

Analysis of Metabolic Networks

Structure, Properties, Visualization

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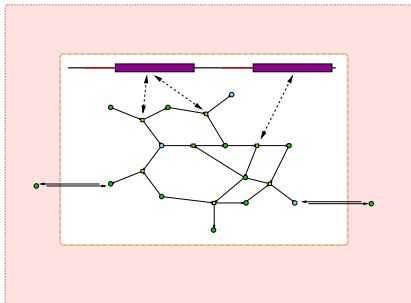
Chair for Bioinformatics
University of Leipzig

TBI-Winterseminar, Bled, February 14-21

Outline

- Simulation
- Motivation
- Visualization
- General network analysis
- Metabolic network analysis
- Outlook

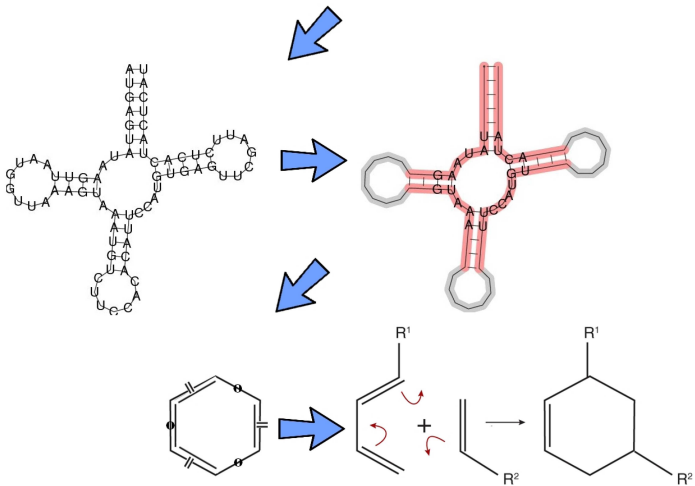
Simulation



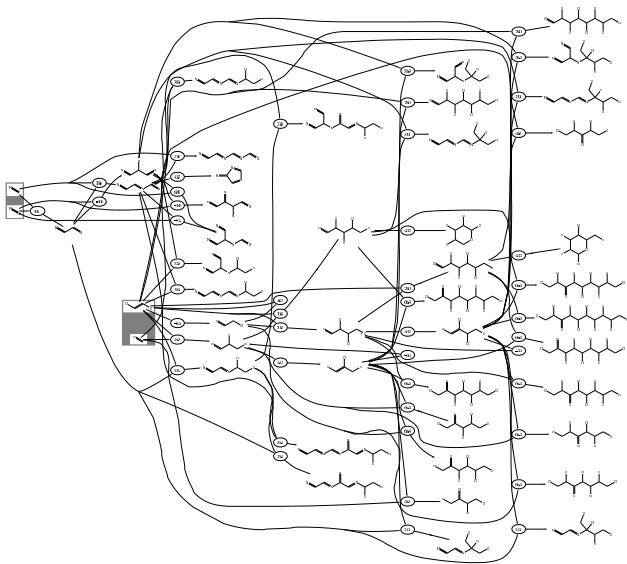
- Bag of ribozymes.
- Algebraic chemistry model.
- Exchange of molecules with the environment.

