Expansion and Exploration of Prebiotic Chemical Reaction Spaces through Rule Based Modeling

Nino Lauber

39th TBI Winterseminar

15th Februar 2024, Bled

Introduction

Motivation: Origins of Life (OL) Research

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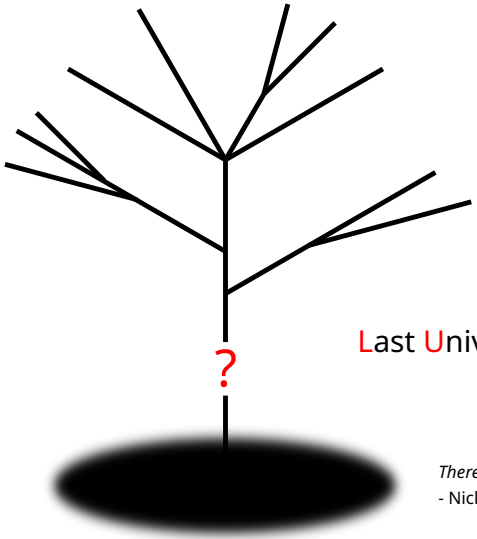

Last Universal Common Ancestor

LUCA

There is a black hole at the heart of biology.
- Nick Lane, The Vital Question

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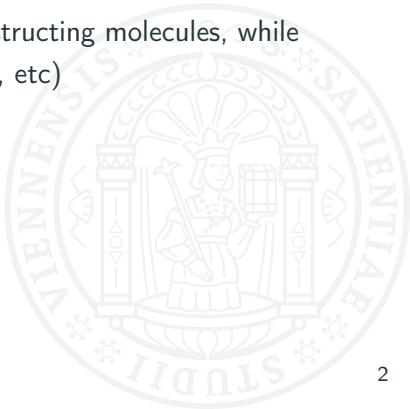

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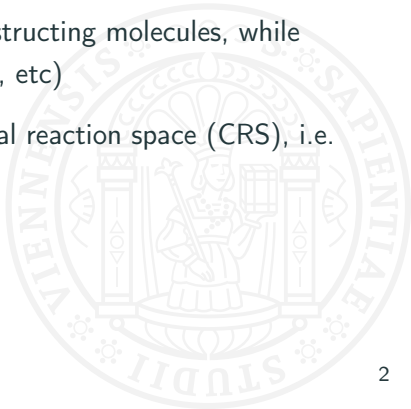
- Many lines of research focus on a **similar logic** of constructing molecules, while varying reaction conditions (catalysts, temperature, pH, etc)
- Need for a way to systematically **trace out** the chemical reaction space (CRS), i.e. the space of **possible reactions** of a given system.



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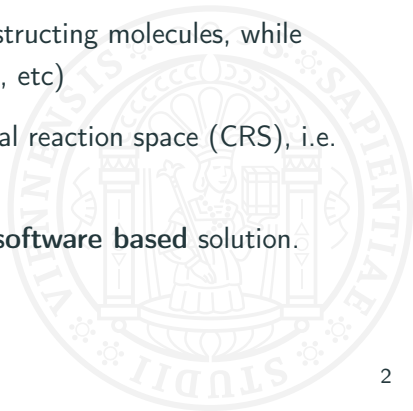
- Need for a way to systematically **trace out** the chemical reaction space (CRS), i.e. the space of **possible reactions** of a given system.
- Expansion and analysis of a CRS can be done using a **software based** solution.



