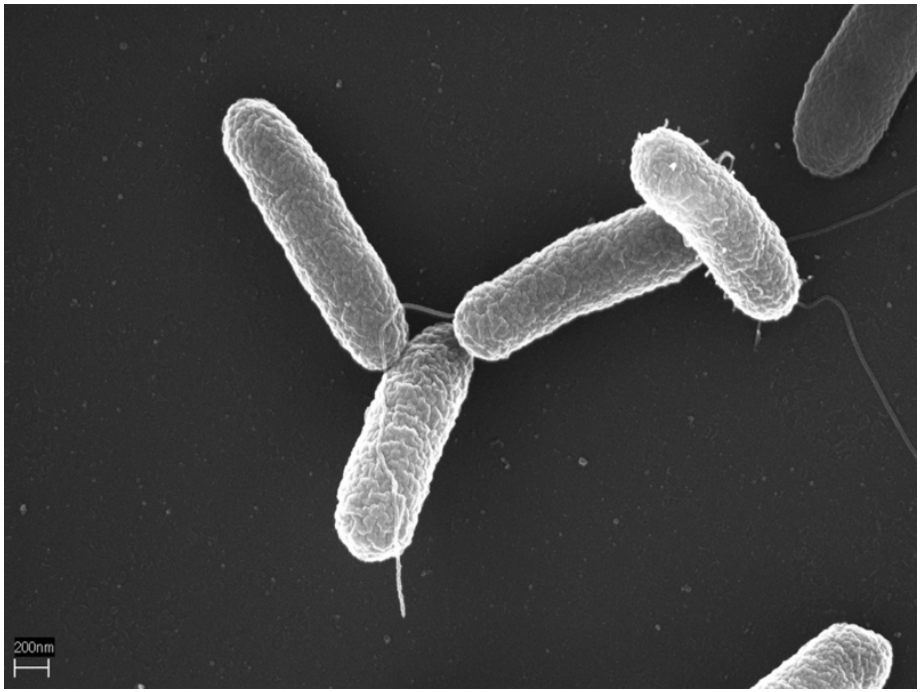
Application: Drug targets in *S. typhimurium*

Salmonella typhimurium



- Gram negative enteric bacterium.
- Pathogen of Humans and other mammals.
- Closely related to other, more pathogenic *Salmonella* serotypes.
- Commonly used as a representative *Salmonella* model.

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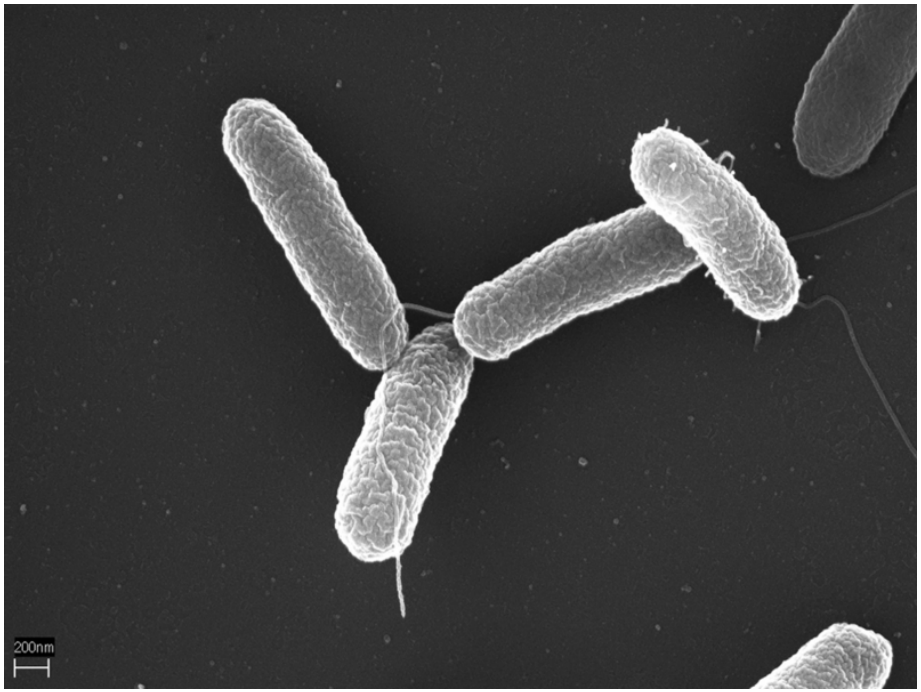

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Can we identify reactions whose inhibition will inhibit growth?

Genome-scale model of *Salmonella* metabolism

- Model constructed as an assembly of modules:
  - 816 Reactions extracted from BioCyc
  - 61 Transport reactions
  - 35 Additional reactions
- Final model consisting of 912 reactions and 783 metabolites

