A new simulation: going metabolic

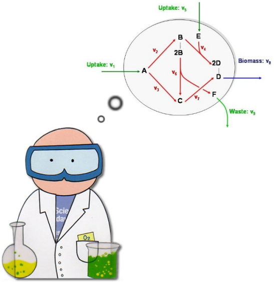
Alexander Ullrich

Institute for Theoretical Chemistry
University of Vienna

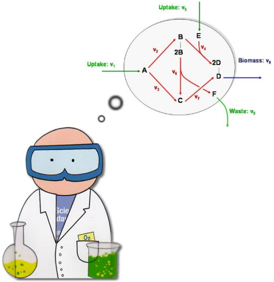
November 3, 2008

WHY?

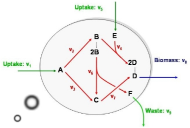
Why go metabolic?

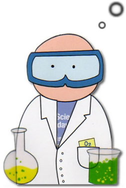


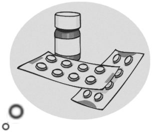
Why go metabolic?

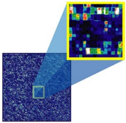


Why go metabolic?

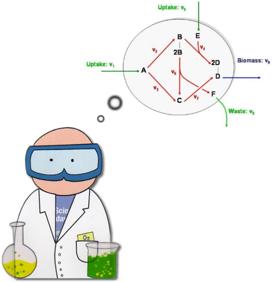




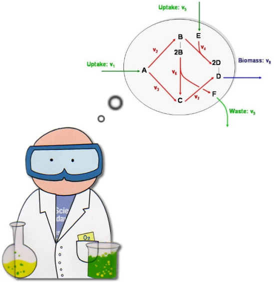


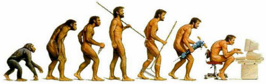


Why simulate?

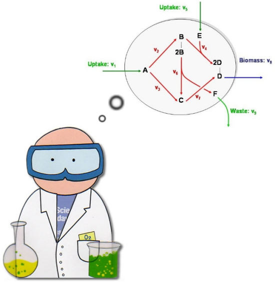


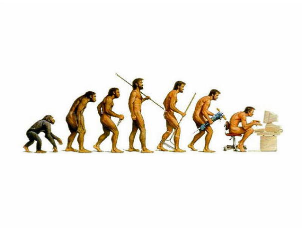
Why simulate?

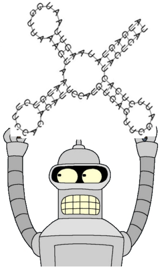




Why simulate?





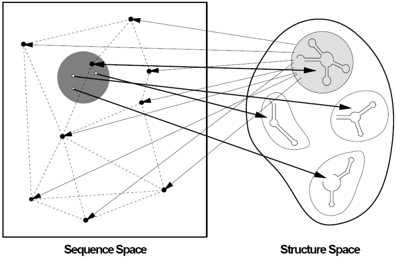


HOW?

Cell

RNA sequence-to-structure map

- Redundancy: Many more sequences than structures.
- Sensitivity: Small changes in the sequences may lead to large changes in the structure.
- Neutrality: A substantial fraction of mutations does not alter the structure.

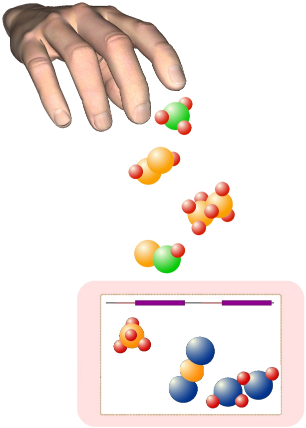


Walter Fontana & Peter Schuster, J. Theor. Biol. 194:491-515 (1998)

