Graph Transformations in an Enzymatic Context

MASTER THESIS PROJECT

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About me

Computer Science master student from the University of Southern Denmark

At the start of thesis

Looking for interesting ideas and difficult problems!

Project Overview

Exploratory work for *hopefully* novel results and applications

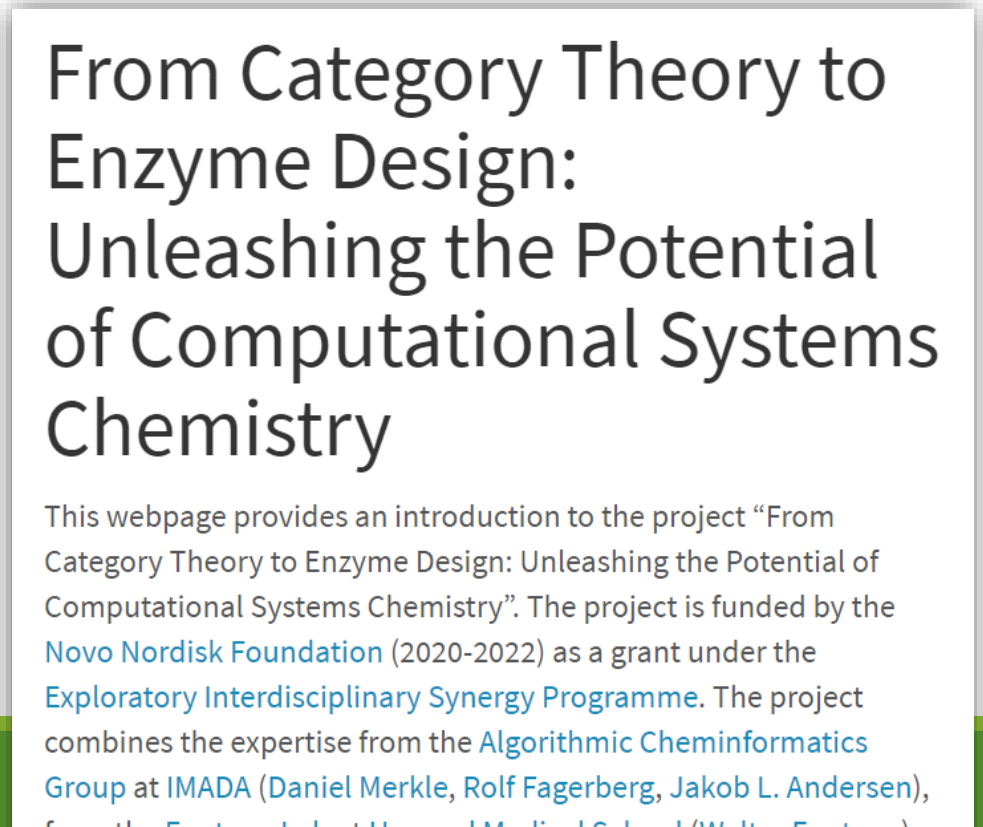
Novo Nordisk Foundation thinks it's exciting too! cheminf.imada.sdu.dk/novo-synergy

A **lot** of work

Presented here is the overarching plan

My role:

- Hopefully help with pre-work
- Method development
- Being kind of naïve on purpose



Applications

Novel enzyme design

Synthetic biology

One-pot designs

MØD + Kappa

Supporting tools for existing discovery techniques

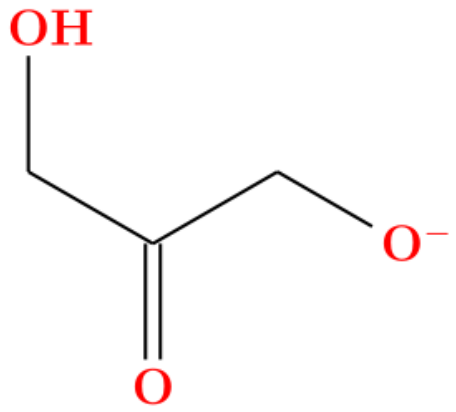
Concrete Steps

1. Rule mining
    1. M-CSA
    2. Infer rules
2. Rule modelling
    1. Generalize to “base knowledge” rule set
    2. Idea: Re-check reaction mechanisms
3. Stochastic simulation
4. Catalytic mechanisms
5. Causality and pathways
6. …