Methods

Rule-Based Expansion of a Chemical Reaction Space

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Expansion of a CRS using the *MØD*[1] software package

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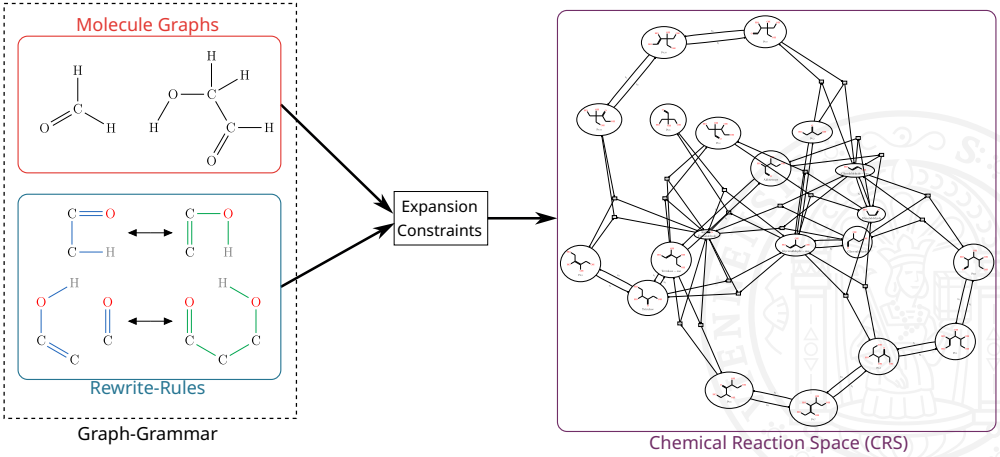

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Any vector $c = (c_1, \ldots, c_m)$ with the property:

$$c \cdot S = 0$$

represents a **conserved moiety** within the CRS[1].

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Given N conserved moieties, any molecule in the system can be represented as a vector: $m = (m_1, \ldots, m_N)^T$, m_i amount of moiety i

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Search for Autocatalytic (AC) Cycles

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Network topological definition of autocatalytic reaction cycles[1]

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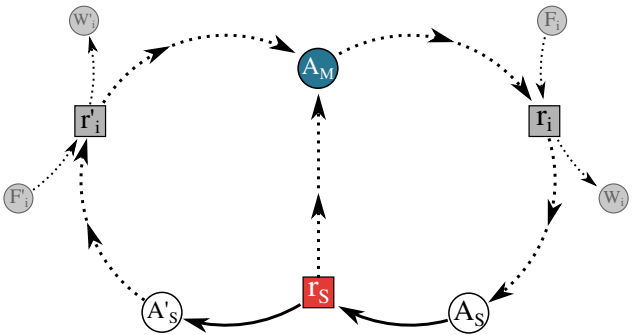

with permission from Phillip Honegger (publication forthcomming)

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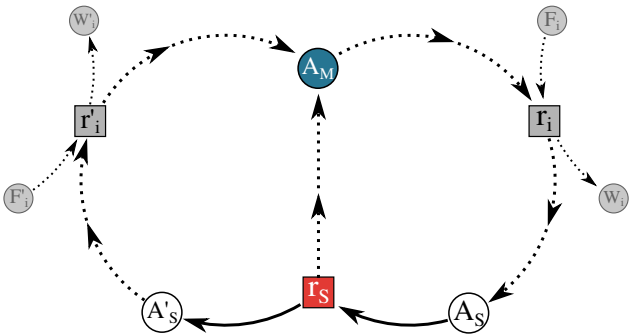

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Search constraints:

- exclusion of molecules
- exclusion of reactions
- maximum cycle length

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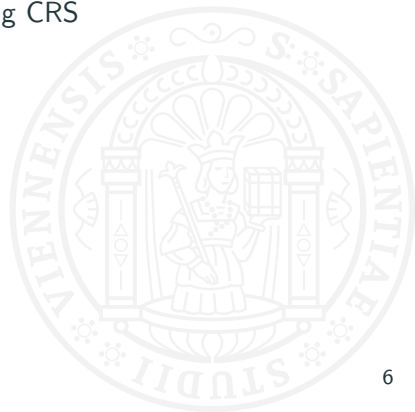

