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Carbon Fixation Pathway Design and the Mystery of Thermodynamics

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40th TBI Winterseminar in Bled

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Carbon Cycle and Natural Carbon Fixation Pathways

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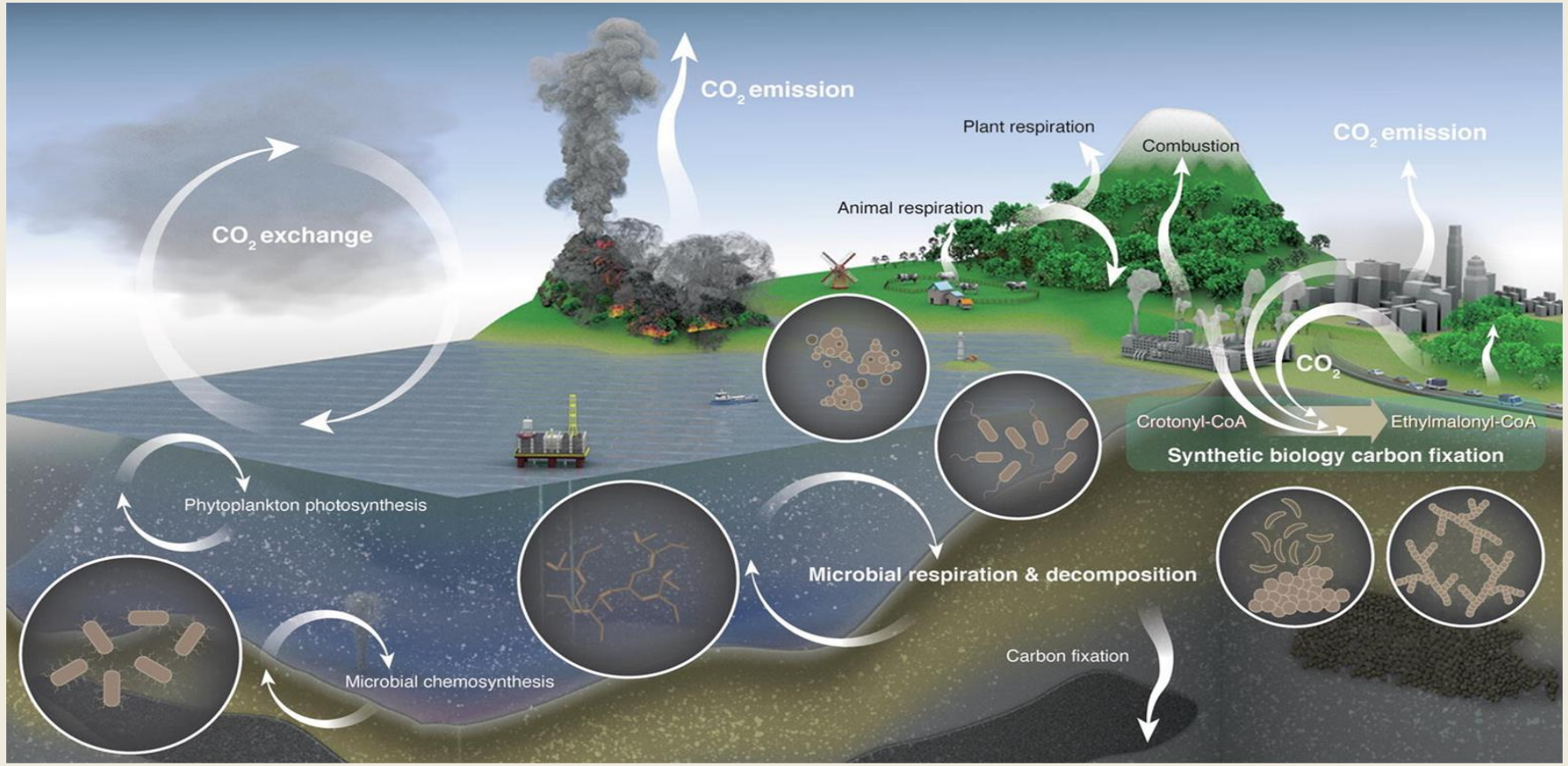

- Inefficient carboxylating enzymes
- High cofactor use
- Oxygen sensitivity

Santos Correa S, Schultz J, Lauersen KJ, Soares Rosado A (2023) Natural carbon fixation and advances in synthetic engineering for redesigning and creating new fixation pathways. J Adv Res 47:75–92. https://doi.org/10.1016/j.jare.2022.07.011

