

Discreet mathematical models applied to genetic regulation of metabolic networks

Objectives

Develop a discreet model that will integrate genetic and metabolic networks

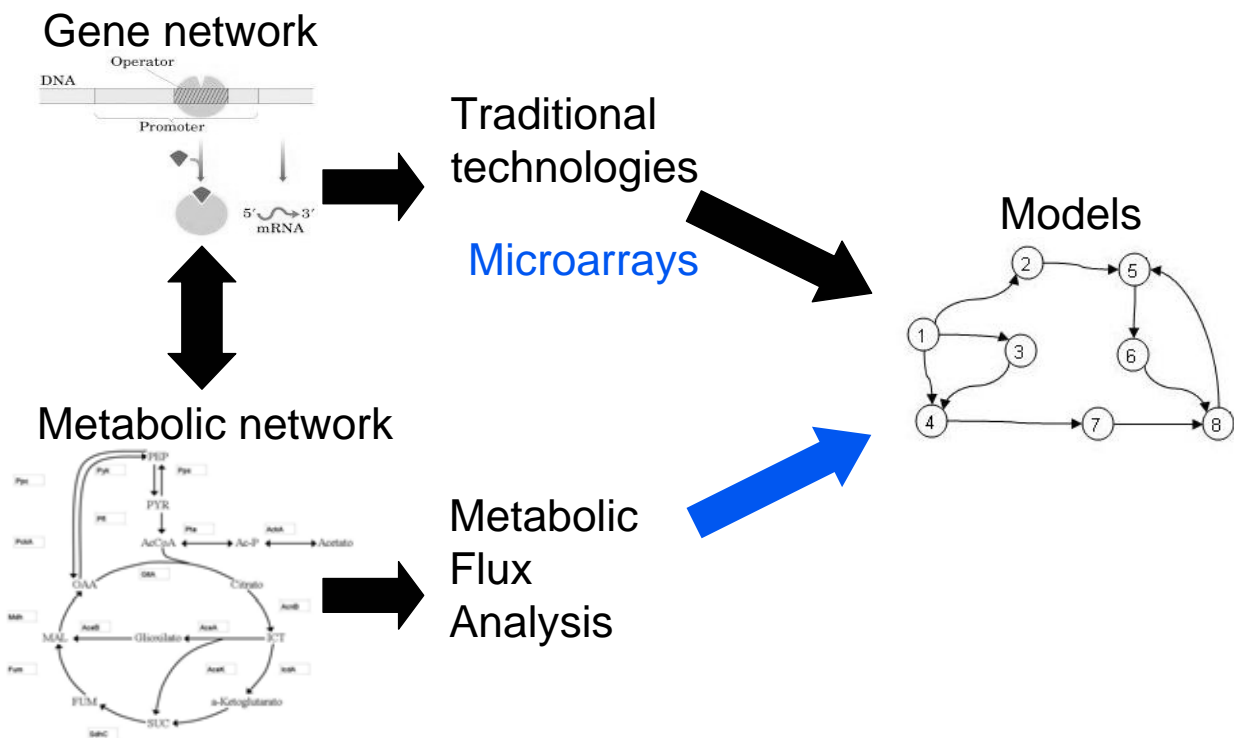
Correlate data on Microarrays and on Metabolic Flux Analysis

Where: Adaptation of *E. coli* to different nutrients

Benefits:

Understanding of biochemical interactions

Find regulators and genes



Phenomena to model

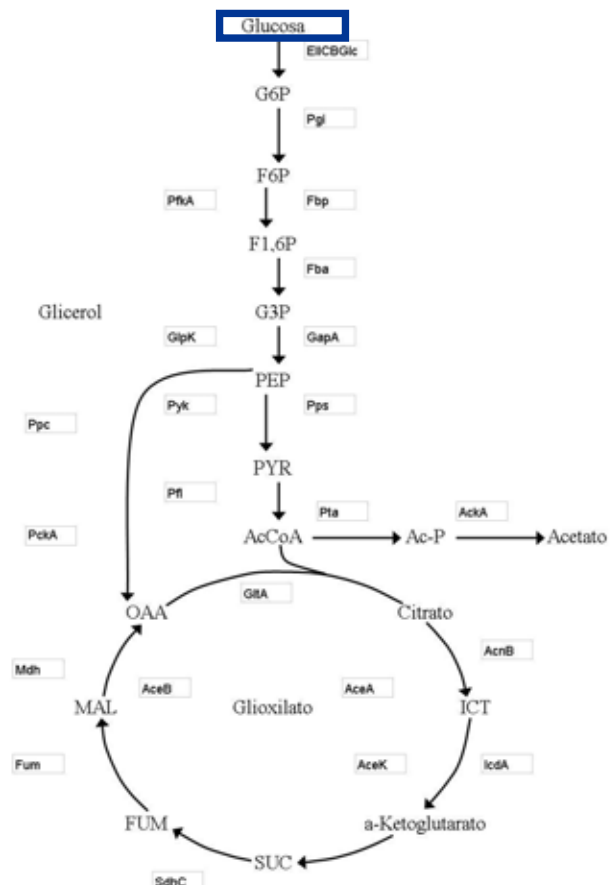
Genetic and metabolic adaptation of *E. coli* to different nutrients

