Catabolic core identification in a *Salmonella* genome-scale model

Hassan Hartman, Oxford Brookes University

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- Theoretical tools for structural analysis of metabolic models scale poorly for large models
- Possible solution - modularization of GSMs to sub-models of manageable size

Modularization of structural models - Reaction Correlation Coefficient

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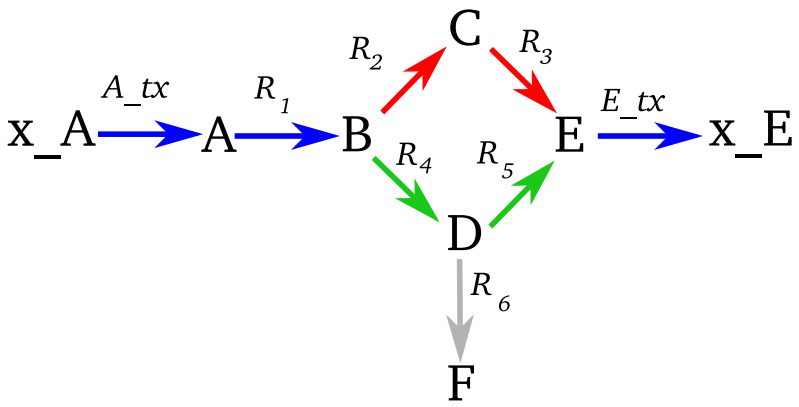
- Quantifies the degree of flux correlation of any pair of reactions for all possible steady-states
- Defined as $cos(K_i, K_j)$, where K_i and K_j are row-vectors of an *orthogonal* kernel matrix

Modularization of structural models - Reaction Correlation Coefficient



$$\mathbf{K}_{\text{orth}} = \begin{bmatrix} 0.34 & 0.37 \\ 0.34 & 0.37 \\ -0.20 & 0.52 \\ -0.20 & 0.52 \\ 0.54 & -0.15 \\ 0.54 & -0.15 \\ 0.34 & 0.37 \end{bmatrix} \Longrightarrow \mathbf{\Phi} = \begin{bmatrix} 1.0 & \mathbf{1.0} & 0.45 & 0.45 & 0.45 & 0.45 & \mathbf{1.0} \\ \mathbf{1.0} & 1.0 & 0.45 & 0.45 & 0.45 & 0.45 & \mathbf{1.0} \\ 0.45 & 0.45 & 1.0 & \mathbf{1.0} & -0.6 & -0.6 & 0.45 \\ 0.45 & 0.45 & \mathbf{1.0} & 1.0 & -0.6 & -0.6 & 0.45 \\ 0.45 & 0.45 & -0.6 & -0.6 & 1.0 & \mathbf{1.0} & 0.45 \\ 0.45 & 0.45 & -0.6 & -0.6 & \mathbf{1.0} & 1.0 & 0.45 \\ \mathbf{1.0} & \mathbf{1.0} & 0.45 & 0.45 & 0.45 & 0.45 & 1.0 \end{bmatrix} \begin{matrix} A\_tx \\ R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ E\_tx \end{matrix}$$

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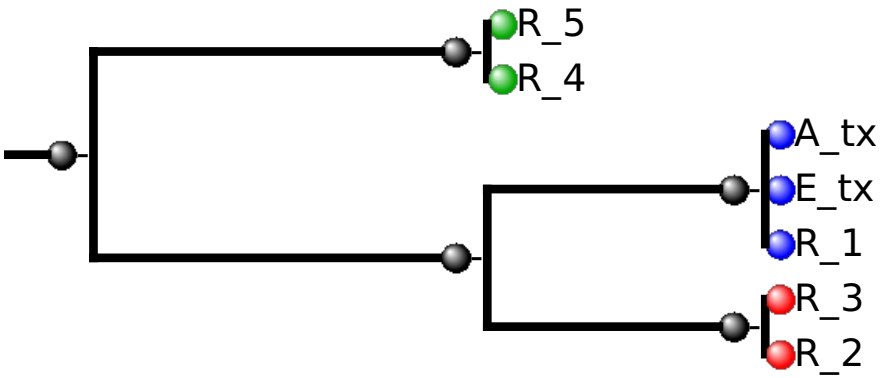
Modularization of structural models - Metabolic trees