Goal - Improve Natural Pathways

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Improvements in agriculture

Increase biomass production by increasing efficiency of CO_2 fixation in plants

Value added chemical production

Produce chemicals using CO_2 as feedstock

Scale-up CO_2 fixation

Mitigate climate change by removing existing CO_2 from the atmosphere

Artificial Pathways

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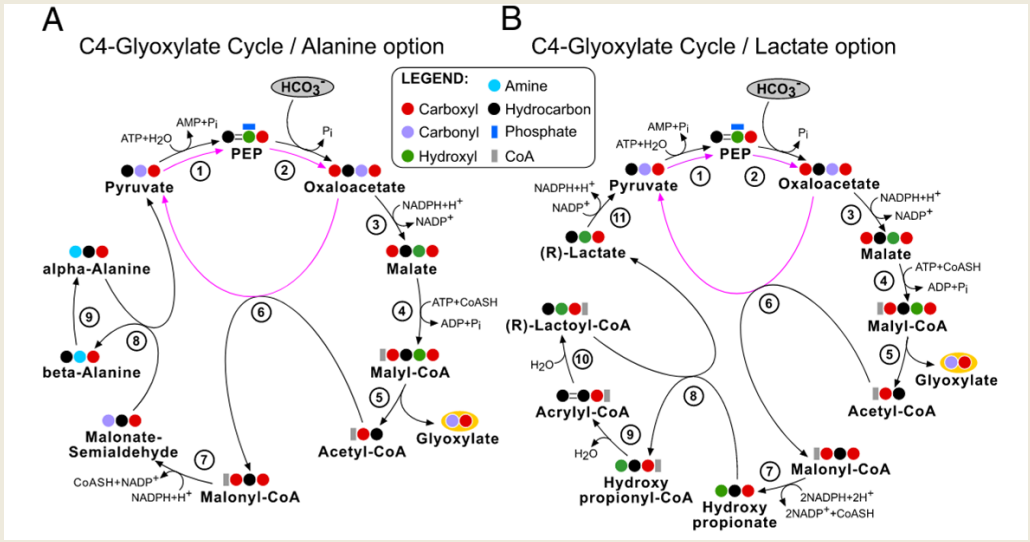
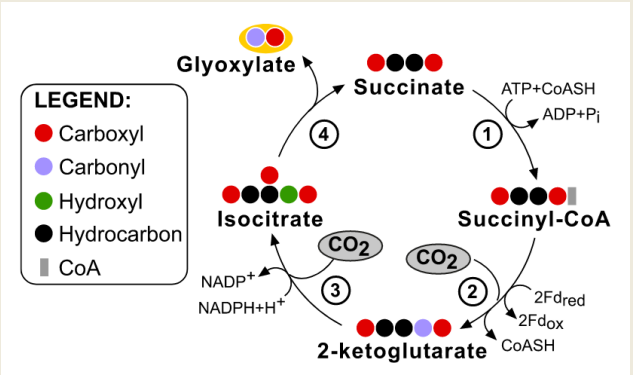
"Better" pathways?

