Randomization of chemical reaction networks

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Widespread use of random chemistry models

SCIENCE ADVANCES | RESEARCH ARTICLE

SYSTEMS BIOLOGY

Universal scaling across biochemical networks on Earth

Hyunju Kim[1,2]*, Harrison B. Smith[2]*, Cole Mathis[1,3], Jason Raymond[2], Sara I. Walker[1,2,4,5†]

Kim et al 2019, Sci Adv 5:eaau0149 | doi:10.1126/sciadv.aau0149

Scaling laws in enzyme function reveal a new kind of biochemical universality

Dylan C. Gagler[a], Bradley Karas[a], Christopher P. Kempes[b], John Malloy[a], Veronica Mierzejewski[a], Aaron D. Goldman[c], Hyunju Kim[a,d,e,1], and Sara I. Walker[a,b,d,e,1]

Gagler et al 2022, PNAS 119(9):e2106655119 | doi:10.1073/pnas.2106655119

JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2012) 9, 1168–1176
doi:10.1098/rsif.2011.0652
Published online 30 November 2011

Evolutionary significance of metabolic network properties

Georg Basler[1,*], Sergio Grimbs[1], Oliver Ebenhöh[2], Joachim Selbig[1,3] and Zoran Nikoloski[1,3]

Mathematical random network models

Purpose of prototype models:

- null models (statistic significance of observed features).
- insight how observed features arise from construction rules.

The most common prototype models:

1. Erdös-Rényi (ER) Model (small-world).
2. Watts-Strogatz (WS) Model (small world + local clustering).
3. Barabási-Alberts (BA) Model (scale-free).

Basic assumption: **A nodes can interact with any other node**.

Assumption fails for chemistry!!

Albert R & Barabási A-L (2002), Statistical mechanics of complex networks, *Rev Mod Phys* **74**:47-97

Randomization strategies for chemical networks

1. Randomize network structure
   a. construct a large network instance
   b. thin out network by random
      - vertex sampling.
      - edge sampling.
      - walk sampling.
2. Randomize network chemistry
   - reaction preception method.
   - mechanistic constraints on rections.

Q1: Are networks generated by these strategies chemical?
A: Not necessarily, only if all reactions are mass balanced =;(

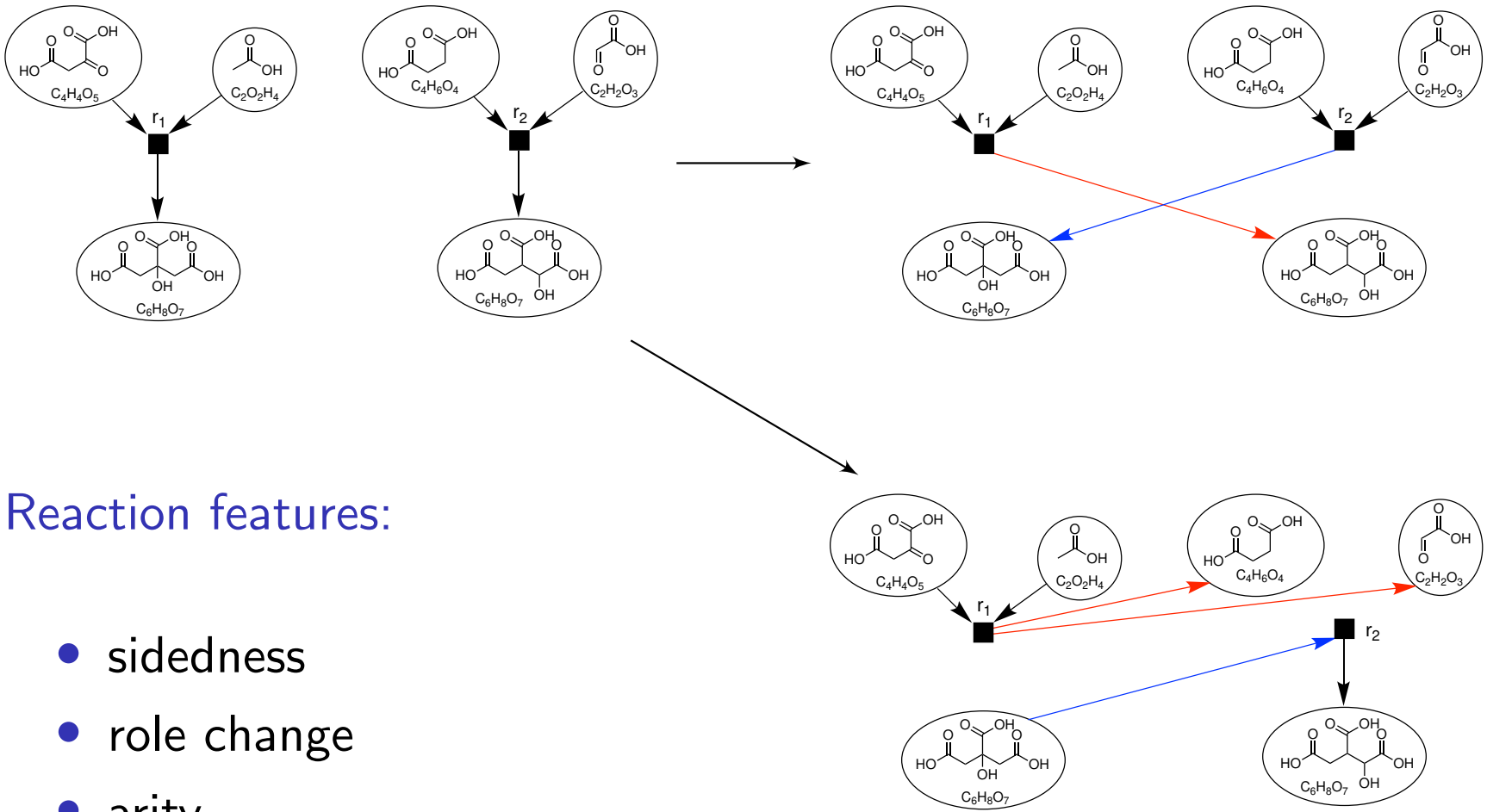
Q2: Is every directed hypergraph a chemical network?
A: No, only if the network is conservative[†] (i.e. mass preserving)!

$$\exists\, m \gg 0 \text{ sucht that } m^T \cdot S = 0$$

[†] Stefan Müller, Christoph Flamm, Peter F Stadler, What makes a reaction network "chemical"? J Cheminfo 14:63, 2022 doi:10.1186/s13321-022-00621-8

What to preserve in chemical reactions . . .

. . . apart from mass?

