In silico Evolution of Early Metabolism

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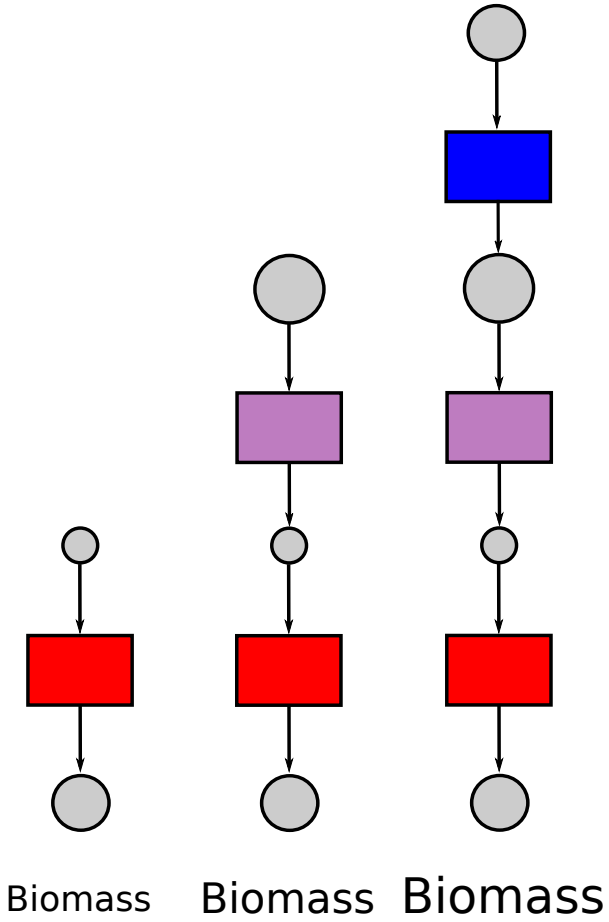
Motivation

- Understand evolutionary mechanisms of biological systems
- Study the early development of metabolism
  - not observable by conventional approaches
- Analyse different hypotheses for pathway evolution
  - finding scenarios for observations in present data
- Answers beyond analyzing real-world data

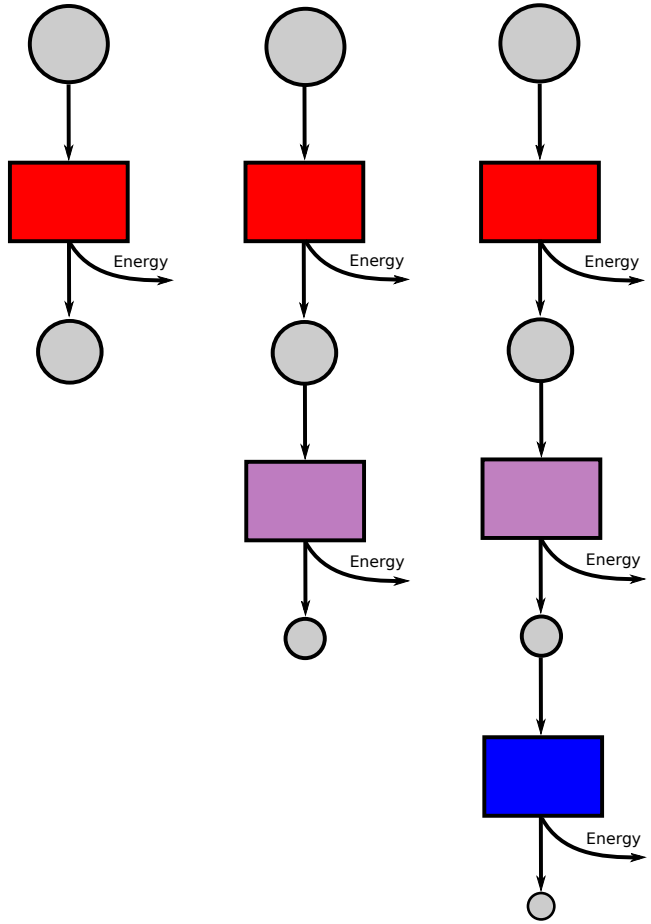
$\longrightarrow$ a multi-scale computational model of early metabolism

Retrograde Evolution



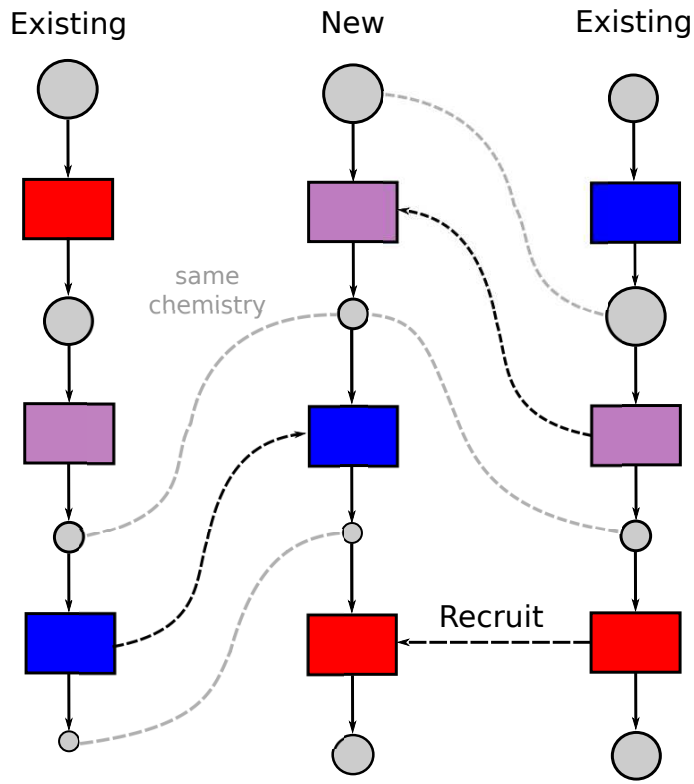
- End-product can be derived from more and more distant metabolites
- Example: glycolytic pathway, histidine biosynthesis

Forward Evolution



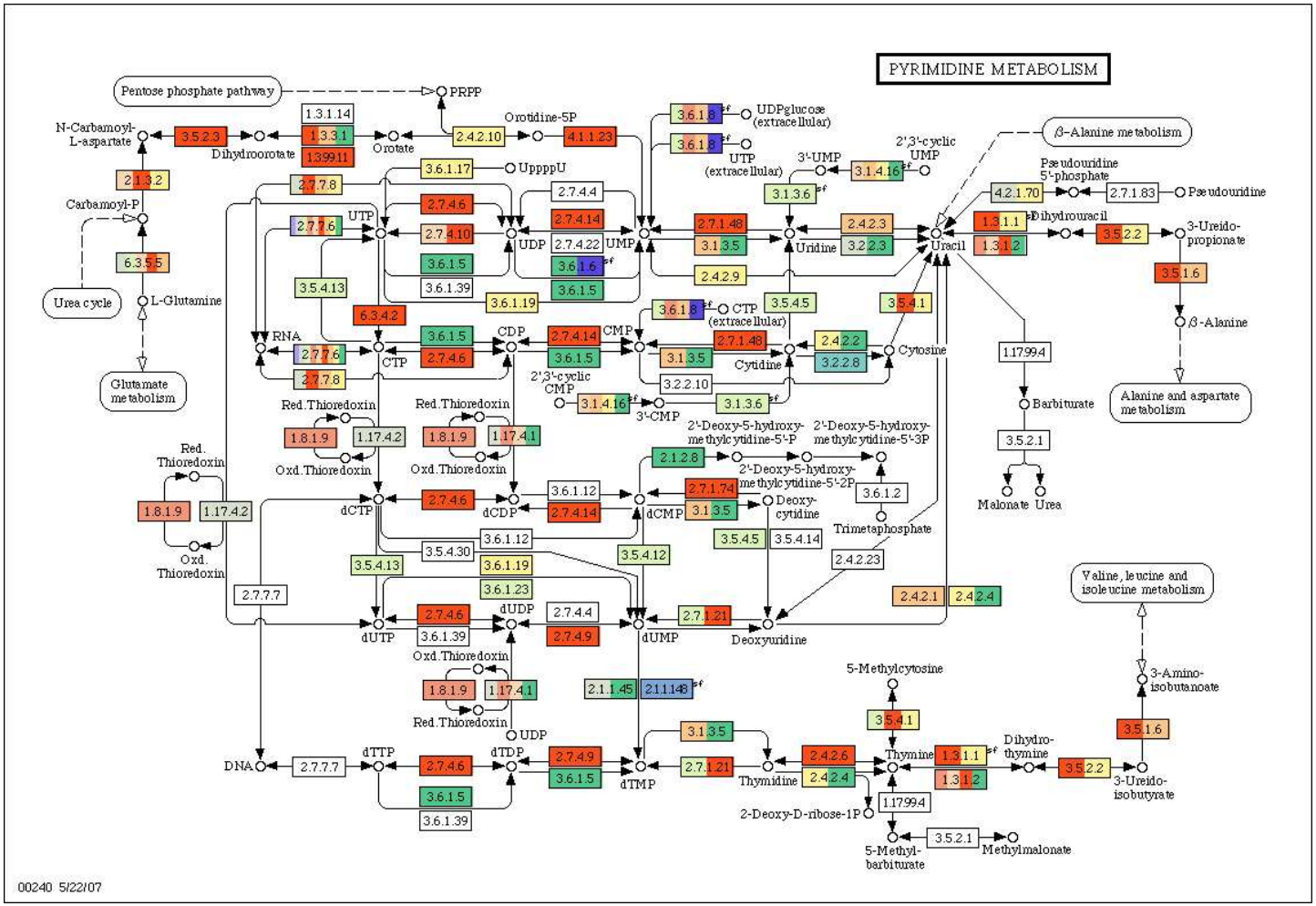
- more efficient extraction through deeper break-down of metabolites
- Example: isoprene lipid pathway