Measures of feasibility

- **Thermodynamics**
- Kinetics
- Topology
- Efficiency
- Oxygen-sensitivity

highest activities

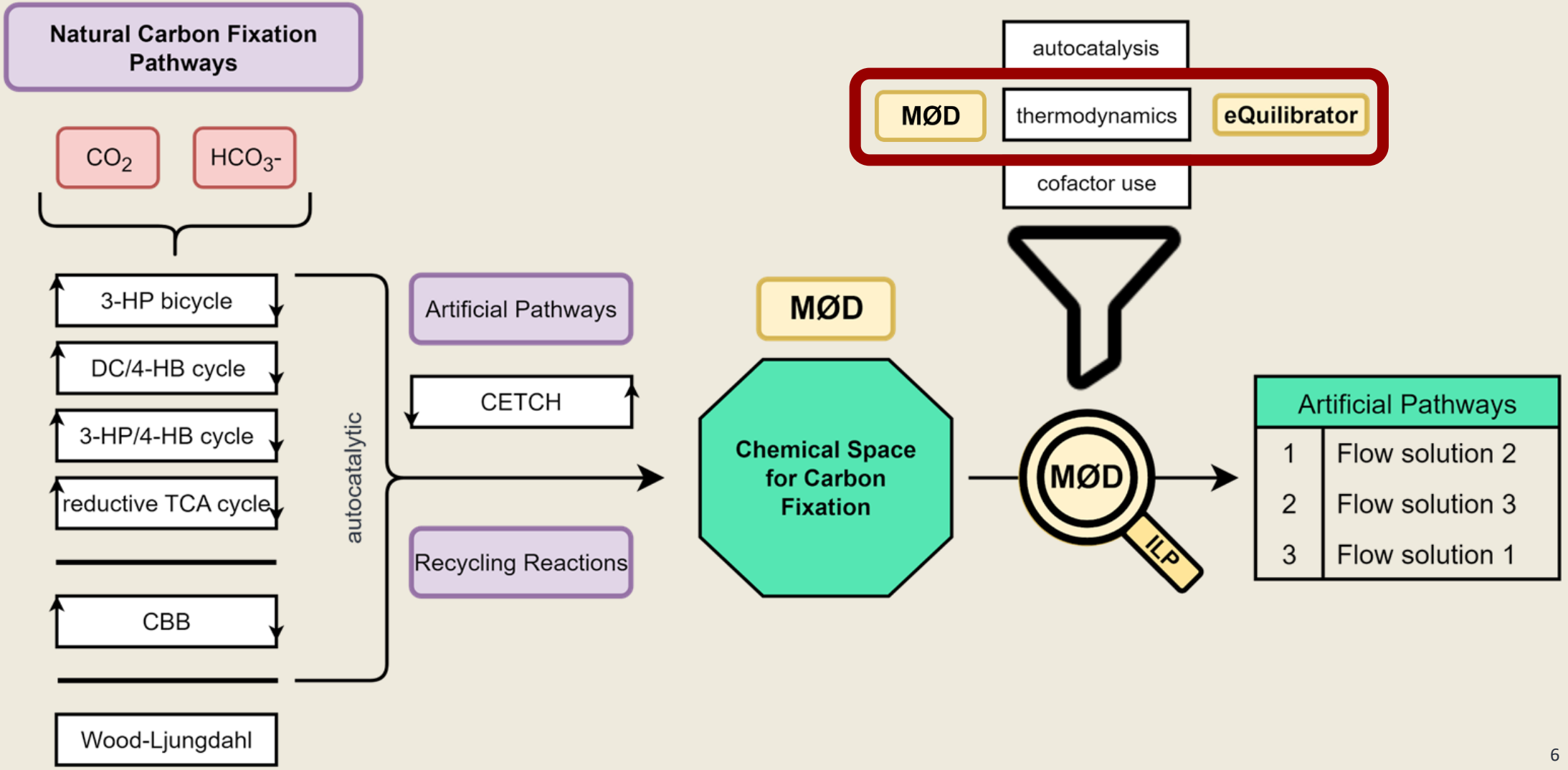




shortest pathway

Bar-Even A, Noor E, Lewis NE, Milo R (2010) Design and analysis of synthetic carbon fixation pathways. Proc Natl Acad Sci 107:8889–8894. https://doi.org/10.1073/pnas.0907176107

Workflow for Pathway Discovery



Thermodynamics – Requirements and Considerations

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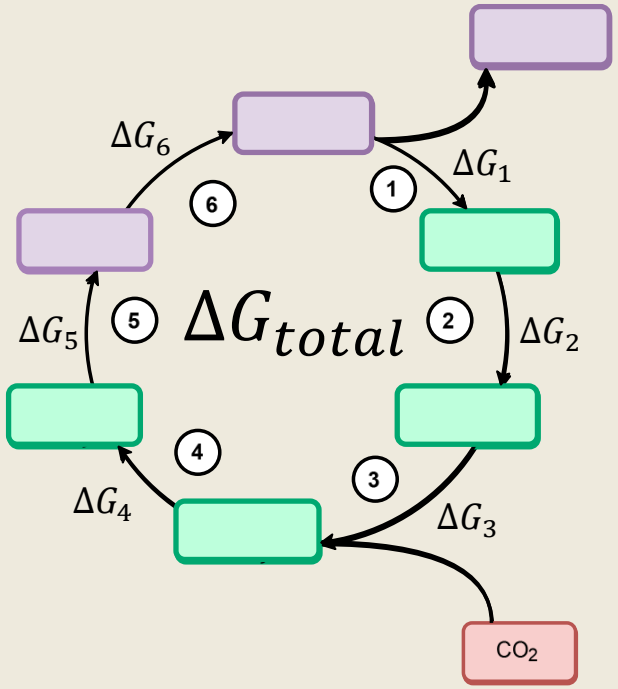
$$\Delta G_{total} = \Delta G_1 + \Delta G_2 + \cdots + \Delta G_6$$