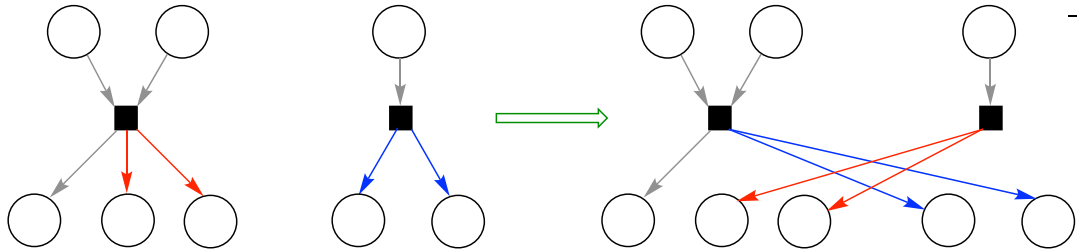


Reaction features:

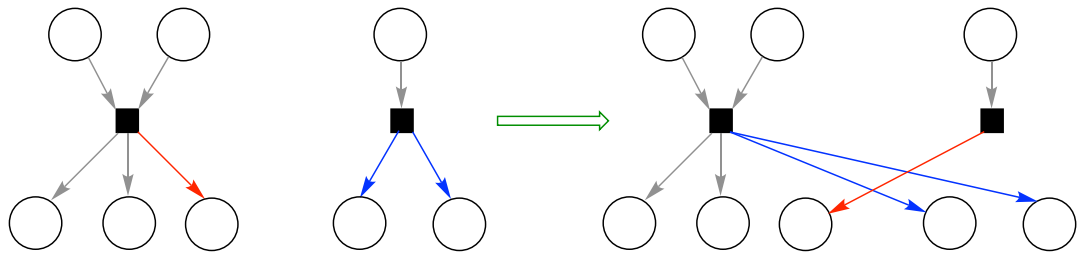
- sidedness
- role change
- arity

Rewiring strategies 1/2

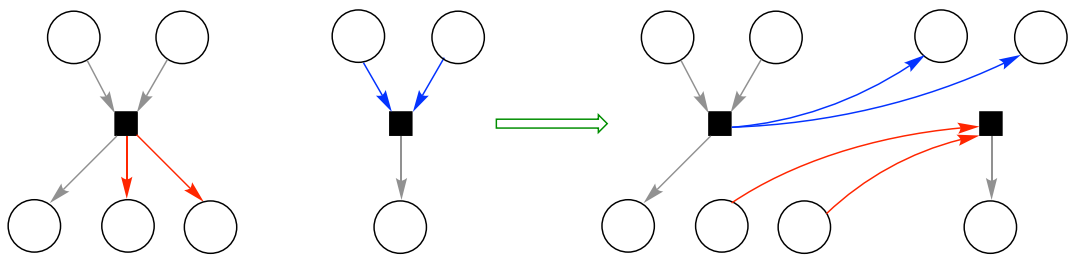
111 - One-sided, no role-change, preserve arity



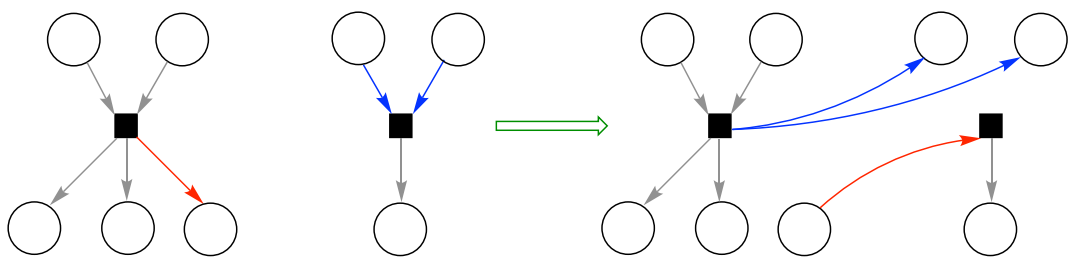
110 - One-sided, no role-change, vary arity



101 - One-sided, allow role-change, preserve arity



100 - One-sided, allow role-change, vary arity



Op	MF	Mdeg	Rdeg	Mdeg_{tot}
111	Y	Y	Y	Y
110	Y	Y	N	Y
101	Y	N	Y	Y
100	Y	N	N	Y

Operation 3-digit code:

1st digit . . . one-sided (only educt or product side of reaction)

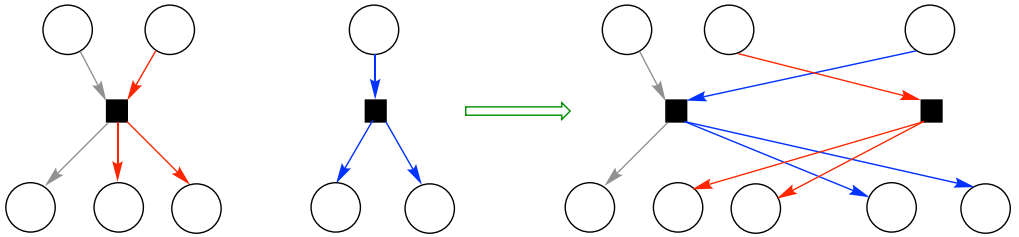
2nd digit . . . role change (educts become products and vice versa)

3rd digit . . . arity (number of educts and products of a reaction)

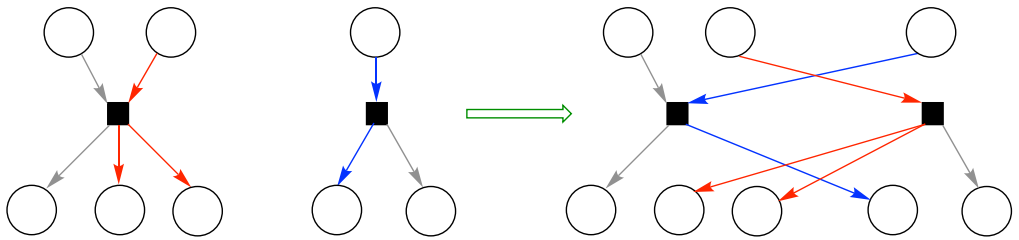
Op . . . operation; **MF** . . . molecular formula; **Mdeg** . . . in/out degree of molecule node; **Rdeg** . . . reaction node degree; $\textbf{Mdeg}_{\textbf{tot}}$ . . . total degree of molecular node

Rewiring strategies 2/2

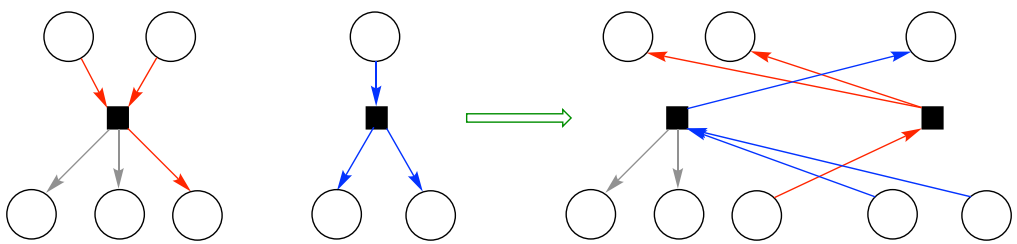
011 - Two-sided, no role-change, preserve arity



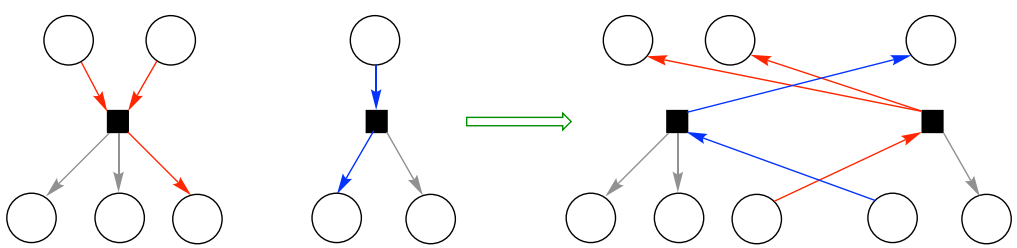
010 - Two-sided, no role-change, vary arity