- Matrix Φ can be visualized as a hierarchical tree

Linear Programming in metabolic modelling - Flux Balance Analysis

- FBA - optimal assignment of reaction fluxes, given a “goal” (e.g. growth yield maximization, flux minimization), and a set of constraints (e.g. rates of nutrient uptake, rates of biomass production)

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- FBA - optimal assignment of reaction fluxes, given a “goal” (e.g. growth yield maximization, flux minimization), and a set of constraints (e.g. rates of nutrient uptake, rates of biomass production)
- Most applications of FBA concerned with analysis of solutions obtained with fixed constraints

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- The Φ matrix gives the reaction correlations based on all possible steady states
- Flux correlations can also be obtained by FBA
- Variation of LP-constraints allows sampling of thermodynamically feasible subset of possible steady states
- Strategic choice of constraints allows exploration of physiologically relevant responses

Method - FBA application to correlation analysis

$$
\begin{array}{lll}
\text{minimise} & : & |\mathbf{v}| \qquad \longleftarrow \text{objective} - \text{min. sum of fluxes} \\
\text{subject to} & \left\{ \begin{array}{ll} \mathbf{Nv} = \mathbf{0} & \longleftarrow \text{steady state constraint} \\ v_j = t_j & \longleftarrow \text{output transporters fixed} \\ v_{\text{ATPase}} = J_{\text{ATPase}} & \longleftarrow \text{ATP hydrolysis variable} \end{array} \right.
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- Similarity in reaction flux response visualized using a metabolic tree

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- Model constructed as an assembly of modules:
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  - Additional reactions (31)
- Final model consisting of 911 reactions and 783 metabolites

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- Aerobic minimal media: Glucose, ammonia, sulphate, oxygen
- Fixed production rate of biomass precursors: Amino acids, DNA, RNA, cell envelope component