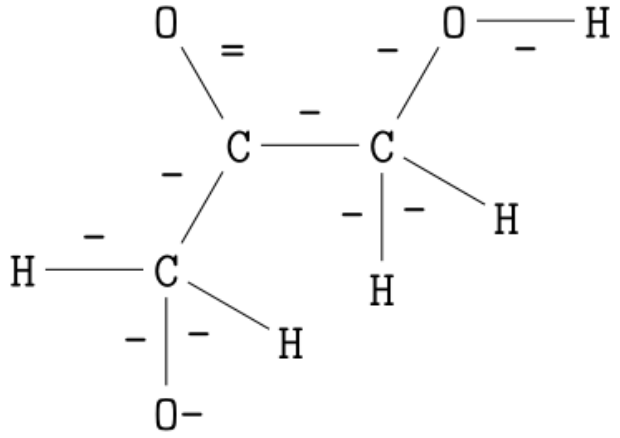
Rules

Modelling of Molecules

Def: a molecule is a labelled, connected, simple, undirected graph.



(a) Chemical depiction.



(b) Visualisation of underlying model.

Vertex label $\equiv$ chemical element and charge

$$\{\mathsf{H}, \mathsf{He}, \mathsf{Li}, \mathsf{Be}, \mathsf{B}, \mathsf{C}, \mathsf{N}, \mathsf{O}, \ldots, \mathsf{Uuo}\} \times \mathbb{Z}$$

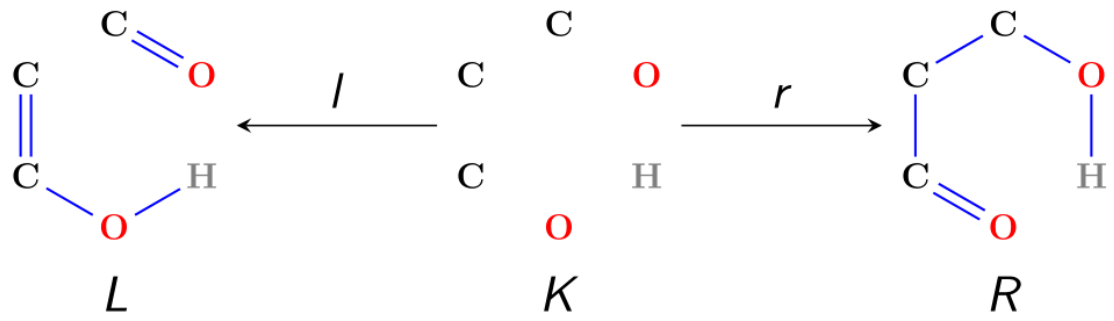
Edge label $\equiv$ bond type

$$\{\textsc{Single}, \textsc{Double}, \textsc{Triple}, \textsc{Aromatic}\}$$

Graph Transformation Rules

Vertices and edges are either deleted, preserved, or added.

As a Double Pushout (DPO) rule $p = (L \xleftarrow{l} K \xrightarrow{r} R)$:

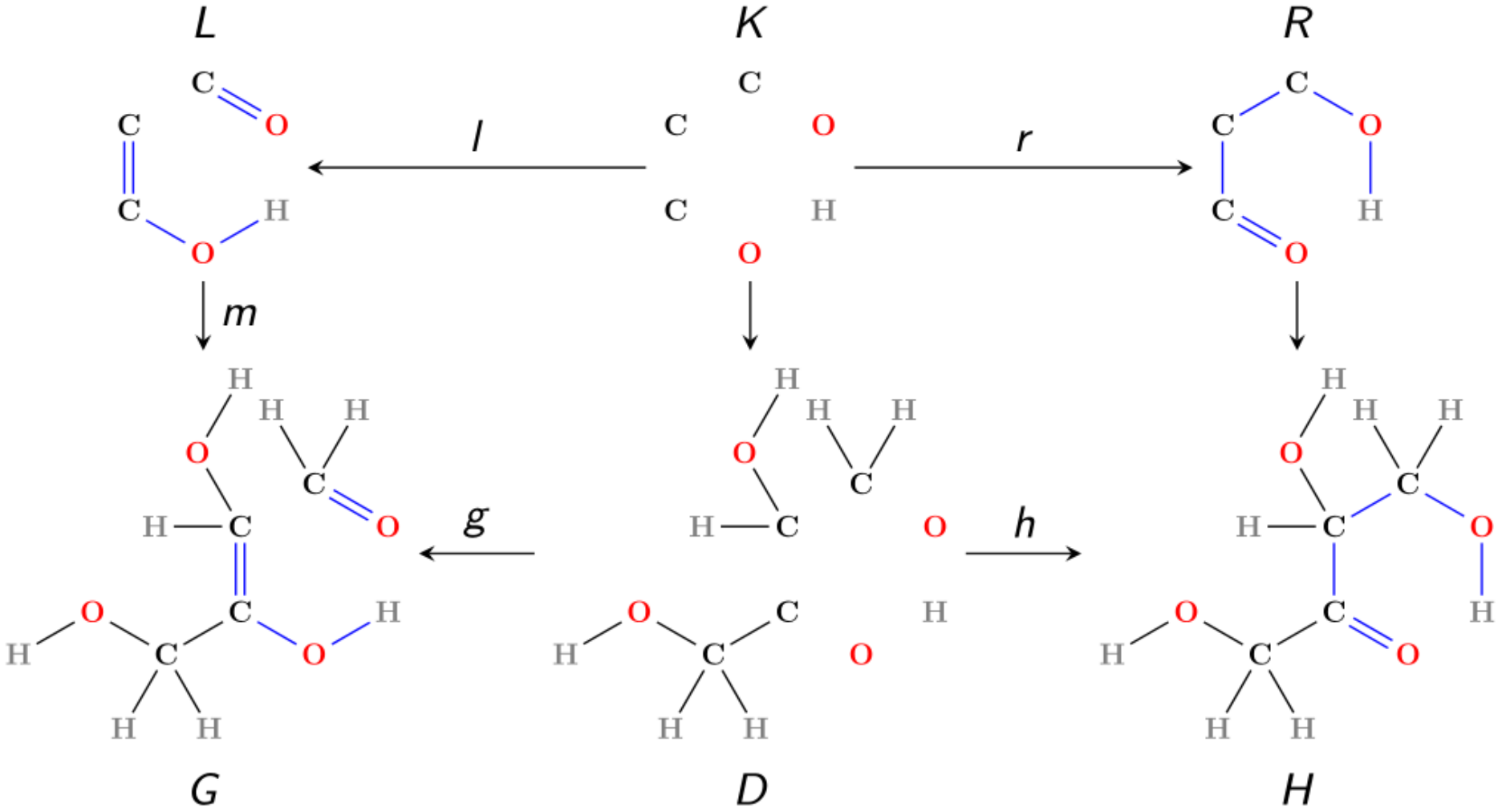


Semantics

- $L \backslash K$ is deleted.
- K is preserved.
- $R \backslash K$ is added.
- Both l and r are monomorphisms.