Method - FBA application to *Salmonella* metabolism

$$
\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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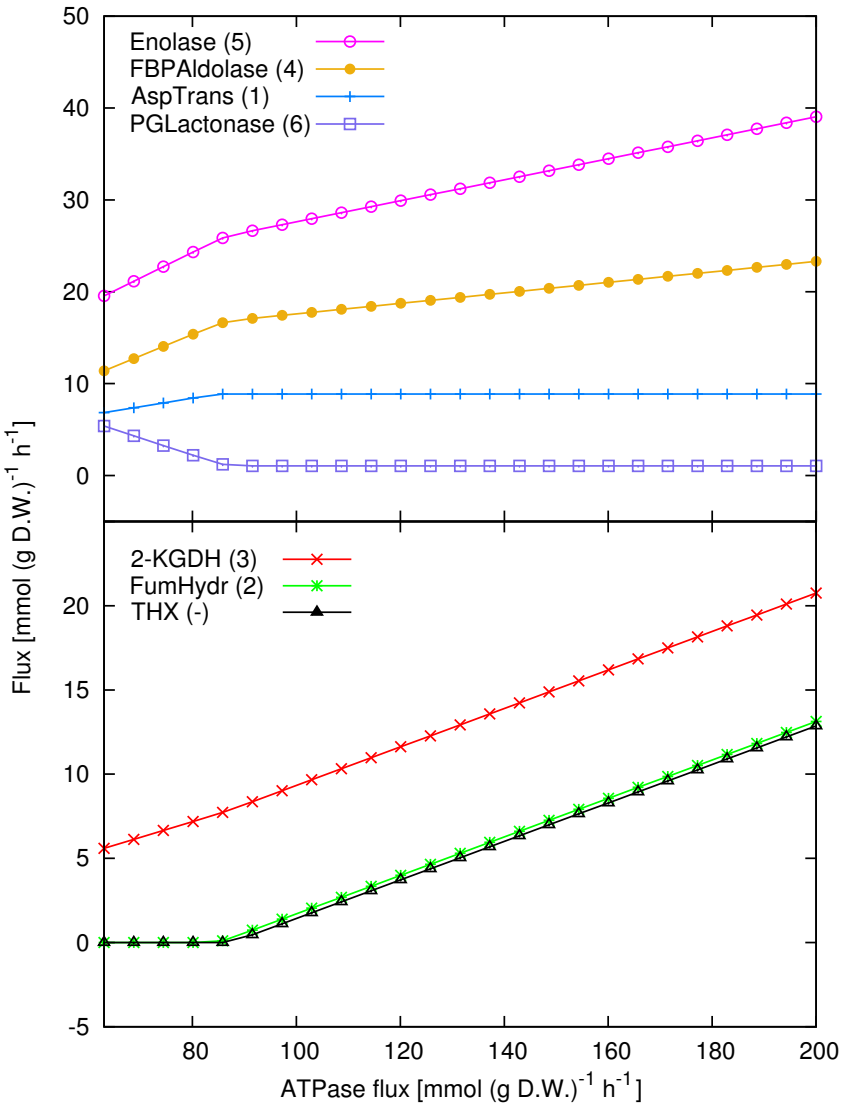
- Aerobic minimal media: Glucose, ammonia, sulphate, oxygen
- Fixed production rate of biomass precursors: Amino acids, DNA, RNA, cell envelope component
- Repeatedly solve with increasing ATP demand.

Results - general properties of flux solution

- 304 reactions, out of 912, required for biomass precursor synthesis
- 33 reactions responsive to ATP demand variation

Response to varying demand for ATP



Application: Drug targets in *S. typhimurium*

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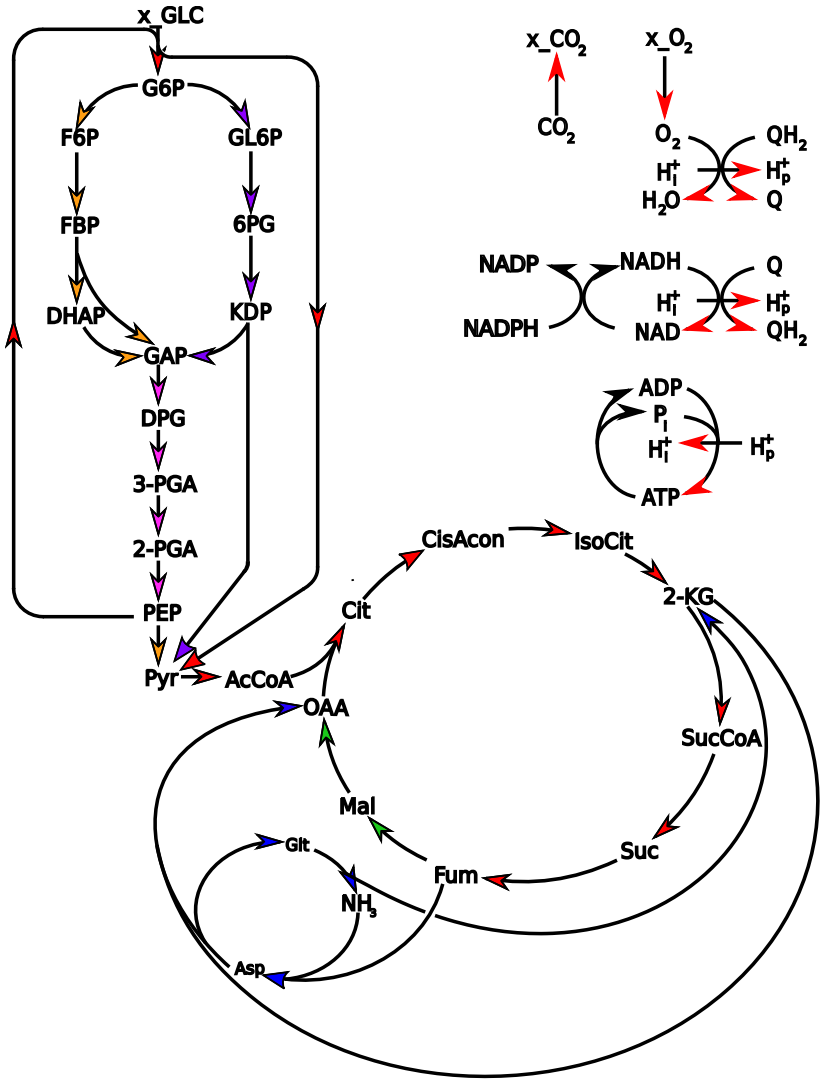

