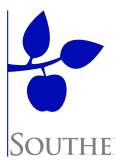
MedØlDatschgerl and Beyond

Jakob Lykke Andersen, Christoph Flamm,
Daniel Merkle, Peter F. Stadler

Department of Mathematics and Computer Science
University of Southern Denmark

Bled, February 2012



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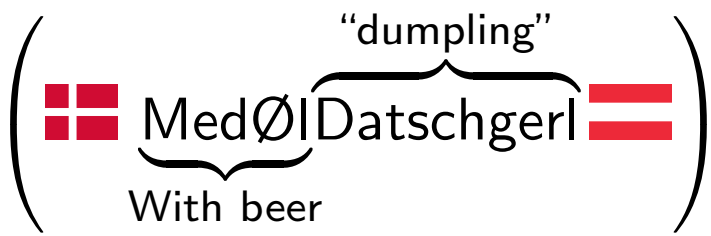

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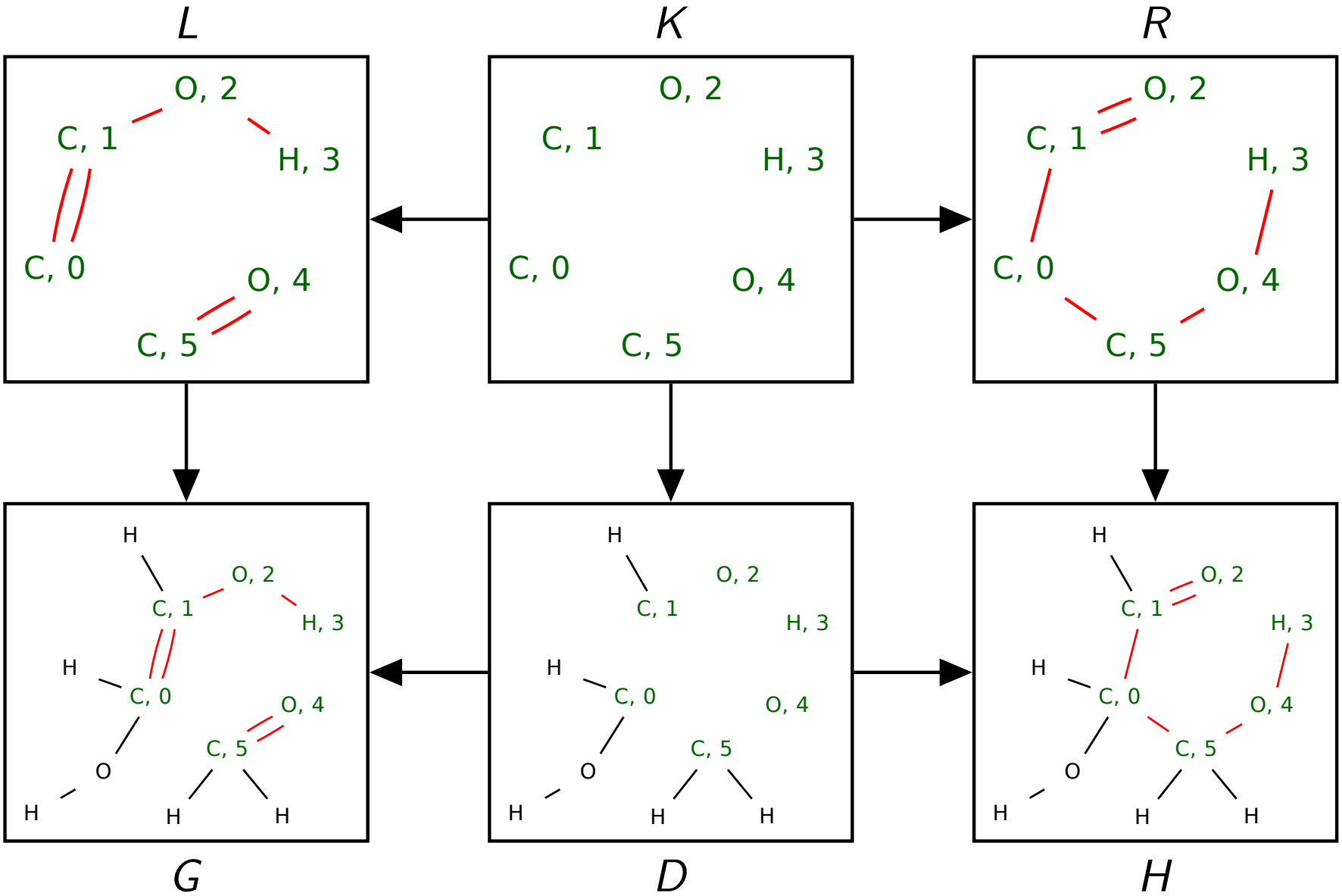
Graph Transformation - Double Pushout Approach

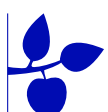


Graph Grammars

Grammar: $\mathcal{H} = (\mathcal{G}, \mathcal{R})$, starting graphs and transformation rules

Example: Formose

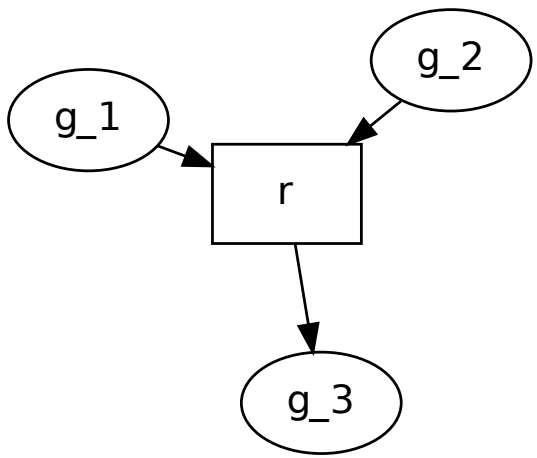
- Starting graphs:
  - g_0 formaldehyde
  - g_1 glycolaldehyde
- Transformation rules:
  - r_0 keto-enol-tautomerism, one direction
  - r_1 keto-enol-tautomerism, the other direction
  - r_2 aldol addition, one direction
  - r_3 aldol addition, the other direction



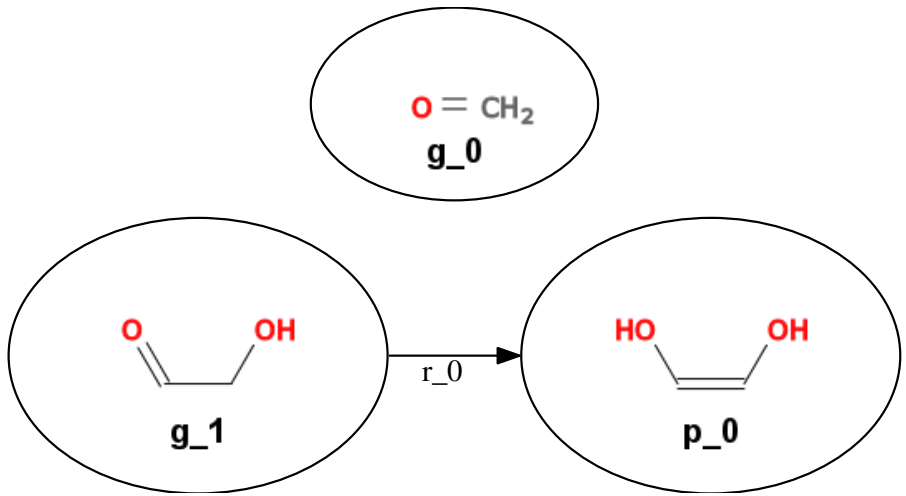
Derivation Graphs (Reaction Networks)