E.g., see [Ehrig et al., Fundamentals of Algebraic Graph Transformation, 2006]

Rule Application



50 Shades of Rule Composition

From Chemical Reactions to Higher Levels of Abstraction

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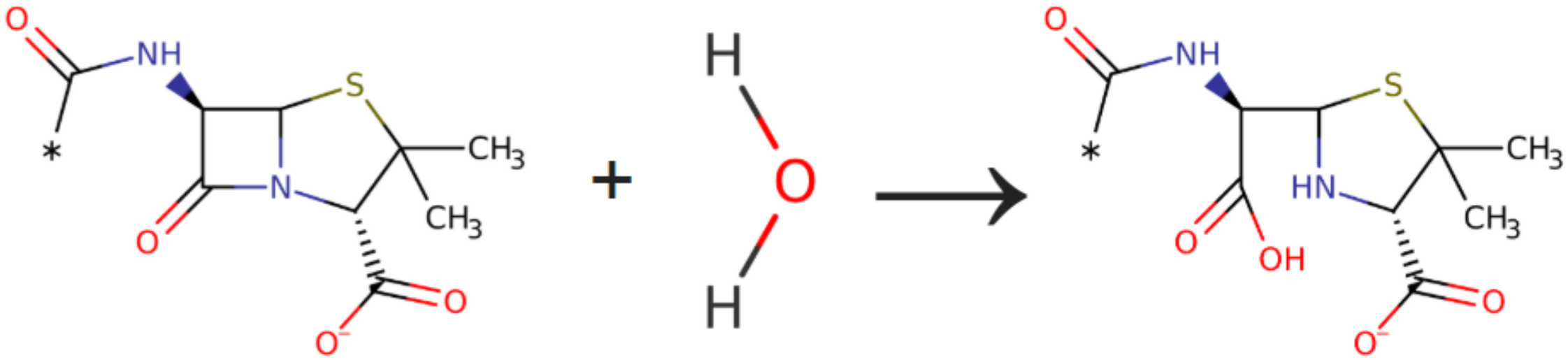
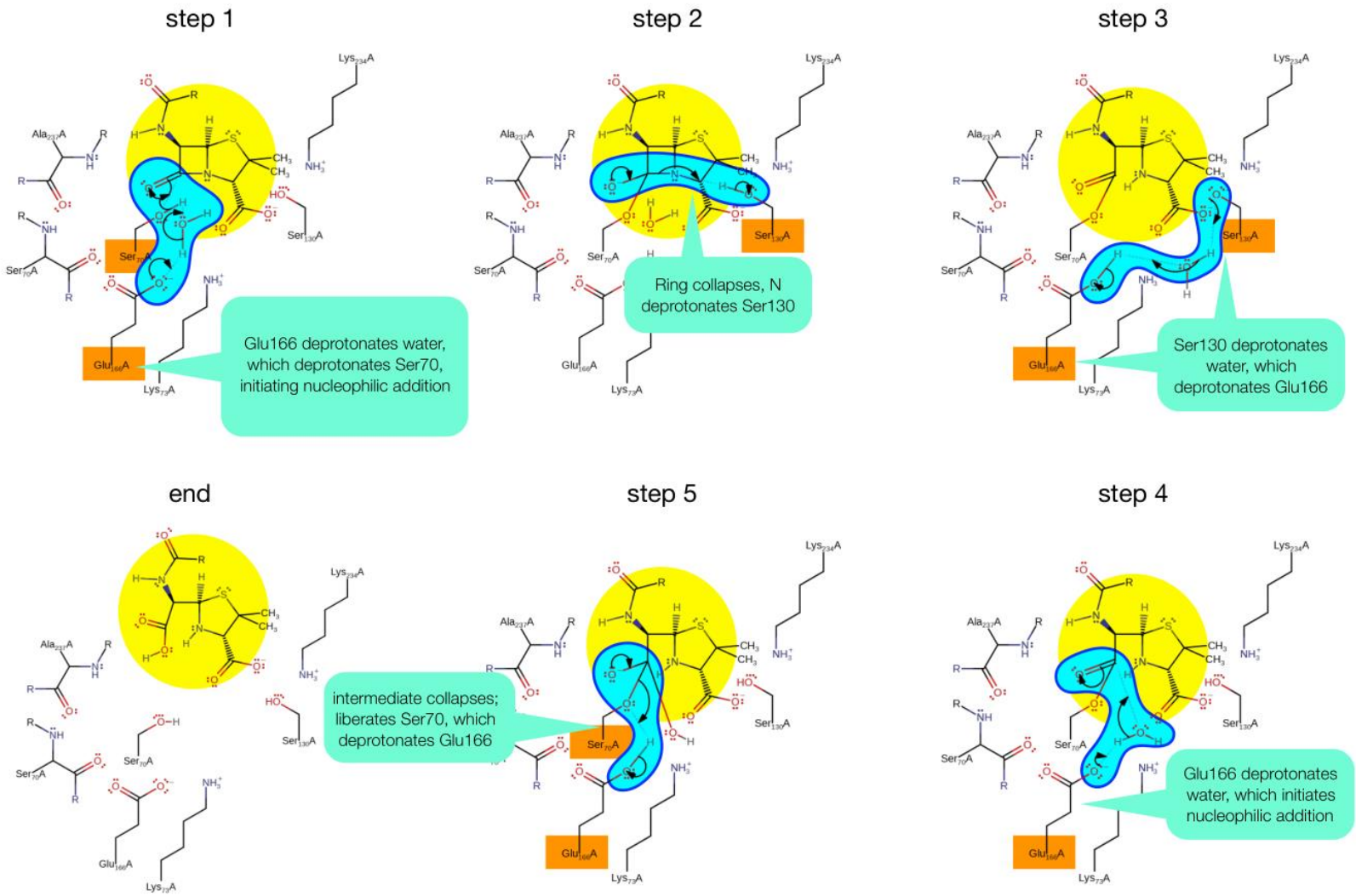
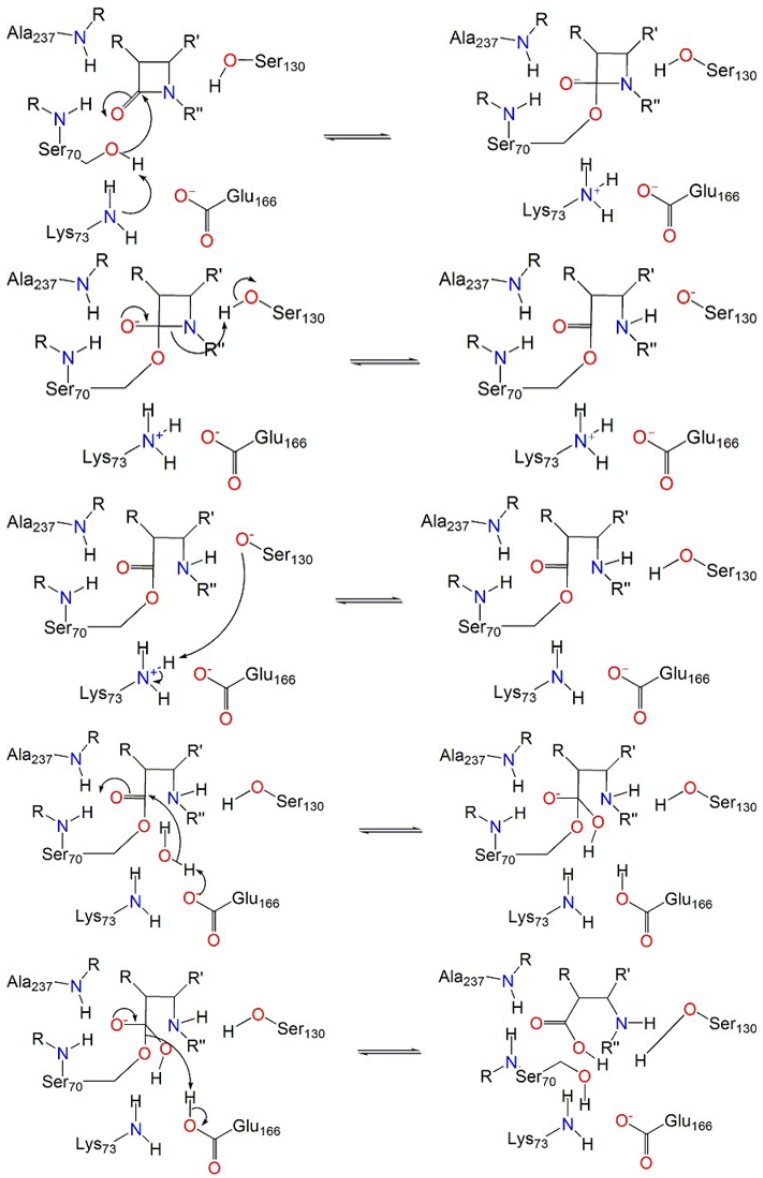
Abstract. Graph rewriting has been applied quite successfully to model