Results - general properties of flux solution

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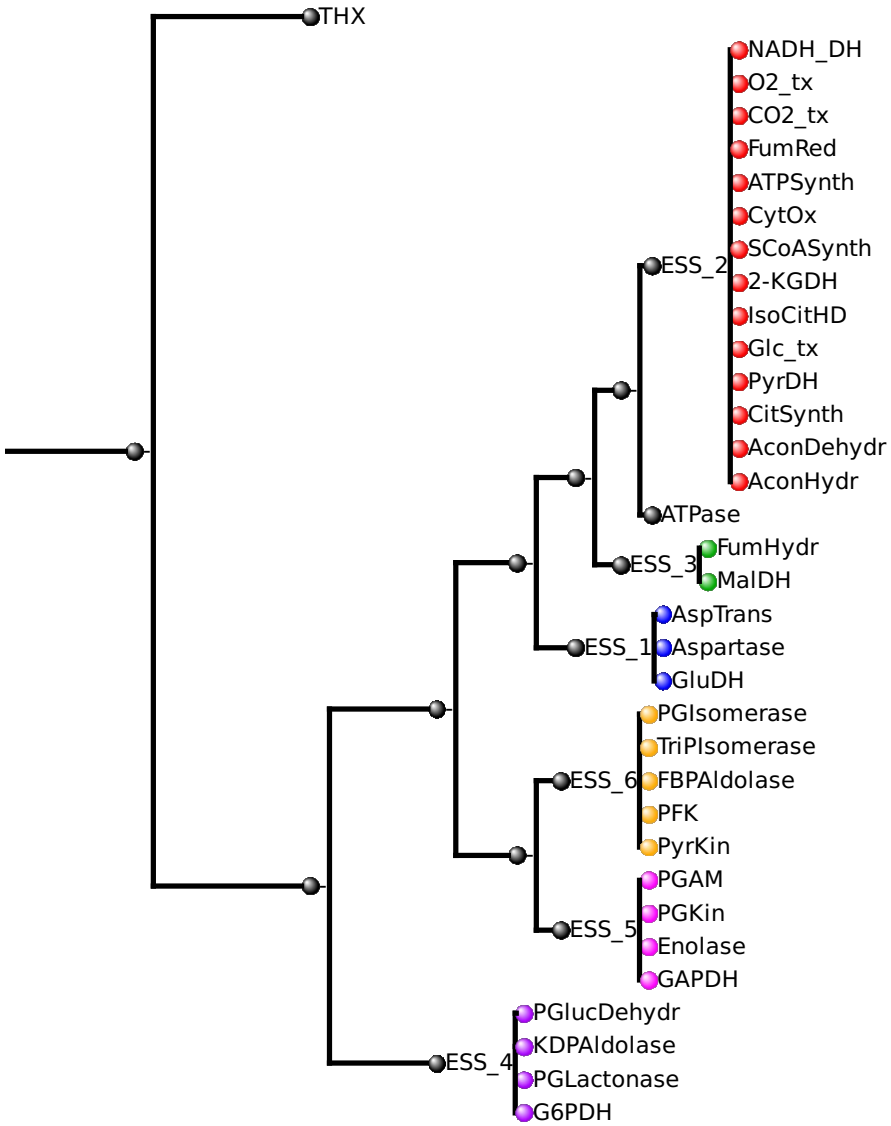
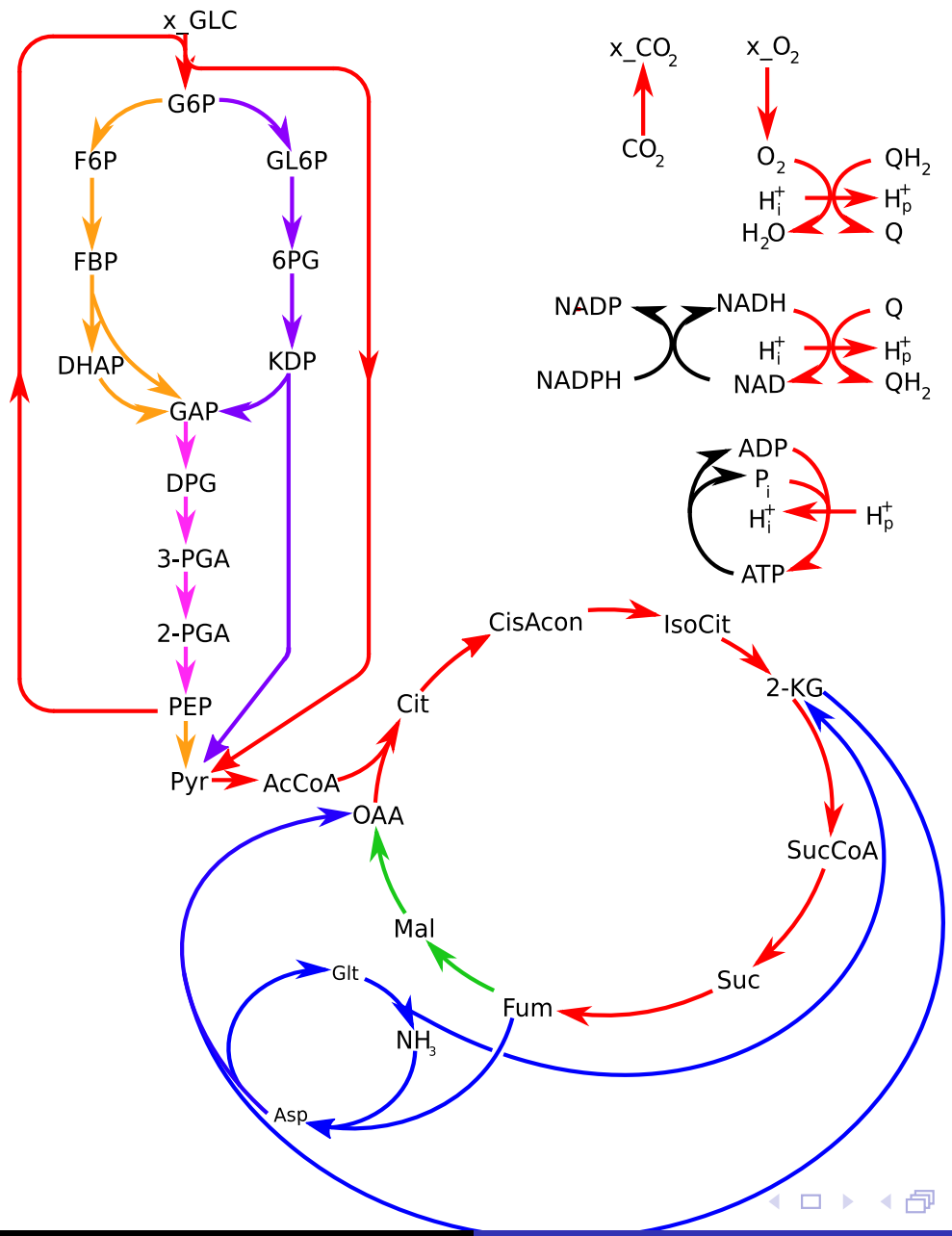
- Catabolic core model composed of ATPase and responsive reactions
- Metabolic tree constructed based on subspace of solutions obtained by ATPase variation