Patchwork Evolution



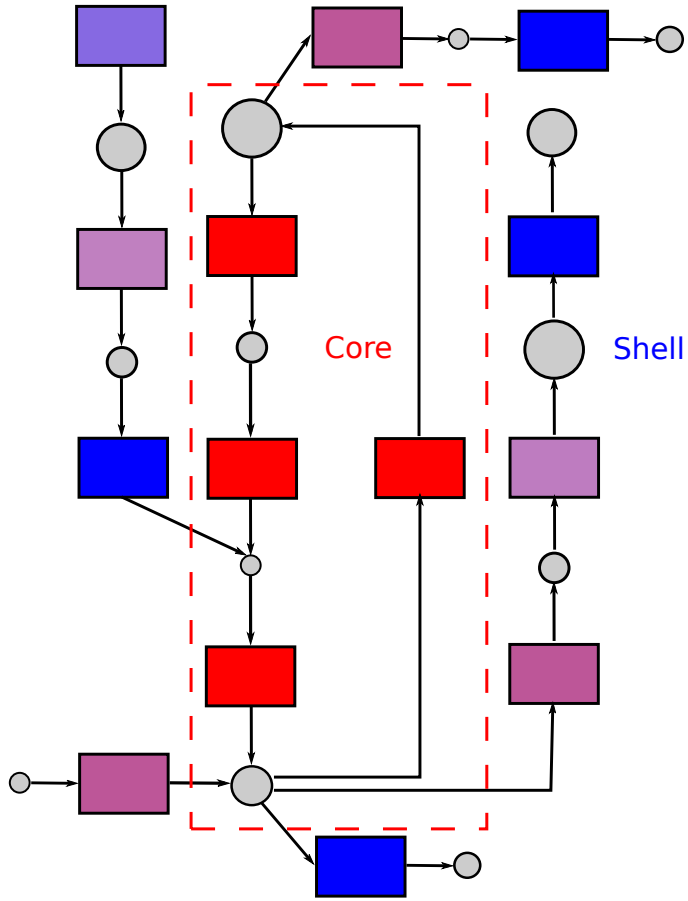
- Enzyme Recruitment from other Pathways
- Example: TIM β/α-barrel fold architecture in modern metabolism

Patchwork Evolution



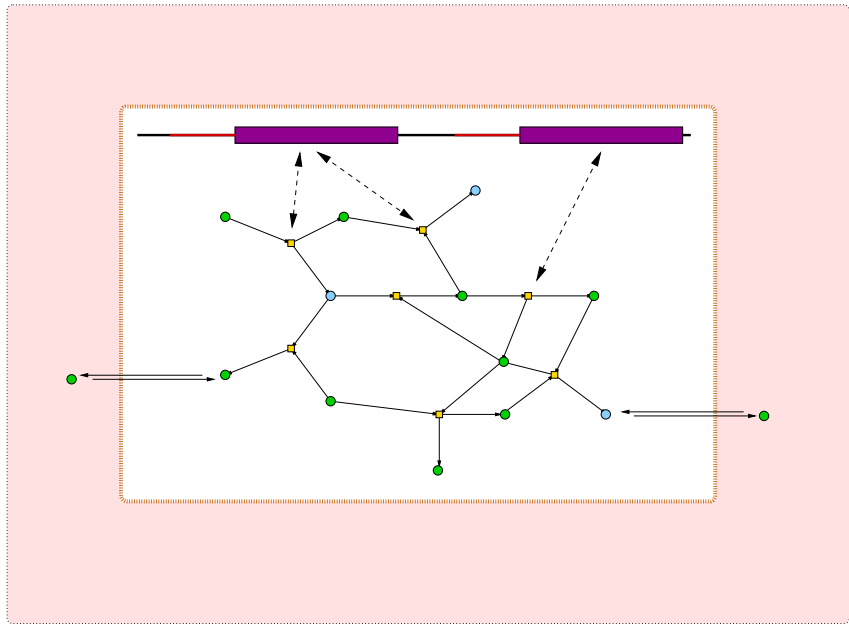
- Pyrimidine metabolism (from MANET)

Shell Hypothesis



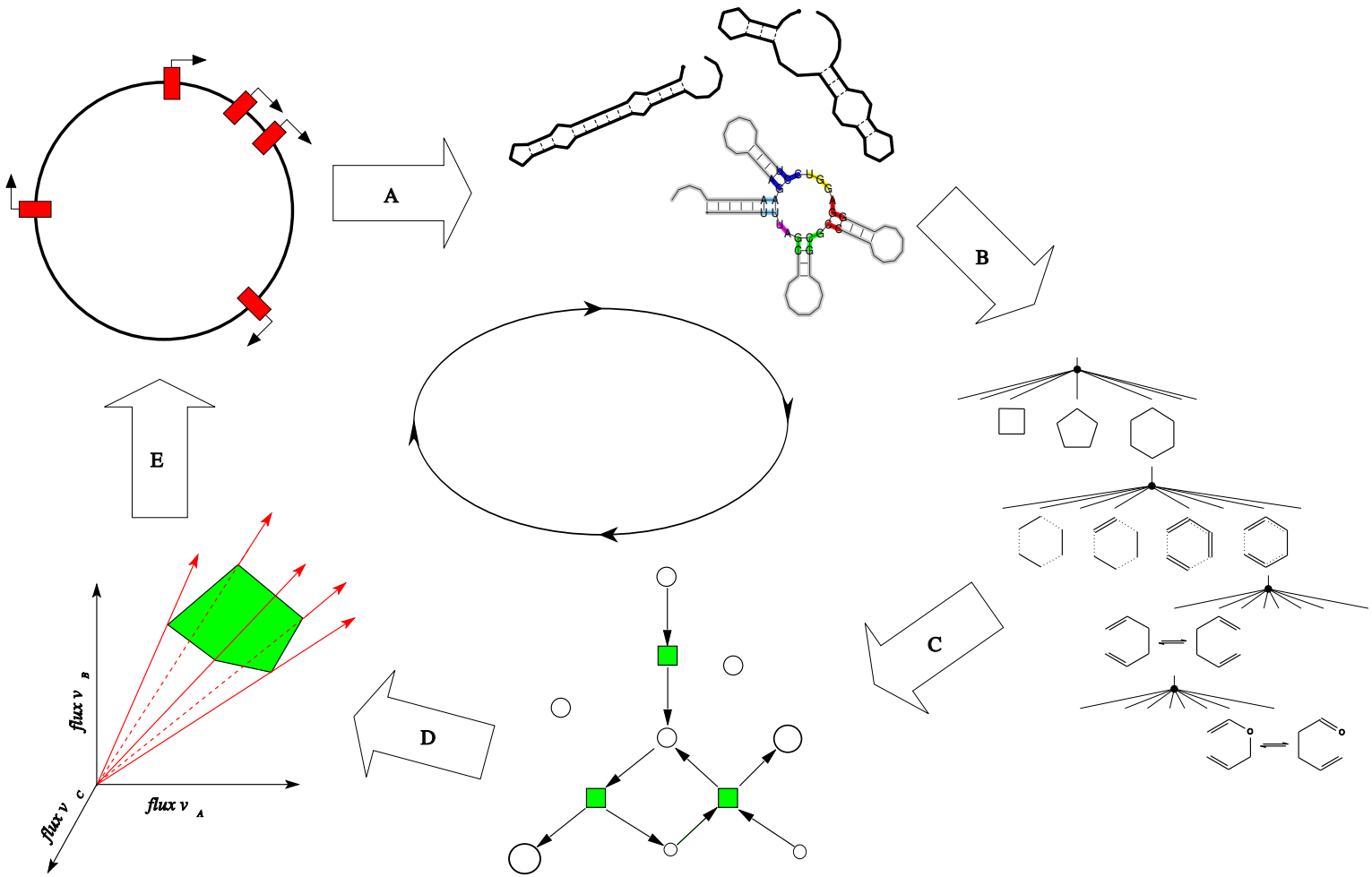
- A core from which pathways can be recruited
- Example:auto-catalytic core of the reductive citric acid cycle