$$\Delta G = \Delta G^0 + RT \ln Q \qquad Q = \frac{c_{products}}{c_{reactants}}$$

$$\Delta G^0 = \sum \Delta G_f^0{}_{products} - \sum \Delta G_f^0{}_{reactants}$$

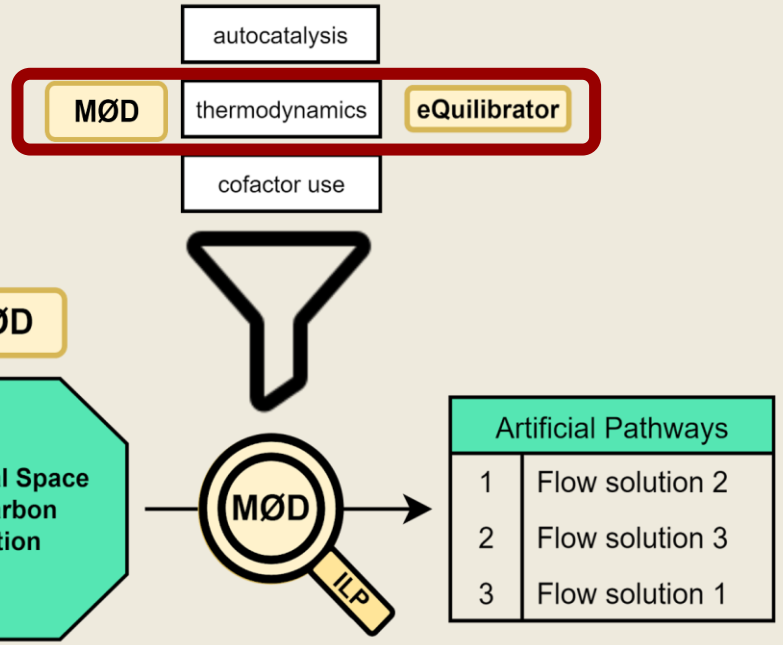
→ **MØD** Optimize energy and find concentrations to fit

ΔG	Gibbs Free **Energy Change**
ΔG°	**Standard** Gibbs Free Energy Change
R	Universal Gas Constant
ΔGf°	Standard Gibbs Free **Energy of Formation**
Q	Reaction Quotient
T	Temperature



$\Delta\ G_f^0$ → **eQuilibrator**

pH = 7, concentration = 1 mM



Elad Noor, Hulda S. Haraldsdóttir, Ron Milo, and Ronan M. T. Fleming; PLOS Computational Biology 2013 doi:10.1371/journal.pcbi.1003098.