Simulation

AUGAGUUAUAGUUAAUGGUAAAAGUAAAUGUCUUCACACAUUCCAUGUGAGUUUCGAUUUCUACGUACUGAU

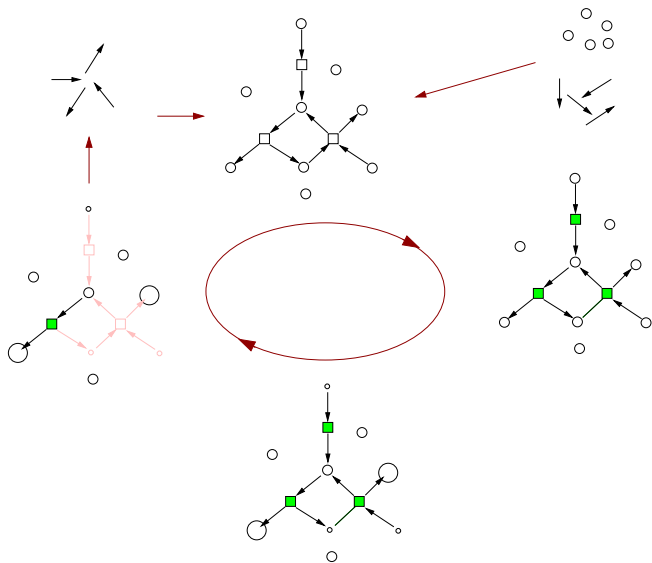


Simulation



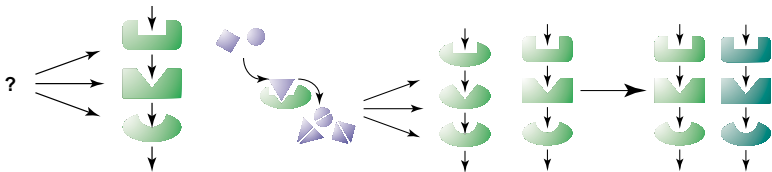
cyanide, formaldehyde glycol; aldolcondensation, tautomerization

Simulation



Motivation

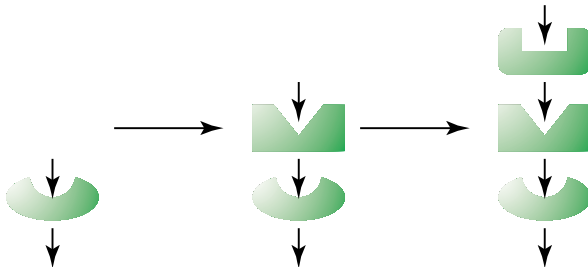
- Study the early development of metabolism
 - Evolution of pathways (different scenarios)