Simulation

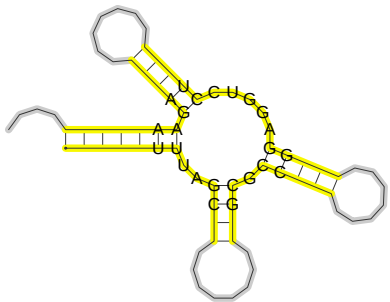


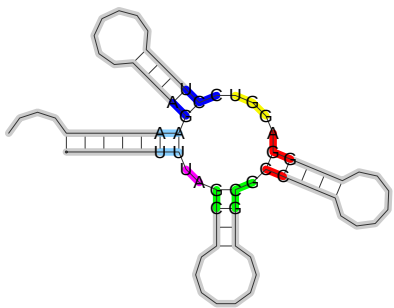
- Protocellular entity
- Bag of ribozymes
- Algebraic chemistry model
- Exchange of molecules with the environment

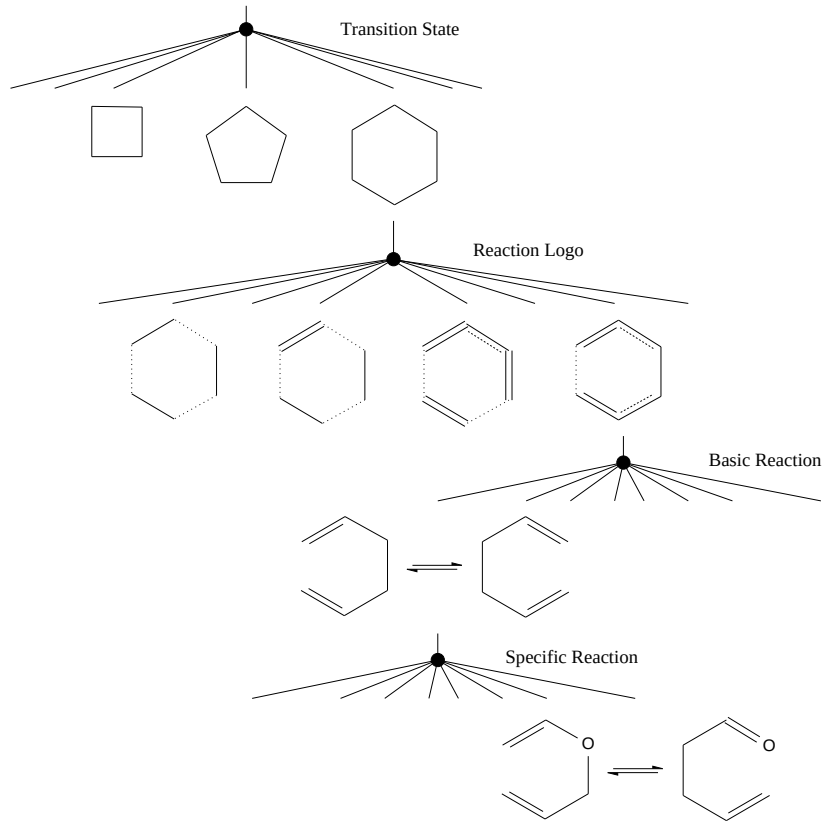
Simulation - Overview



Simulation - G2P Mapping