001 - Two-sided, allow role-change, preserve arity



000 - Two-sided, allow role-change, vary arity



Op	MF	Mdeg	Rdeg	Mdeg_{tot}
111	Y	Y	Y	Y
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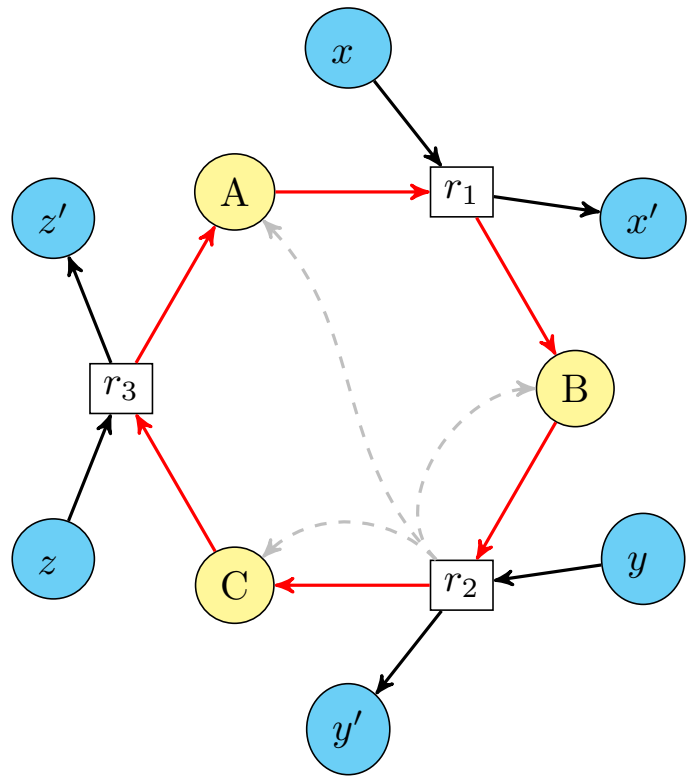
(Auto)Catalyst as Sets

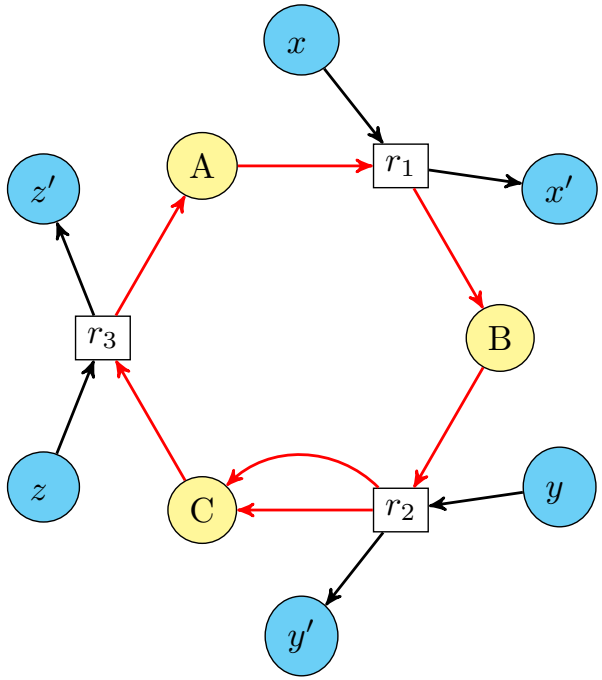
$$\mathrm{x} + \mathrm{y} + \mathrm{z} \overset{\{\mathrm{A,B,C}\}}{\rightleftharpoons} \mathrm{x}' + \mathrm{y}' + \mathrm{z}'$$

1. Rate acceleration: $r_1 - r_3$ must together proceed faster than the spontanious process.
2. Set of catalysts is conserved.
3. Each reaction involve:
   - catalysts.
   - at least 1 catalyst as reactant.
   - at least 1 catalyst as product.
4. The production of a species from the set of catalysts depends on the presence of another species from the set of catalysts.



3 + 4 induce the presence of a cycle. Species ○ show turnover, species ○ remain conserved.
For catalysis ignore gray dashed arrows.

The stoichiometric matrix S



$$\mathrm{x} + \mathrm{A} \xrightarrow{r_1} \mathrm{B} + \mathrm{x}'$$

$$\mathrm{y} + \mathrm{B} \xrightarrow{r_2} 2{\cdot}\mathrm{C} + \mathrm{y}'$$

$$\mathrm{z} + \mathrm{C} \xrightarrow{r_3} \mathrm{A} + \mathrm{z}'$$

	r_1	r_2	r_3
x	-1	0	0
x’	1	0	0
y	0	-1	0
y’	0	1	0
z	0	0	-1
z’	0	0	1
A	-1	0	1
B	1	-1	0
C	0	2	-1

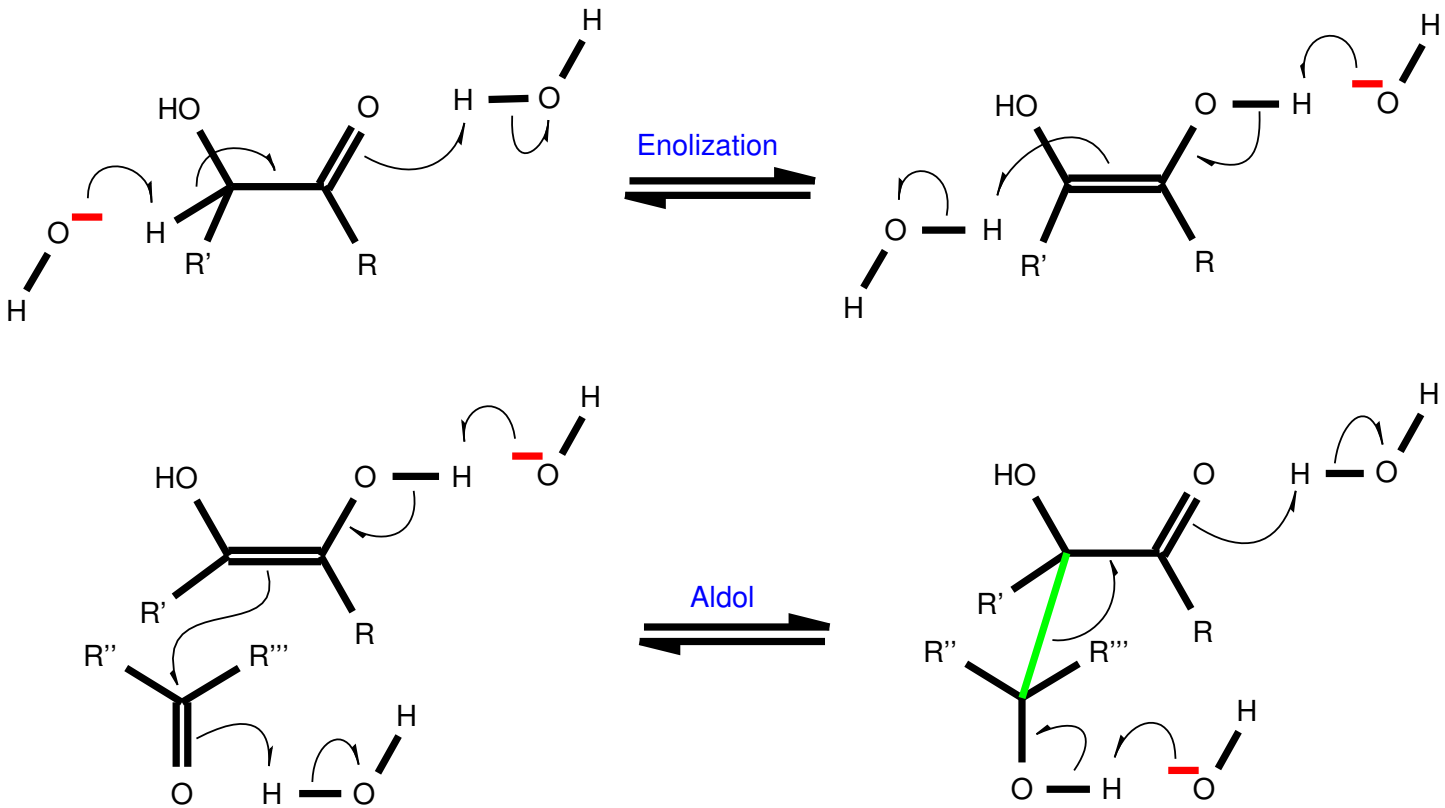
Note that a catalyst, which enters and exits a reaction with the same stoichiometry, has as well a zero entry in S. The yellow highlighted region is a restriction of the S to the autocatalytic cycle. The species in the cyan region are considered externl to the autocatalytic cycle, and are thought to be chemo-stated.