Substrates: Glucose, Glycerol and Acetate

Glycolysis and TCA

8 possible substrate combinations → 8 Phenotypes

Phenomena has been described using Microarrays (MA) and Metabolic Flux Analysis (MFA)



Phenomena to model

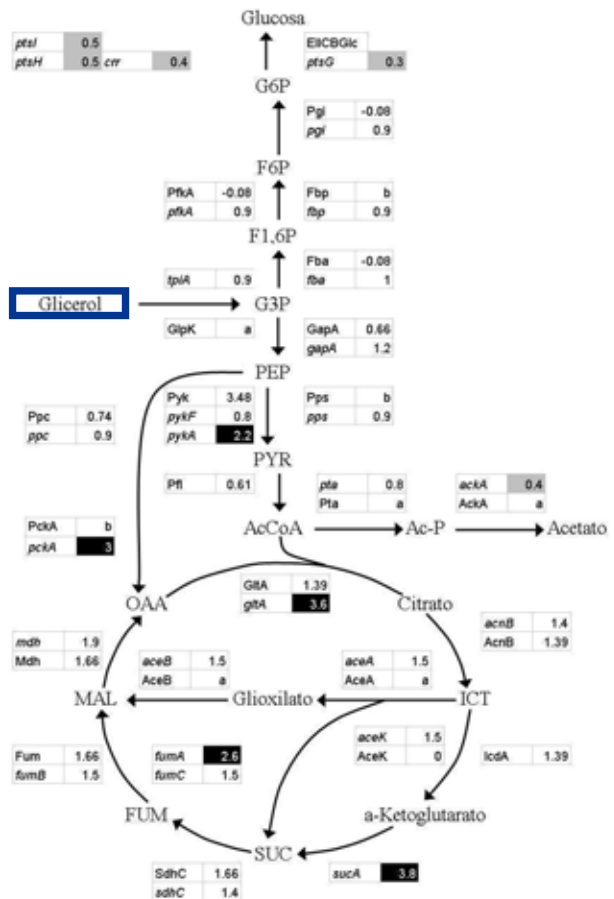