Flow Query Examples - Thermodynamics

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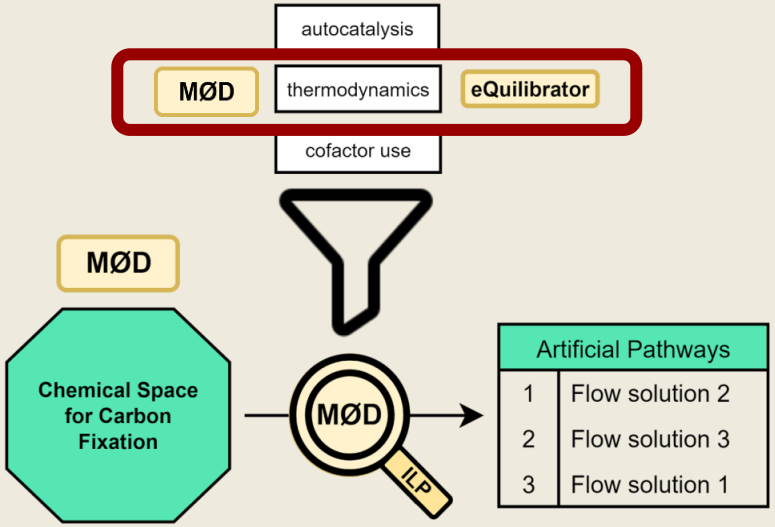
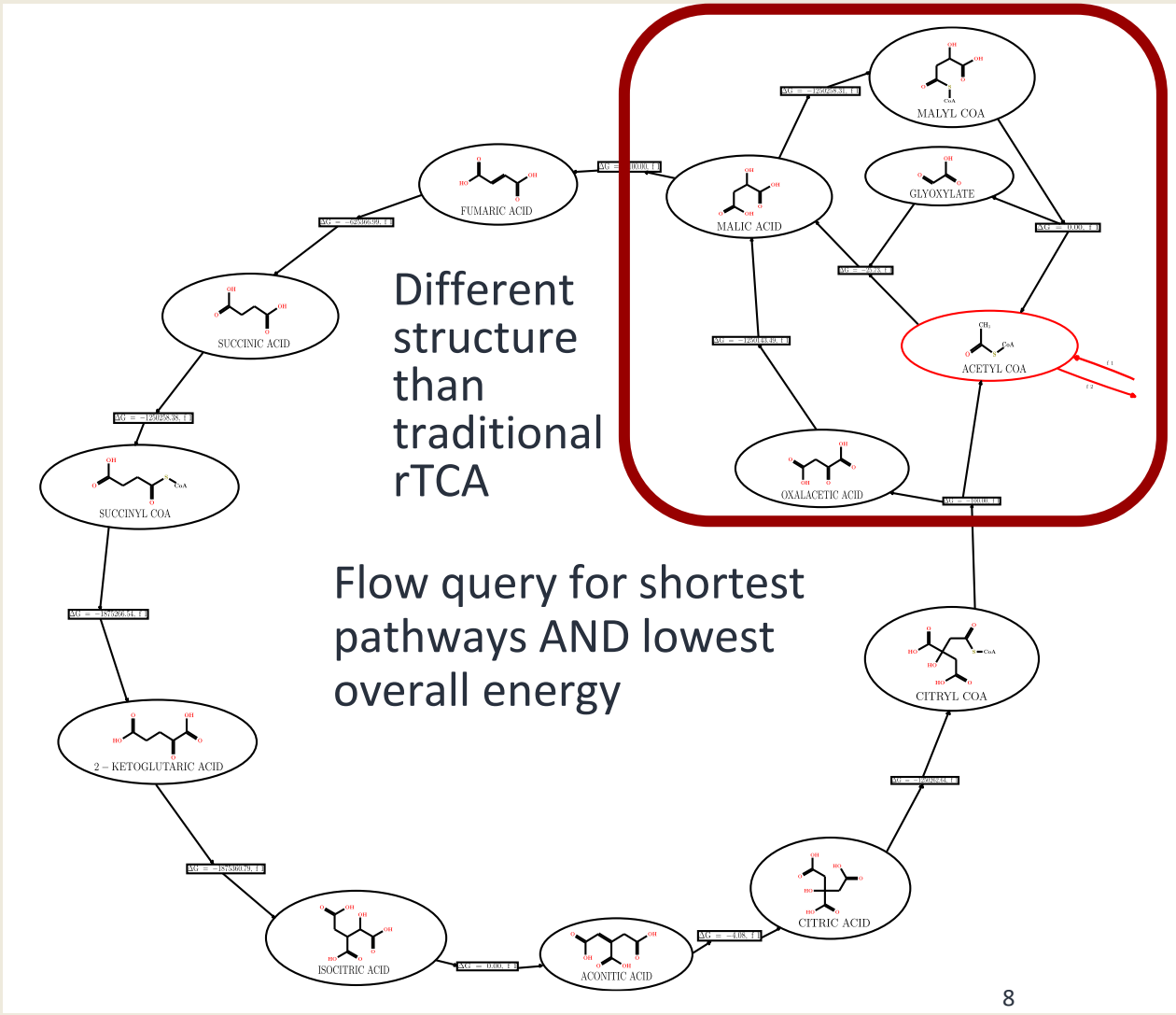
Optimisation for **minimal Energy** on flow

