Thermodynamic Feasibility of Pathways

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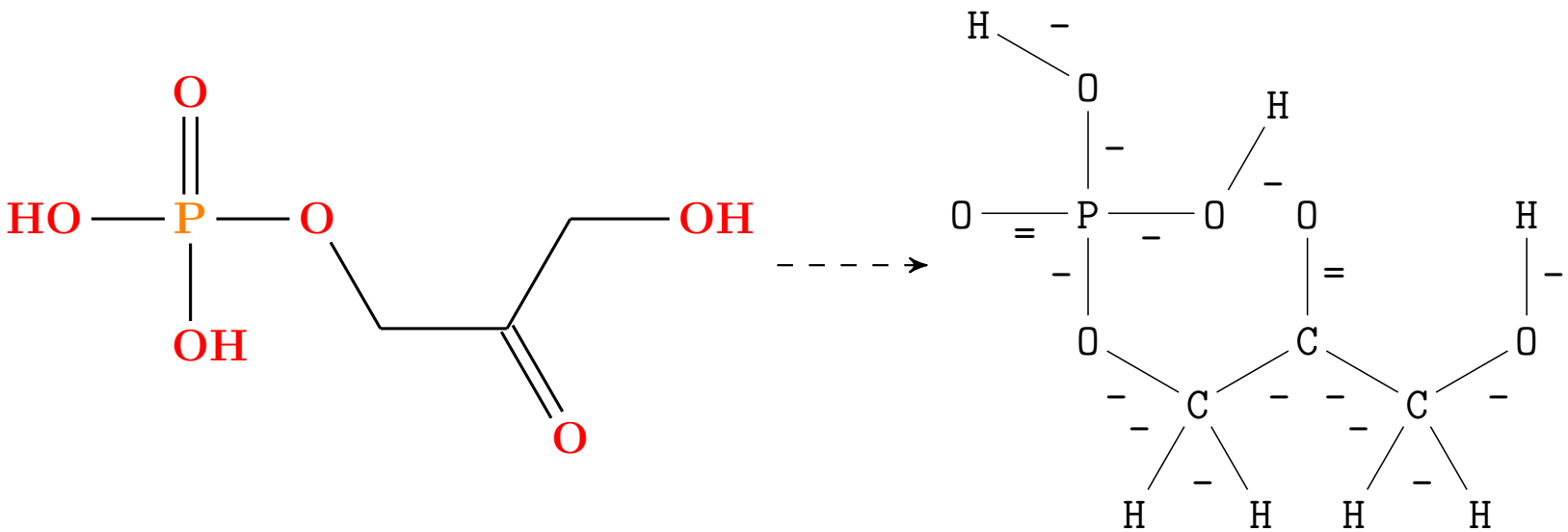
Bled, February 2016

Modelling and Analysis of Chemical Systems

1. Model molecules as labelled graphs.



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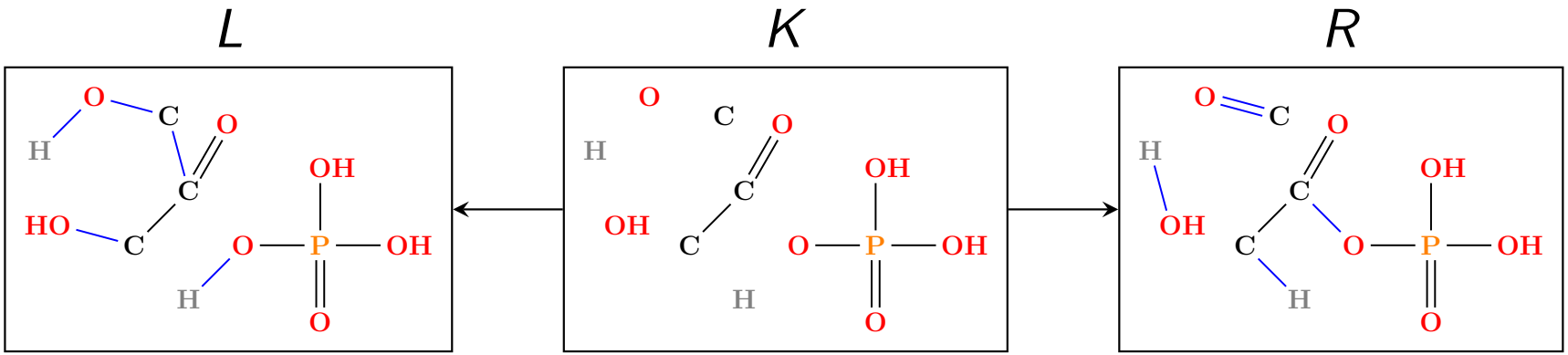
2. Model reaction types and graph transformation rules.