Primer: Carbohydrate Chemistry $(CH_2O)_n$

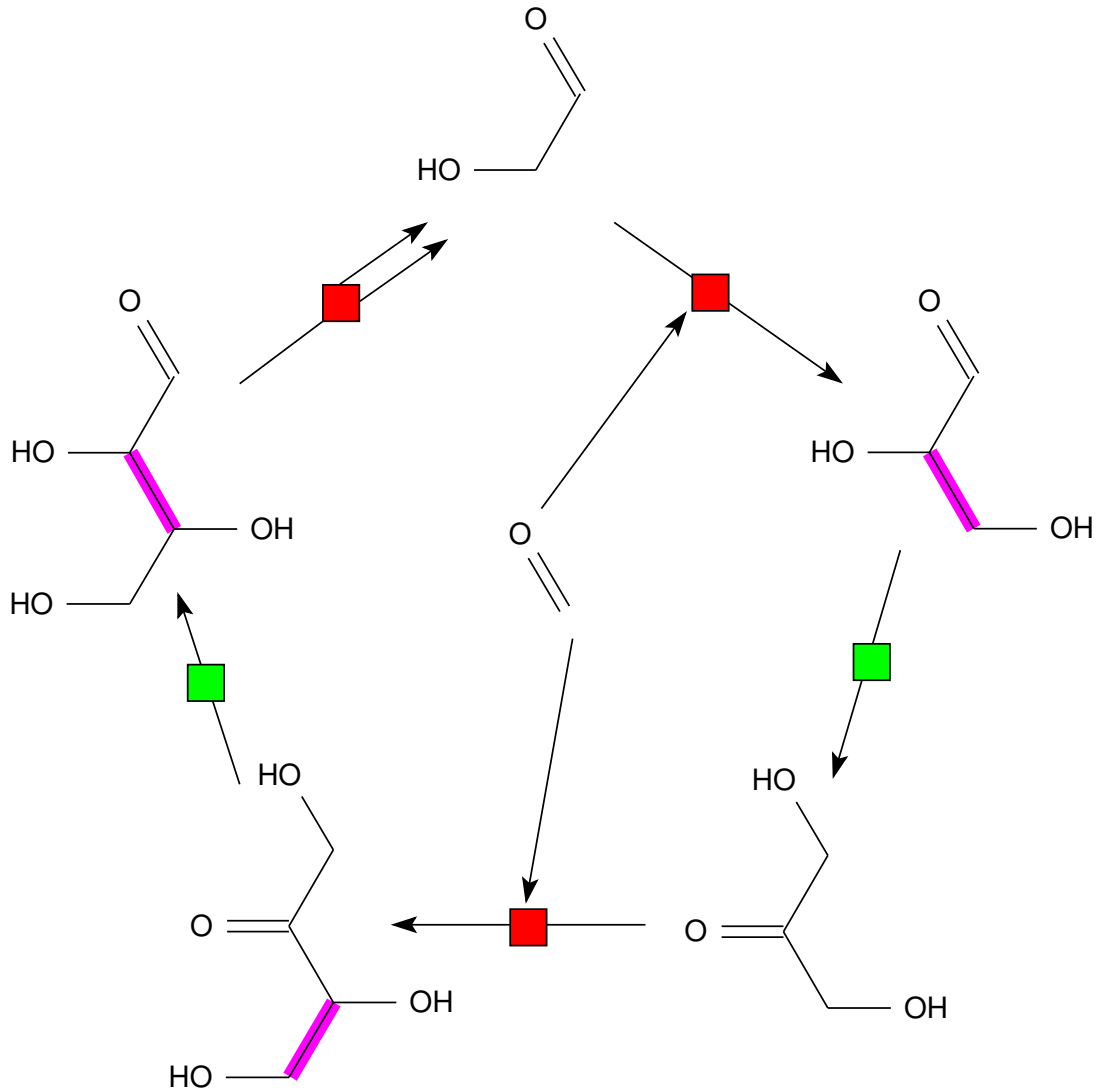
Sugars are organic compounds with an C:H:O ratio of 1:2:1.

The reactivity of sugars is largely dominated by the carbonyl group ($C=O$) and the vicinal alcohol groups ($HO-C-C-OH$).

The keto-enol isomerization reaction and the aldol condensation a $C-C$ bond formation reaction are of importance.