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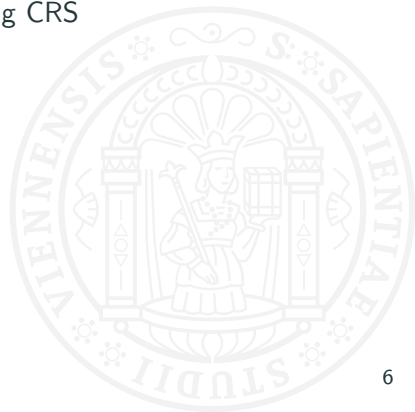

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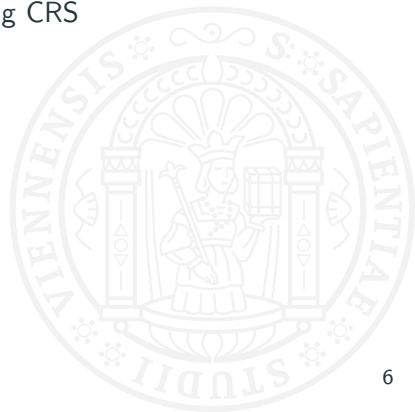

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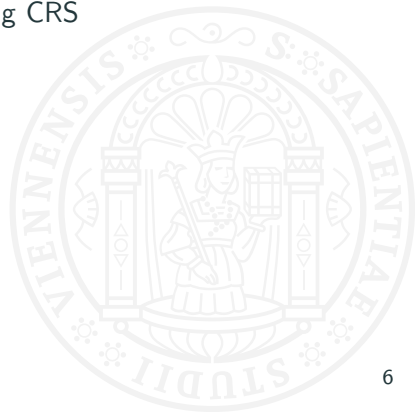
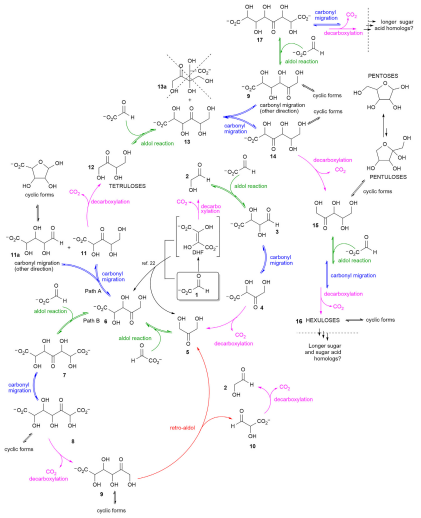
- Analyze the **properties** of the found pathways



Case Study: Glyoxylose Reaction

Reaction System

Reaction System



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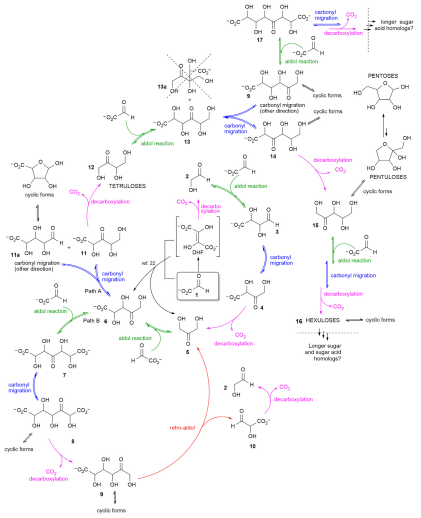

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Initially present Molecules:

- Glyoxylate
- Glycolaldehyde

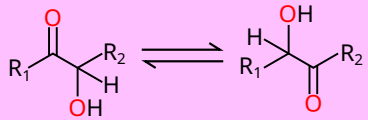
Four types of reactions:

- Carbonyl Migration
- (Retro)-Aldol
- Decarboxylation

Reaction Grammar

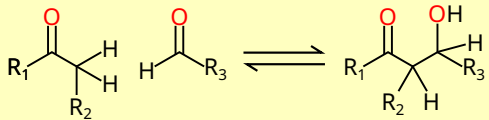
Reaction Grammar

1



R_1: C, H
R_2: C, H

2



R_1: C, H
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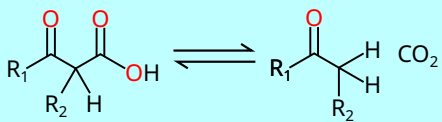
R_3: C, H