Results - metabolic tree



Results - catabolic network



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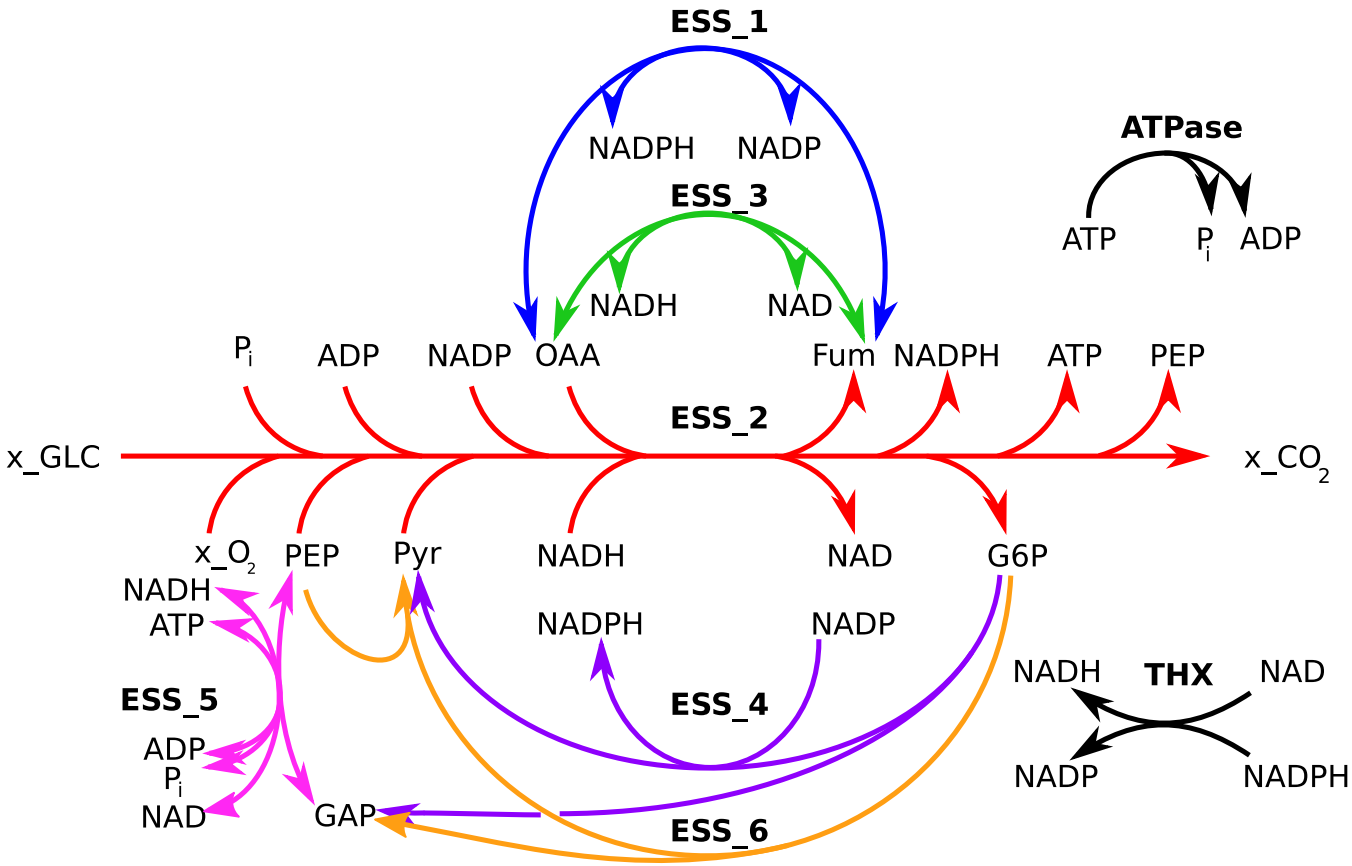
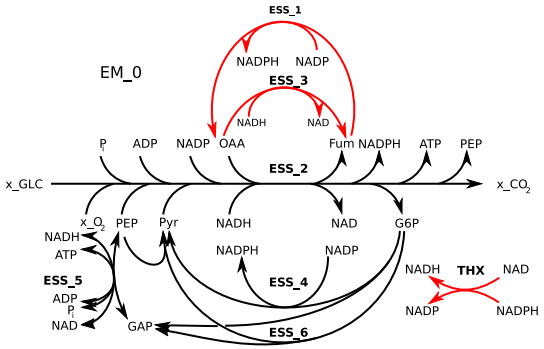
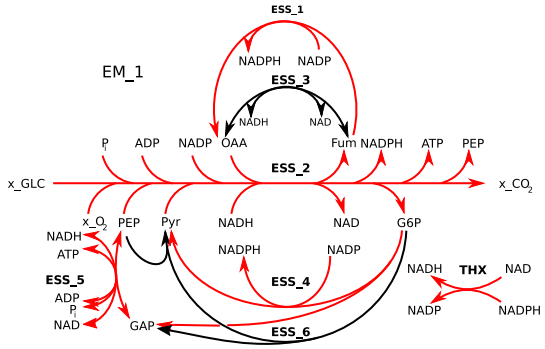
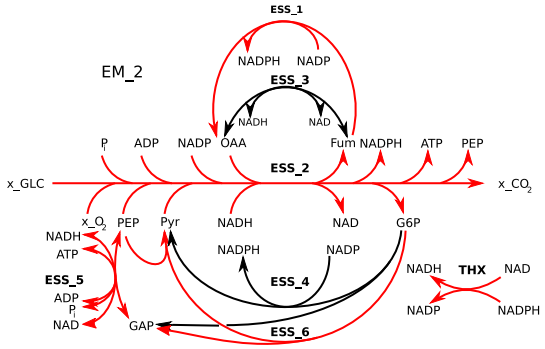


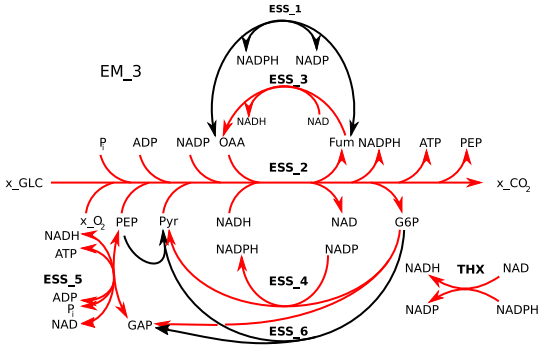
- Catabolic network condensed to enzyme subsets