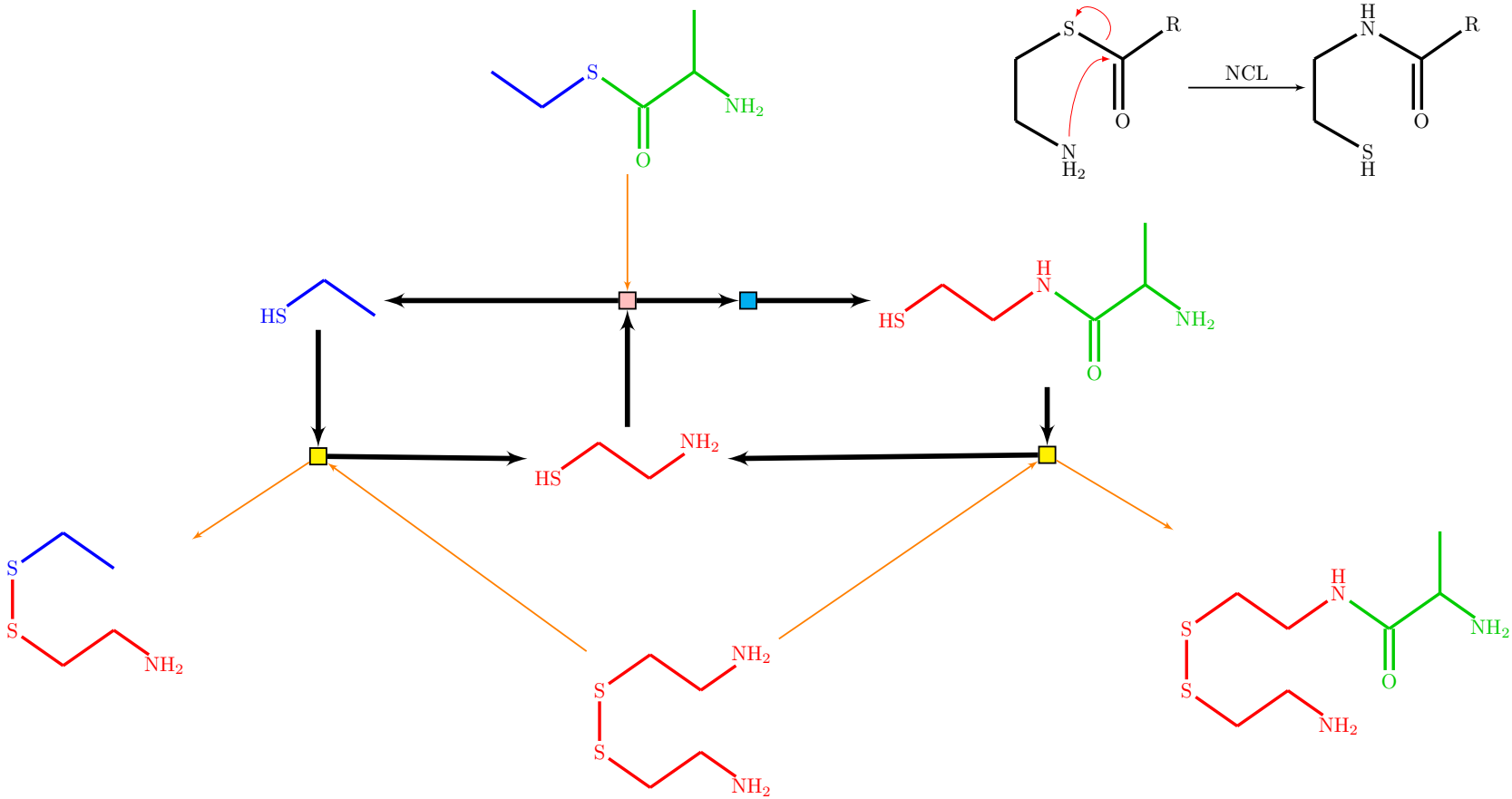


Core Cycle of the Formose Process



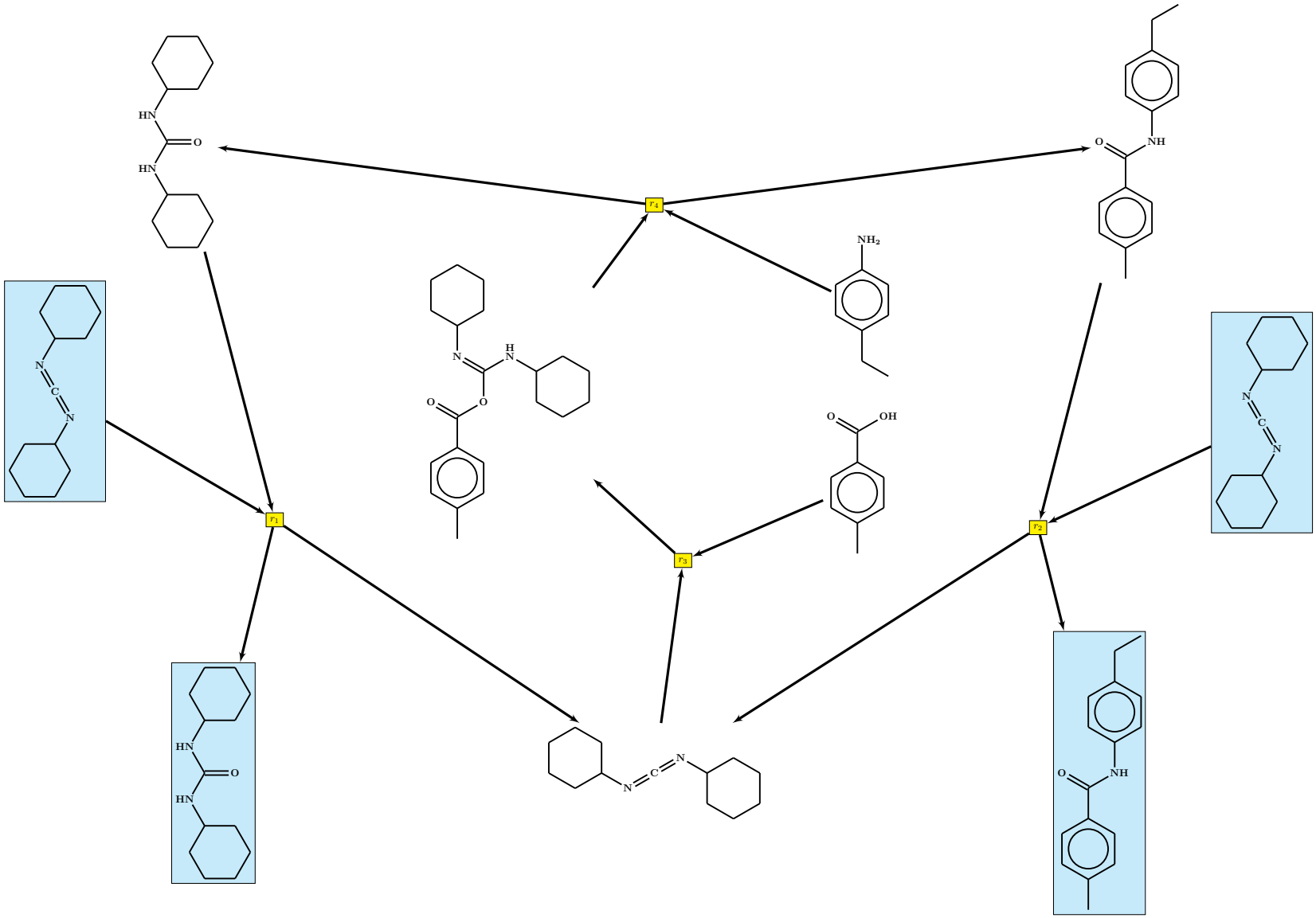
Type 1 autocatalytic core; keto-enole isomerization, Aldol / retro-Aldol reaction. Note that the reaction sequence from glycolealdehyde to erytrose is compressed into a single reaction (r_1) in the type 1 autocatalytic core figure. Butlerov AM (1861), Einiges über die chemische Structur der Körper, *Zeitschrift für Chemie* **4**:549-560;

Amino acid thioesters, cystamine autocatalytic system



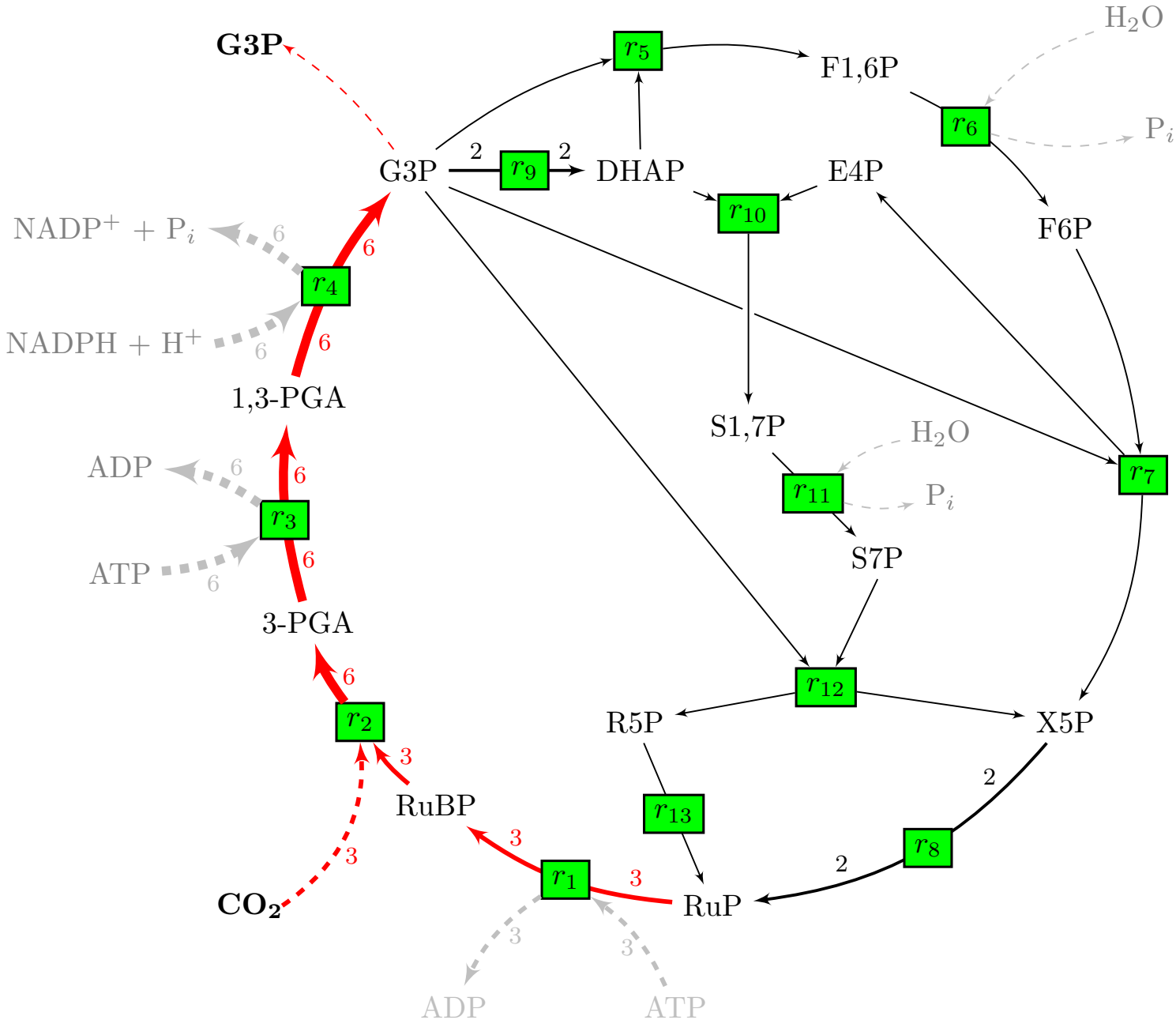
Type 3 autocatalytic core; The reaction chemistry is thiol-disulfide exchange ■, thiol-thoester exchange ■ and native chemical ligation ■; orange arrows connect food or wast molecules to the autocatalytic cycle, which has a type 3 topology; cystamine (in the center) is the "autocatalyst"; [Semenov et al Nature 2016]