Input: a graph grammar (e.g., Formose)
Output: a directed hypergraph of (all) graph derivations

Visualization: $\{g_1, g_2\} \overset{r}{\Rightarrow} g_3$ is represented as

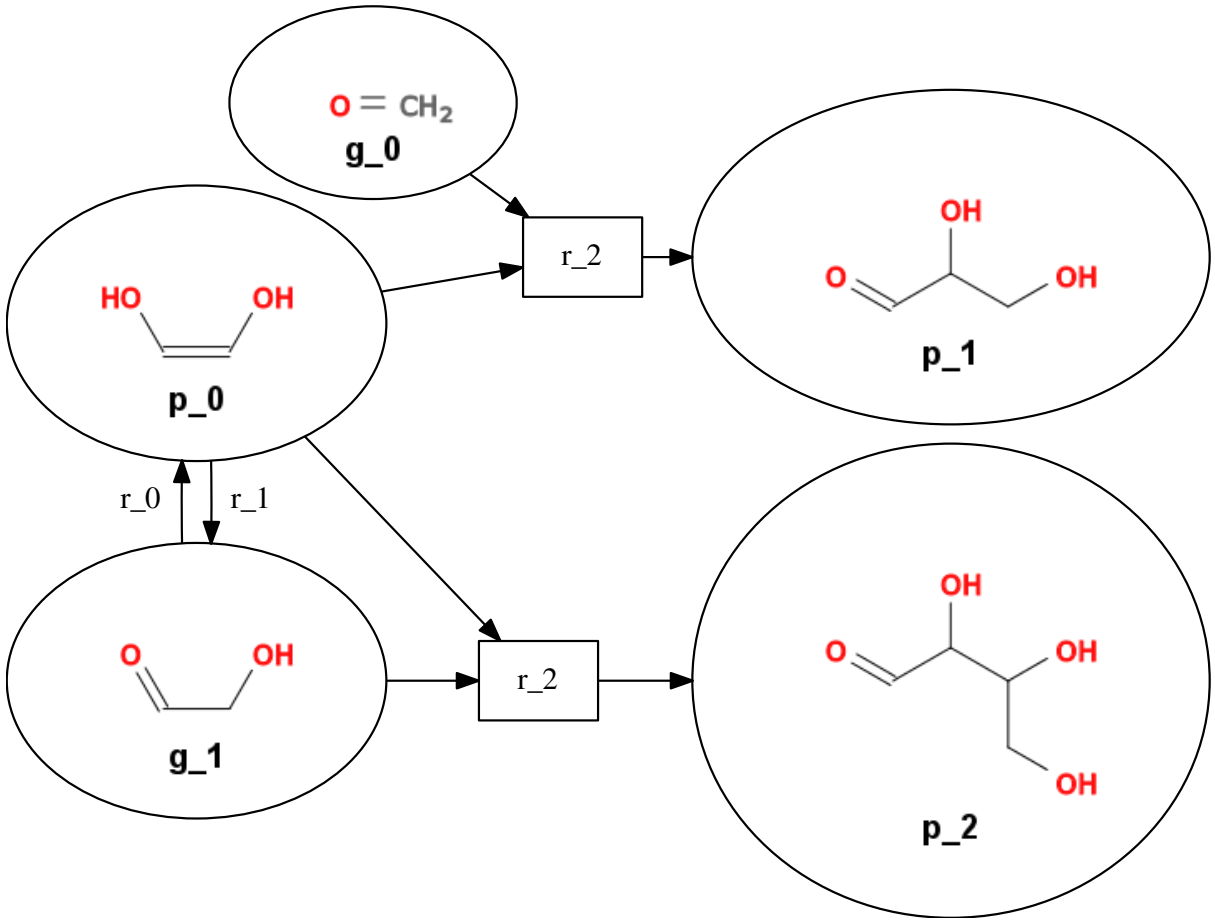


Reaction Network of Formose



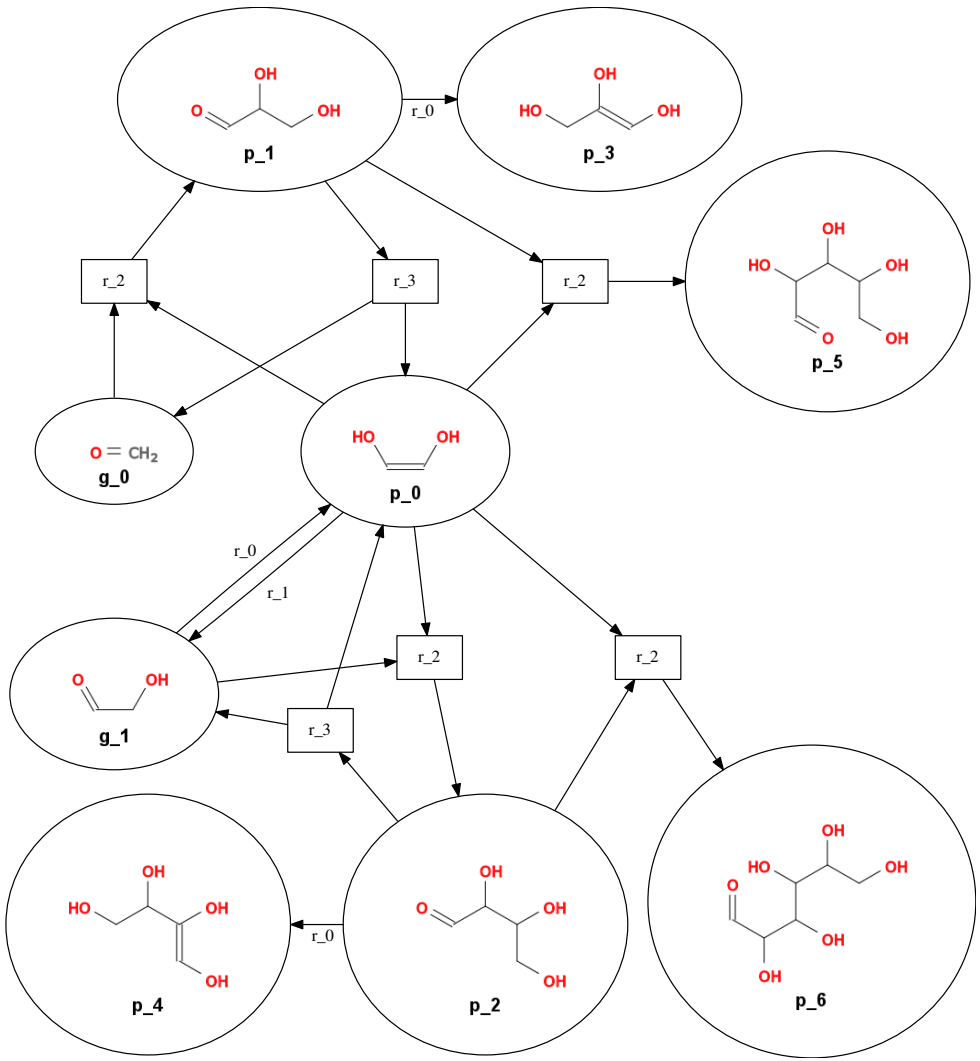
Generation 1

Reaction Network of Formose



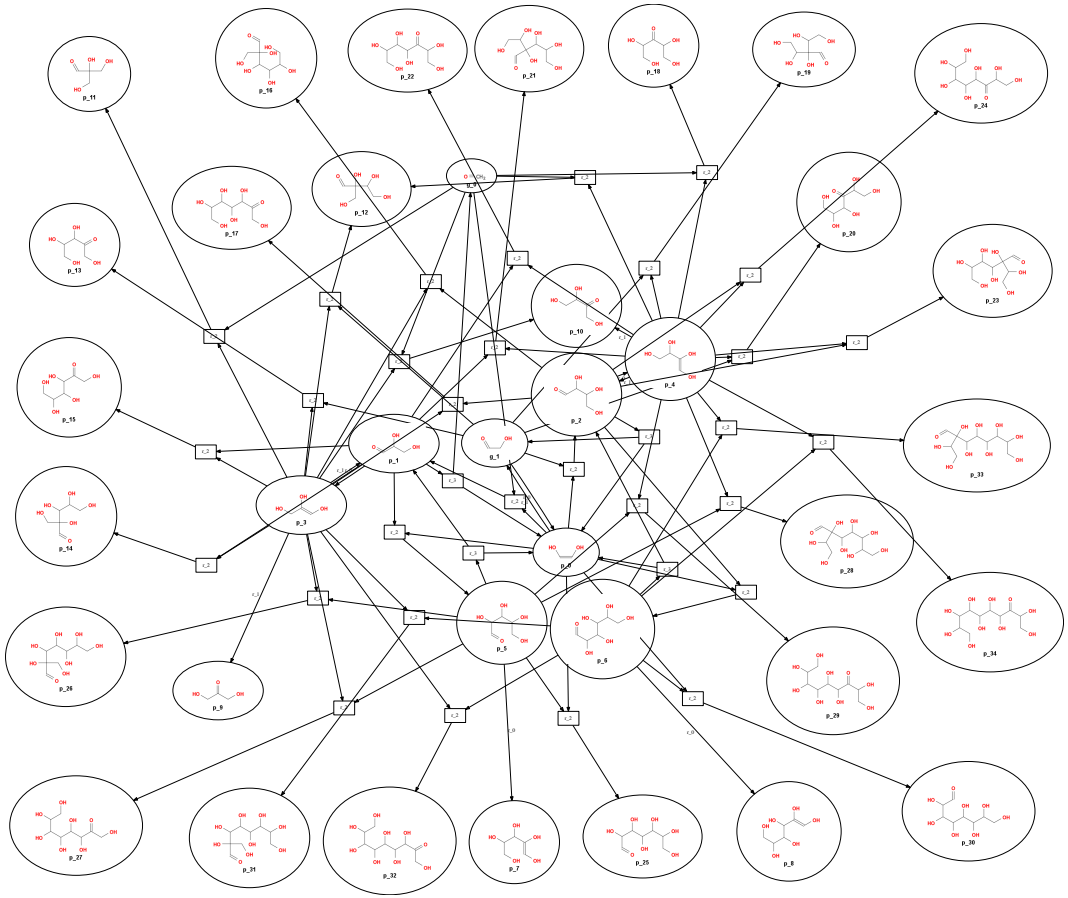
Generation 2

Reaction Network of Formose



Generation 3

Reaction Network of Formose



Generation 4

Pathways in Reaction Networks

Idea: use network flows as model for chemical pathways,
and find interesting flows

Problem: derivation graphs are hypergraphs

Solution: use integer linear programming (ILP)

Examples of interesting questions::

General pathway:

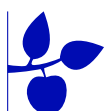
$$6 \text{ ribulose-5-phosphate} \rightarrow 5 \text{ fructose-6-phosphate}$$

Is it possible? and how?

Autocatalysis:

$$2 \text{ formaldehyde} + 1 \text{ glycolaldehyde} \rightarrow 2 \text{ glycolaldehyde}$$

Is it possible? and how?



Basis Model

Input: a derivation graph, (V, E)

Augment with input and output edges:

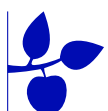
$$E_I = \{e_{in}^v = (\emptyset, \{v\}) | v \in V\} \qquad \bar{E} = E \cup E_I \cup E_O$$
$$E_O = \{e_{out}^v = (\{v\}, \emptyset) | v \in V\}$$

Variables:

$$x_e \in \mathbb{N}_0 \quad , \quad \forall e \in \bar{E}$$

Constraints:

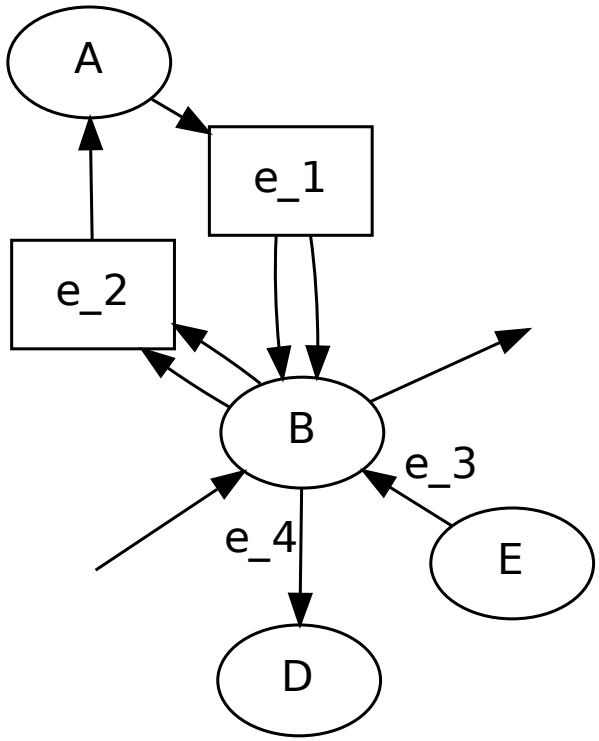
$$\sum_{e \in in(v)} x_e = \sum_{e \in out(v)} x_e \quad , \quad \forall v \in V$$



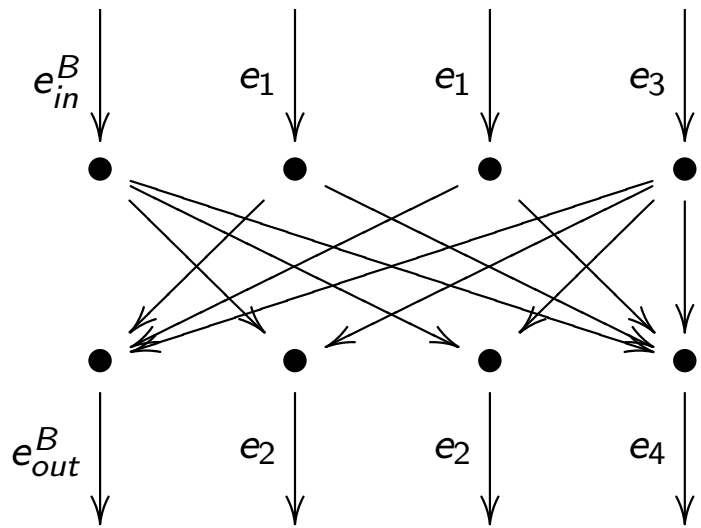
Change of the Basis Model

Replace each vertex with a bipartite graph

Part of a derivation graph



B



The extension Autocata

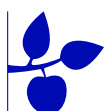
Variables:

$$Z_v \in \{0,1\} \quad , \quad \forall v \in V$$
$$Z_v^{in} \in \{0,1\} \quad , \quad \forall v \in V$$