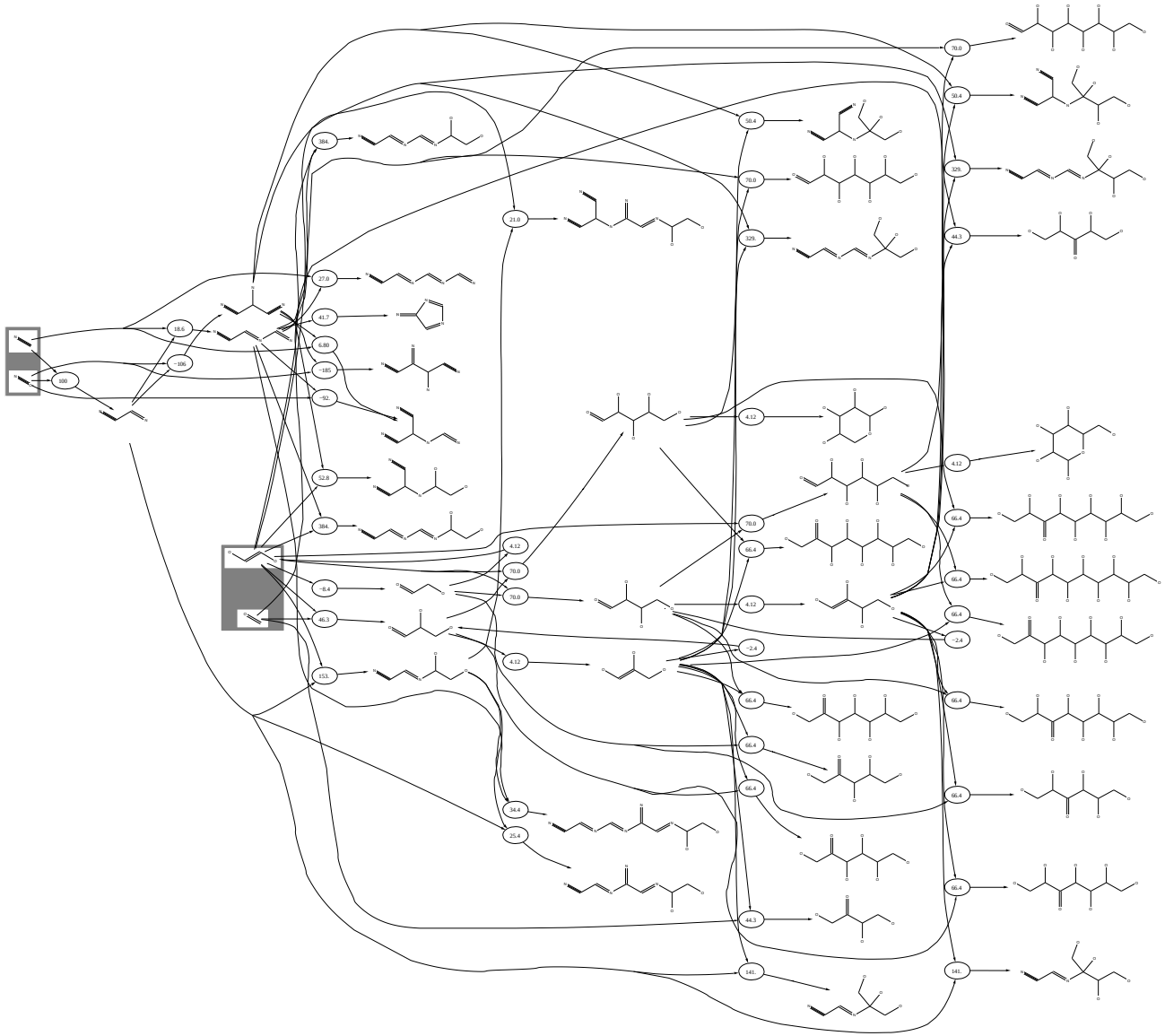






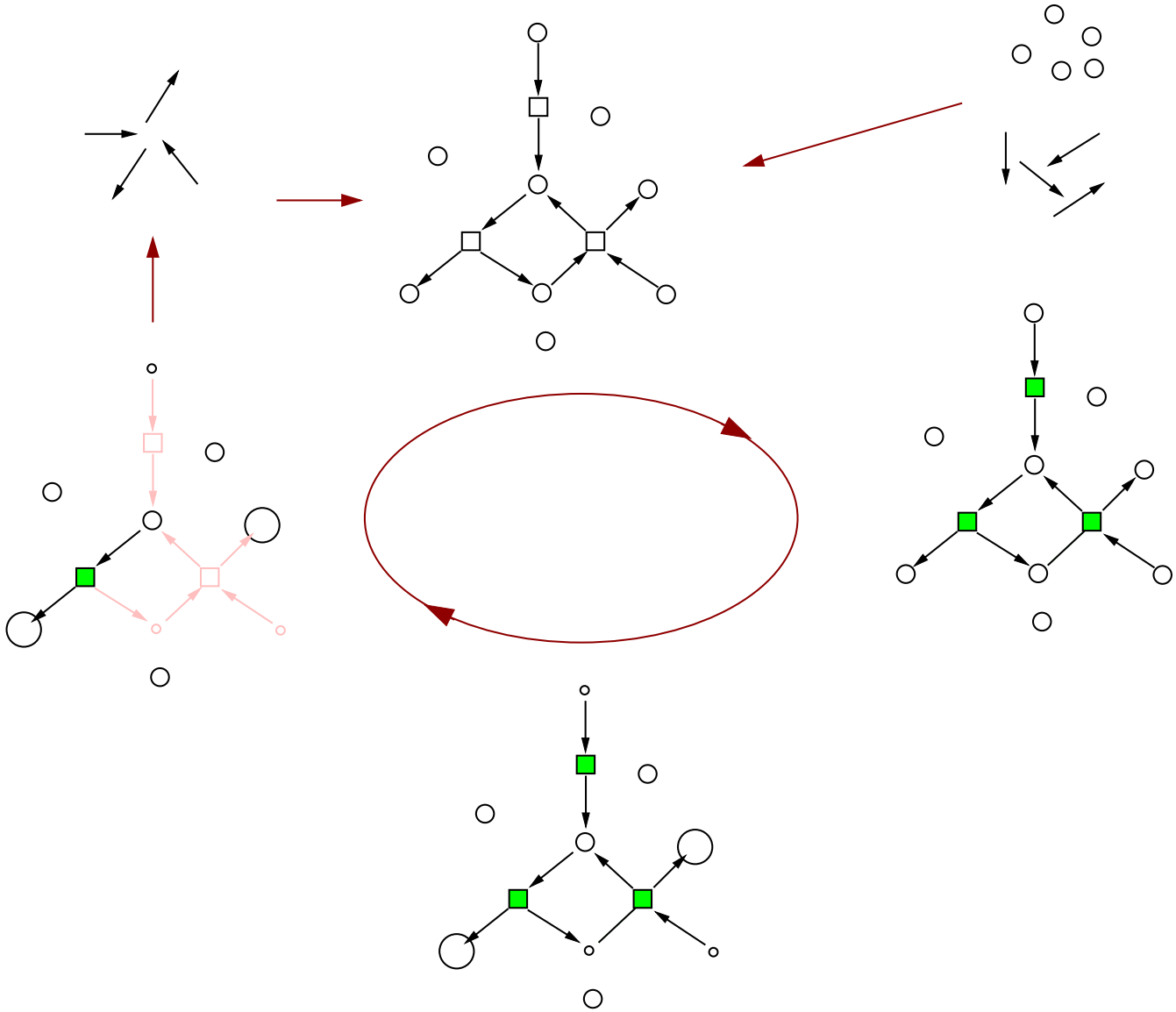
- RNA genes, Ribozymes
- ITS (Fujita) hierarchy, Chemical reaction, Graph-rewrite rule

Simulation - Growth



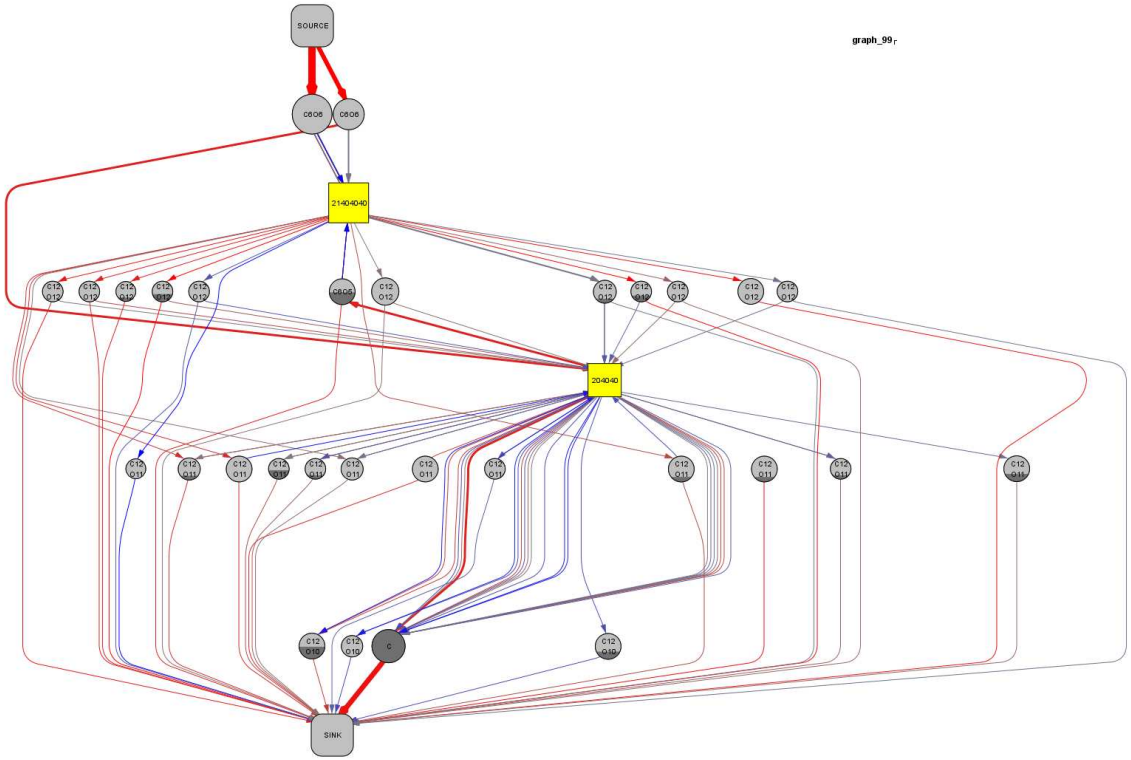
cyanide, formaldehyde glycol; aldolcondensation, tautomerization