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- The reactions whose flux increases in response to increasing ATP demand form a single connected network:
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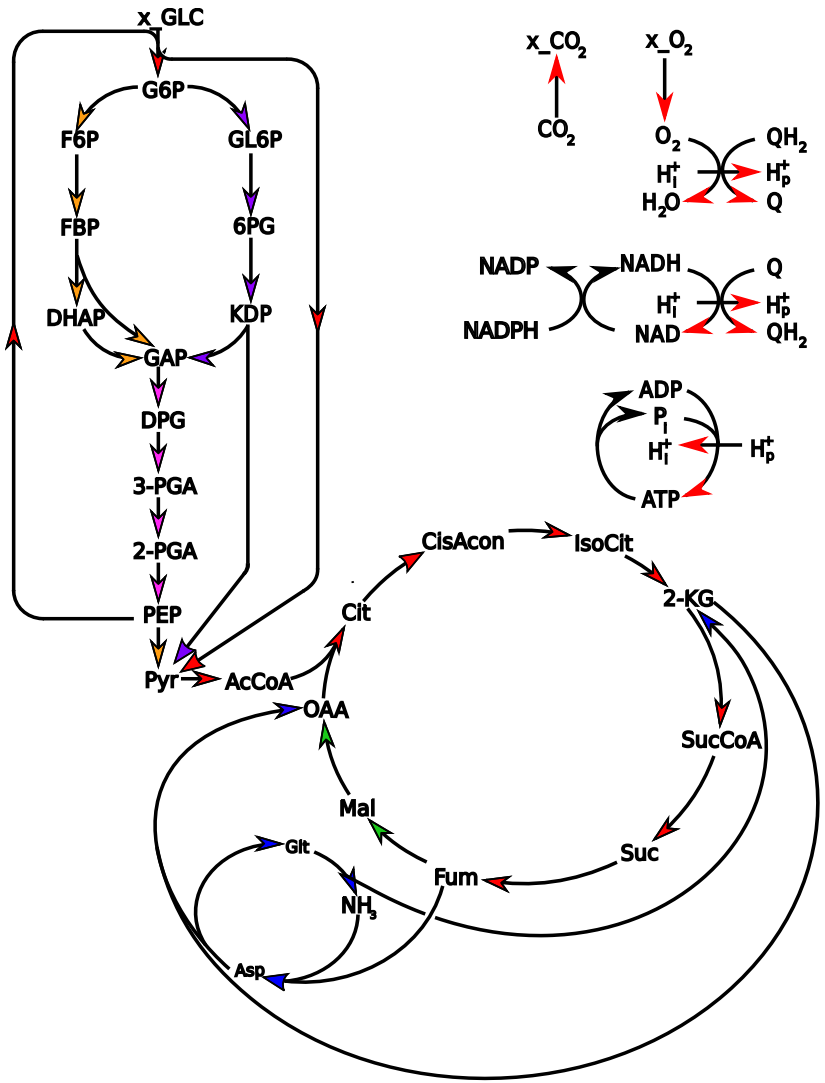

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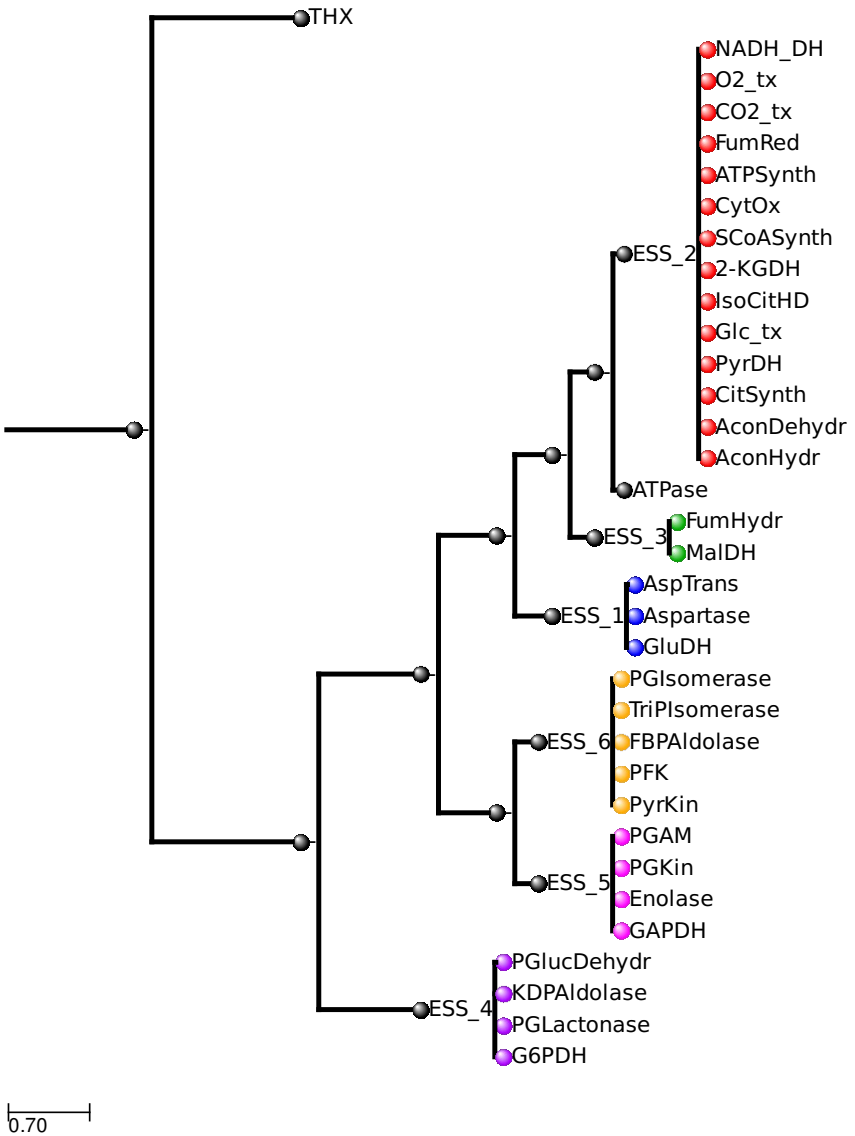