- Analysis of the metabolic networks
 - network structure
 - network properties

Pathway Evolution

Retrograde Evolution

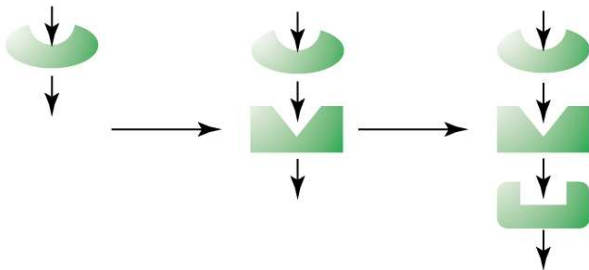


End-product can be derived from more and more distant metabolites

Example: glycolytic pathway, histidine biosynthesis

Pathway Evolution

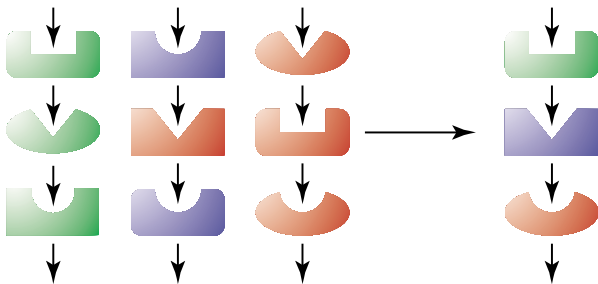
Forward Evolution



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

Pathway Evolution

Patchwork Evolution



Enzyme Recruitment from other Pathways

Pathway Evolution

Comparison
red = older, blue = younger

Retrograde Evolution



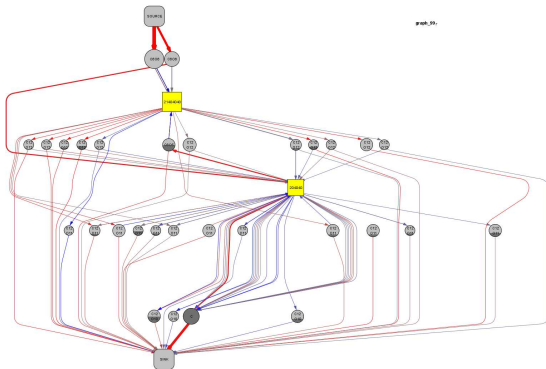
Forward Evolution



Patchwork Evolution



Visualization



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

Visualization

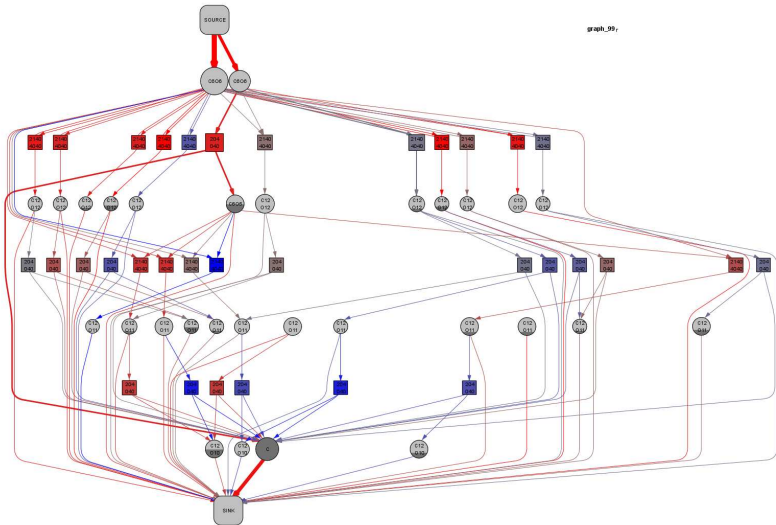
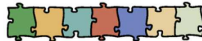
Retrograde Evolution



Forward Evolution

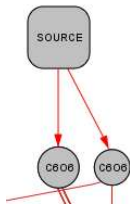


Patchwork Evolution

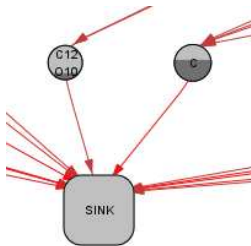


Visualization

Flow

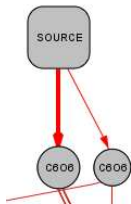


Concentration

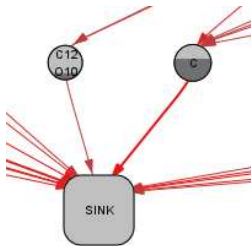


Visualization

Flow

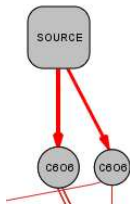


Concentration

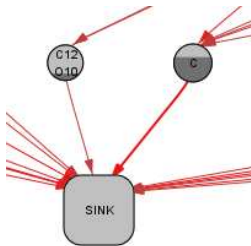


Visualization

Flow

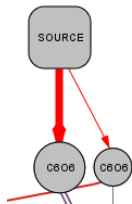


Concentration

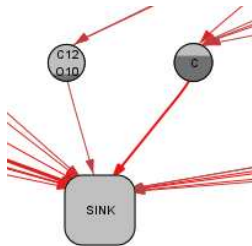


Visualization

Flow

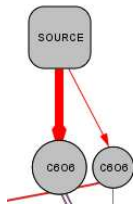


Concentration

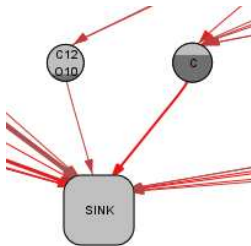


Visualization

Flow

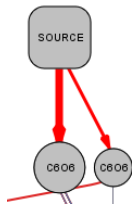


Concentration

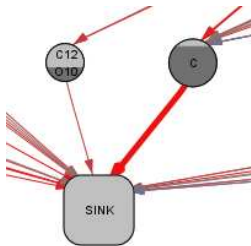


Visualization

Flow



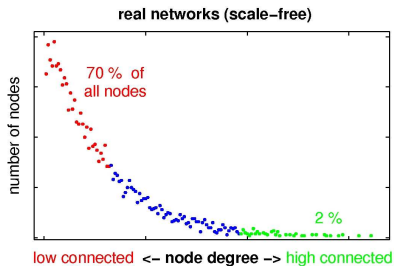
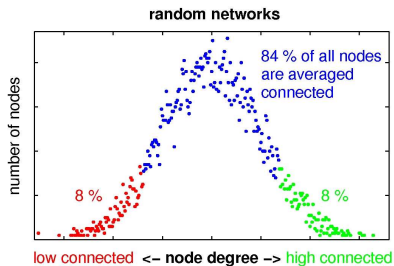
Concentration