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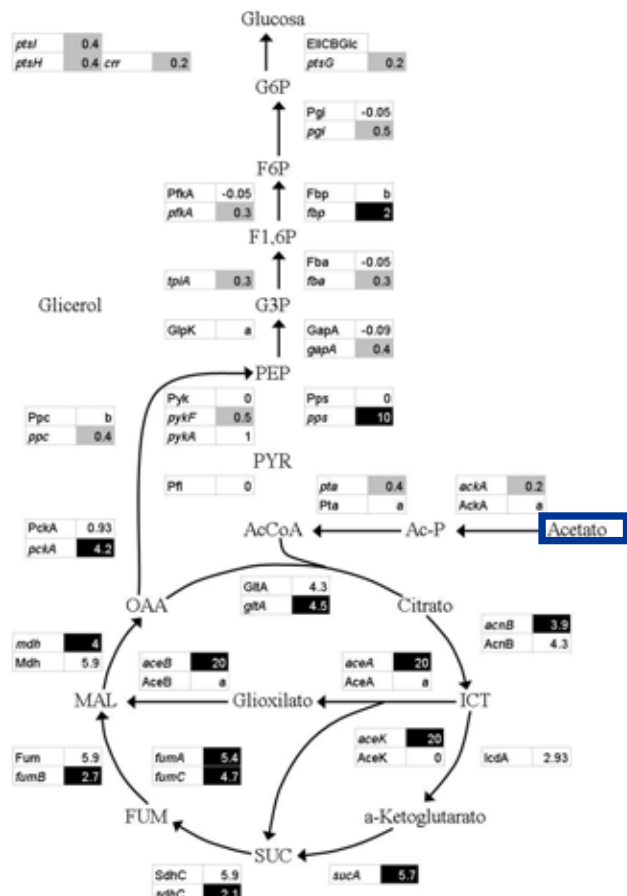
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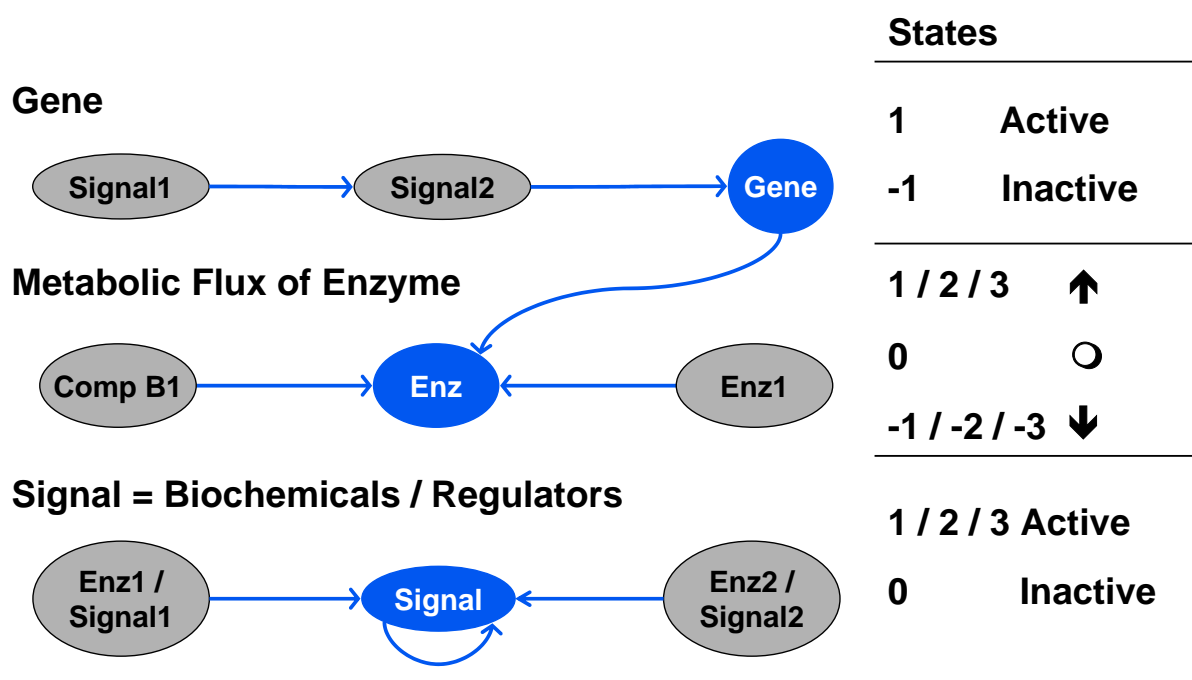
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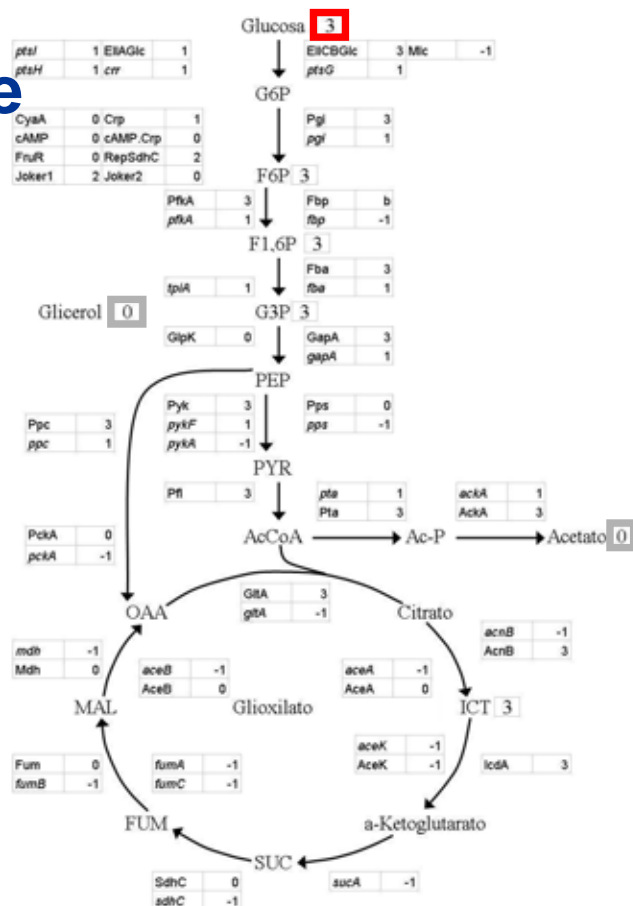