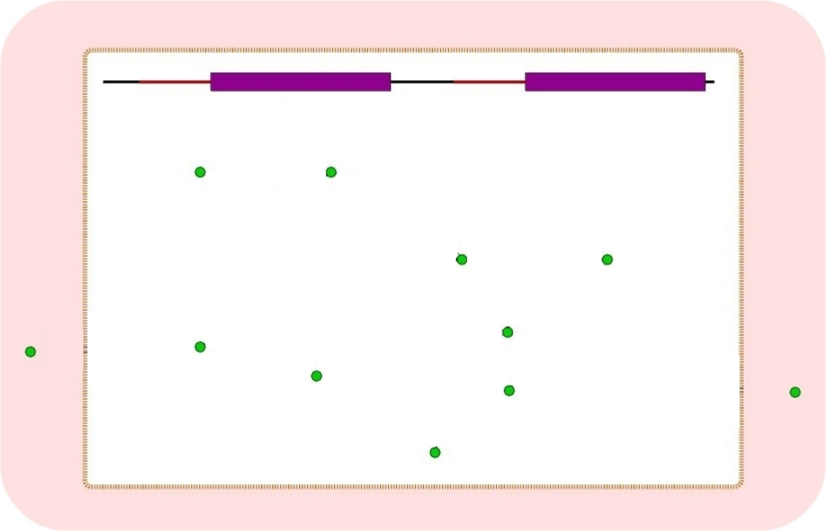
Cell with Genome

Adding Metabolites

- Molecules are abstracted to vertex and edge labeled graphs
- Neighborhood relations are preserved by this abstraction.
- Spacial properties (e.g. Chirality, E/Z isomery) can be handled by extending the label set.
- Use graph-indices and QM to calculate physical properties

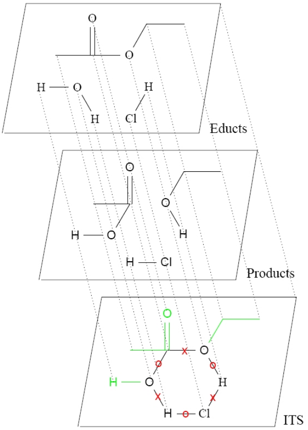


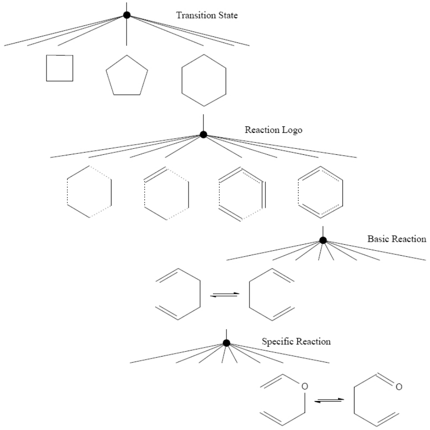
Cell with Genome and Metabolites



Reaction Classification

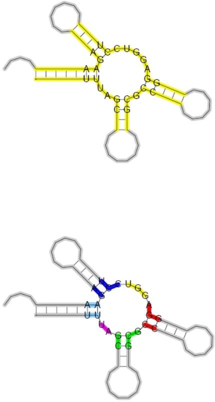
$$CH_3CO_2Et + HCl + H_2O \rightleftharpoons CH_3CO_2H + EtOH + HCl$$

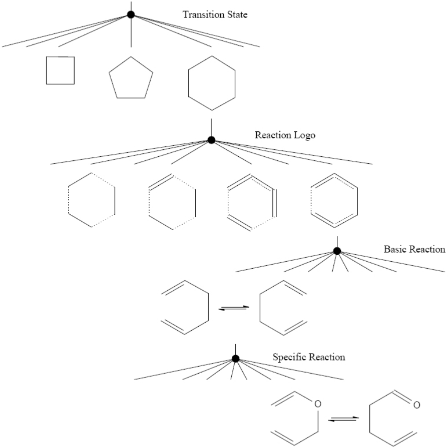




Fujita, Hendrickson, ...

