.
- Separate compartments for chloroplast and mitochondrion.

Model Compartments



Analysing the Model

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- Minimise total flux (proxy for minimum protein investment).
- $\mathbf{t}\mathbf{x}$ represents fluxes in biomass transporters $\mathbf{v}_{i..j}$
- ν is the photon flux. Solve for a range of values.

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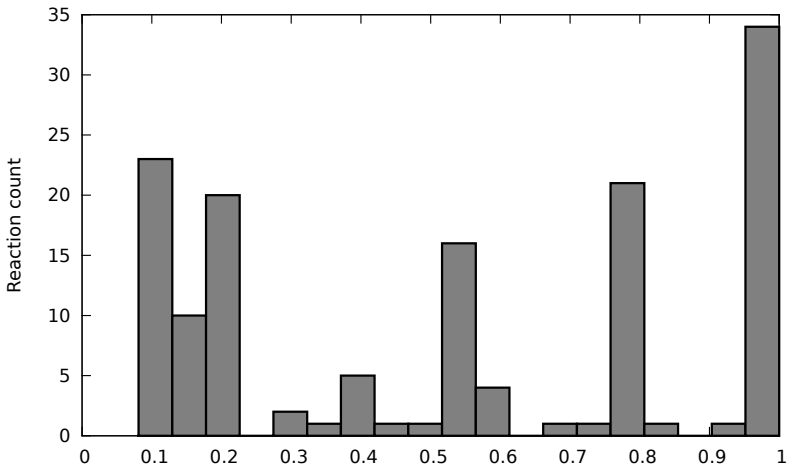
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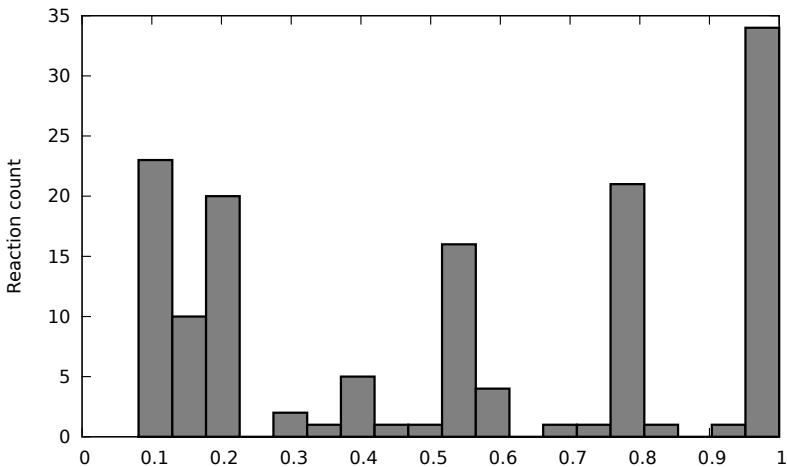
Results

- 309 reactions required for biomass synthesis.
- 142 showed some response to varying photon flux.
- Most responses were weak.