Rebeck's Autocatalytic System

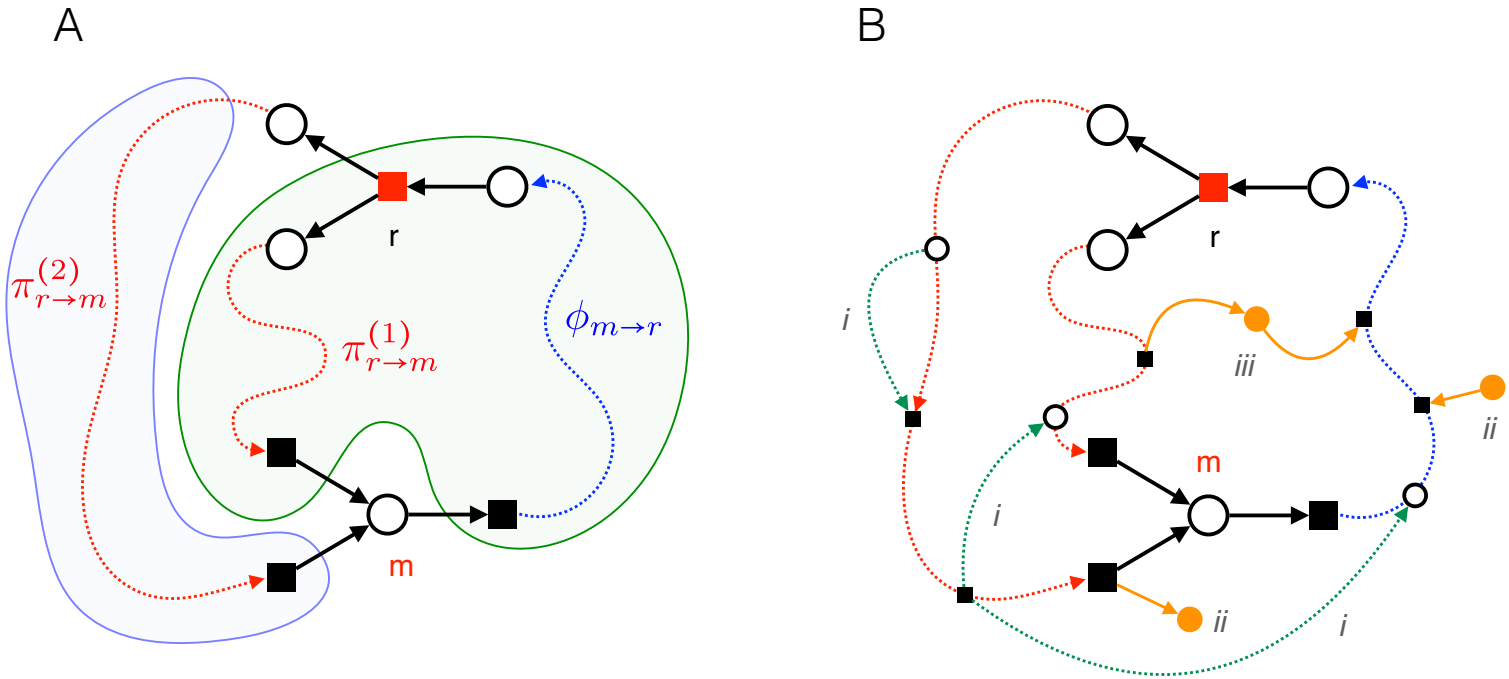


Type 3 autocatalytic core; Molecules in cyan boxes are sequestered in a molecular cage. The synthesis of the autocatalytic species and its storage, occures temporally, spatially, and chemically distinct from the process that depletes the store in an autocatalytic fashion. [Chen et al PNAS 2001]