Desired constraints:

$$Z_v = 1 \Leftrightarrow 0 < x_{in}^v < x_{out}^v$$
$$Z_v^{in} = 1 \Leftrightarrow 0 < x_{in}^v$$

$$\sum_{v \in V} Z_v \geq 1$$



The extension Autocata

Constraints:

$$Z_v^{in} \leq x_{in}^v \tag{1}$$

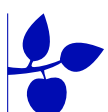
$$M \cdot Z_v^{in} \geq x_{in}^v \tag{2}$$

$$Z_v \leq x_{in}^v \tag{3}$$

$$x_{in}^v < x_{out}^v + M \cdot (1 - Z_v) \tag{4}$$

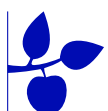
$$M \cdot Z_v \geq x_{out}^v - x_{in}^v - M \cdot (1 - Z_v^{in}) \tag{5}$$

x_{in}^v		x_{out}^v	${}^1Z_v^{in}$	${}^2Z_v^{in}$	${}^3Z_v$	${}^4Z_v$	${}^5Z_v$
0		0	0	–	0	0	–
0		42	0	–	0	–	–
42		0	–	1	–	0	–
	$=$		–	1	–	0	–
	$<$		–	1	–	–	1
	$>$		–	1	–	0	–

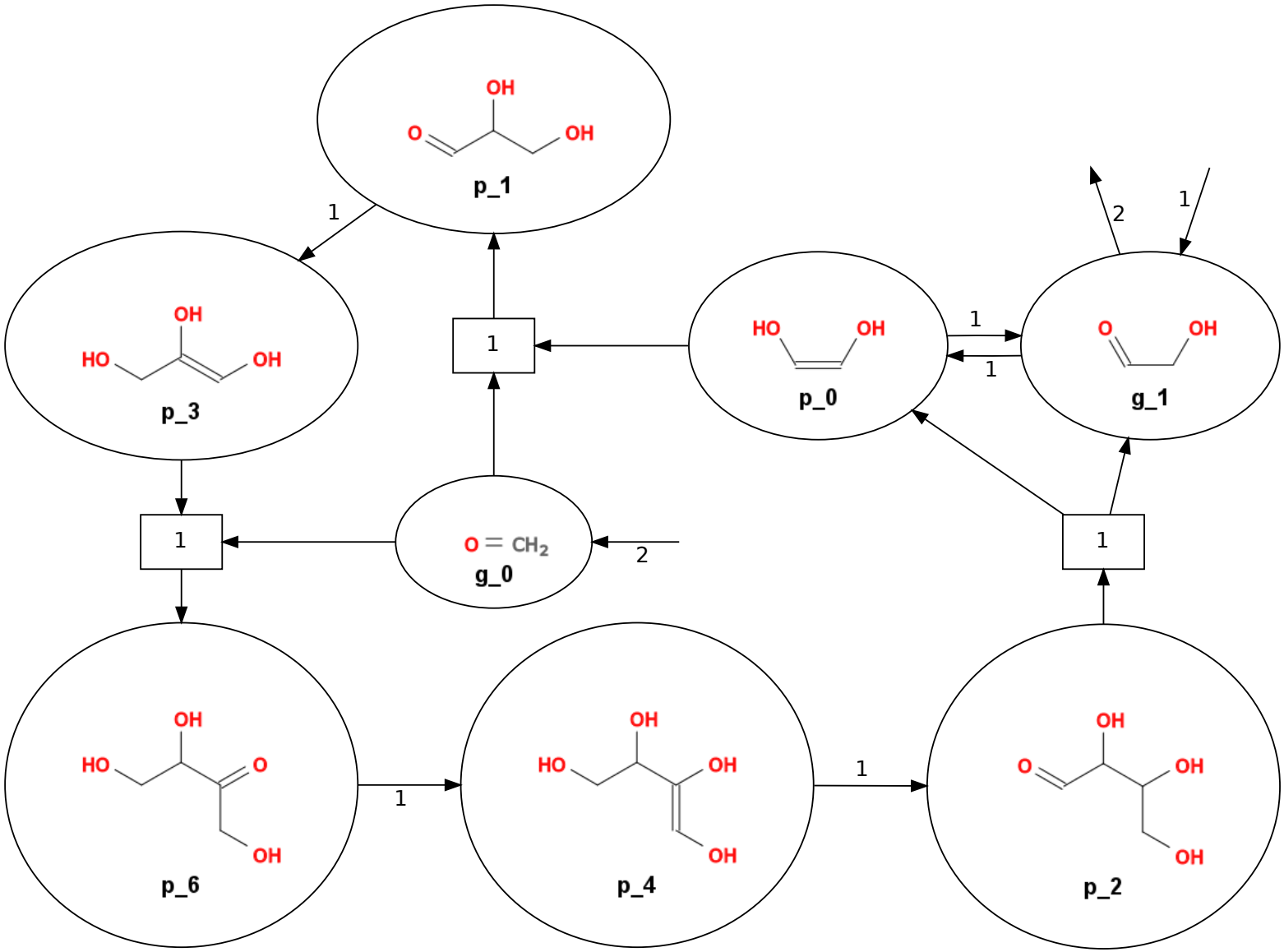


MedØlDatschgerl Code – Detection of Autocatalysis

```
load smiles    C=O
               OCC=O    ;
load r    keto_enol_forward.gml
          keto_enol_backward.gml
          aldol_addition_forward.gml
          aldol_addition_backward.gml    ;
dg size 16
autocata sources input; sinks sources;
list autocata
print dg
set DGFlow::printOnlyFiltered false
set DGFlow::printOnlyFlowLabels true
print autocata
```



Autocatalysis in Formose



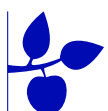
Autocatalysis in Metabolic Networks

Computational identification of obligatorily autocatalytic replicators embedded in metabolic networks
[Kun et al. Genome Biology 2008]

Networks:

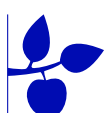
- *Escherichia coli*
- *Heliobacter pylori*
- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*
- *Methanosarcina barkeri*

Runs: for each network, run the detection with each internal molecule added to the input and output sets, individually
2898 runs in total ($\approx$ 3 days with 17 computers (3 cores each))



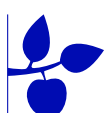
Autocatalysis in Metabolic Networks

Networks	Auto. molecules	Molecules	Percentage
Escherichia coli	226	625	36%
Heliobacter pylori	118	412	29%
Staphylococcus aureus	193	577	35%
Mycobacterium tuberculosis	255	740	34%
Methanosarcina barkeri	143	558	26%



Autocatalysis in Metabolic Networks

32 molecules, autocatalytic in all 5 networks					
13dpg	4pasp	gdp	nad	ppi	ump
23dhdp	adp	gln-L	nadh	prpp	utp
26dap-M	arg-L	gmp	nadp	pser-L	
2pg	aspsa	gtp	nadph	so3	
3pg	atp	hom-L	pep	thdp	
3php	coa	lac-L	phom	udp	



Model for Catalysis, Part 1 of 2

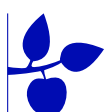
$$0 < x^v_{in} - x^v_{out} + M \cdot (1 - Z^{>}_v) \quad (1) \qquad 0 < x^v_{out} - x^v_{in} + M \cdot (1 - Z^{<}_v) \quad (3)$$

$$M \cdot Z^{>}_v \geq x^v_{in} - x^v_{out} \quad (2) \qquad M \cdot Z^{<}_v \geq x^v_{out} - x^v_{in} \quad (4)$$

$$1 - Z^0_v \leq x^v_{in} + x^v_{out} \quad (5)$$

$$M \cdot (1 - Z^0_v) \geq x^v_{in} + x^v_{out} \quad (6)$$

x^v_{in}		x^v_{out}	${}^1Z^{>}_v$	${}^2Z^{>}_v$	${}^3Z^{<}_v$	${}^4Z^{<}_v$	${}^5Z^0_v$	${}^6Z^0_v$
0		0	0	–	0	–	1	–
0		42	0	–	–	1	–	0
42		0	–	1	0	–	–	0
	$=$		0	–	0	–	–	0
	$<$		0	–	–	1	–	0
	$>$		–	1	0	–	–	0