3



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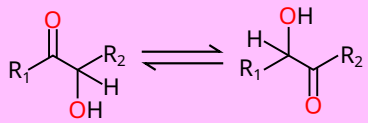
Reaction Grammar

1



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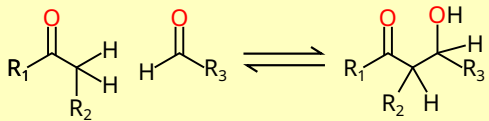

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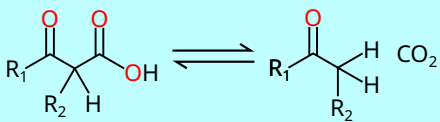

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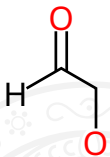
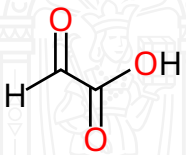
Glycolaldehyde (GLYC)



Glyoxylate (GLX)



Results

CRS Expansion

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Expansion constraint:

- no molecules with **more than** 8 C-atoms

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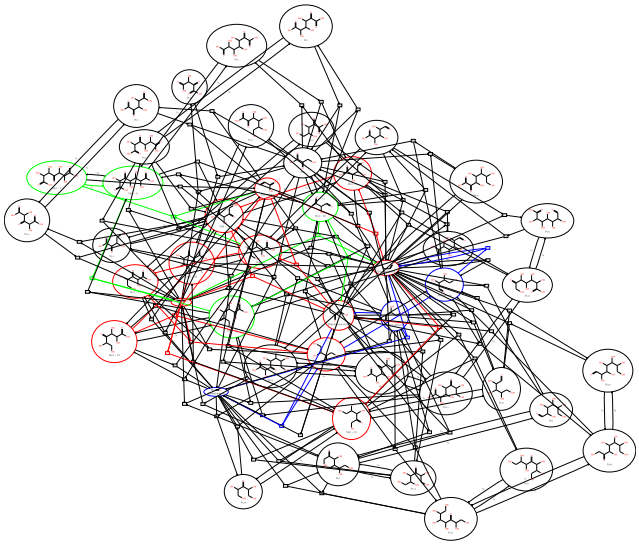

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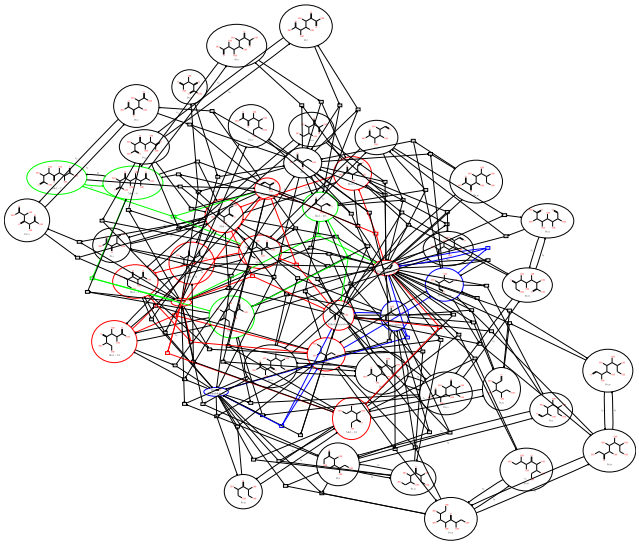

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General CRS properties:

- 46 Molecules
- 156 Reactions

Conserved Moieties

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Two conserved moieties found in expanded CRS:

- H_2CO-moiety (carbonyl-, alcohol-group)
- CO_2-moiety (acid-group)

Any molecule in the CRS can be **decomposed** into a **combination** of them

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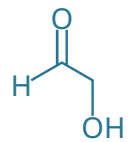
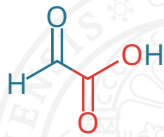