Calvin–Benson–Bassham Cycle



Finding Autocatalysis in reaction networks



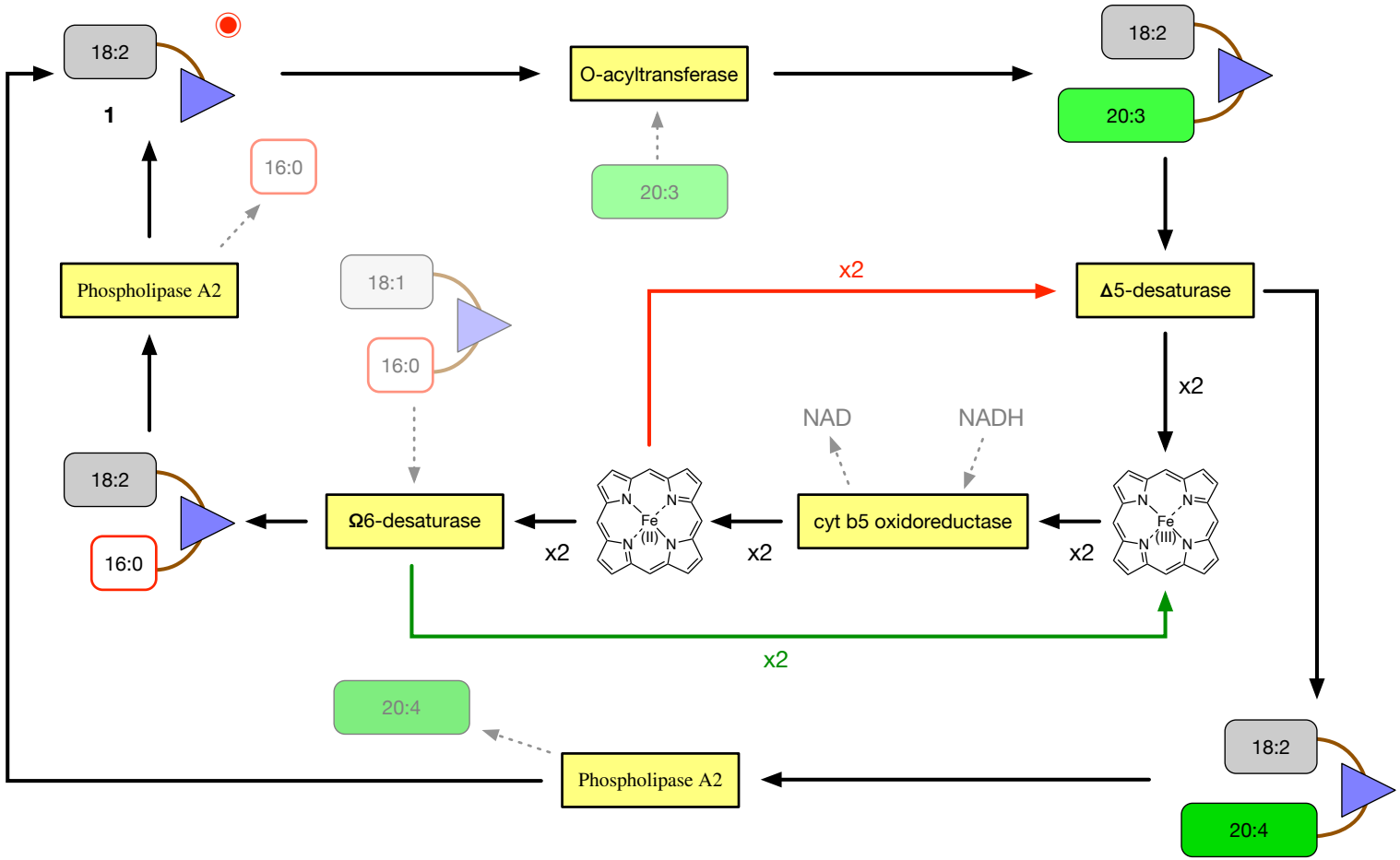
A Find autocatalytic skeleton:

1. Find fission and merging points.
2. Connect fission and merginf points by paths.

B Embed autocatalytic skeleton in hypergraph:

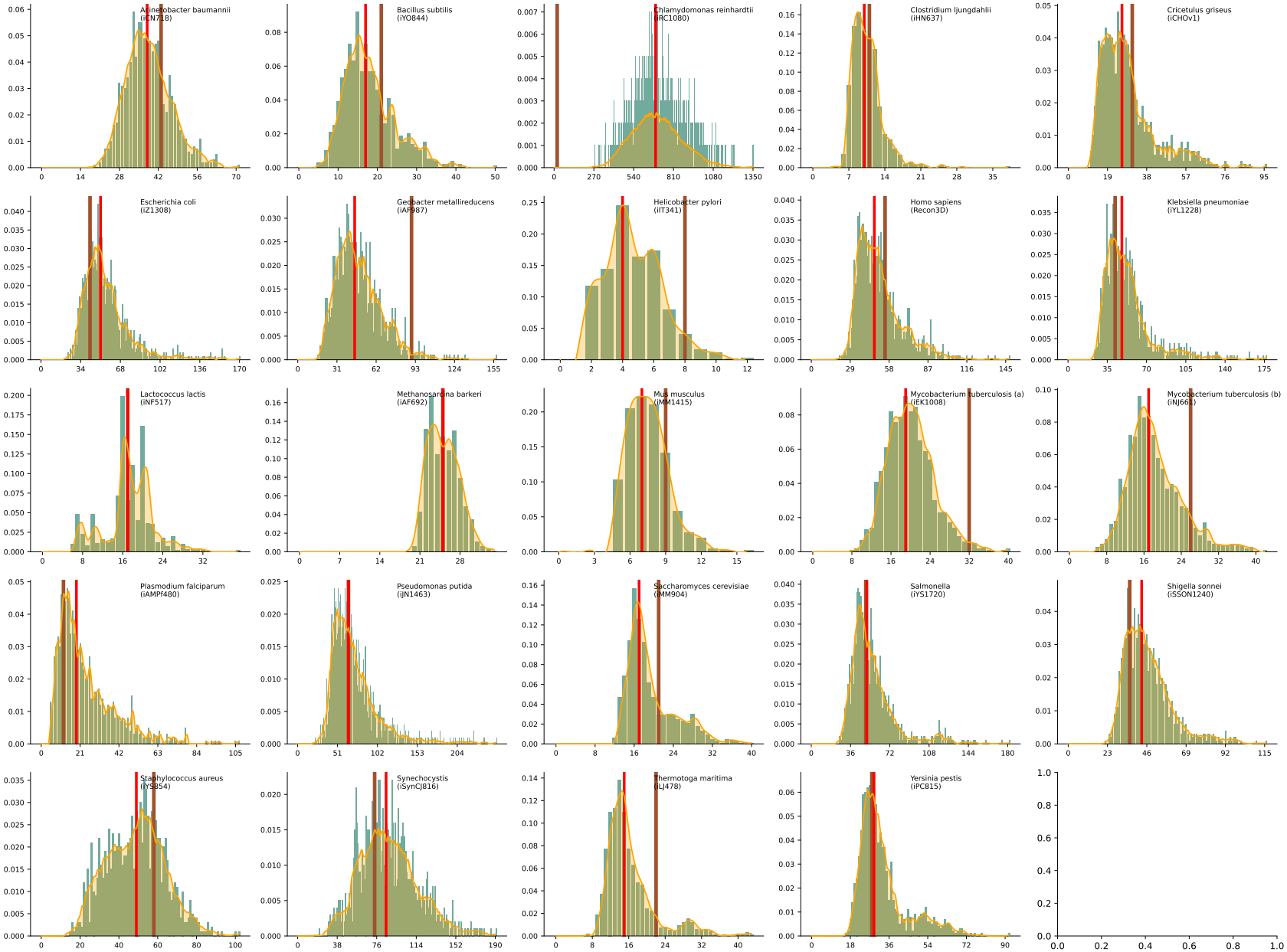
1. Insert induced edges (highlighted in green labeled i).
2. Add species and edges attached to sceleton reaction nodes. (highlighted in yellow; nodes: ii immediate substrates and products; iii mediator species).

Poly-unsaturated fatty acid system (PUFA)



Red bull's eye marks autocatalytic species. Reactions are yellow boxes. Skeleton connected by black arrows. Red / green cross-links are introduced in embeding phase and render the network catalytic.