Model for Catalysis, Part 2 of 2

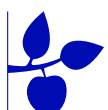
$$Z_v^c \geq 1 - Z_v^< - Z_v^> - Z_v^0 \tag{7}$$

$$0 \leq x_{in}^v - x_{out}^v + M \cdot (1 - Z_v^c) \tag{8}$$

$$0 \leq x_{out}^v - x_{in}^v + M \cdot (1 - Z_v^c) \tag{9}$$

$$Z_v^c \leq x_{in}^v + x_{out}^v \tag{10}$$

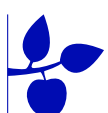
x_{in}^v	x_{out}^v	${}^7Z_v^c$	${}^8Z_v^c$	${}^9Z_v^c$	${}^{10}Z_v^c$
0	0	–	–	–	0
0	42	–	0	–	–
42	0	–	–	0	–
	$=$	1	–	–	–
	$<$	–	0	–	–
	$>$	–	–	0	–



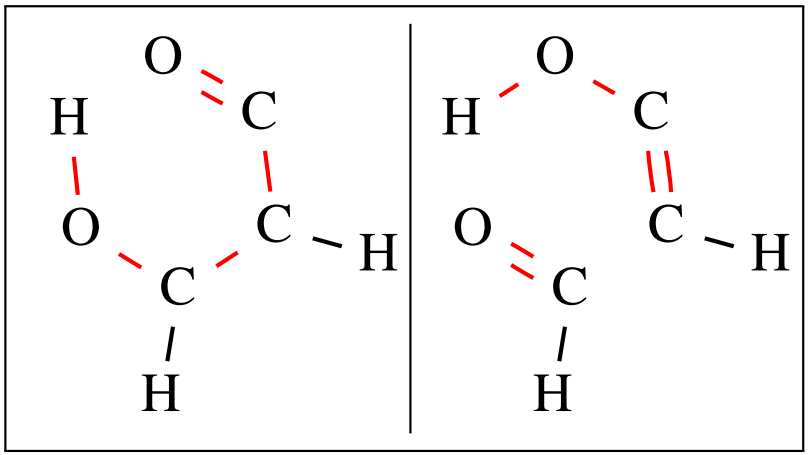
The Pentose-phosphate Pathway

$$6 \text{ ribulose-5-phosphate} \rightarrow 5 \text{ fructose-6-phosphate}$$

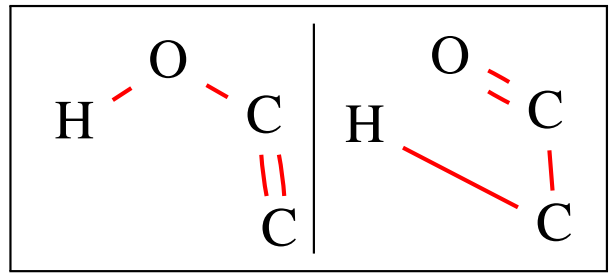
Is it possible? and how?



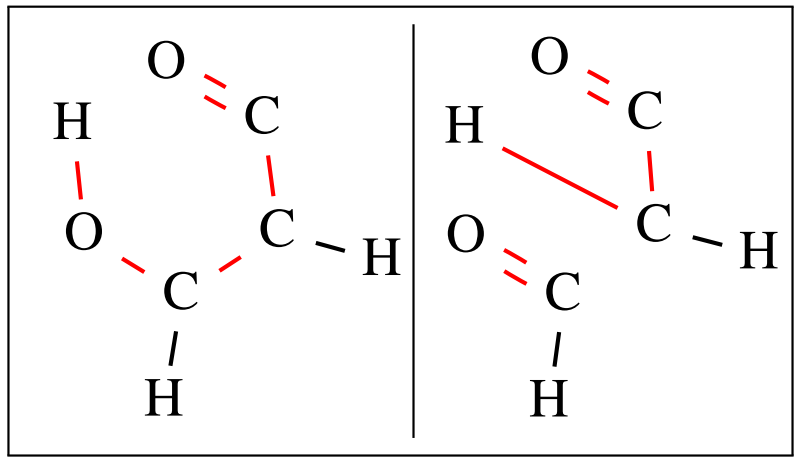
Composition of Rules



r_1: aldol-addition, backwards



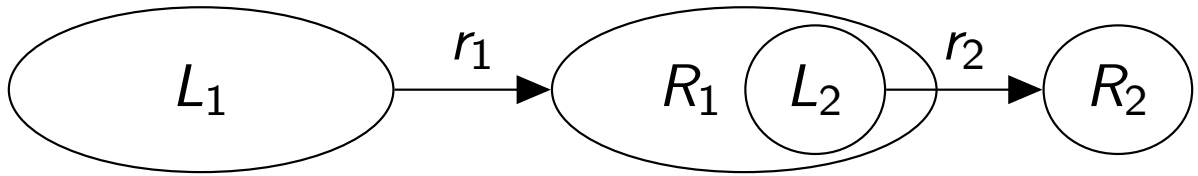
r_2: keto-enol-tautomerisation



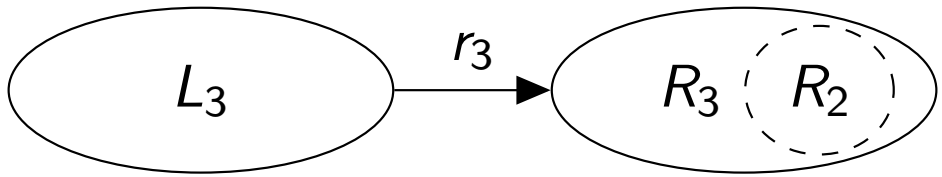
$r_2 \circ r_1$

Composition of Rules

Abstract example:

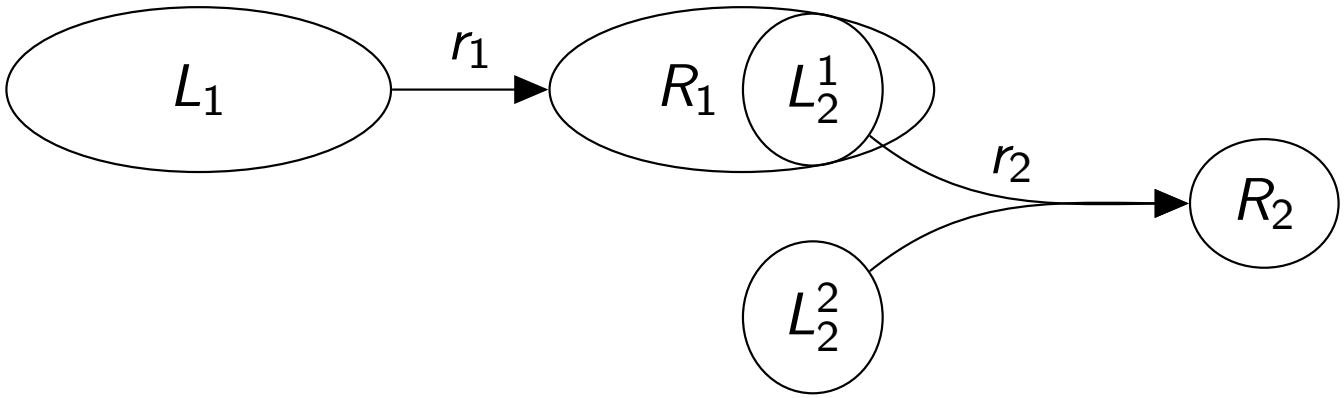


$$r_1 = (L_1, K_1, R_1),\ r_2 = (L_2, K_2, R_2)$$

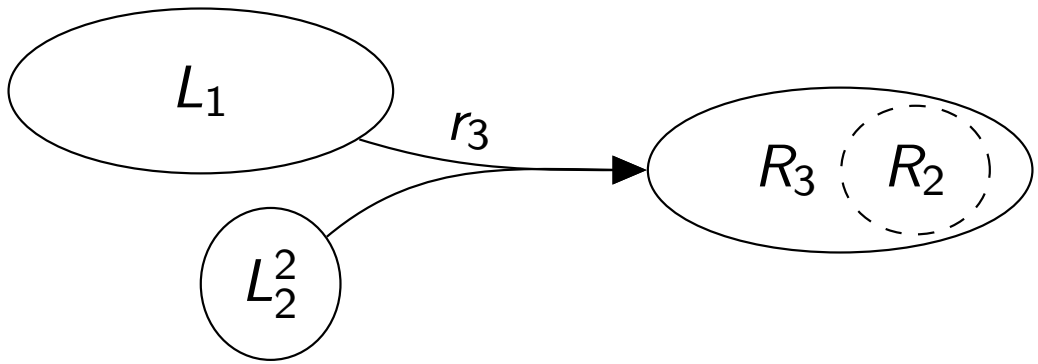


$$r_3 = r_2 \circ r_1 = (L_3, K_3, R_3)$$

Partial Composition

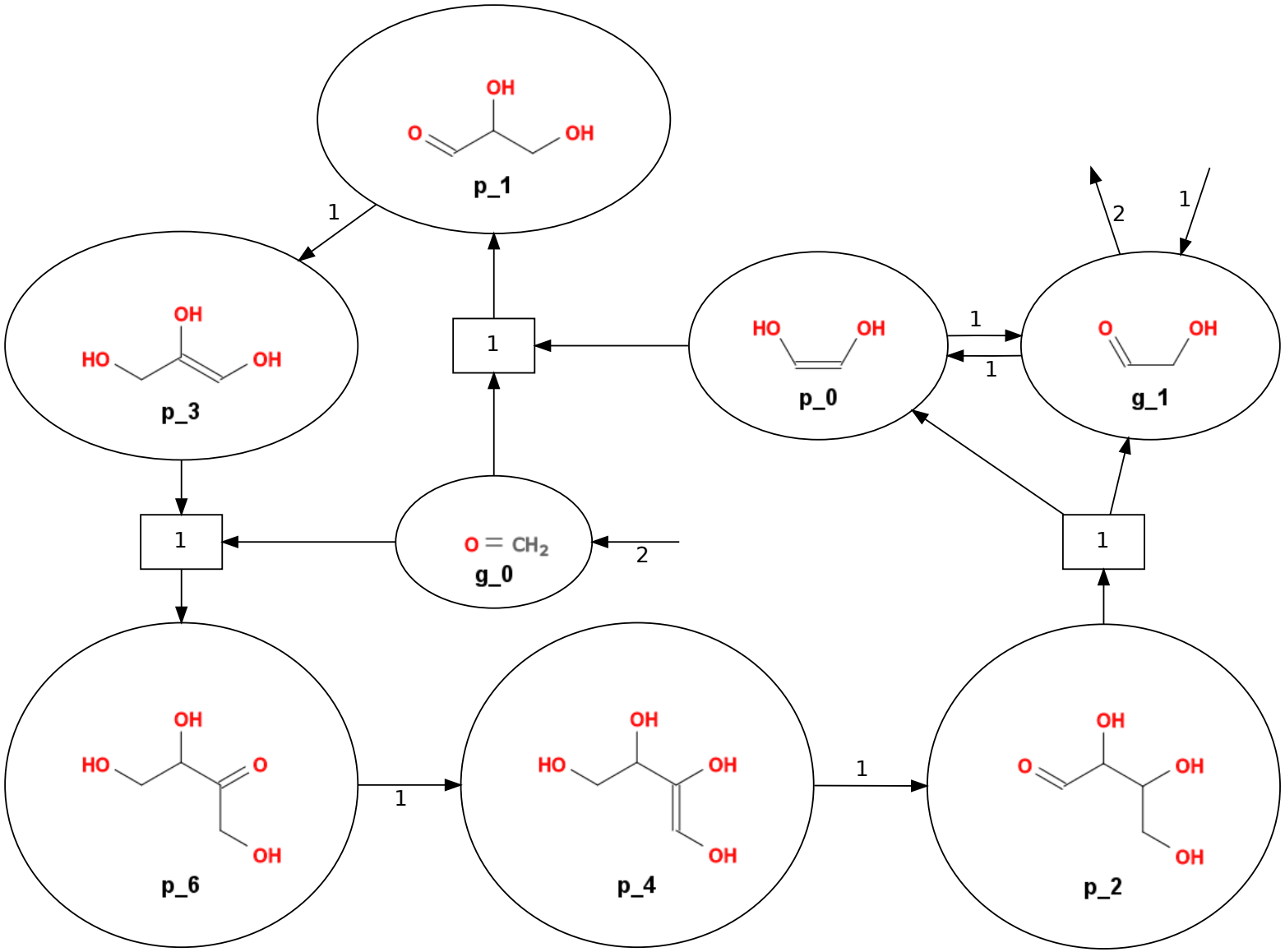


$$r_1 = (L_1, K_1, R_1),\ r_2 = (\{L_2^1, L_2^2\}, K_2, R_2)$$

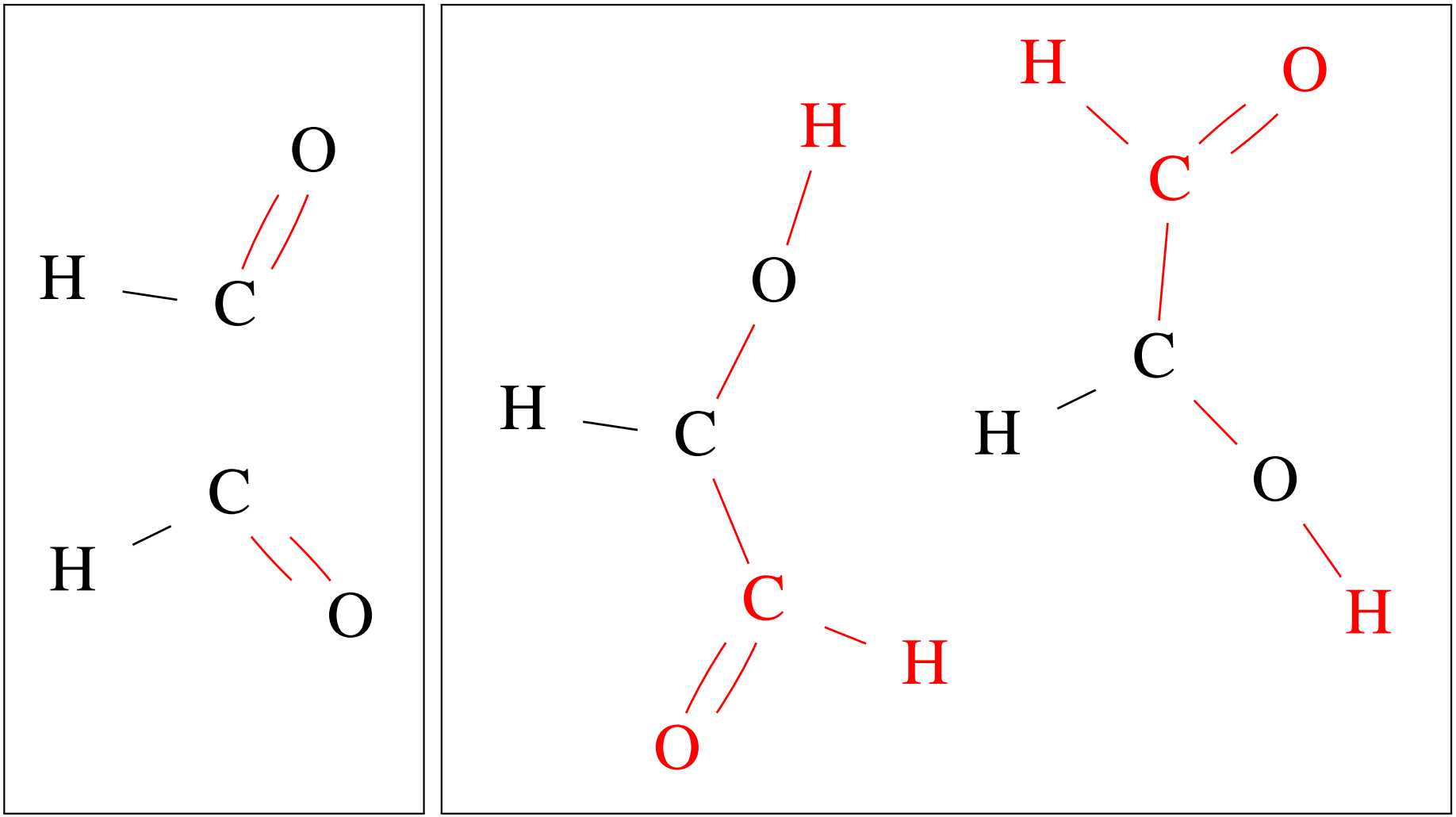


$$r_3 = r_2 \circ r_1 = (\{L_1, L_2^2\}, K_3, R_3)$$

Autocatalysis in Formose



Composition with the Formose Grammar



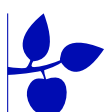
$r_1 \circ r_3 \circ r_1 \circ r_0 \circ r_2 \circ r_0 \circ r_2 \circ r_0 \circ g_1$

Strategies for Derivation Graph Generation

Current algorithm: breadth-first application of rules

`repeat({r1 r2 ... rN})`

Idea: general framework for generation



Strategies for Derivation Graph Generation

Current algorithm: breadth-first application of rules

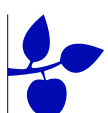
`repeat({r1 r2 ... rN})`

Idea: general framework for generation

Examples:

Limit reaction participation for molecule size:

`repeat( filter(size < 42) . {r1 r2 ... rN} )`



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Idea: general framework for generation

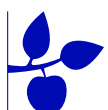
Examples:

Limit reaction participation for molecule size:

`repeat( filter(size < 42) . {r1 r2 ... rN} )`

Prioritize expansion by yield:

`repeat( limit[-10]{r1 r2 ... rN} . sort(yield) )`