BUT

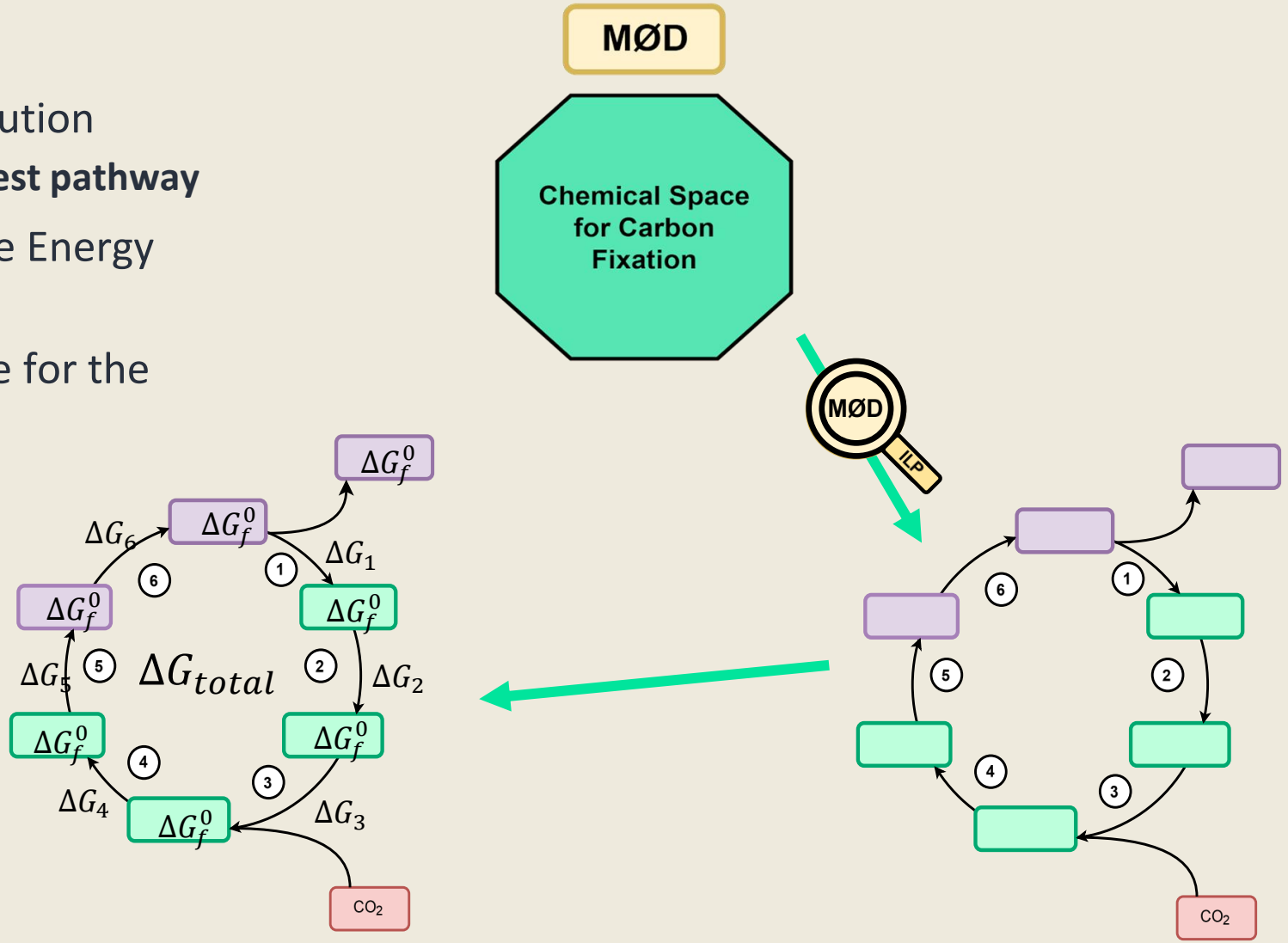
Currently facing problems with the concentration range of our solutions → outside of biochemically feasible range





Flow Query – Thermodynamic Post-Annotation

- First find a flow query solution
  - **Optimisation** for **shortest pathway**
- THEN calculate Gibbs Free Energy Change of the reactions
- Gives a feasiblity measure for the solutions



Flow Query – Thermodynamic Post-Annotation

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- First find a flow query solution
  - **Optimisation** for **shortest pathway**
- THEN calculate Gibbs Free Energy Change of the reactions
- Gives a feasiblity measure for the solutions