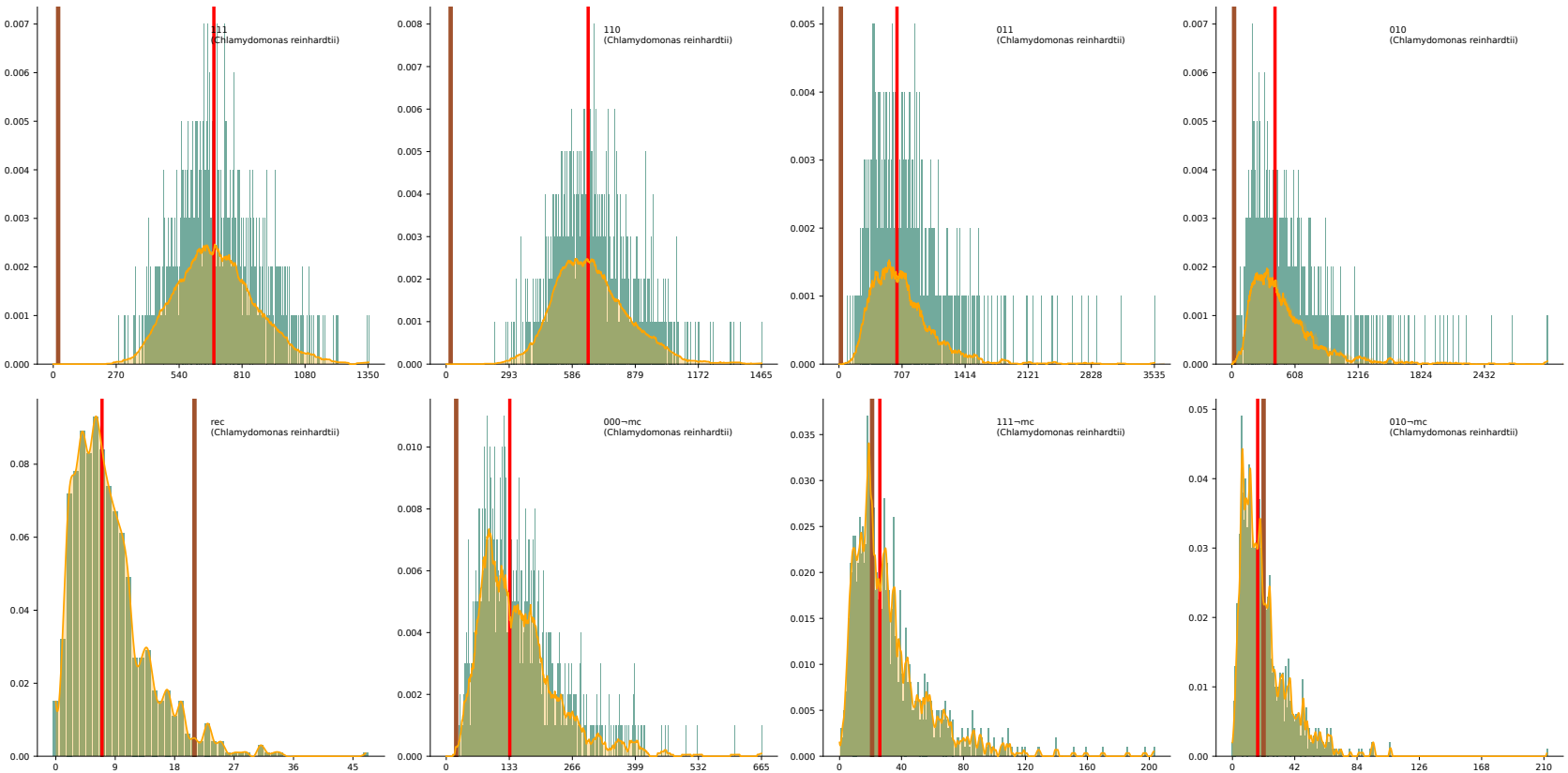
Using Strategy 111 to randomize GEMs



GEM . . . genome-scale metabolic models

Chlamydomonas reinhardtii

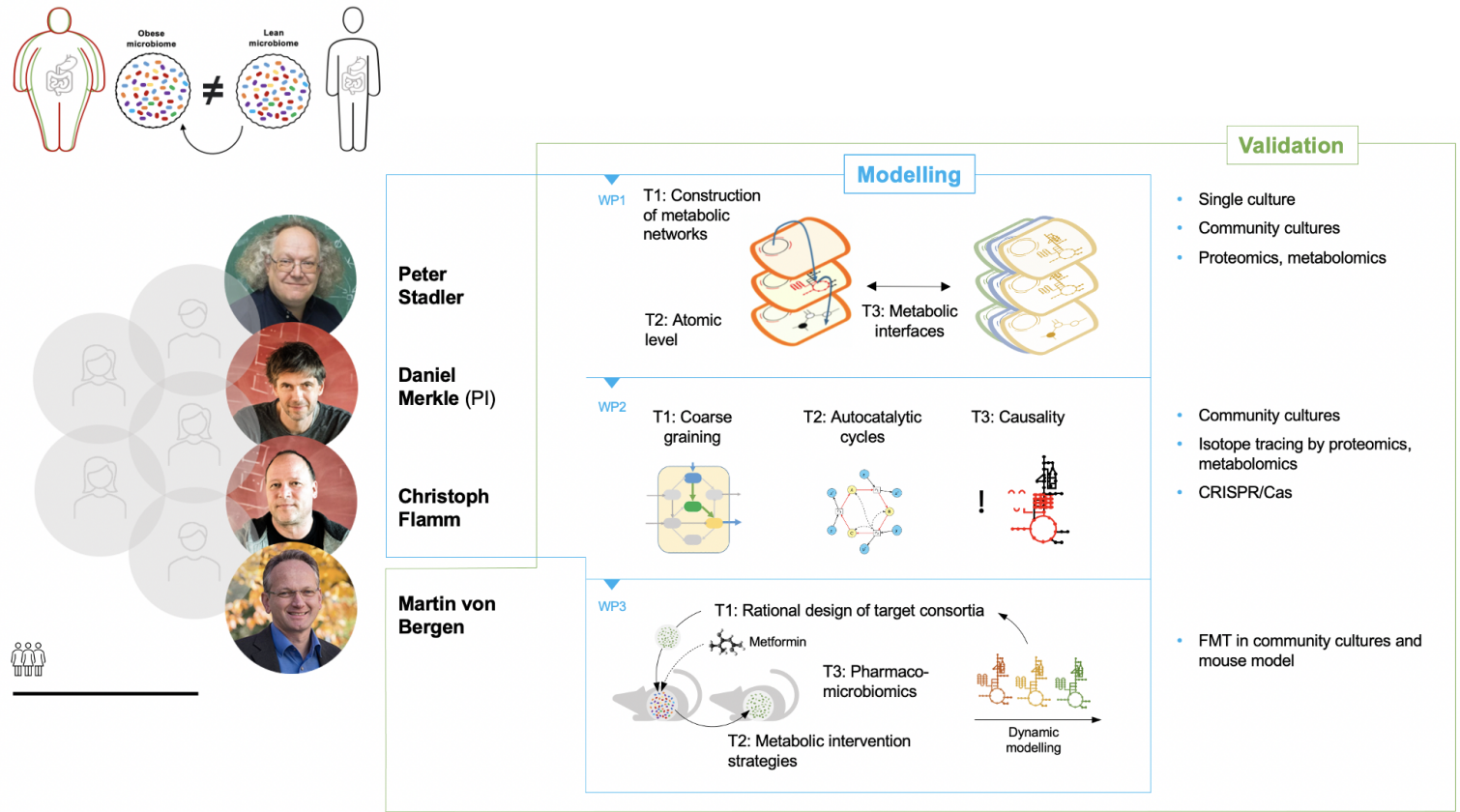
Single-celled green alga.
Extended lipid metabolism.



Conclusion

1. A formalism for Chemistry must be **expressive enough** to capture the major characteristics of reactive systems:
   - mass conservation.
   - structural change.
   - atom-to-atom mappings.
2. Graph grammar formalization has the right level of abstraction.
3. Chemical reaction space is vast, hence:
   - computational exploration is indispensable.
   - hyperflows allows to search for complex reaction patterns.
   - automated atom tracking in reaction networks is important.
4. Computational methods can be a powerful way to gain insight into complex chemistry.

Mathematical Modelling for Microbial Community Induced Metabolic Diseases



MATOMIC

Novo Nordisk Foundation Challenge Programme

!!! Postdoc Position availabel in Vienna !!!

Novo Nordisk Foundation grant NNF21OC0066551 (45 mio. DKK, 2022–2028).

Further reading

Andersen JL, Flamm C, Merkle D, Stadler PF.

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Autocatalytic, bistable, oscillatory networks of biologically relevant organic reactions.
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