$\begin{pmatrix} 2 \\ 0 \end{pmatrix}$

Glyocolaldehyde (GYC)



$\begin{pmatrix} 1 \\ 1 \end{pmatrix}$

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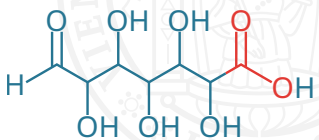

$\begin{pmatrix} 6 \\ 1 \end{pmatrix}$

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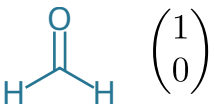
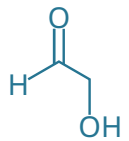
Furthermore, define a set of **basis-species** (molecules with only one of each moiety):



Formaldehyde (FORM) $\begin{pmatrix}1\\0\end{pmatrix}$

CO_2 $\begin{pmatrix}0\\1\end{pmatrix}$



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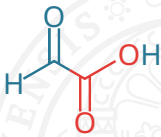

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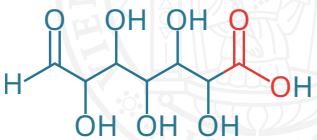

$\begin{pmatrix}6\\1\end{pmatrix}$

Conserved Moieties: Reaction Path A

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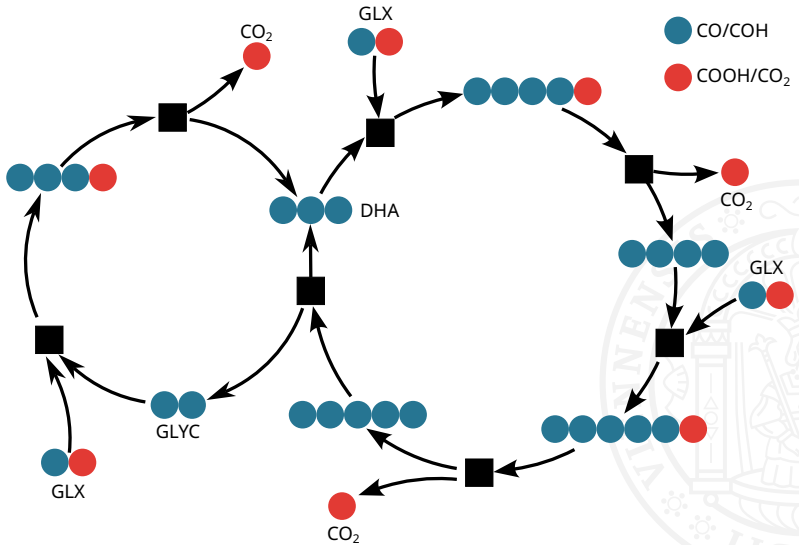

Conserved Moieties: Reaction Path B

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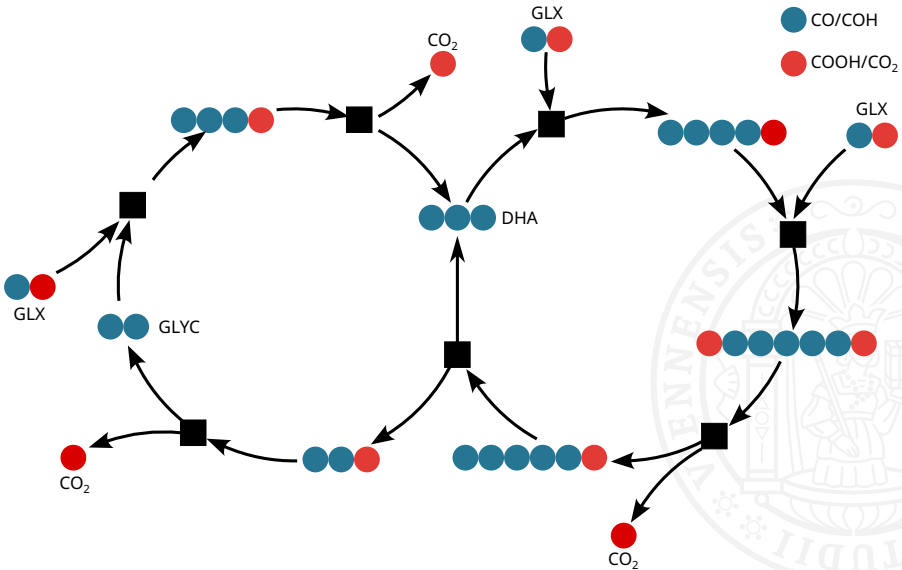