Example: Carbon rearrangement

- Aldolase: $\text{ketone} + \text{aldehyde} \longrightarrow \text{ketone}$
- Aldose-Ketose: $\text{aldehyde} \longrightarrow \text{ketone}$
- Ketose-Aldose: $\text{ketone} \longrightarrow \text{aldehyde}$
- Phosphohydrolase: $\text{H}_2\text{O}+\text{CnP} \longrightarrow \text{Cn}+\text{Pi}$
- Phosphoketolase $\text{Pi}+\text{ketone} \longrightarrow \text{carbonyl} + \text{CnP}_{+\text{water}}$
- Transaldolase: $\text{Cn}+\text{Cm} \longrightarrow \text{C(n+3)}+\text{C(m-3)}$
- Transketolase: $\text{Cn}+\text{Cm} \longrightarrow \text{C(n+2)}+\text{C(m-2)}$

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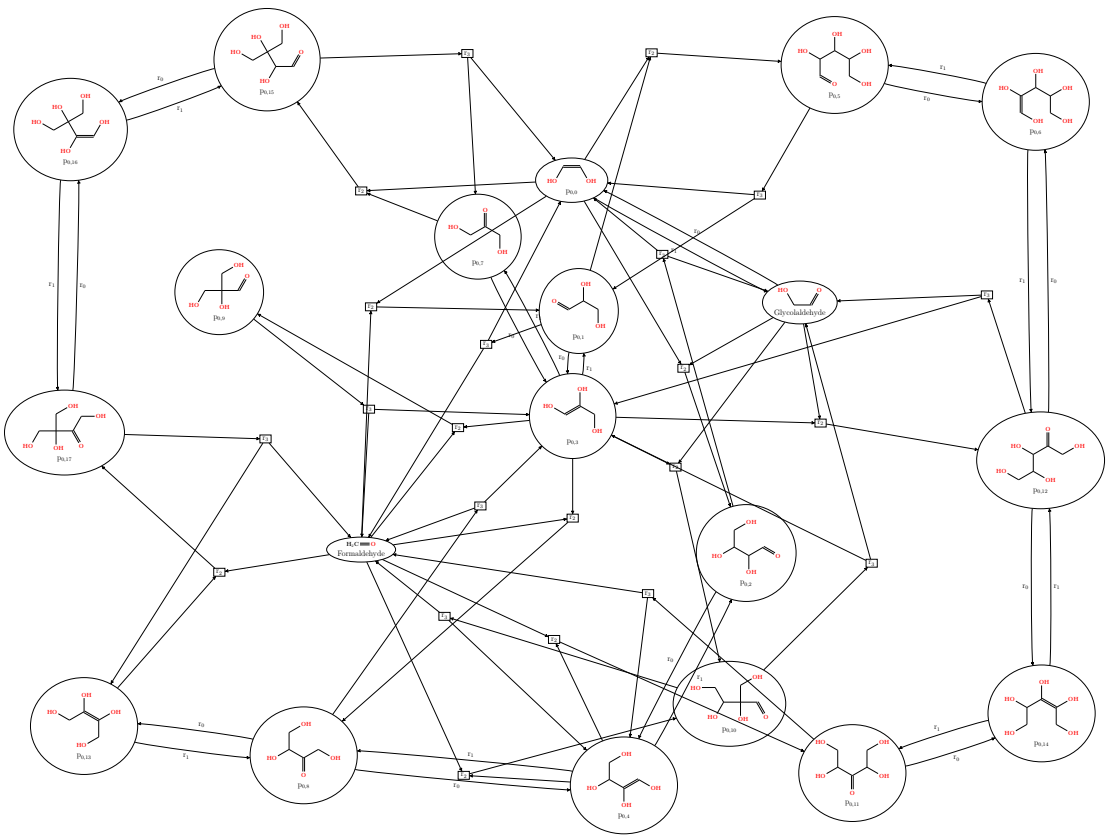
3. Generate a reaction network.

```
dg = dgRuleComp(inputGraphs,
    addSubset(inputGraphs) >> rightPredicate[
        lambda d: all(countCarbon(a) <= 5 for a in d.right)
    ](      repeat(inputRules)    )
)
dg.calc()
```