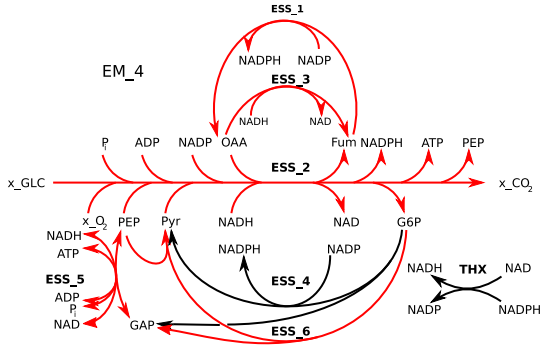
Results - elementary modes

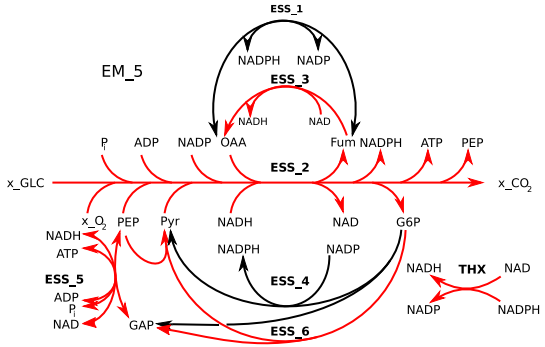


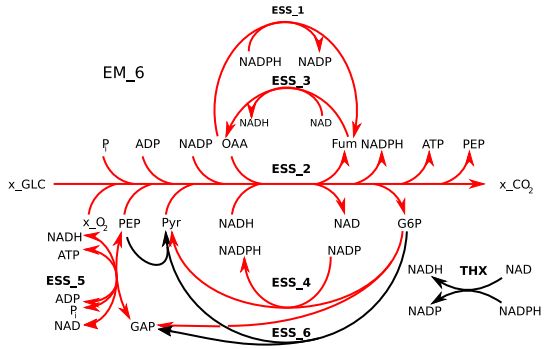




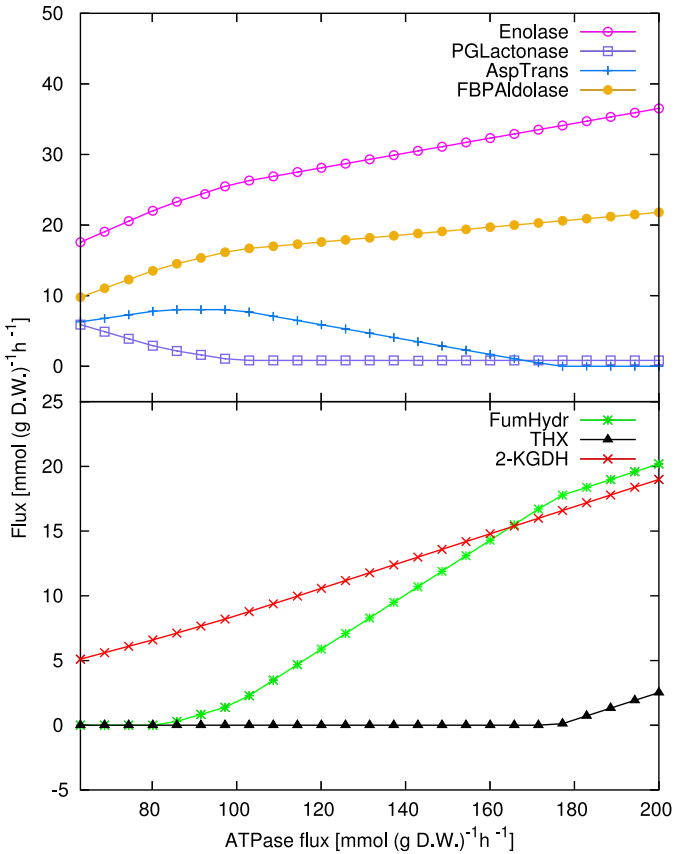






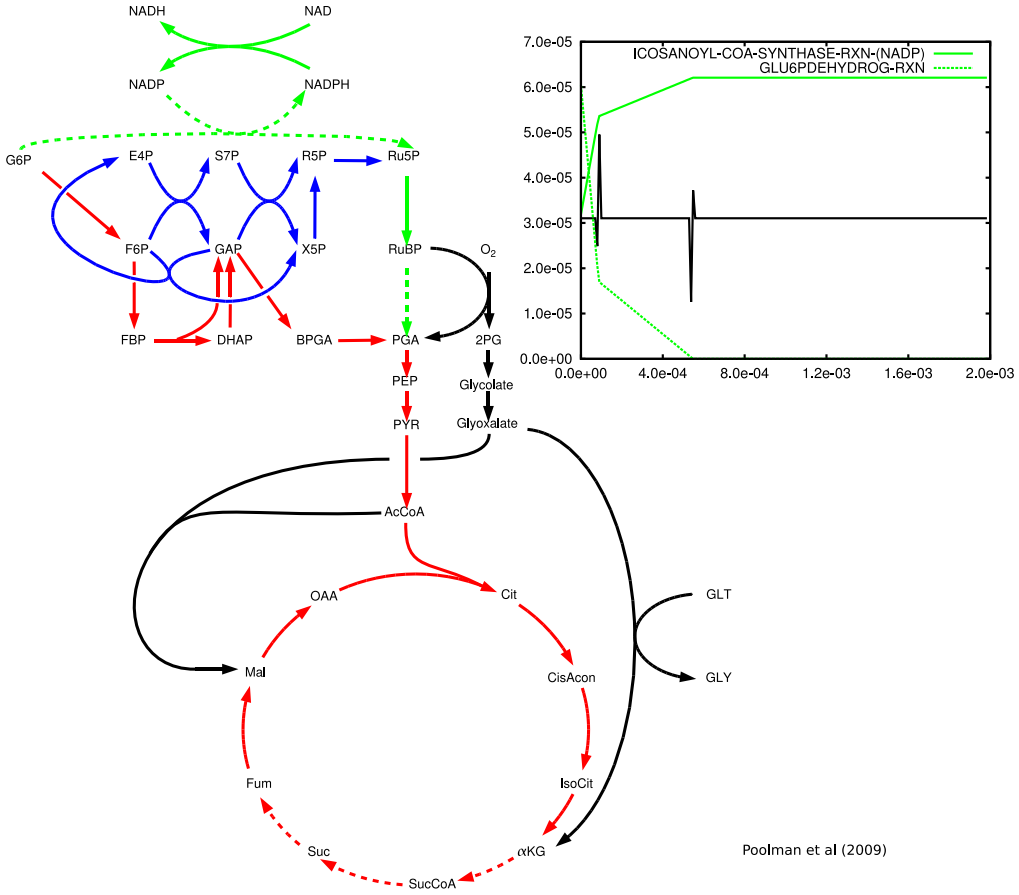


Results - flux responses



- Flux response pattern indicate a shift from NADPH yielding to NADH yielding flux distribution

Comparison with *Arabidopsis* GSM



- Functional similarity between E-D and Ox. PPP: decreased flux concomitant with increased ATPase flux

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- ATPase probing allows unbiased extraction of functional catabolic core
- Infection-relevant application: analysis suggests a small set of EMs relevant for targeting ATP regeneration

Acknowledgment

- Oxford Brookes University
  - Dr. Mark Poolman
  - Prof. David Fell
- Animal Health and Veterenary Laboratories Agency
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