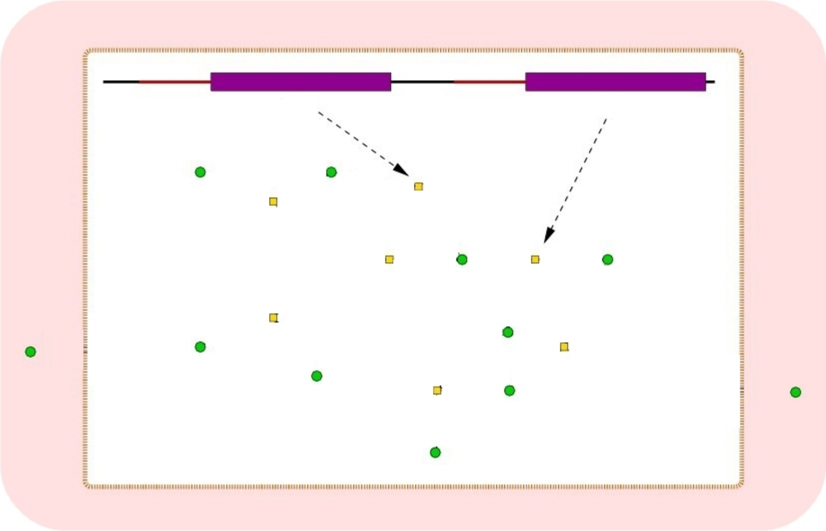
From structure to function



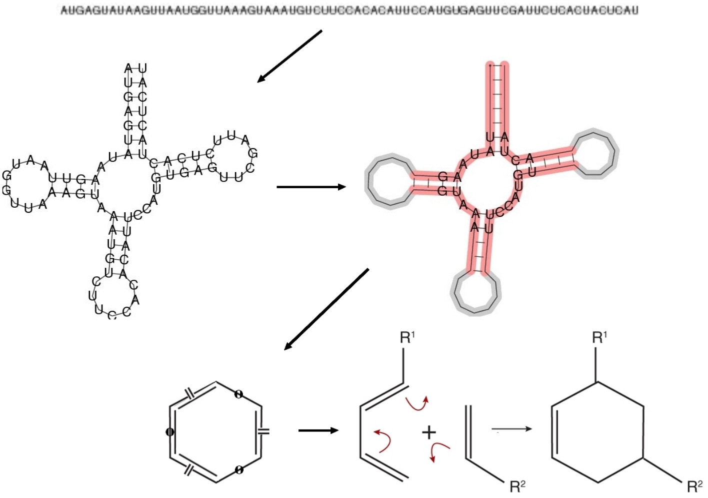


Neutrality is higher than in the RNA sequence-to-structure map.