AC-Cycle Search

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General constraints:

- GLX, FORM, CO_2 excluded as on-cycle species
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1. "Strict" Search
   - only aldol-addition with GLX
   - maximum 7 reactions

$\Rightarrow$ 43 AC-Cycles

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Two main search strategies on the CRS:

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   - maximum 7 reactions

$\Rightarrow$ 43 AC-Cycles

2. "Relaxed" Search
   - general aldol-additions
   - maximum 4 reactions

$\Rightarrow$ 3144 AC-Cycles

AC-Cycle Energies

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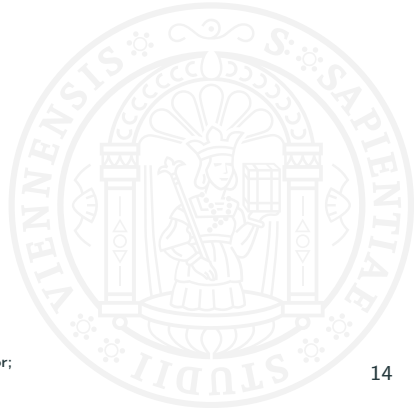
Calculate reaction energy $\Delta_r G^\circ$ using the *eQuilibrator*[1] software package



[1] M. E. Beber, M. G. Gollub, D. Mozaffari, K. M. Shebek, A. I. Flamholz, R. Milo & E. Noor; **Nucleic Acids Res.** 50(D1): D603–D609; 2022.

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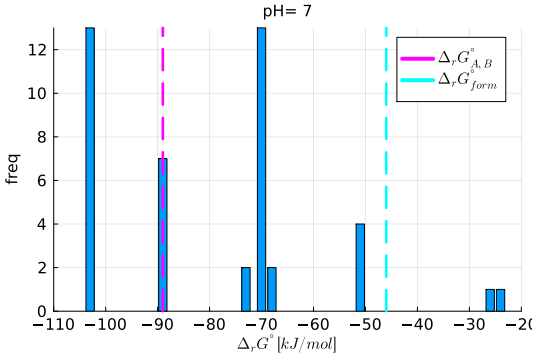
"Strict Search" AC-Cycles:



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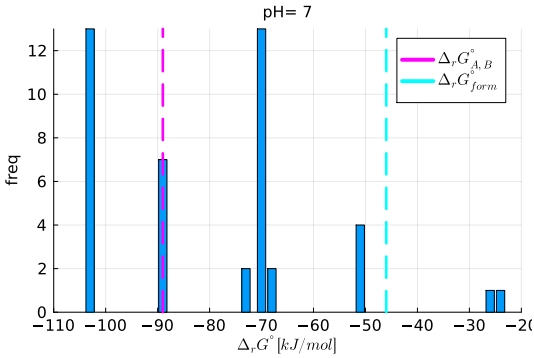
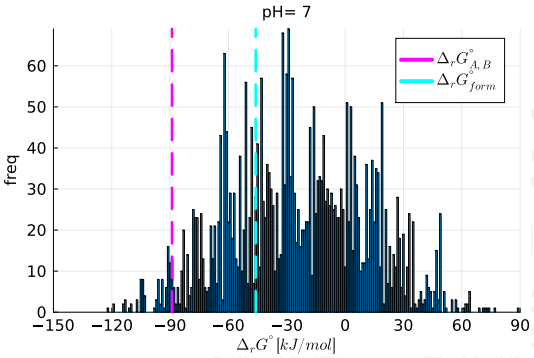