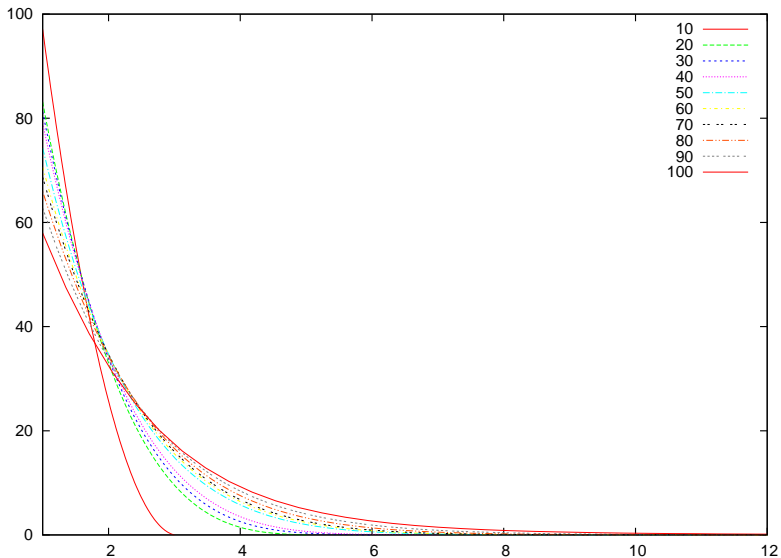
Animation

General network analysis

- Connectivity Distribution
 - small vs big
 - early vs evolved
- Centrality, Entropy, ...
 - simulated vs real world



Connectivity Distribution



Metabolic network analysis

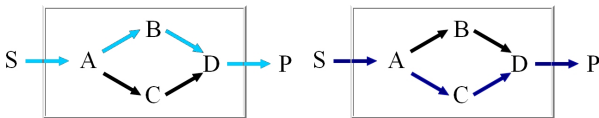
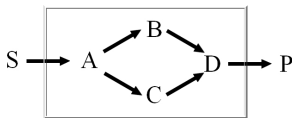
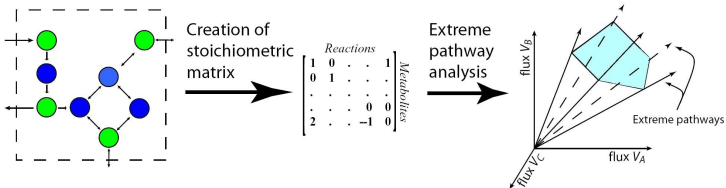
We have sets of edges forming meaningful complex entities



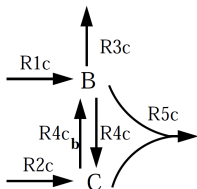
pathways

- number of pathways → flexibility
- change in case of single/multiple knockouts → robustness
- number of acceptable knockouts → robustness

Metabolic Pathway Analysis



Metabolic Pathway Analysis



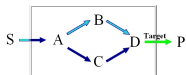
$$N_C = \begin{matrix} & R1c & R2c & R3c & R4c_b & R4c & R5c \\ \begin{pmatrix} 1 & 0 & -1 & 1 & -1 & -1 \\ 0 & 1 & 0 & -1 & 1 & -1 \end{pmatrix} & B \\ & C \end{matrix}$$

$$K_C' = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0.5 & -0.5 & -0.5 & 1 \\ 0.5 & 0.5 & -0.5 & 0 \end{pmatrix} \begin{matrix} R1c \\ R2c \\ R3c \\ R4c_b \\ R4c \\ R5c \end{matrix}$$