Application: Drug targets in *S. typhimurium*

- The reactions whose flux increases in response to increasing ATP demand form a single connected network:
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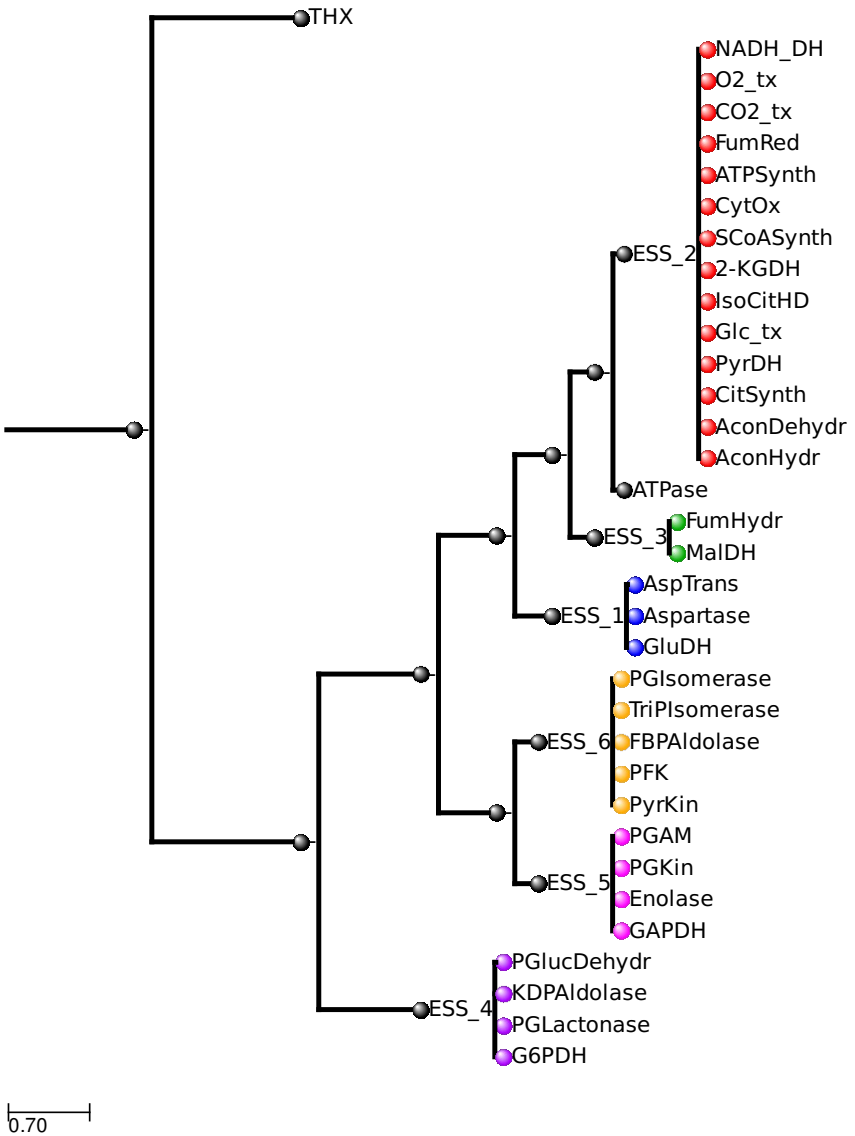
- This identifies 6 sets of reactions with similar responses



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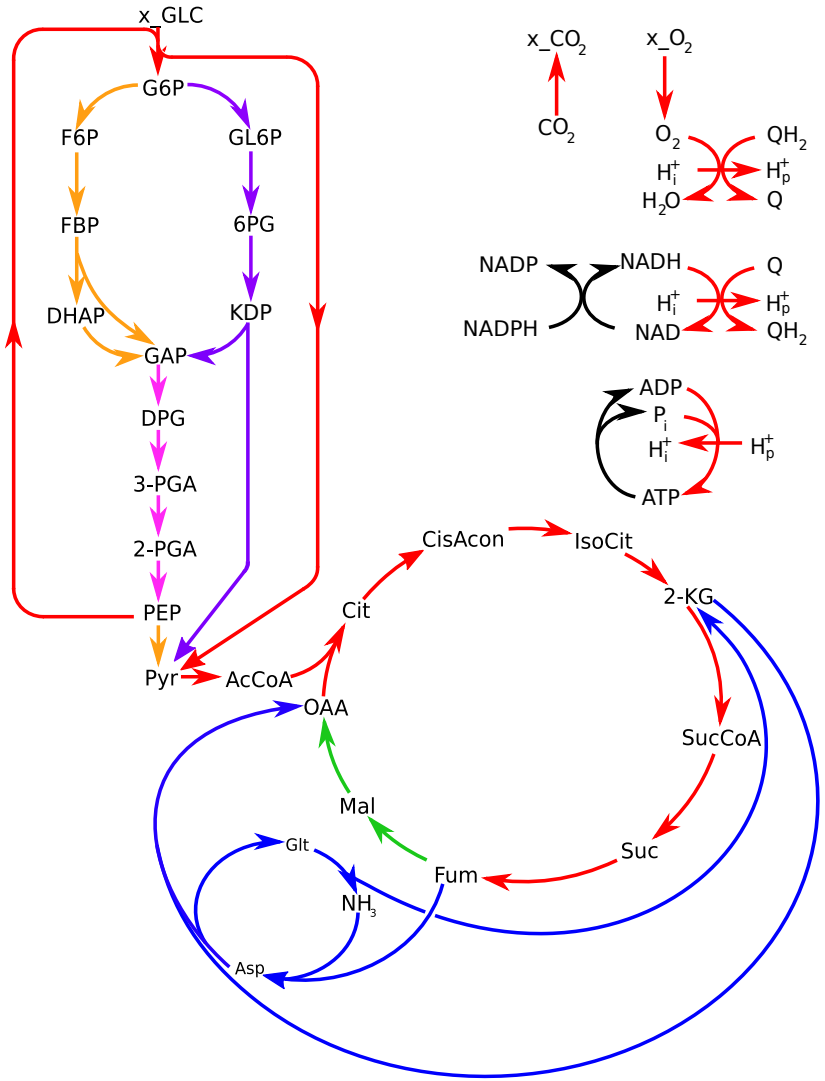
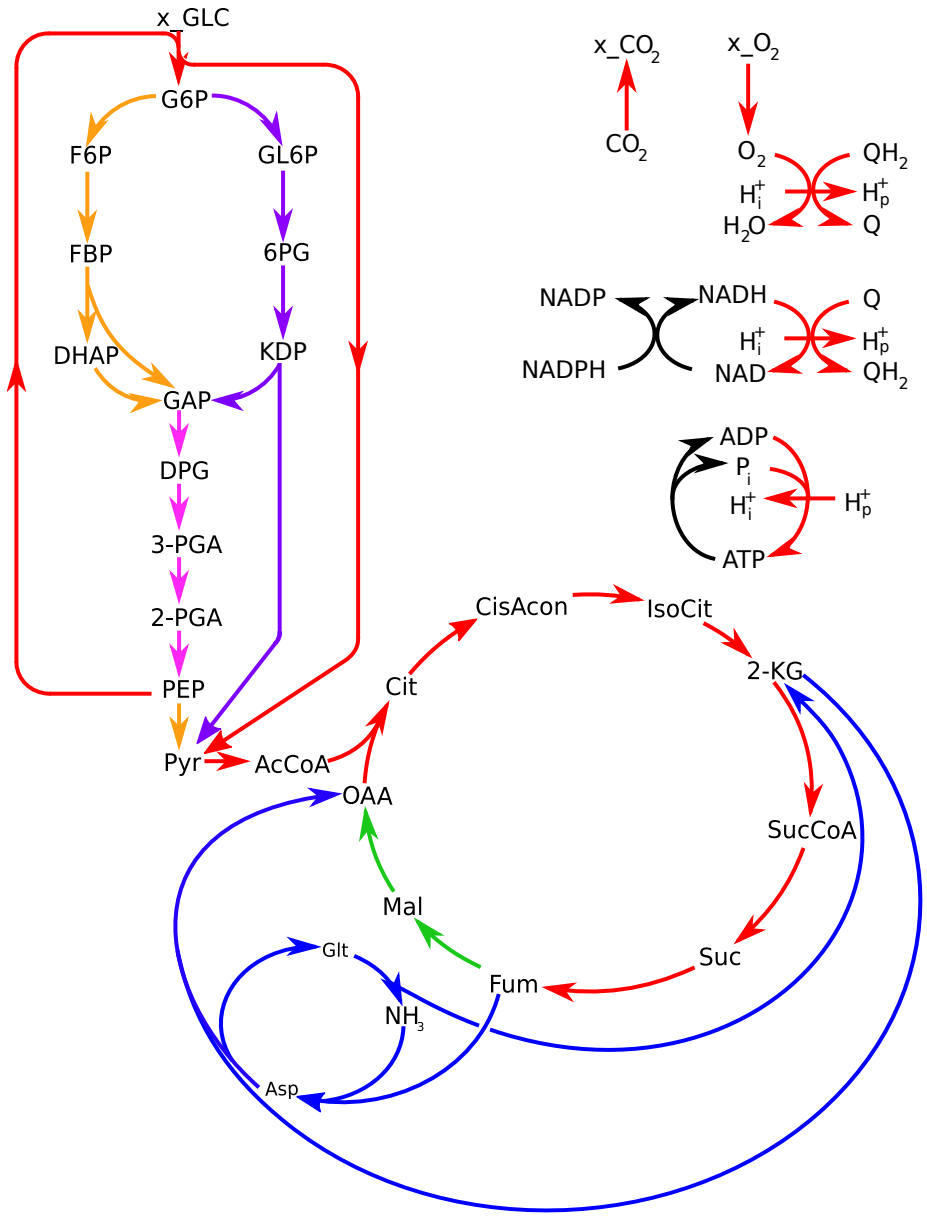