Strategies for Derivation Graph Generation

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Idea: general framework for generation

Examples:

Limit reaction participation for molecule size:

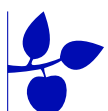
`repeat( filter(size < 42) . {r1 r2 ... rN} )`

Prioritize expansion by yield:

`repeat( limit[-10]{r1 r2 ... rN} . sort(yield) )`

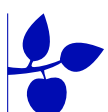
Catalan:

```
repeat( unmark . repeat[3](deleteNode) .
                                repeat(fixEdge) . mark )
```



Summary

- Generation of reaction networks from grammars
- Model for chemical pathways: flows in hypergraphs with ILP
- Strict model for autocatalysis and catalysis
- Detection of autocatalysis in metabolic networks
- Composition of transformation rules



Summary

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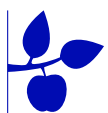
Future work:

- Pathways, catalysis, and autocatalysis in more chemistries (Citric acid cycle, Calvin cycle, HCN, ...)
- Detection of polymerization (Terpene, Polyketide, HCN, ...)
- Synthesis planning
- Strategy framework for network generation
- (Use graph grammars to solve more games)



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- Daniel Merkle
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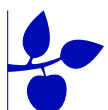
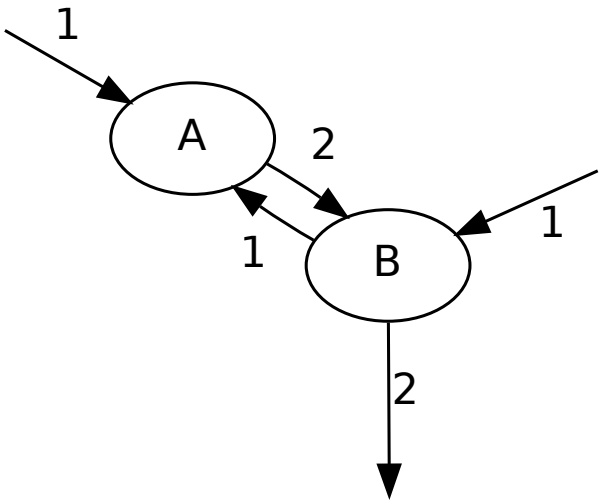
- Peter F. Stadler
- Martin Mann