Cell with Genome, Metabolites and Enzymes

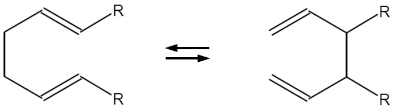


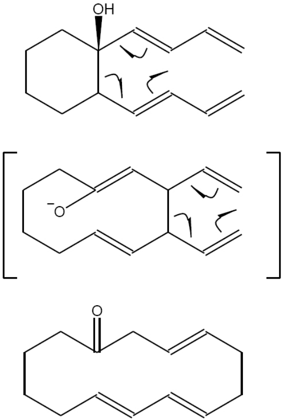
From gene to function



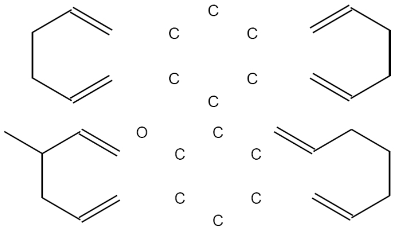
Chemical Reaction as Graph Rewrite Rule

Cope Rearrangement



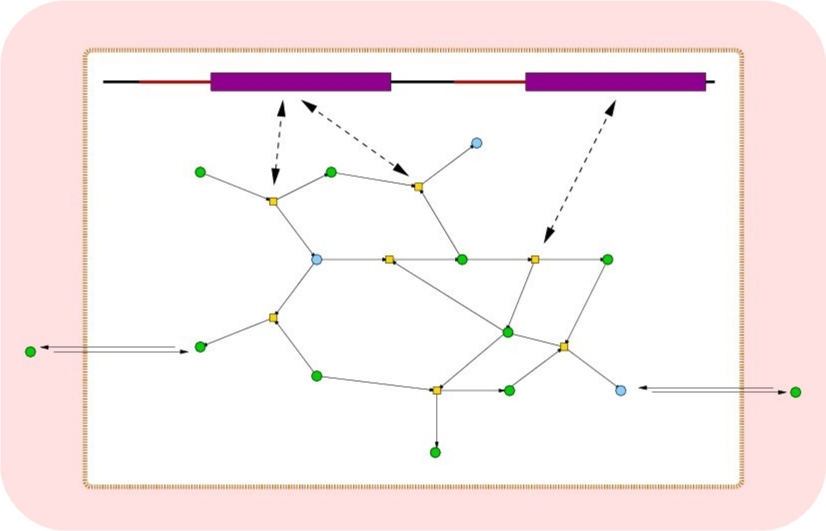


Rewrite Rules



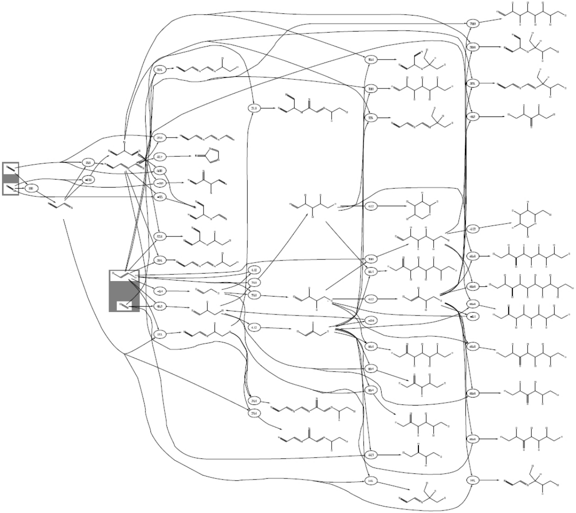
Graph-grammars are a context sensitive language!

The Cell



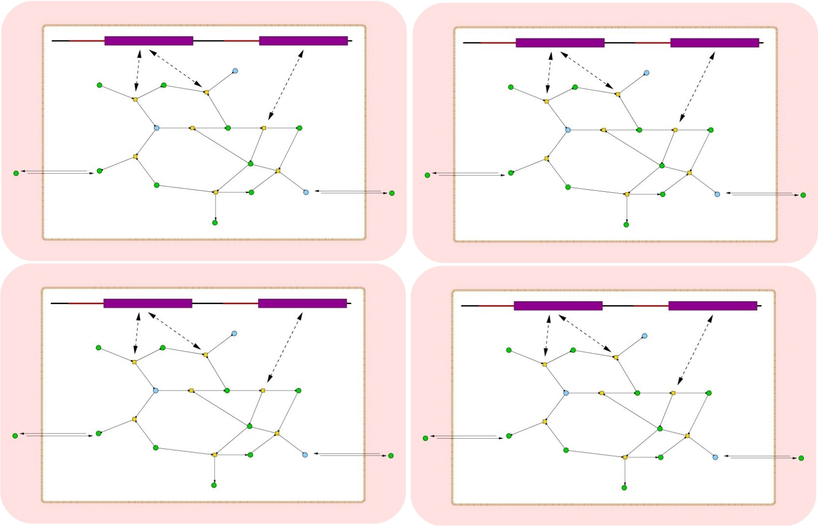
THE NEXT STEP!