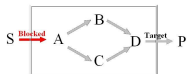
$$R^5 = \begin{pmatrix} \times & 0 & \times & \times & 0 & 0 \\ 0 & 0 & \times & 0 & \times & 0 \\ 0 & 0 & 0 & \times & 0 & \times \\ 0 & \times & 0 & 0 & \times & \times \\ \frac{\times}{0.5} & \frac{\times}{0} & \frac{0}{1} & \frac{0}{0} & \frac{0}{1} & \frac{0}{-1} \end{pmatrix} \begin{matrix} R1c \\ R2c \\ R3c \\ R4c_b \\ R4c \\ R5c \end{matrix}$$

$$R^6 = \begin{pmatrix} \times & 0 & \times & \times & 0 & 0 \\ 0 & 0 & \times & 0 & \times & \times \\ 0 & 0 & 0 & \times & 0 & \times \\ 0 & \times & 0 & 0 & \times & \times \\ \times & \times & 0 & 0 & 0 & 0 \\ \times & 0 & \times & 0 & \times & 0 \end{pmatrix} \begin{matrix} R1c \\ R2c \\ R3c \\ R4c_b \\ R4c \\ R5c \end{matrix}$$

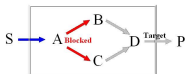
Acceptable Knockouts



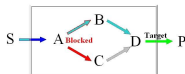
Minimal Knockout sets



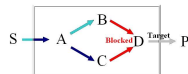
$\{S \rightarrow A\}$



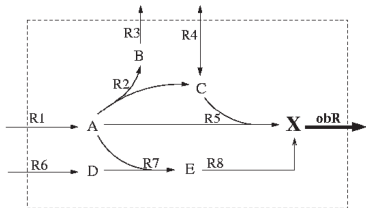
$\{A \rightarrow B, A \rightarrow C\}$



$\{A \rightarrow C\}$ is not a MKS



$\{B \rightarrow D, C \rightarrow D\}$

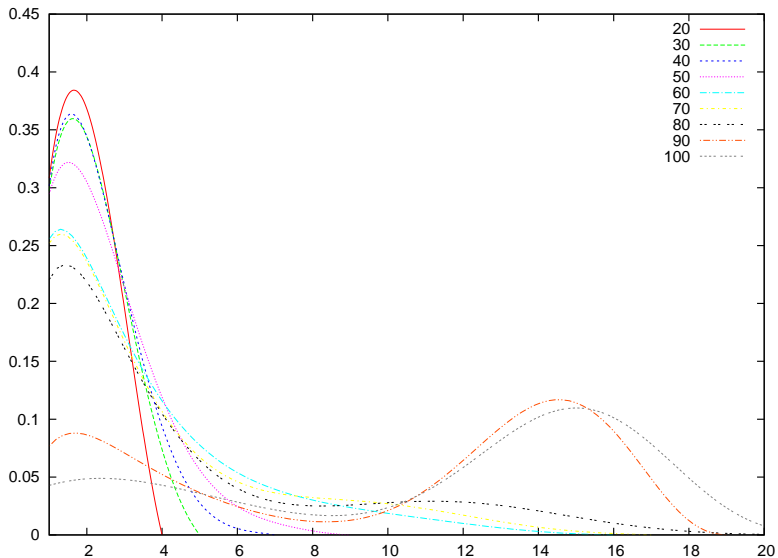


	R1	R2	R3	R4	R5	R6	R7	R8	obR
Elementary modes									
EM1	1	1	1	-1	0	0	0	0	0
EM2	1	0	0	0	0	1	1	1	1
EM3	2	1	1	0	1	0	0	0	1
EM4	1	0	0	1	1	0	0	0	1

Minimal cut sets (objective reaction: obR)

MCS0										×
MCS1	×									
MCS2					×	×				
MCS3					×		×			
MCS4					×				×	
MCS5		×		×		×				
MCS6			×	×		×				
MCS7		×		×			×			
MCS8			×	×			×			
MCS9		×		×					×	
MCS10			×	×					×	
F_i	1	1/3	1/3	1/3	1/2	3/8	3/8	3/8	3/8	1