Application: Drug targets in *S. typhimurium*

- In the isolated catabolic core the correlated reactions form 6 subsets.



Application: Drug targets in *S. typhimurium*

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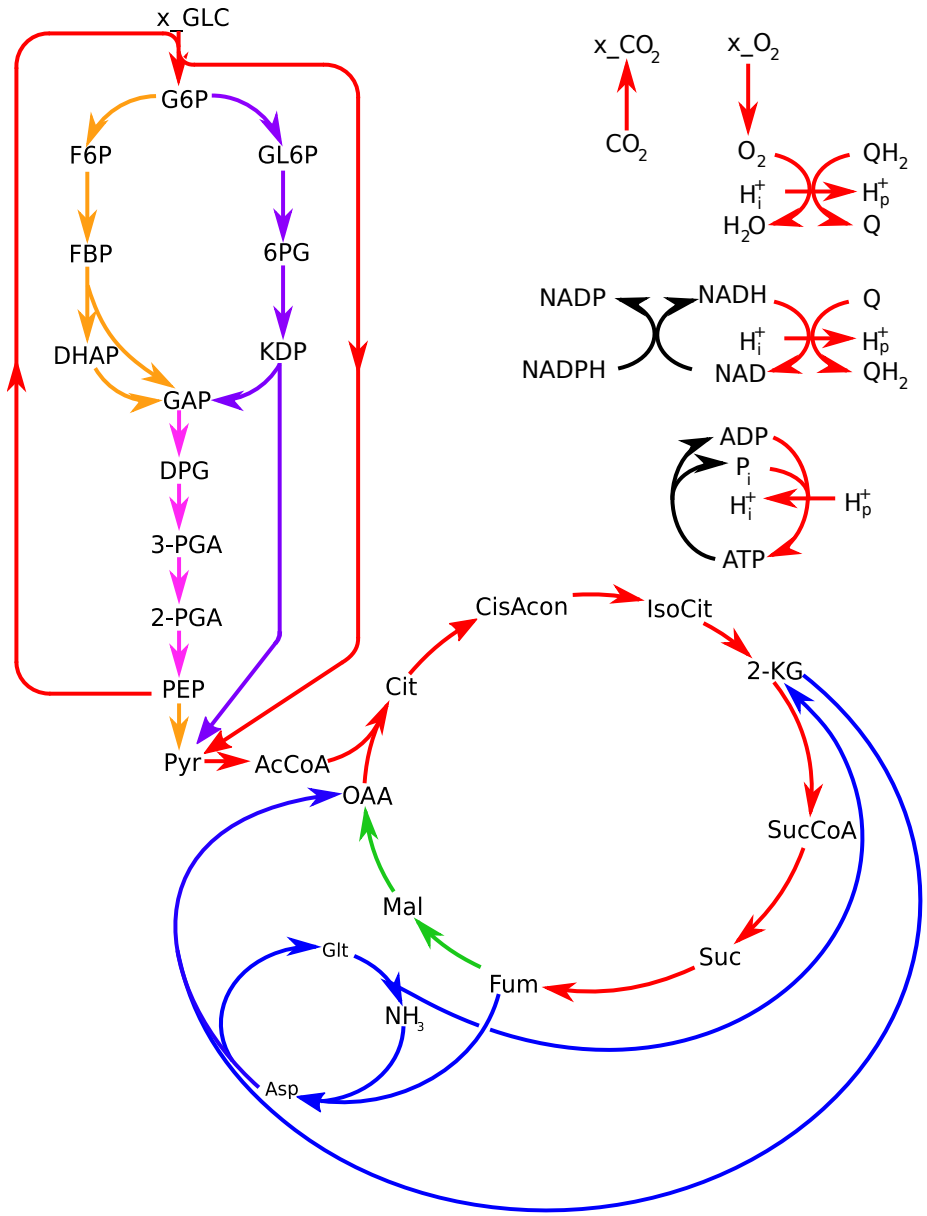
- There are 5 elementary modes producing ATP.