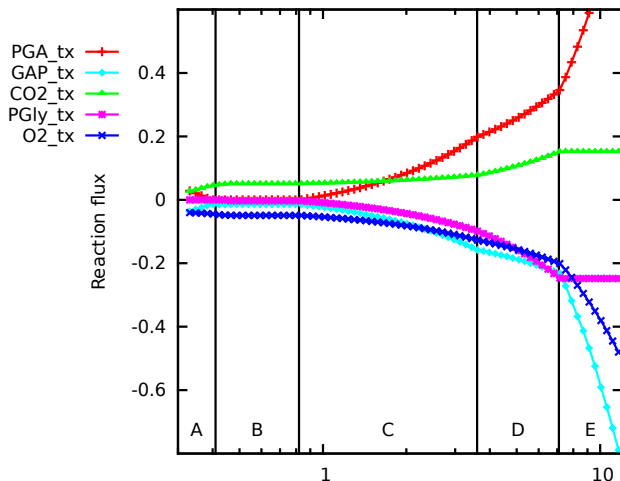


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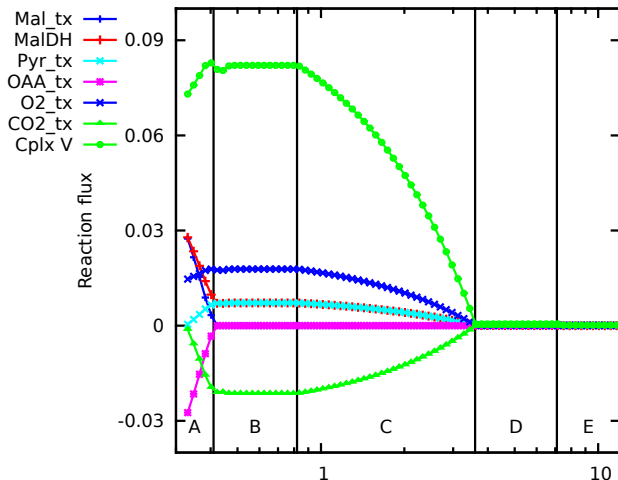
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Chloroplast response.

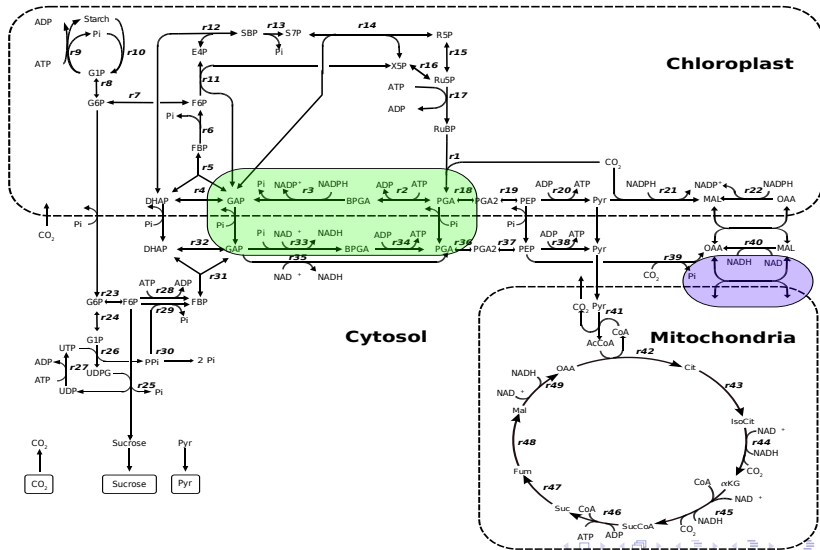


Mitochondrial response.

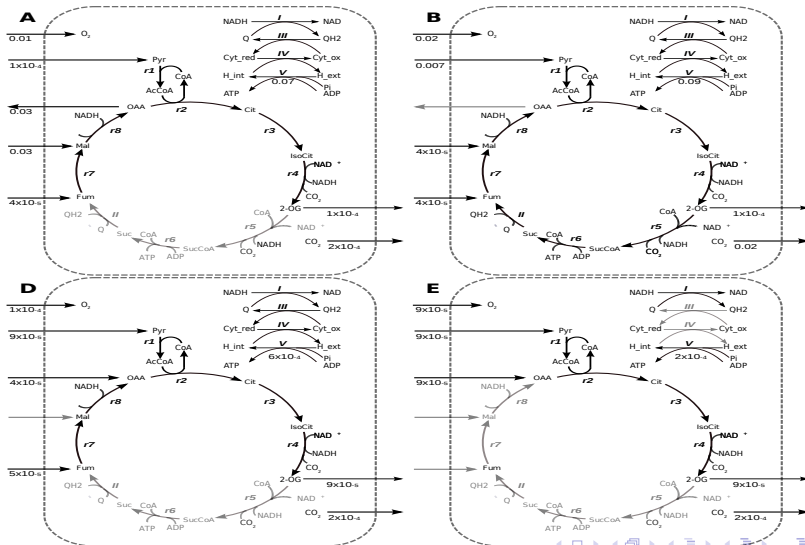


Results

Active shuttles.



Mitochondrial flux modes.



Conclusions

- Analysing the model greatly simplifies a complex network:
 - ① Only 300 from 1700 reactions to account for autotrophic growth.
 - ② Of these 30 are identified significantly responding to variations in light.
- We propose that optimal energy metabolism in plants requires coordinated responses in the three major compartments.

Thanks to



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