Simulation - Stochastic Network Generator



Faulon, J-L, (2001) J Chem Inf Comput Sci 41:894-908

Simulation - Network

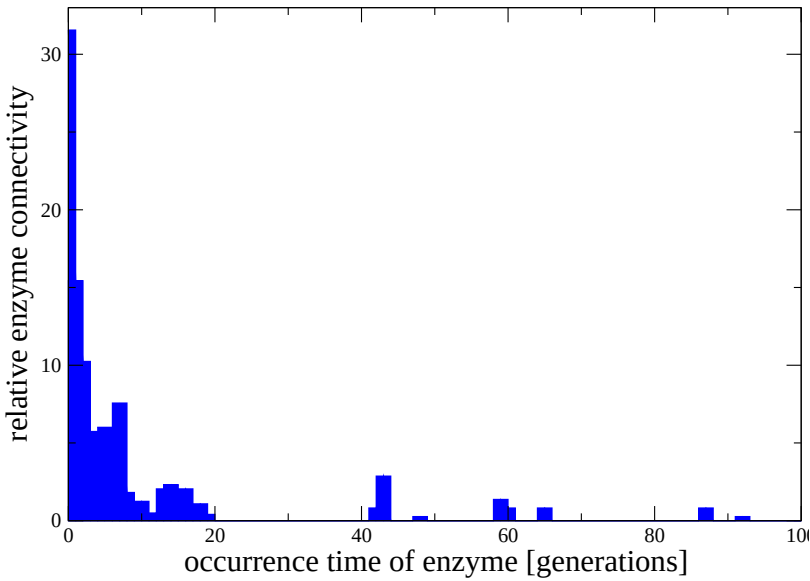


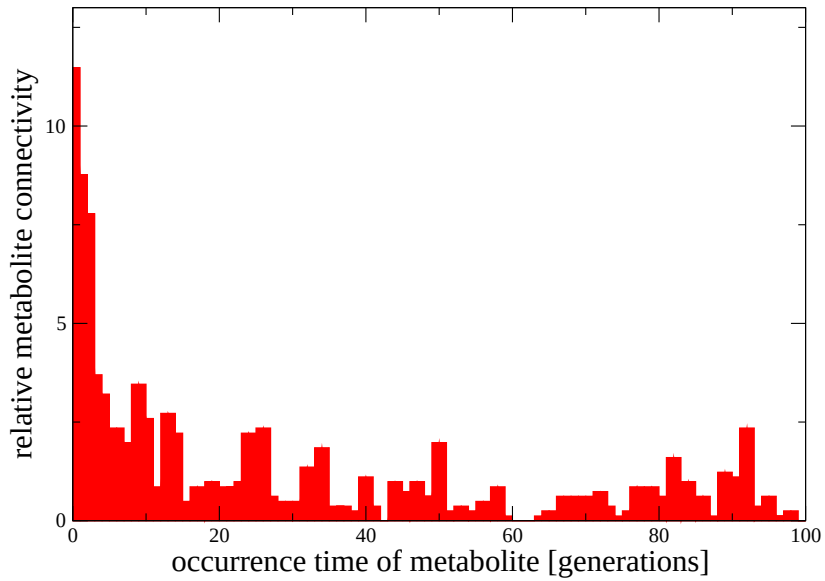
- bidirectional, bipartite graph
- nodes: metabolites (gray circles), enzymes (yellow squares)
- edges: participation in the same reaction
- dot layout: flow of mass downwards in the graph (if possible)

Results

- Quantitive Analysis
  - Connectivity vs Age (Time of Occurence)
  - Evolution of Pathways (Direction)
- Study on Example
  - Evolution of Pathways (Life-time of enzymes, molecules)
  - Geneaology (History of Genes)

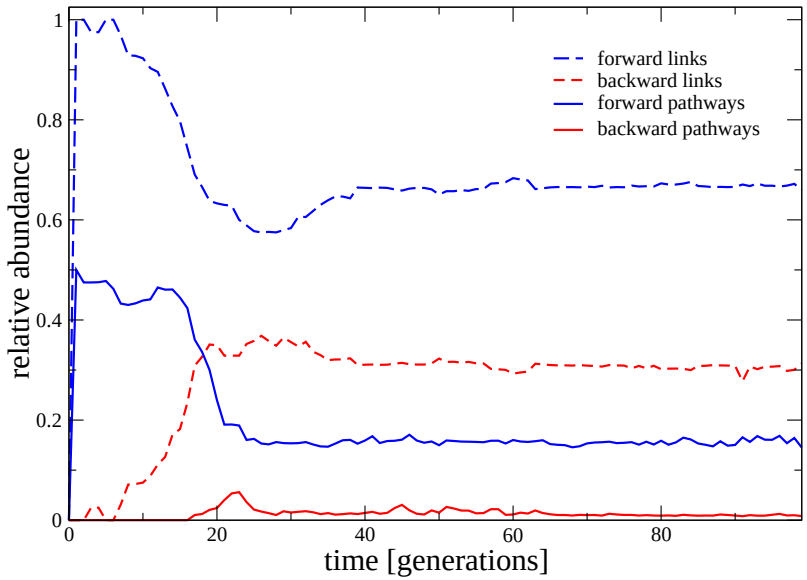
Results - QA

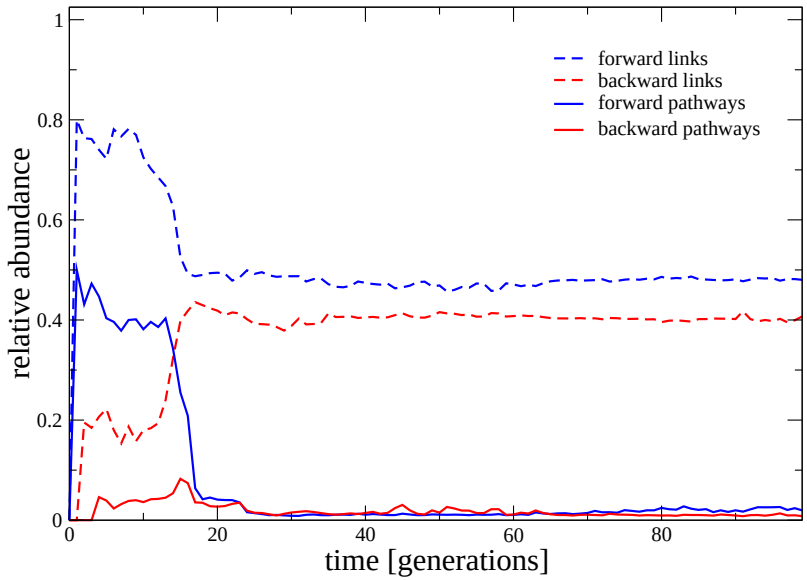




- Highly connected metabolites (hubs) originate from early generations.
- Enzymes from later stages have higher specificty.