- Measure of feasibilty in biochemical context
  - **Count of ATP molecules used**

Optimsation for maximized CO2 input with fewest reactions

0.1.1 Solution 0

Overall Data

Objective value (integral): 3

Vertex/Graph	In	Out	OA
ACETYL COA	1	20	1
ADP	1	0	0
AMP	0	39	0
ATP	38	0	0
CO2	38	0	0
CoASH	19	0	0
Fdox	0	38	0
Fdred	38	0	0
H2O	0	18	0
NAD+	0	19	0
NADH	19	0	0
NADP+	0	38	0
NADPH	38	0	0
PPi	0	38	0
Pi	0	1	0
hplus	95	0	0

Optimsation for shortest pathway for autocatalytic acCoA

0.1.1 Solution 0

Overall Data

Objective value (integral): 13

Vertex/Graph	In	Out	OA
ACETYL COA	1	2	1
ADP	0	1	0
AMP	0	2	0
ATP	3	0	0
CO2	2	0	0
CoASH	1	0	0
Fdox	0	2	0
Fdred	2	0	0
NAD+	0	1	0
NADH	1	0	0
NADP+	0	2	0
NADPH	2	0	0
PPi	0	2	0
Pi	0	1	0
hplus	5	0	0

Outlook

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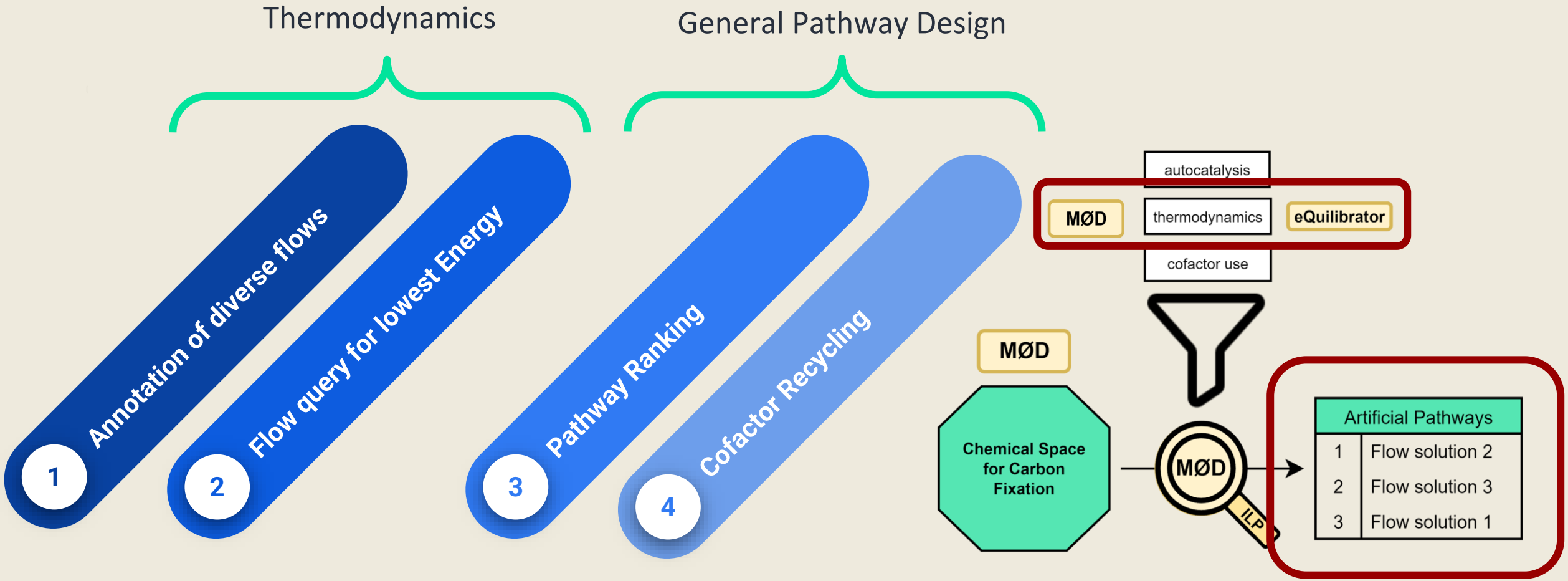

Thank You for Your Attention!

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Nino Lauber PhD

TBI Group

& other TACsy Students and Professors