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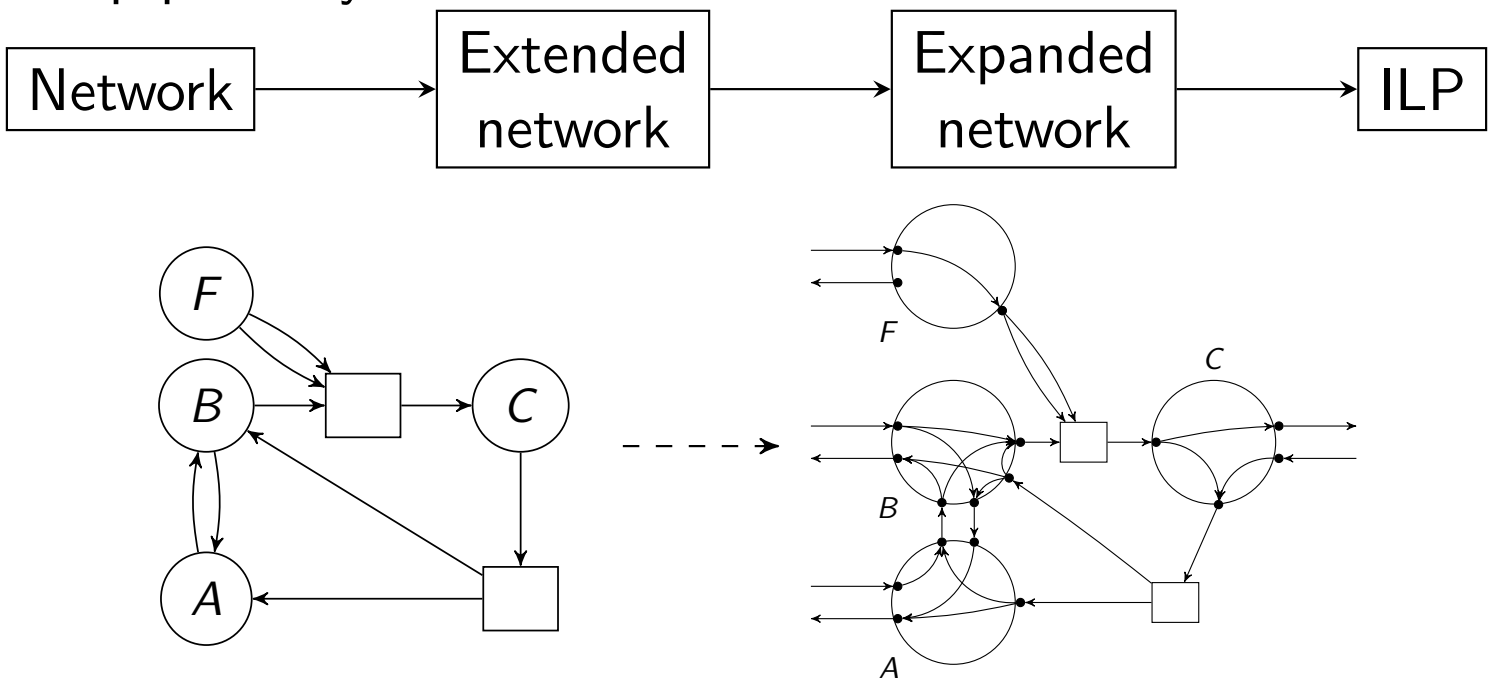
4. Set up pathway model.



Conservation constraints:

$$\sum_{e \in \delta^+_{\widetilde{E}}(v)} m_v(e^+) f(e) - \sum_{e \in \delta^-_{\widetilde{E}}(v)} m_v(e^-) f(e) = 0 \qquad \forall v \in \widetilde{V}$$