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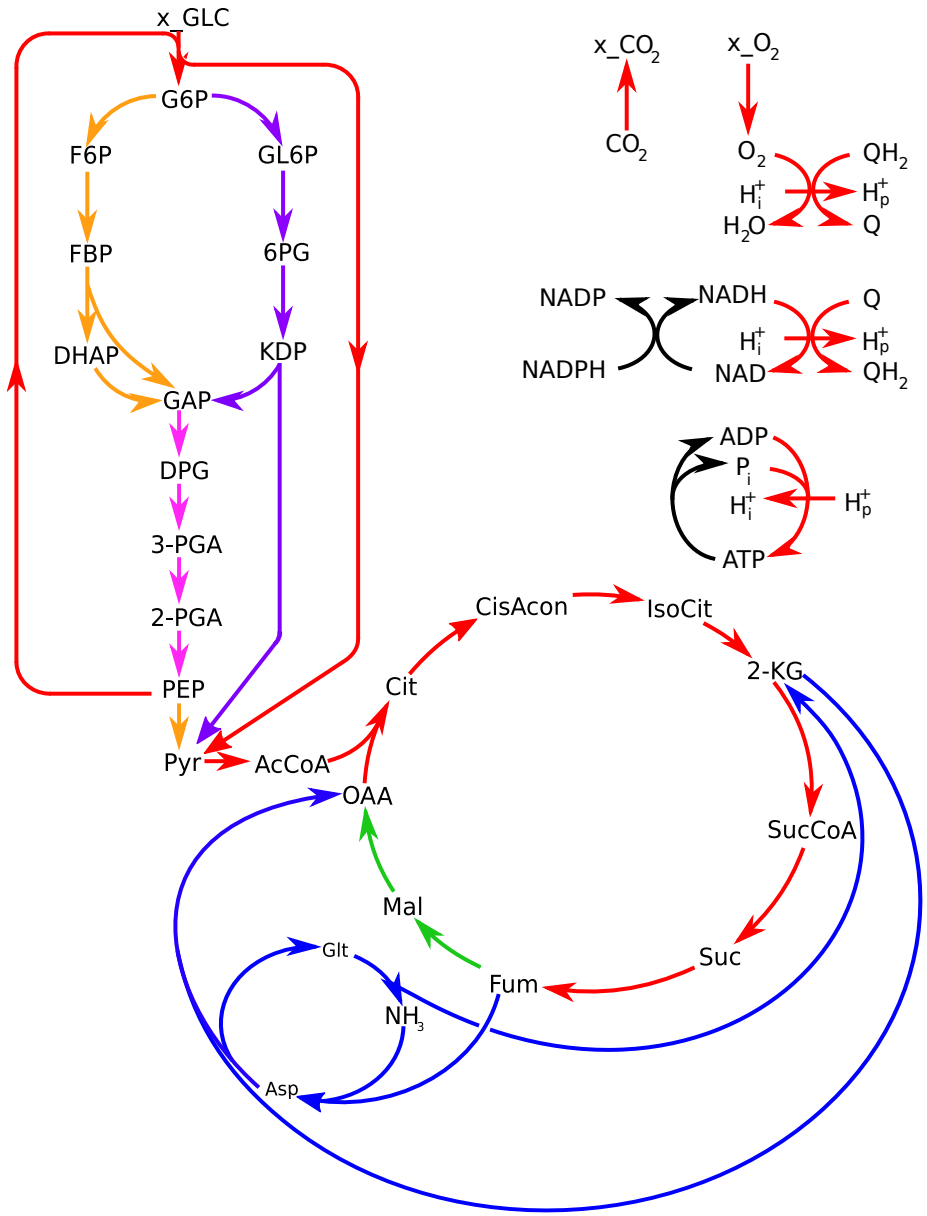
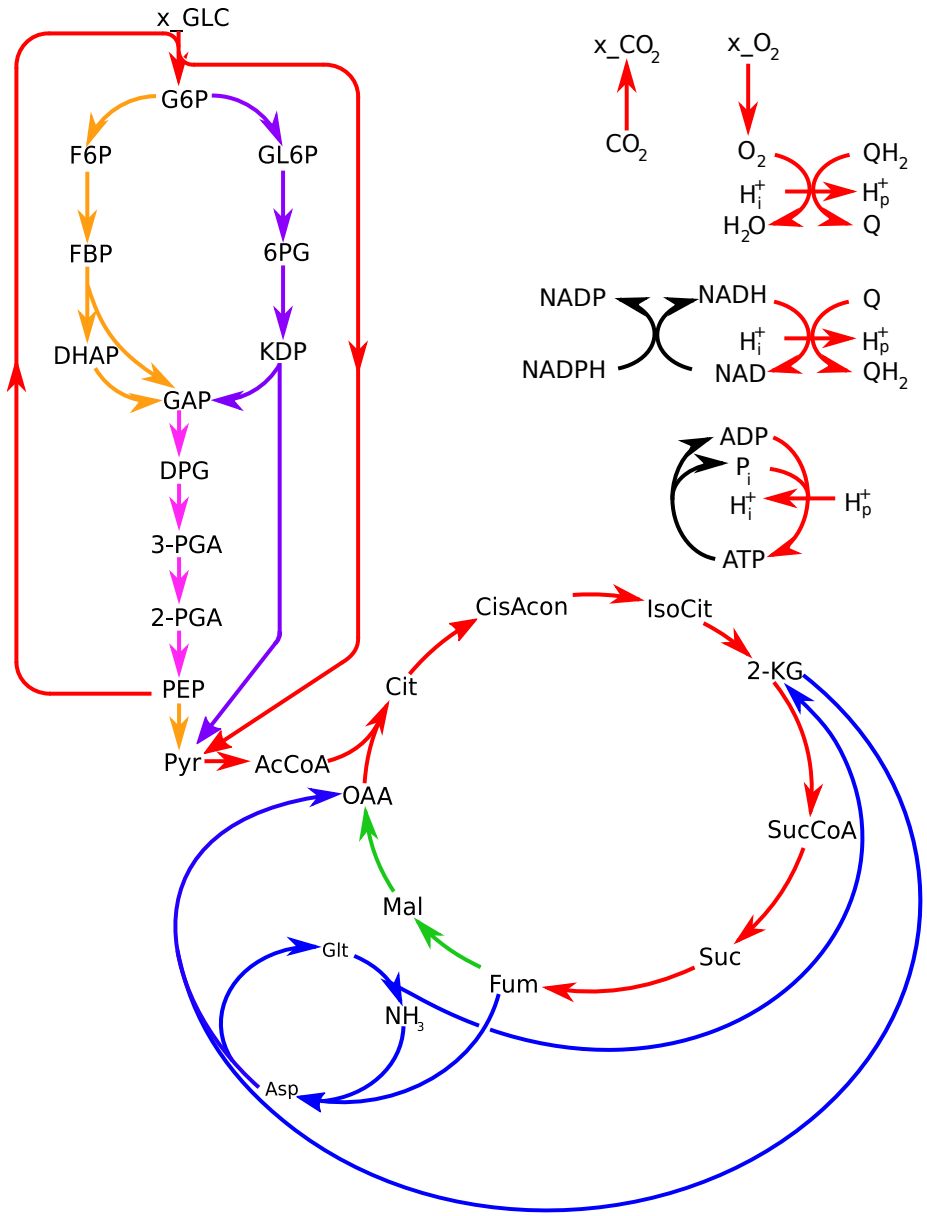
- There are 5 elementary modes producing ATP.
- Note the involvement of nitrogen metabolism.