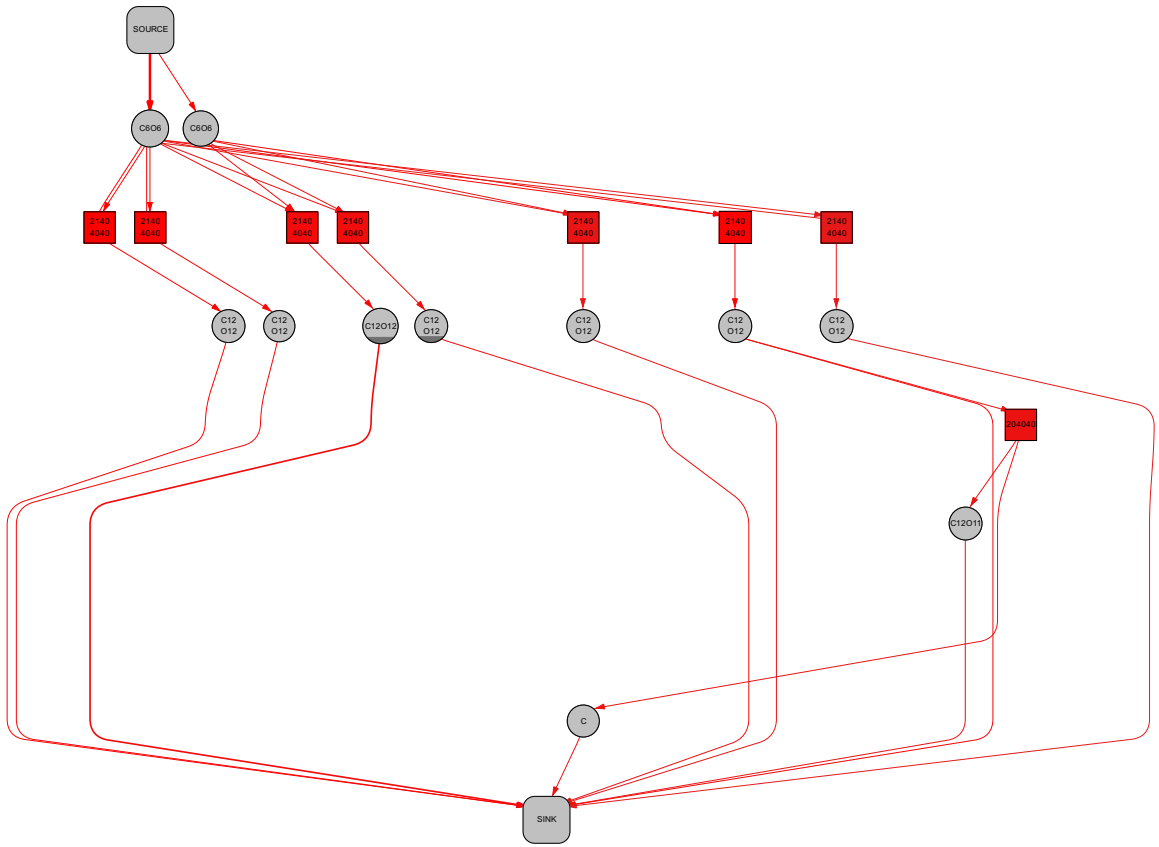
Results - QA



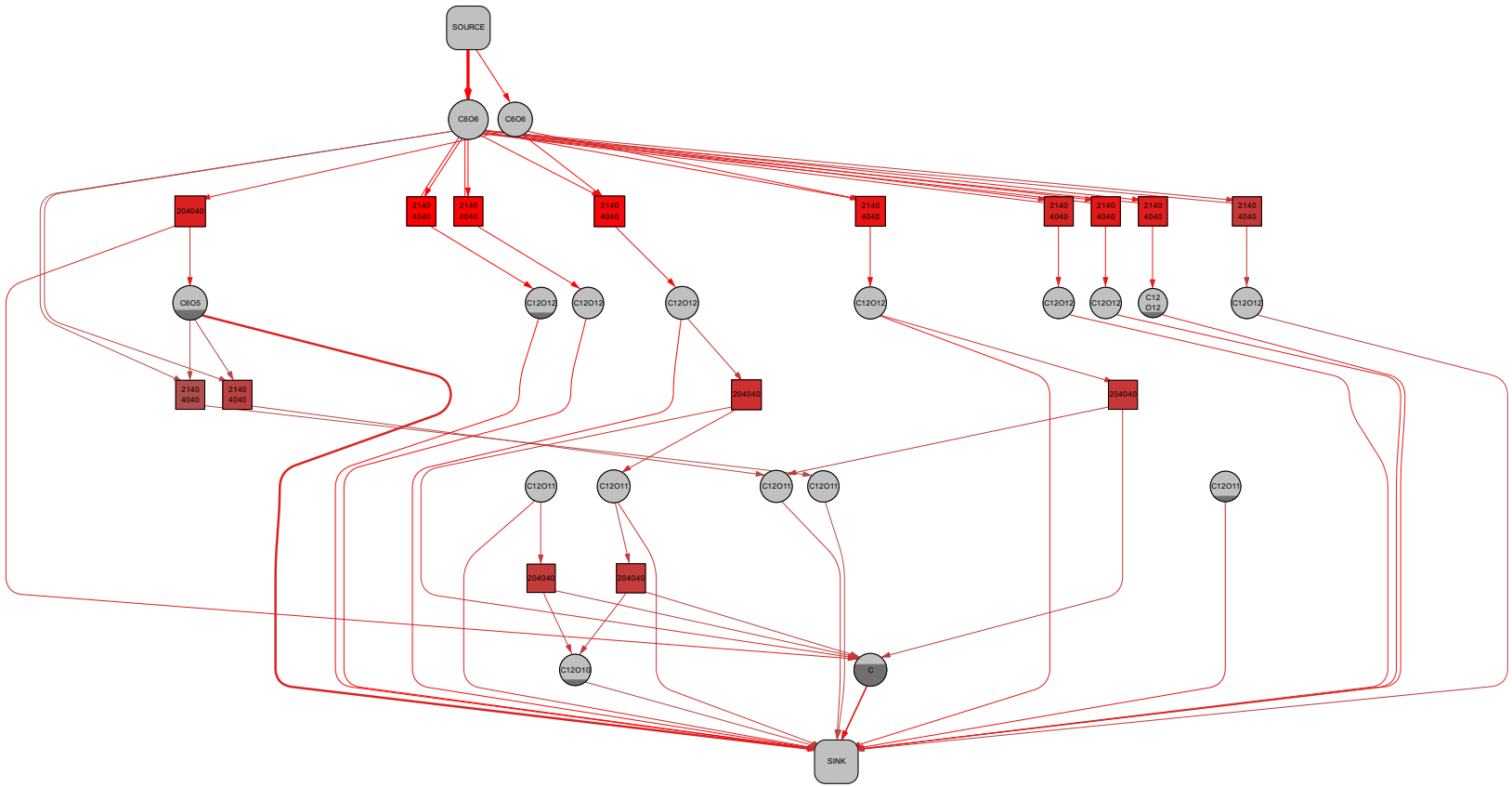


- First generations are dominated by forward evolution.
- When a certain network size is reached, enzyme recruitment takes over.
- A core of pathways from early generations is kept.