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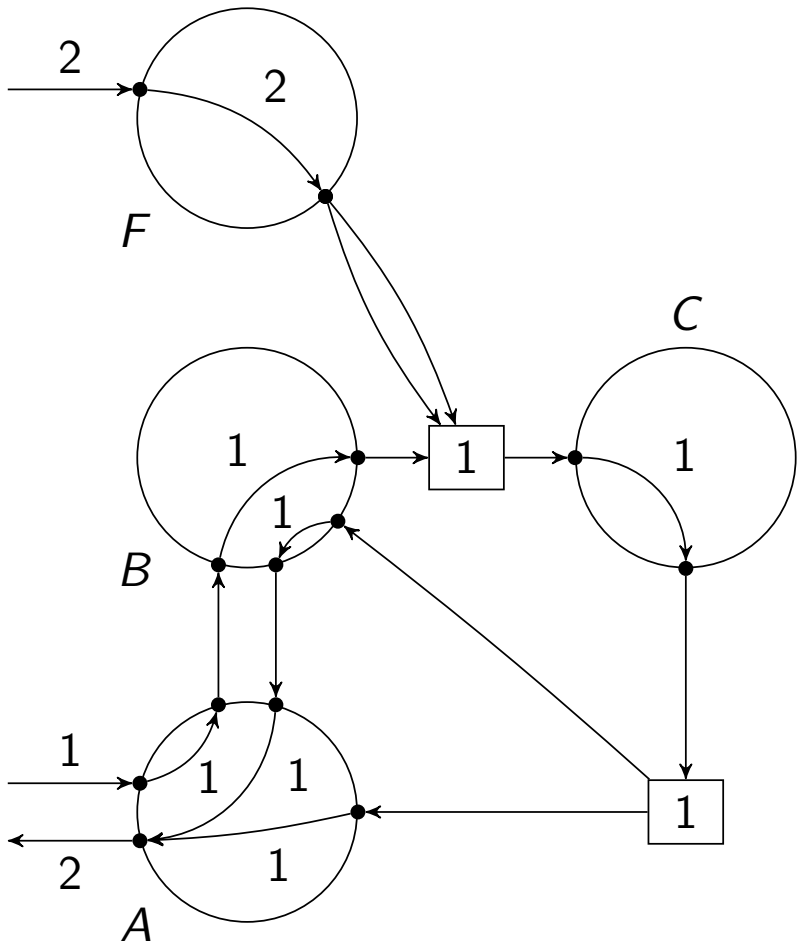
5. Formulate pathway question.

Example: Given 2 formaldehyde and 1 glycolaldehyde, how can 2 glycolaldehyde be produced through autocatalysis.



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6. Enumerate many alternate pathways.

Example (Formose):

Network: all molecules with at most 9 carbon atoms (284 molecules, 978 reactions).

	Maximum #C						
Reactions used	4	5	6	7	8	9	Sum
6	0	0	1	1	1	2	5
7	0	0	0	0	0	2	2
8	1	5	7	17	37	68	135
9	0	0	12	12	37	69	130
10	0	12	50	274	849	—	≥ 1185
11	0	5	41	190	738	—	≥ 974
							≥ 2431

Feasibility

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Are all of those pathways feasible in reality?

Reality is complicated...

Idea: Add constraints from thermodynamics.
Not an entirely new idea:

Thermodynamics-Based Metabolic Flux Analysis
C. S. Henry, L. J. Broadbelt, V. Hatzimanikatis
Biophysical Journal 2007

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Each molecule v has

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The actual change of energy:

$$\Delta G(e) = \Delta G^\circ(e) + RT \ln K(e)$$

with

$$\ln K(e) = \sum_{v \in_m e^-} \ln K(v) - \sum_{v \in_m e^+} \ln K(v)$$

. . . and energy should go down: $\Delta G(e) < 0$.

Thermodynamics using Mixed Linear Programming

Each molecule v has

- a free energy estimate $G^{\circ}_{est}(v)$, with an error estimate $\sigma(v)$.
- a variable for free energy $x_v^{G^{\circ}} \in [G^{\circ}_{est}(v) - \sigma(v); G^{\circ}_{est}(v) + \sigma(v)]$.
- a variable for concentration $x_v^K \equiv \ln K(v)$.

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A reaction e has a variable for change in energy:

$$x_e^{\Delta G} = x_e^{\Delta G^{\circ}} + RT \cdot x_e^K$$

with

$$x_e^{\Delta G^{\circ}} = \sum_{v \in_m e^-} x_v^{G^{\circ}} - \sum_{v \in_m e^+} x_v^{G^{\circ}} \qquad x_e^K = \sum_{v \in_m e^-} x_v^K - \sum_{v \in_m e^+} x_v^K$$

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If energy does not go down, then no flow on the reaction:

$$x_e^{\Delta G} \geq 0 \Rightarrow x_e = 0$$

and in linear form (with a "big M"):

$$x_e^{\Delta G} < M \cdot (1 - x_e^+)$$

(with x_e^+ indicating positive flow on e).

Summary

1. Molecule modelling (MØD + a chemist)
2. Reaction type modelling (MØD + more chemists)
3. Network expansion (MØD)
4. Pathway modelling (MØD + CPLEX)
5. Pathway questions (a chemist)
6. Enumeration of thermodynamically feasible pathways (MØD + Nikolai's stuff (and no chemist!))

Thanks

Earth-Life Science Institute
Tokyo Institute of Technology

ELSI Origins Network

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