"Relaxed Search" AC-Cycles:



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Types of AC-Cycles: "Build-Up" Cycle

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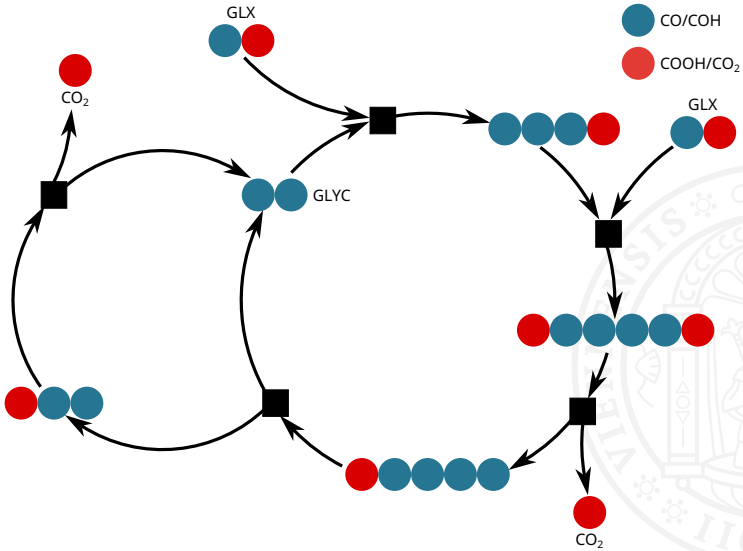

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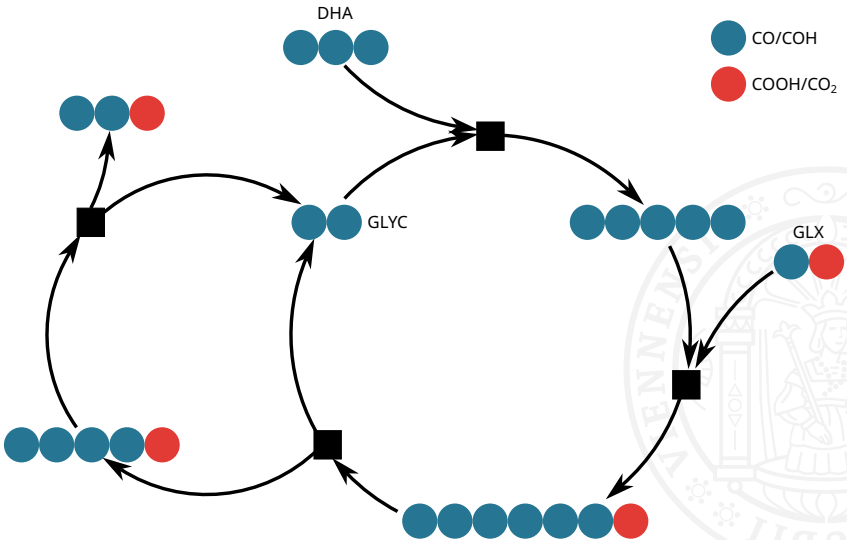

Outlook

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- Investigate and compare the CRSs associated to other types of chemistries

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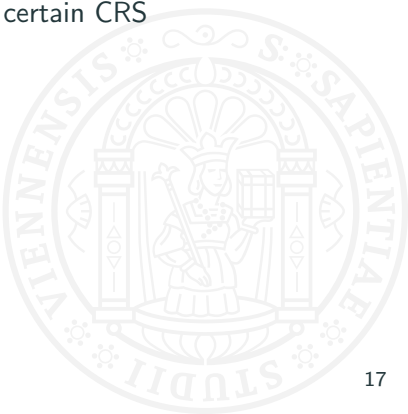
- Investigate and compare the CRSs associated to other types of chemistries
- Find out how **specific** pathways could emerge out of a certain CRS



Outlook

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- Further contrast the role of "build-up" and "recombination" AC-cycles in OL and protometabolism

Thank you for your Attention!

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