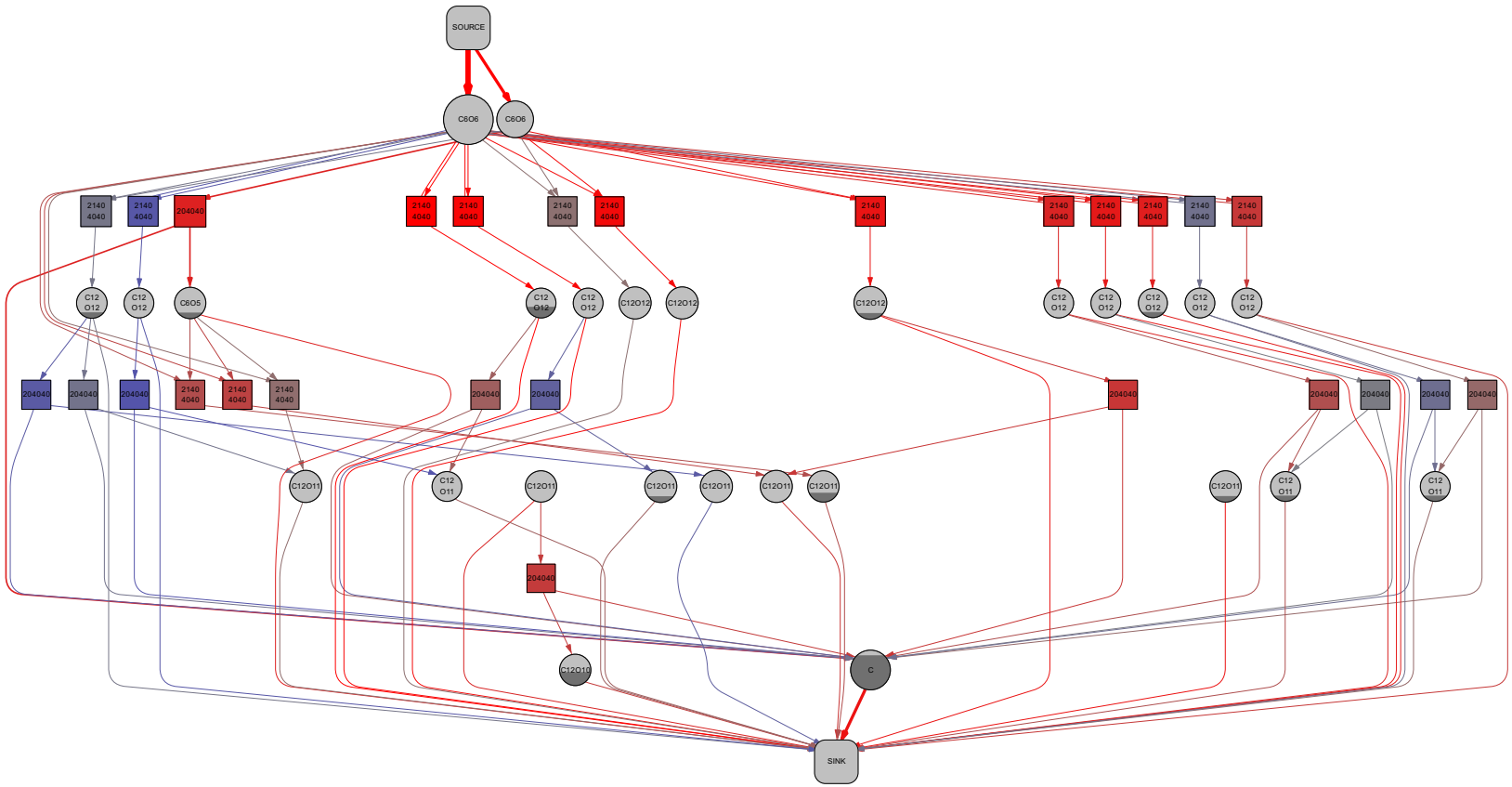
generation 10



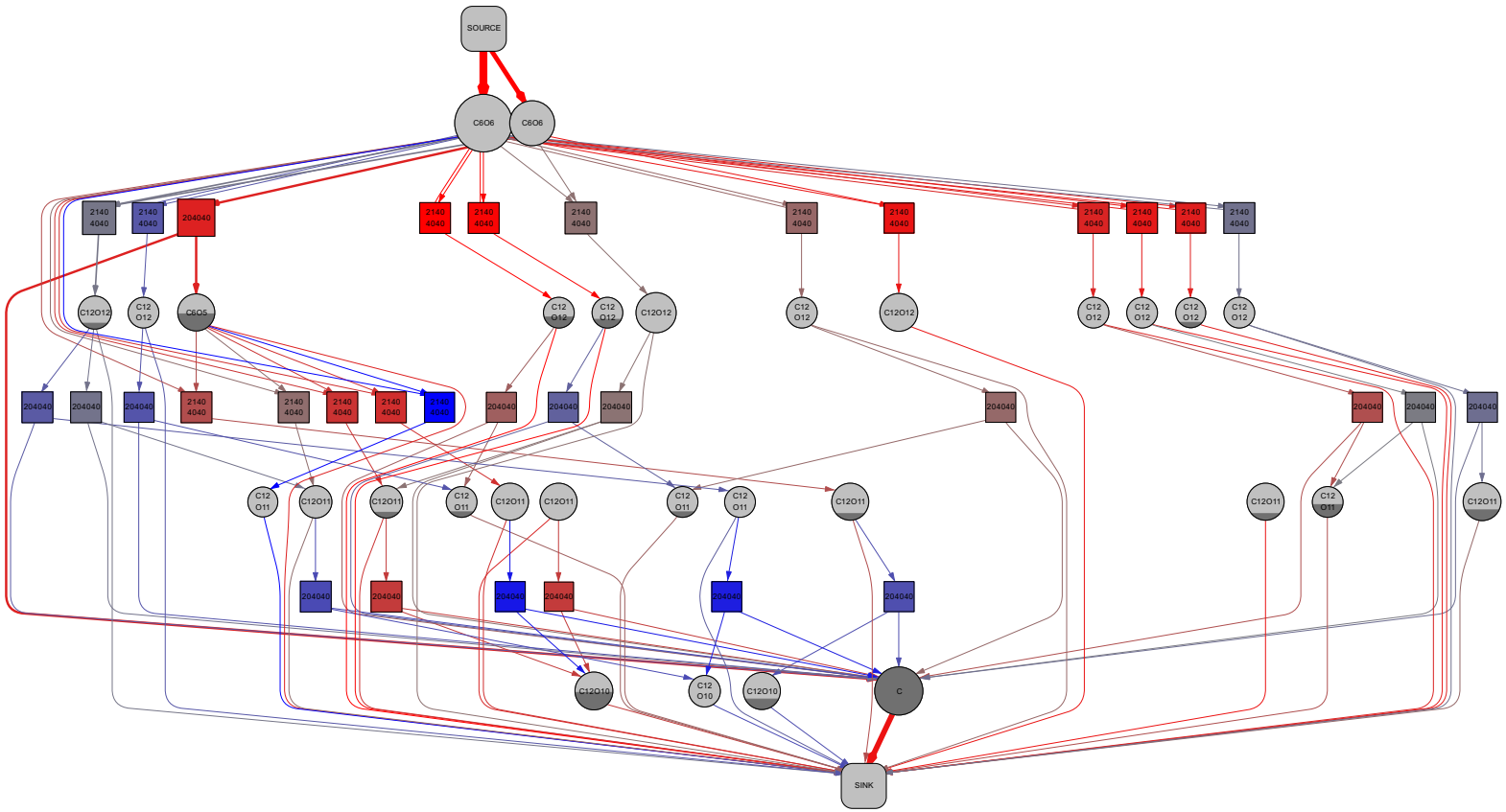
generation 30



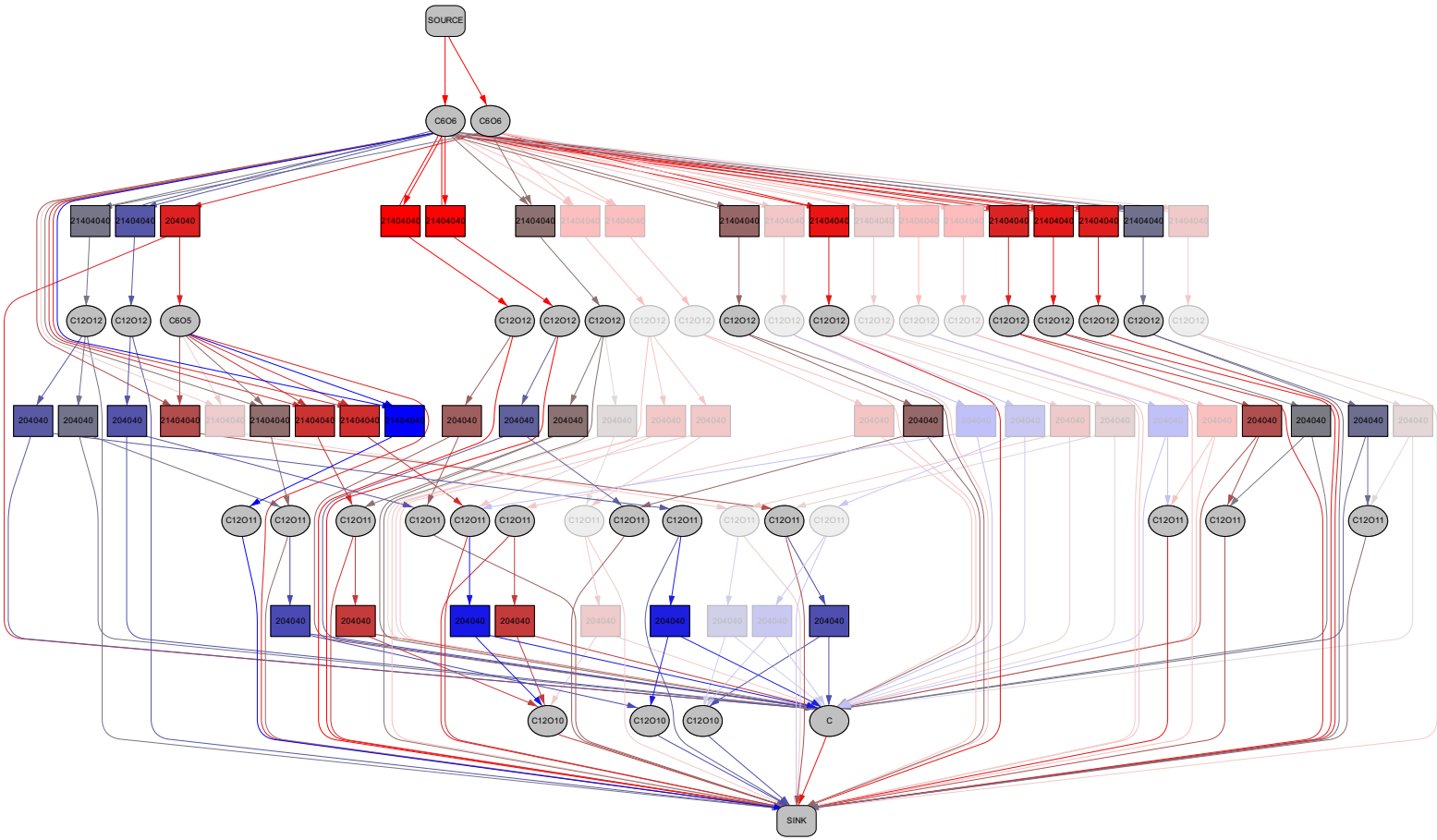
generation 66



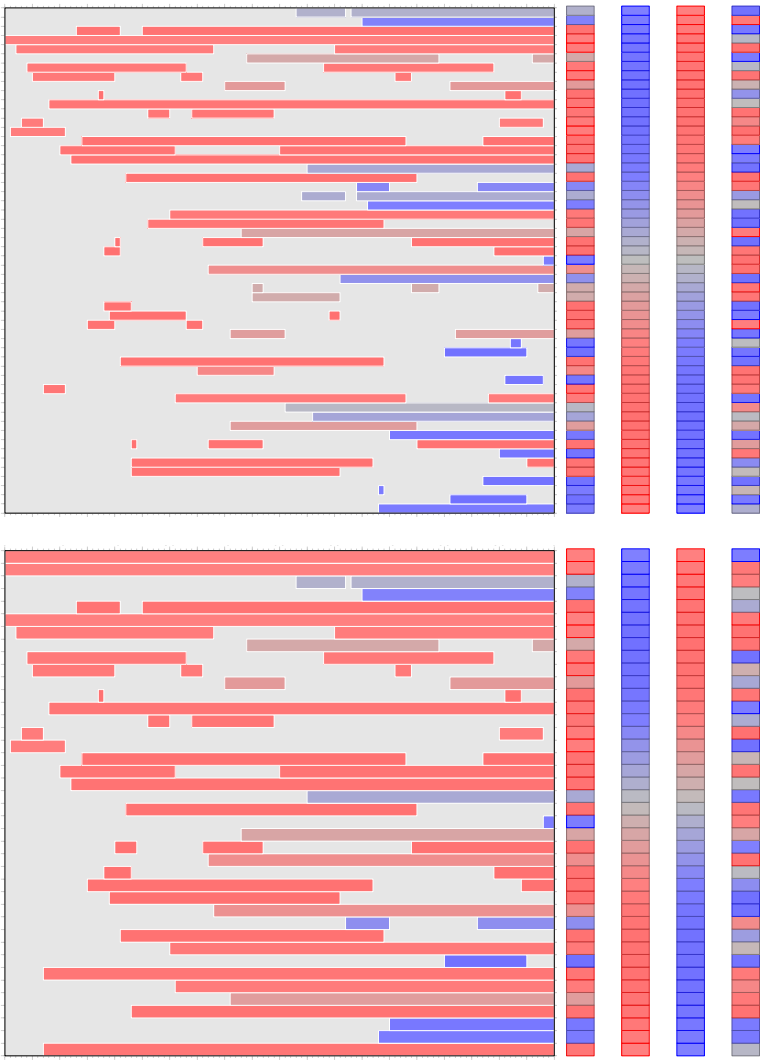
generation 100

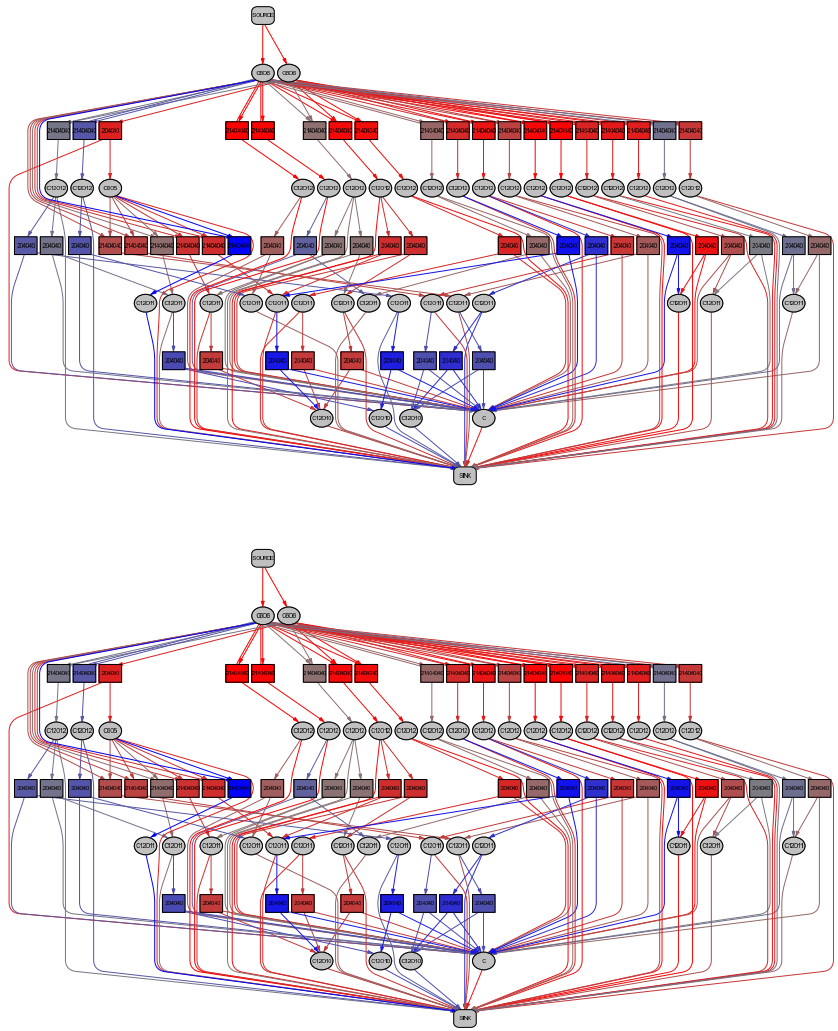


Union graph


SOURCE
C6O6
C6O6
21404040
204040
C12O12
C6O5
C12O11
C12O10
C
SINK

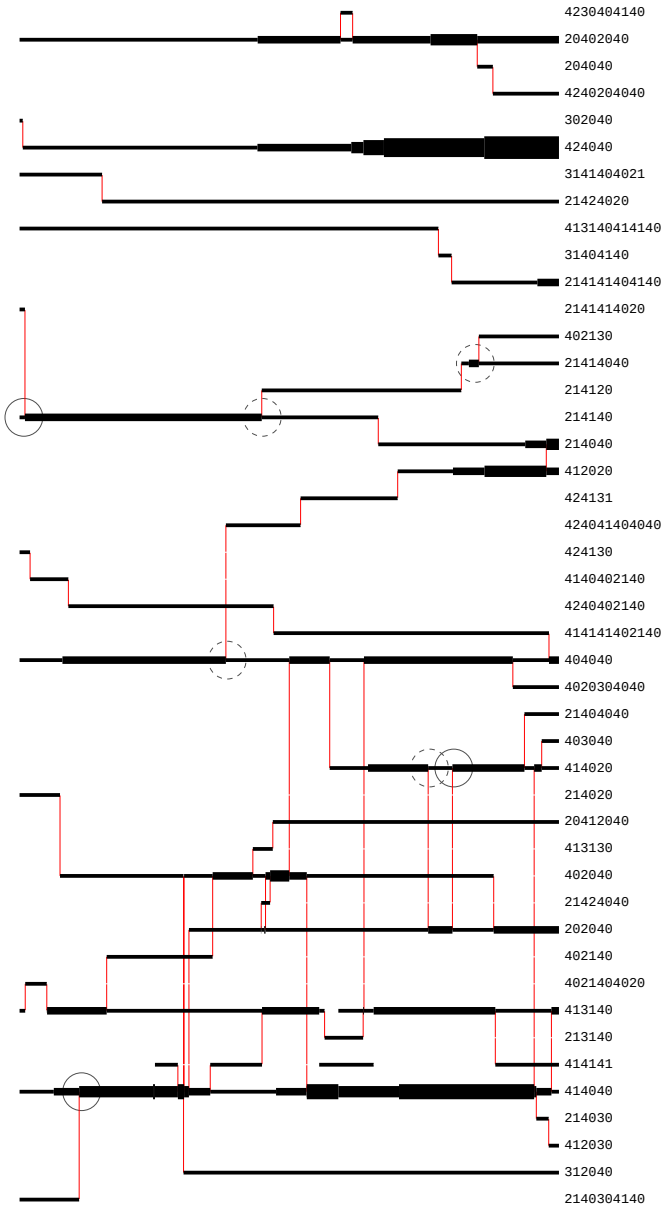
Results - small Example





- Enzyme pattern similar to forward simulation pattern.

Results - small Example



- Genealogy of catalytic functions and gene dosage over 2000 generations.
- Convergent as well as divergent events.

Conclusion

- Summary
  - Computational model of early metabolism
  - Insights in evolution of complex system
  - Combining different pathway evolution hypotheses
  - Explaining hypotheses through scenarios
- Outlook
  - Depletion of Metabolites
  - Changing Environment
  - Similarity between Pathways (Flexibility, Modularity)
  - Robustness towards knockouts

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