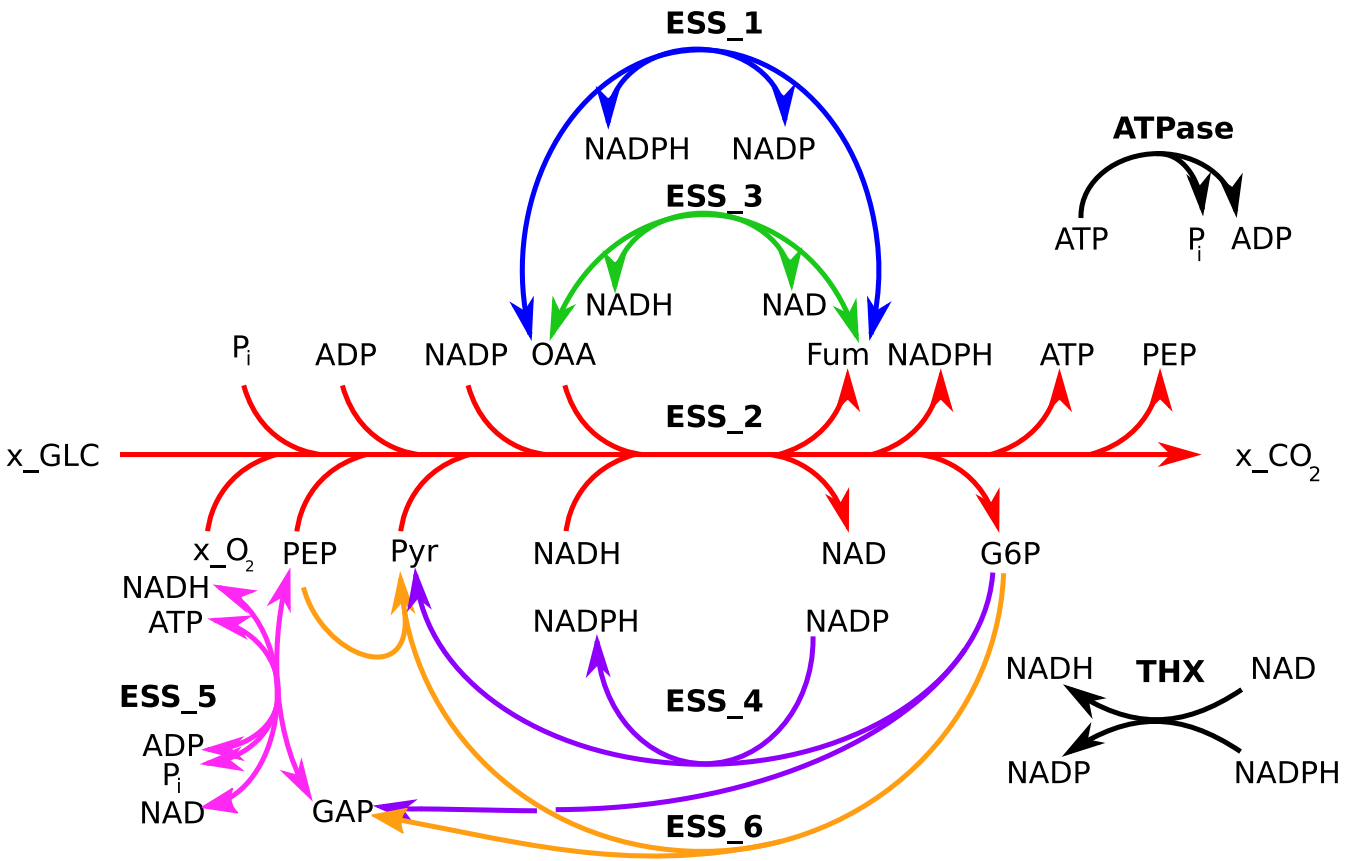


Application: Drug targets in *S. typhimurium*

- In the isolated catabolic core the correlated reactions form 6 subsets.
- There are 5 elementary modes producing ATP.
- Note the involvement of nitrogen metabolism.
- It is now easy catabolic core.