Iterating the Graph Grammar



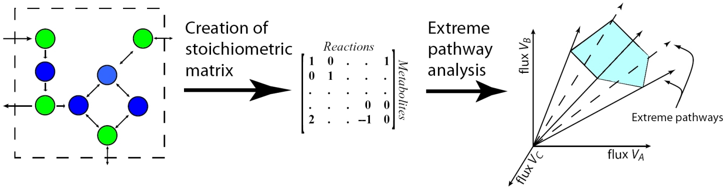
cyanide, formaldehyde glycol; aldolcondensation, tautomerization

Cell-Population

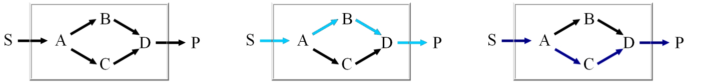


Analysis of the networks

- Metabolic Pathway Analysis

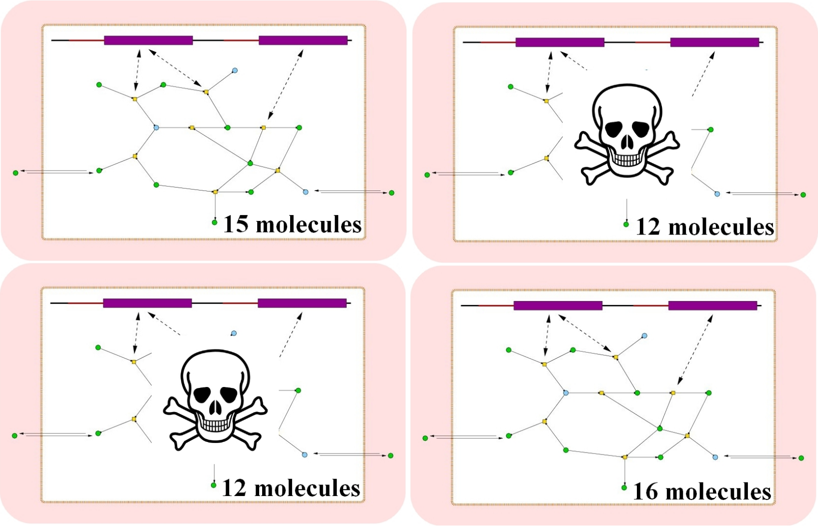


- Pathway Distribution using extreme pathways

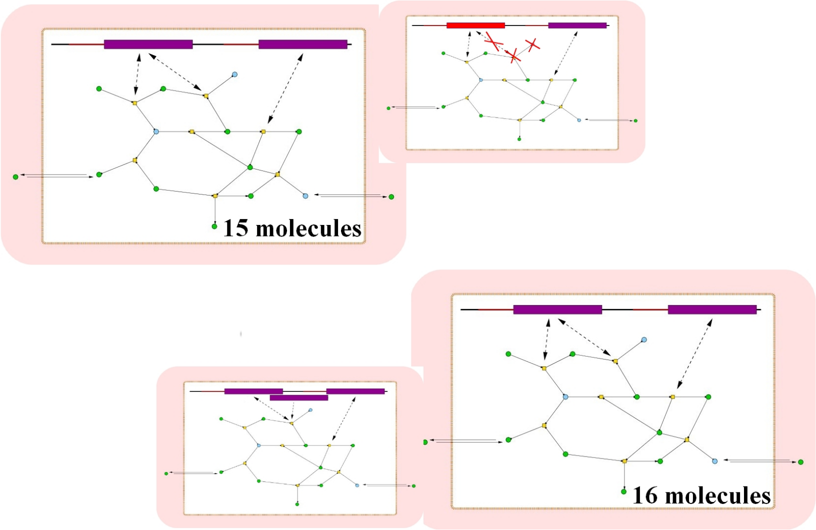


- Calculating the Yield of all extreme pathways
- At least one of those Pathways has optimal Yield