Model Building

1. Define nodes: genes, regulators, biochemical compounds and enzymes
2. Determine interactions
3. Assign state of activation to nodes
4. Describe phenotypes using nodes and states
5. Construction of discrete functions of activation
6. Study of model dynamics: find attractors

Building of discrete functions of activation





Atractor = Phenotype

Each attractor of model corresponds to a phenotype

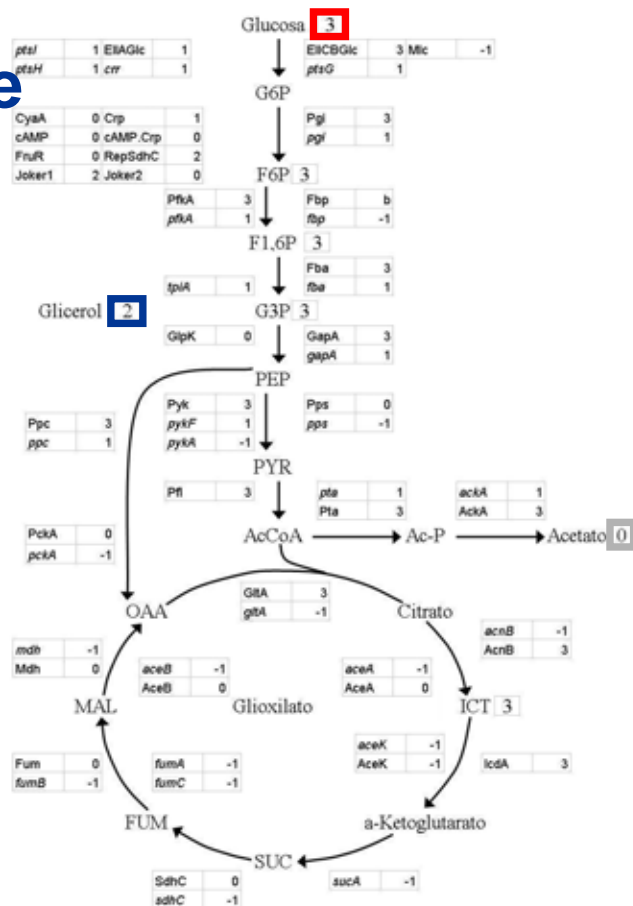
Atractors are very stable

Similarity between Atractors with:

Glucose present

Glycerol present and Glucose absent

Only Acetate present and All others absent



Atractor = Phenotype

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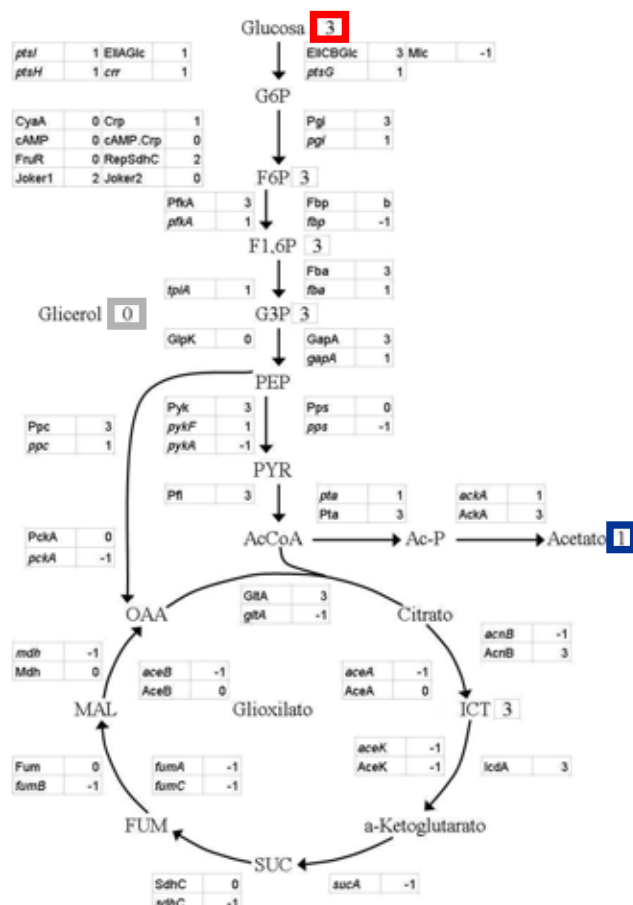
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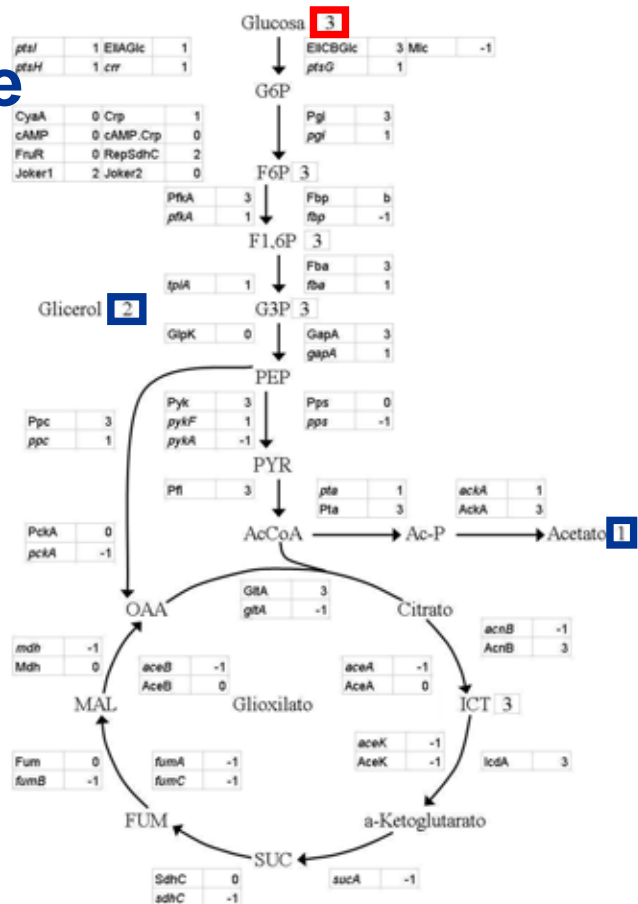
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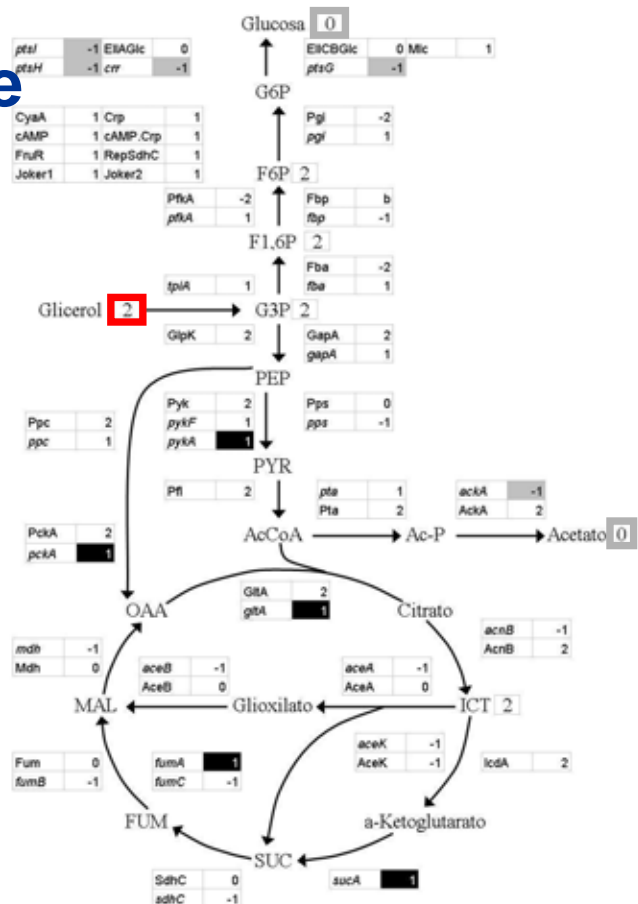