Results - catabolic core - as enzyme subsets

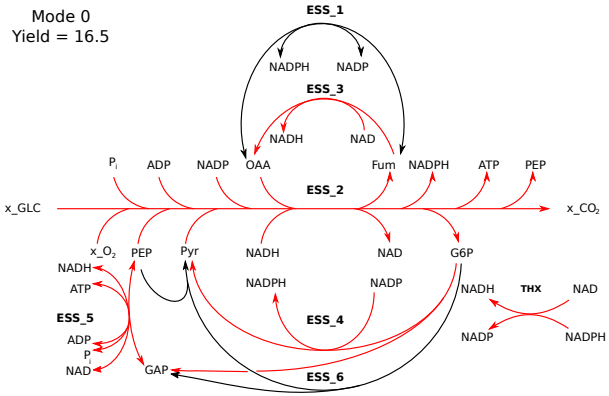


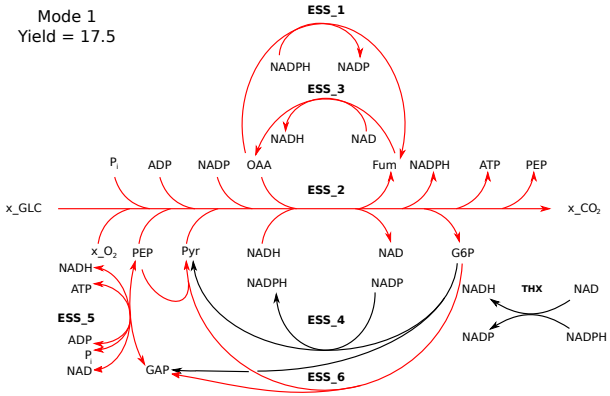
Results - elementary modes of the catabolic core

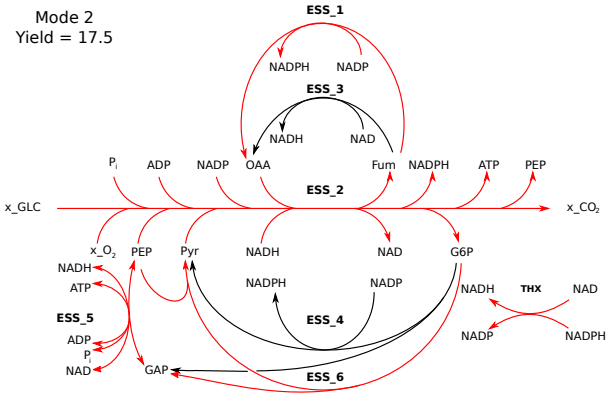
The six reaction subsets can be combined to generate a total of five elementary modes:

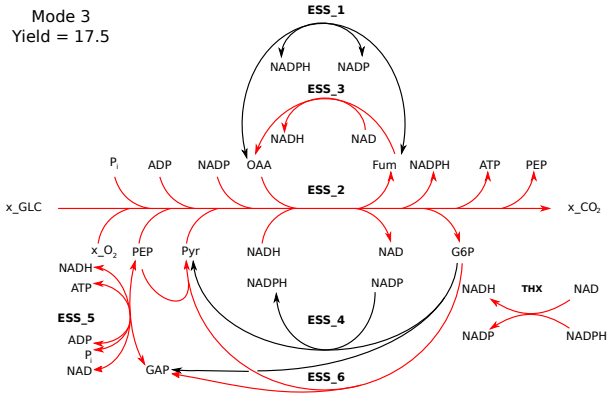
EM 1	1	2	3		5	
EM 2	1	2		4	5	
EM 3	1	2			5	6
EM 4		2	3	4	5	
EM 5		2	3		5	6

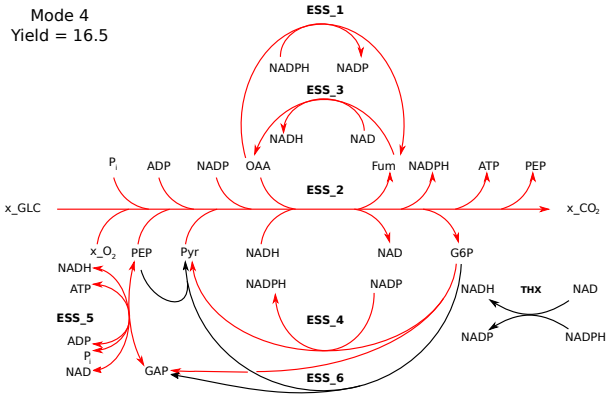
Results - catabolic core

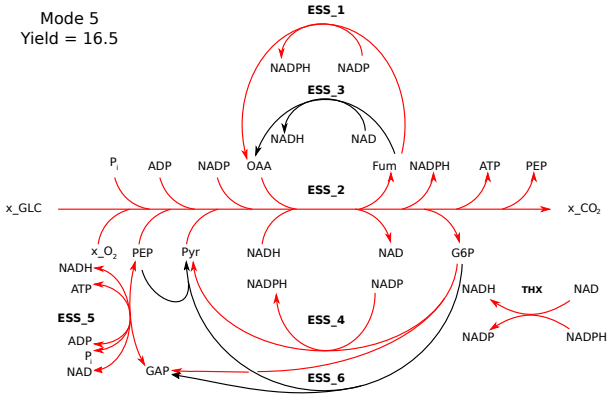












Experimental

F rom this we can identify:

1. Reactions whose removal, singly or in combination, abolish the production of ATP in the catabolic core.
2. Identify the impact this has on the *whole* model.
3. From 2 identify candidates for KO experiments.

Experimental

Hartman *et al.* (2013), *Microbiolgy*,
Identification of potential drug targets in *Salmonella* Typhimurium using metabolic modelling and experimental validation., **vol**, pp pages.

Acknowledgements

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Hartman *et al.* (2014), *Microbiolgy*, Identification of potential drug targets in *Salmonella* Typhimurium using metabolic modelling and experimental validation., **160**, pp 1252–1256.