Knockout set size distribution











Knockout effects

single $R_1 = \frac{\sum_{i=1}^r z^i}{r * z}$

depletion $R_2 = \frac{\sum_{i=1}^n R_1^i}{n}$

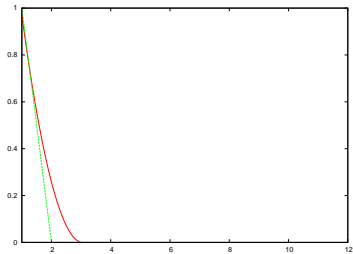
multiple $R_3(k) = \frac{\sum_{i=1}^{s(k)} z^i}{s(k) * z}$

overall $R_3(\leq K) = \sum_{k=1}^K R_3(k) p_k$

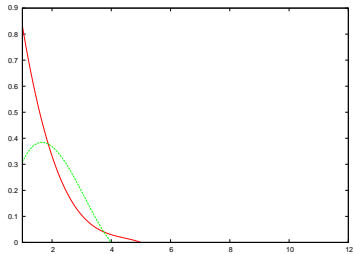
Example system	Number of reactions	Number of elementary modes	$R_1(1)$	$R_1(2)$	$R_1(3)$	$R_1(\leq 3)$
1 	4	2	1/2 = 0.5	1/6 ≈ 0.167	0	0.414
2 	4	2	1/2 = 0.5	1/4 = 0.25	1/8 = 0.125	0.436
3 	4	2	3/8 = 0.375	1/12 ≈ 0.083	0	0.302
4 	4	2	1/4 = 0.25	0	0	0.189
5 	8	2	7/16 ≈ 0.438	3/8 = 0.375	5/16 ≈ 0.313	0.418
6 	8	2	1/2 = 0.5	3/14 ≈ 0.214	1/14 ≈ 0.071	0.416
7 	5	4	13/20 = 0.65	3/8 = 0.375	7/40 = 0.175	0.573
8 	5	3	2/3 ≈ 0.667	2/5 = 0.4	1/5 = 0.2	0.592

Robustness

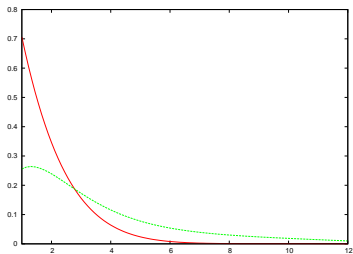
Robustness = 0.51



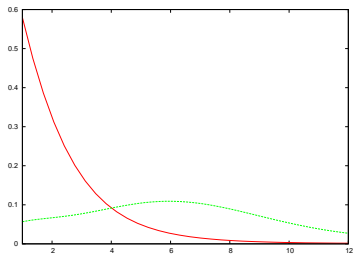
Robustness = 0.67



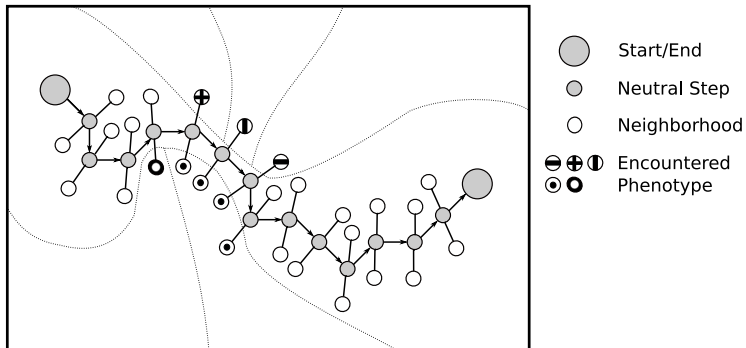
Robustness = 0.75



Robustness = 0.81



Future analysis methods



- Neutral network of a metabolic network (see RNA, GRN)
- Barrier trees of flux distributions (see xtof)

Acknowledgements

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