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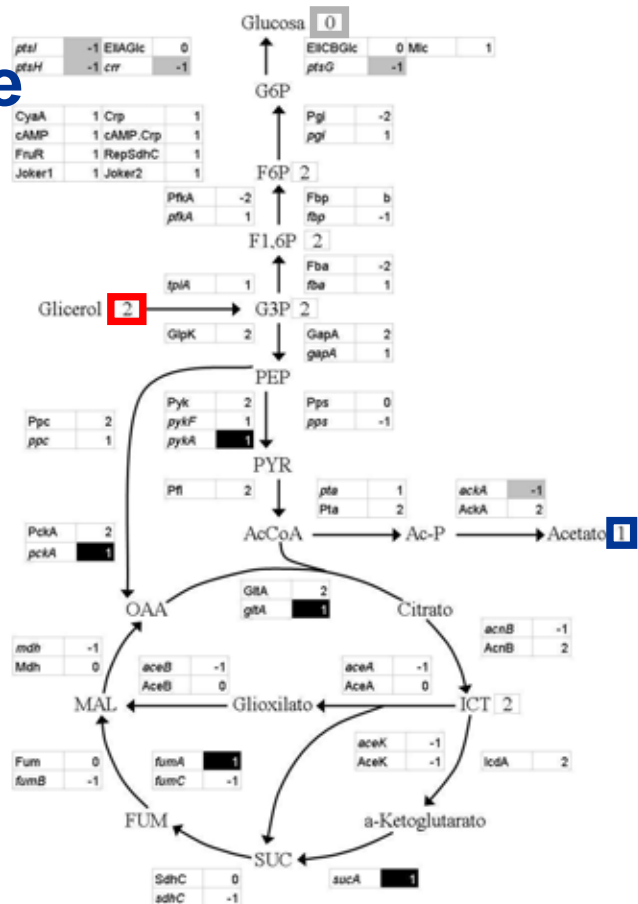
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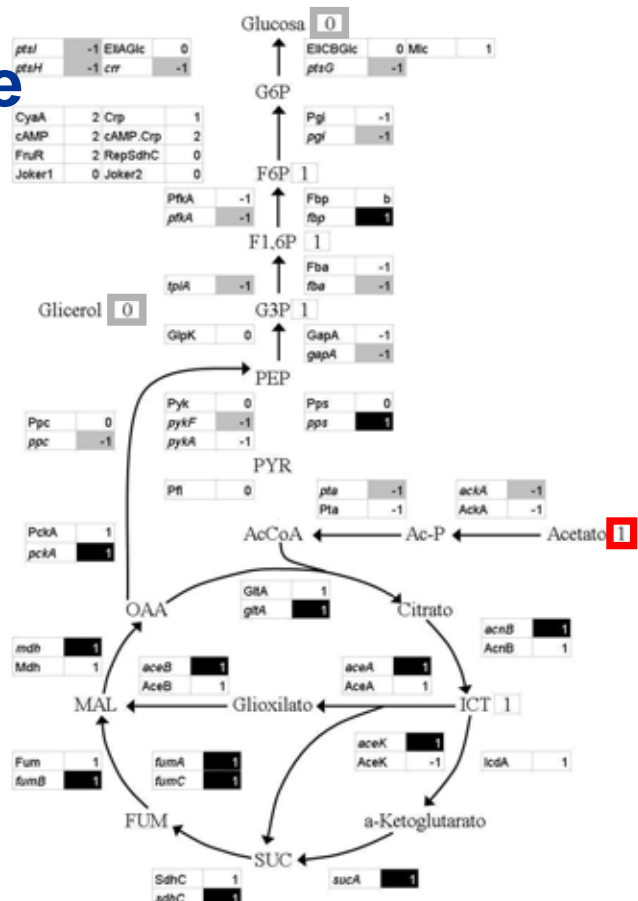
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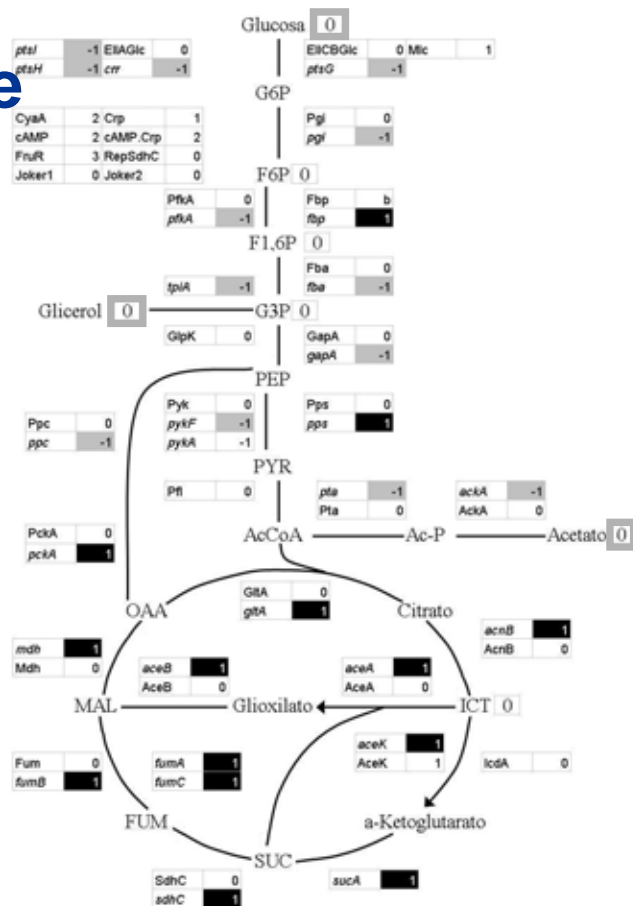
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Network is mathematically simple