Selection

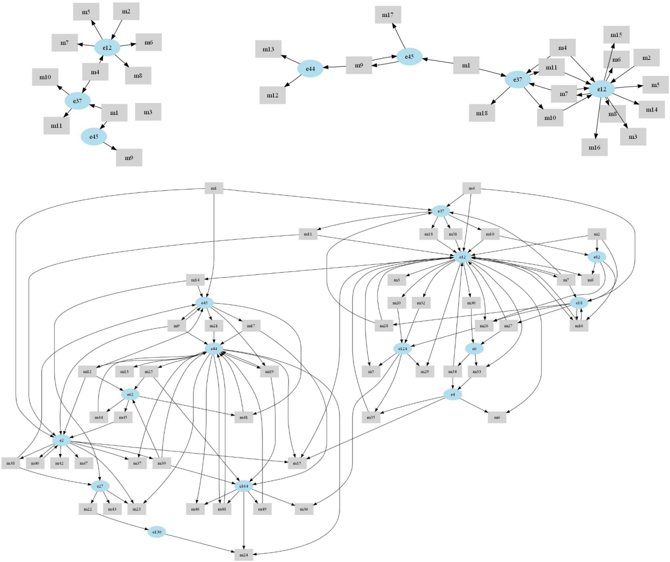


The next Generation

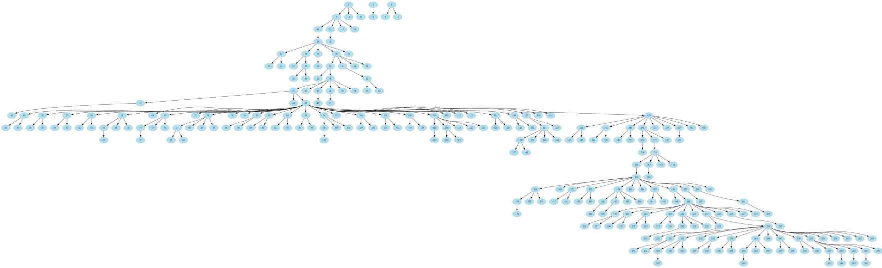


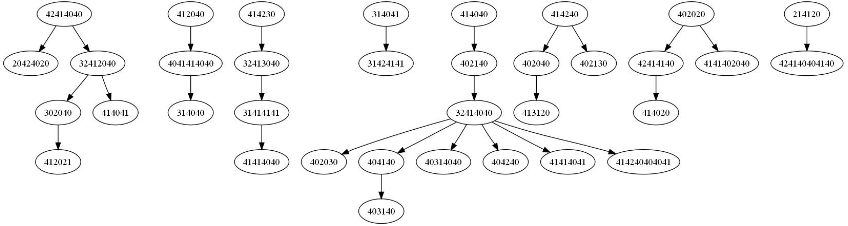
Analysis

Network Graphs

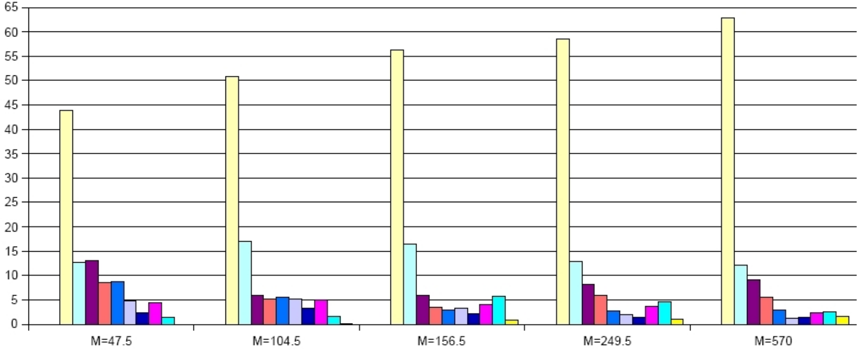


Cell/Enzyme Evolution





Connectivities

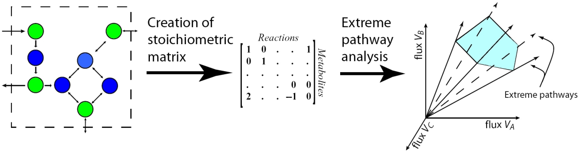


Enzyme	e37	e45	e12	e44	e18	e27	e6	e82	e4	e62	e124	e130	e2
Generation	1	1	1	2	3	3	7	10	14	42	44	51	53
Connectivity	4	5	12	9	4	2	2	2	2	2	3	1	6