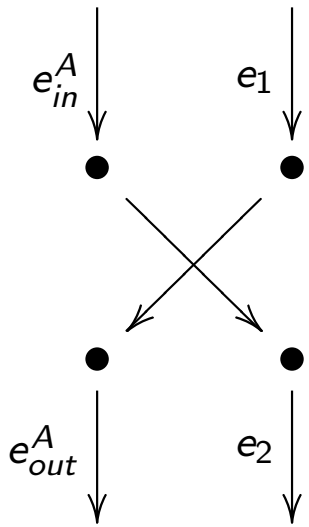


Bonus – Exampple of Problemaic Flow

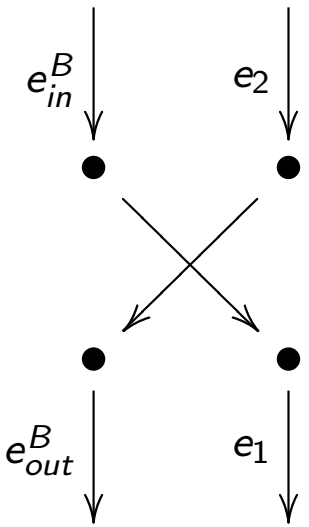
Problematic flow



A



B

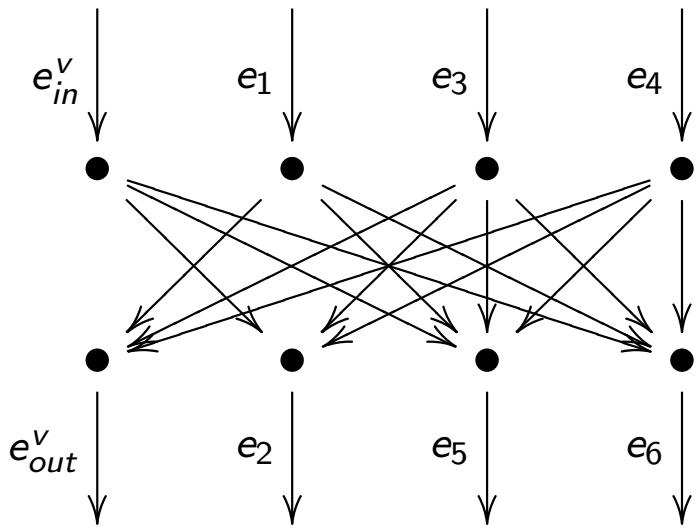


The problematic flow is no longer feasible

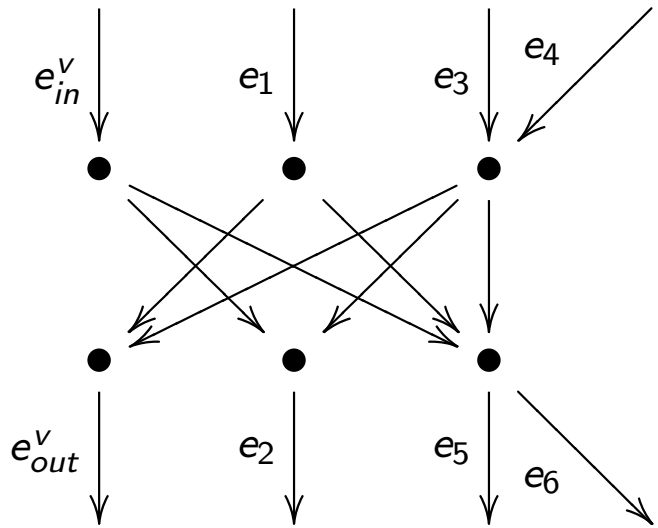
Bonus – Optimization

Example: e_1 is the inverse of e_2

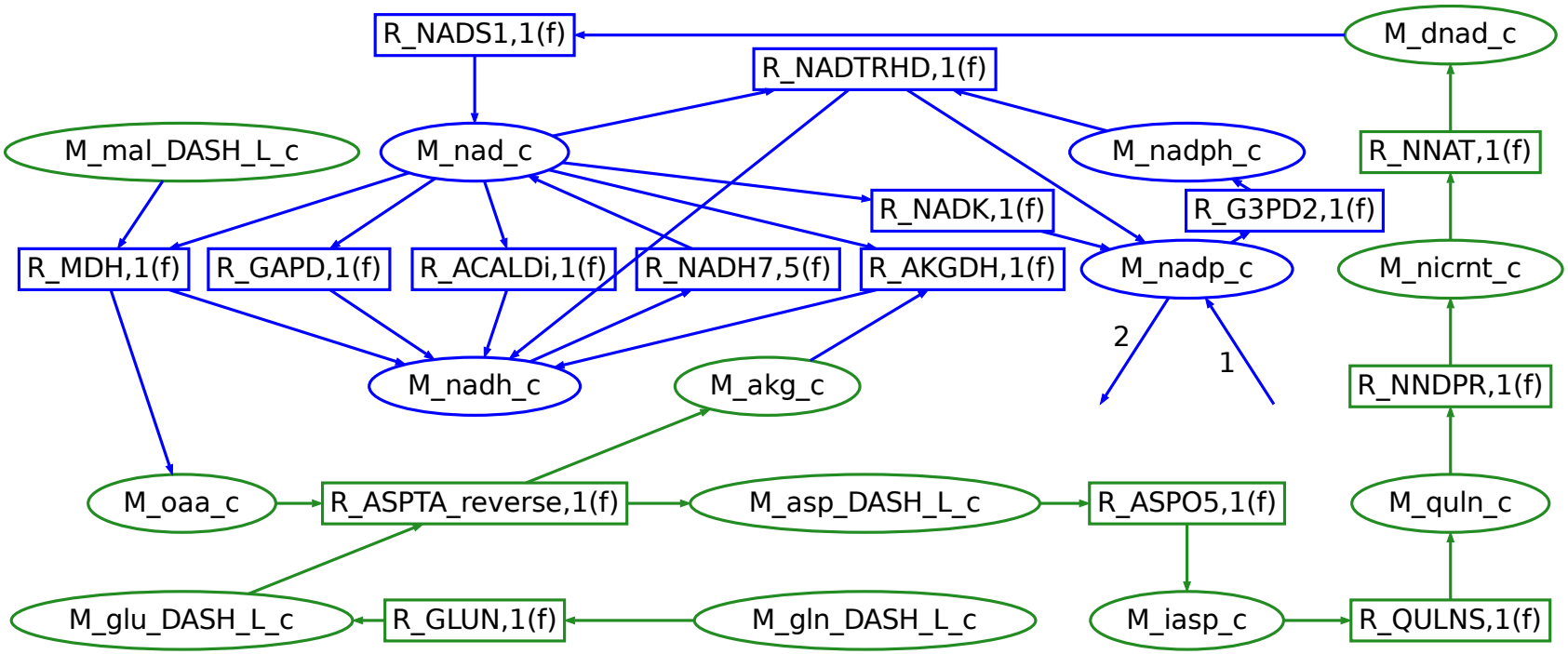
Without optimization



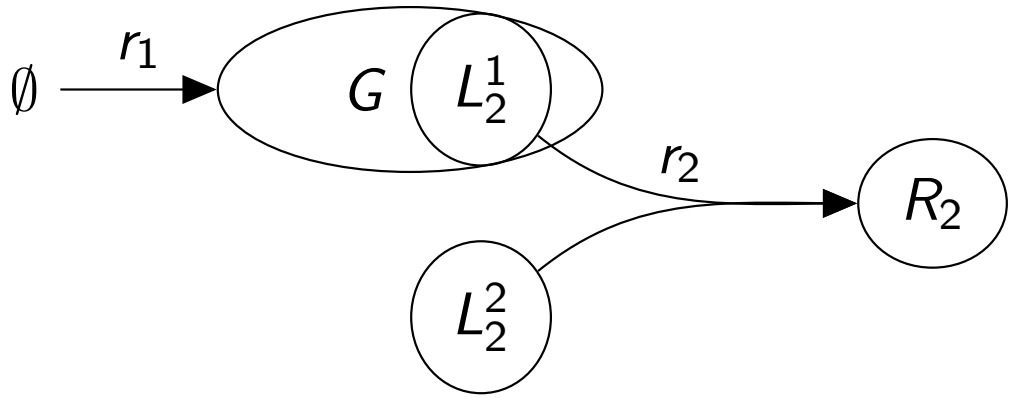
With optimization



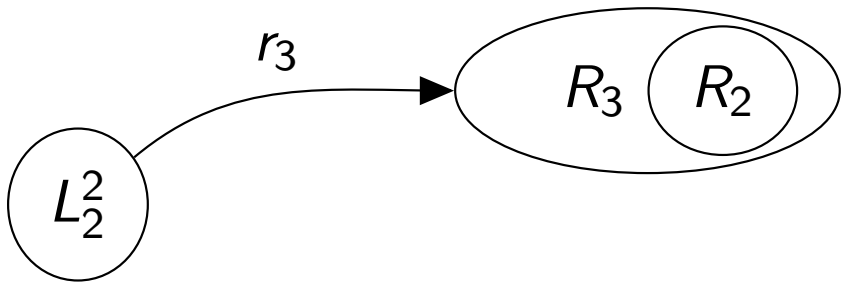
Bonus – Autocatalysis in *Escherichia coli*, NAD^+



Graph Binding



$$r_1 = (\emptyset, \emptyset, G),\ r_2 = (\{L_2^1, L_2^2\}, K_2, R_2)$$



$$r_3 = r_2 \circ r_1 = (L_2^2, K_3, R_3)$$