Depends on Glucose, Glycerol and Acetate

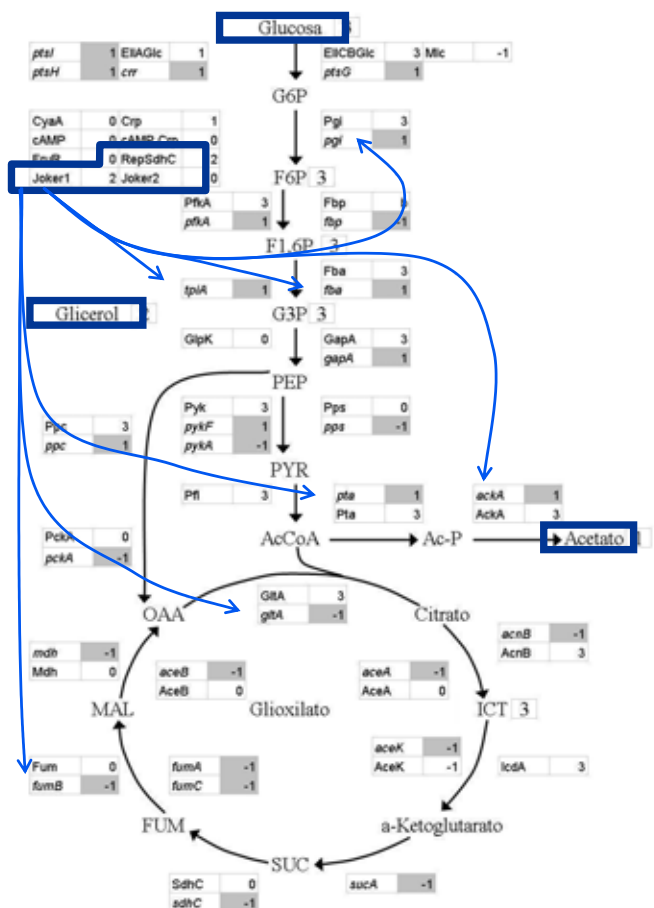
Regulators transmit information

It was necessary to use Fictitious Regulators

The strongest: Joker1

They suggest:

Similar regulation mechanisms
Regulation dependent on PTS



Conclusions

Model

- Simulates successfully behaviour of gene regulation of metabolic networks

- Has stable attractors which are similar to the phenotypes

- Depends on Glucose, Glycerol and Acetate, in order of importance

- Relates the results of MA and MFA

The Model suggests

- Gene activation is similar in the presence and absence of Acetate as carbon source in the medium

- Relation between unknown genes and PTS system should be investigated

Conclusions

Discreet mathematical model that:

- integrates gene regulation of metabolic networks,

- and relates results of MA and MFA