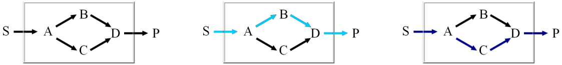
Specificity of enzymes in the example network

Analysis of metabolic networks

- Metabolic Pathway Analysis



- Pathway Distribution using extreme pathways

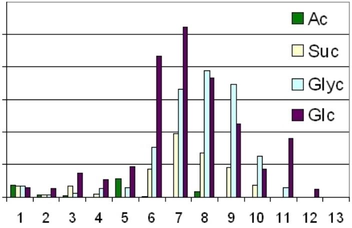


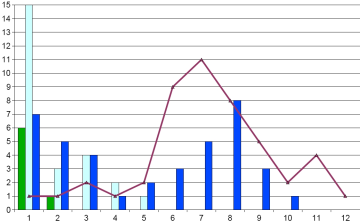
- Knockout Analysis using minimal knockout sets

- Viable Conditions using the notion of biological organizations

Measuring Robustness

- Knockout set size distribution





- Elementary mode measures

$$R_1 = \frac{\sum_{i=1}^{r} z^{(i)}}{r \cdot z}$$

$$R_2 = \frac{\sum_i R_1^{(i)}}{n}$$

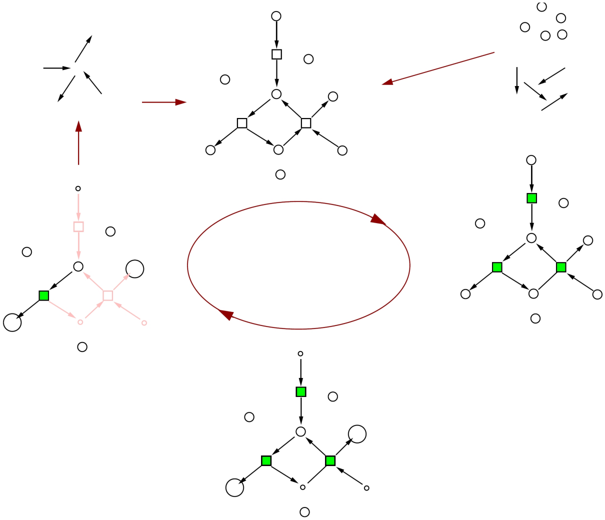
$$R_3 = \min\left\{R_1^{(1)}, R_1^{(2)}, \ldots, R_1^{(n)}\right\}$$

Problems and Solutions

Problems

- Combinatorial Explosion of the Networks
- Open-ended Simulation

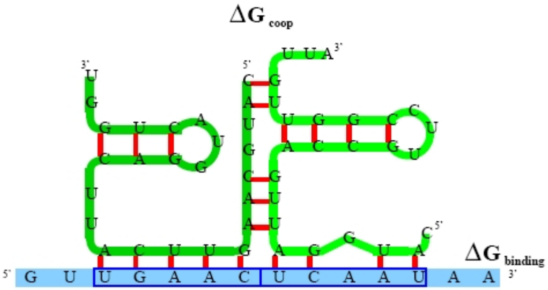
Avoiding Combinatorial Explosion



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

Adding Complexity

- Introduction of further functions for metabolites
  - Biomass, Membrane, Genetic material, . . .
- Introduction of further functions for enzymes
  - Catalyst, Transporter, Transcrition factor, . . .



Thanks to:

- University of Vienna
  - Christoph Flamm
  - The entire TBI-Group (Ilenia, Ronny, Dill, Christian, ...)
- University of Leipzig
  - Peter Stadler
  - Konstantin Klemm
- EBI
  - Lukas Endler
- University of Freiburg
  - Martin Mann
- Wiener Wissenschafts-, Forschungs- und Technologiefonds (WWTF) for Funding

  You for listening!