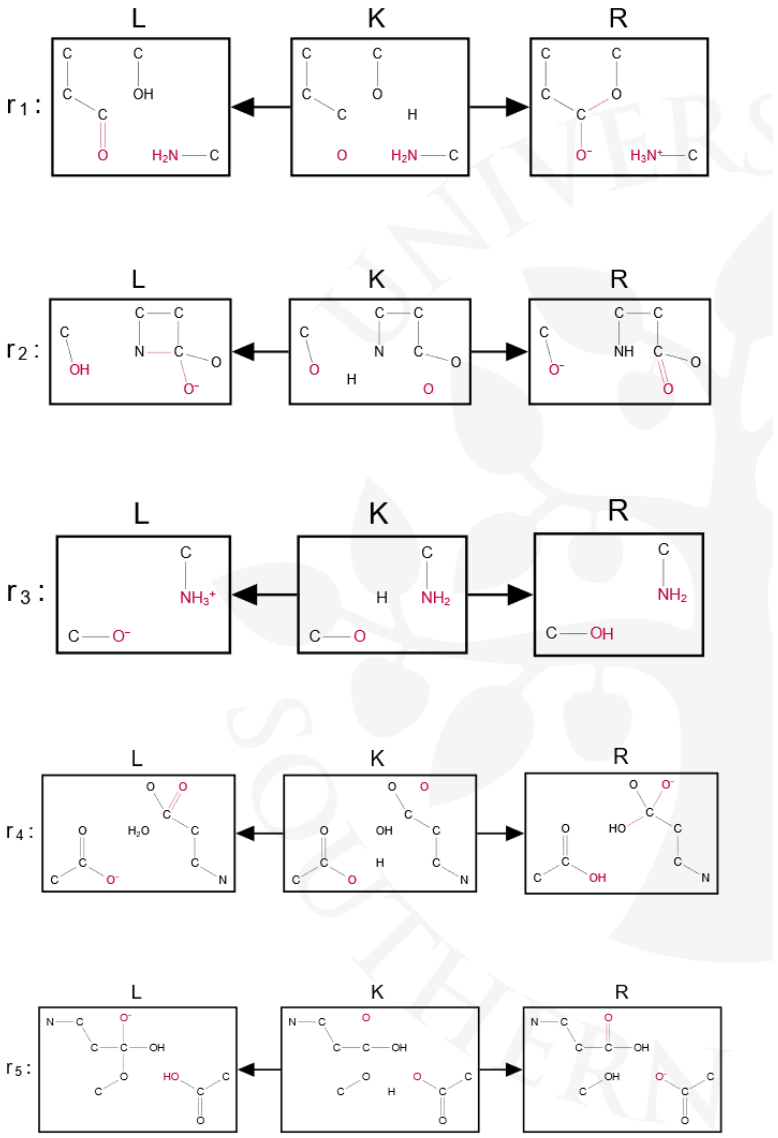


β-Lactamase

The Mechanism of β-lactamase

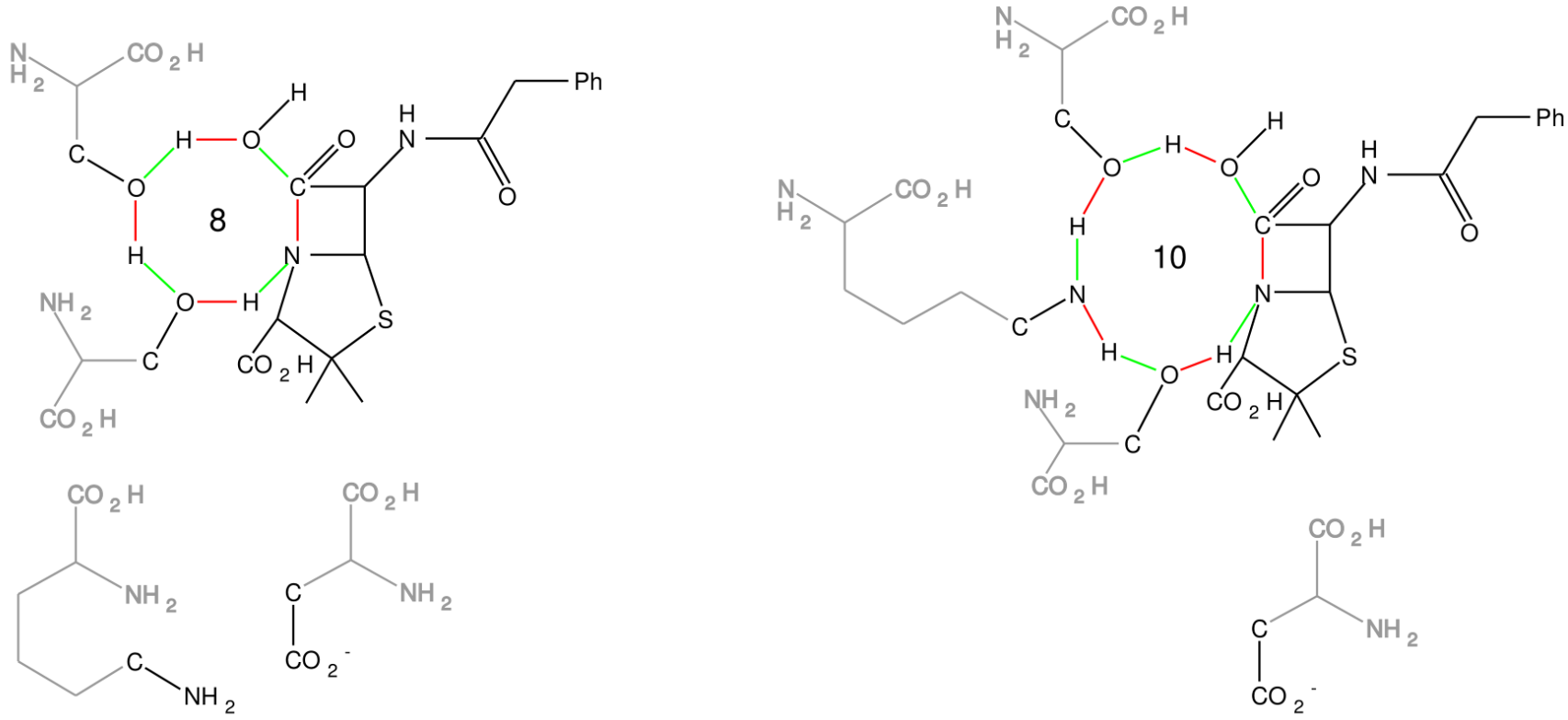



Ala237
Ser130
Ser70
Lys73
Glu166


L
K
R
r1 :
r2 :
r3 :
r4 :
r5 :

Rule Composition - β-Lactamase

$$\iota_G \circ r_1 \circ r_2 \circ r_3 \circ r_4 \circ r_5 \circ \iota_H$$



Stochastic Simulation

Rules implicitly define transitions for stochastic simulations

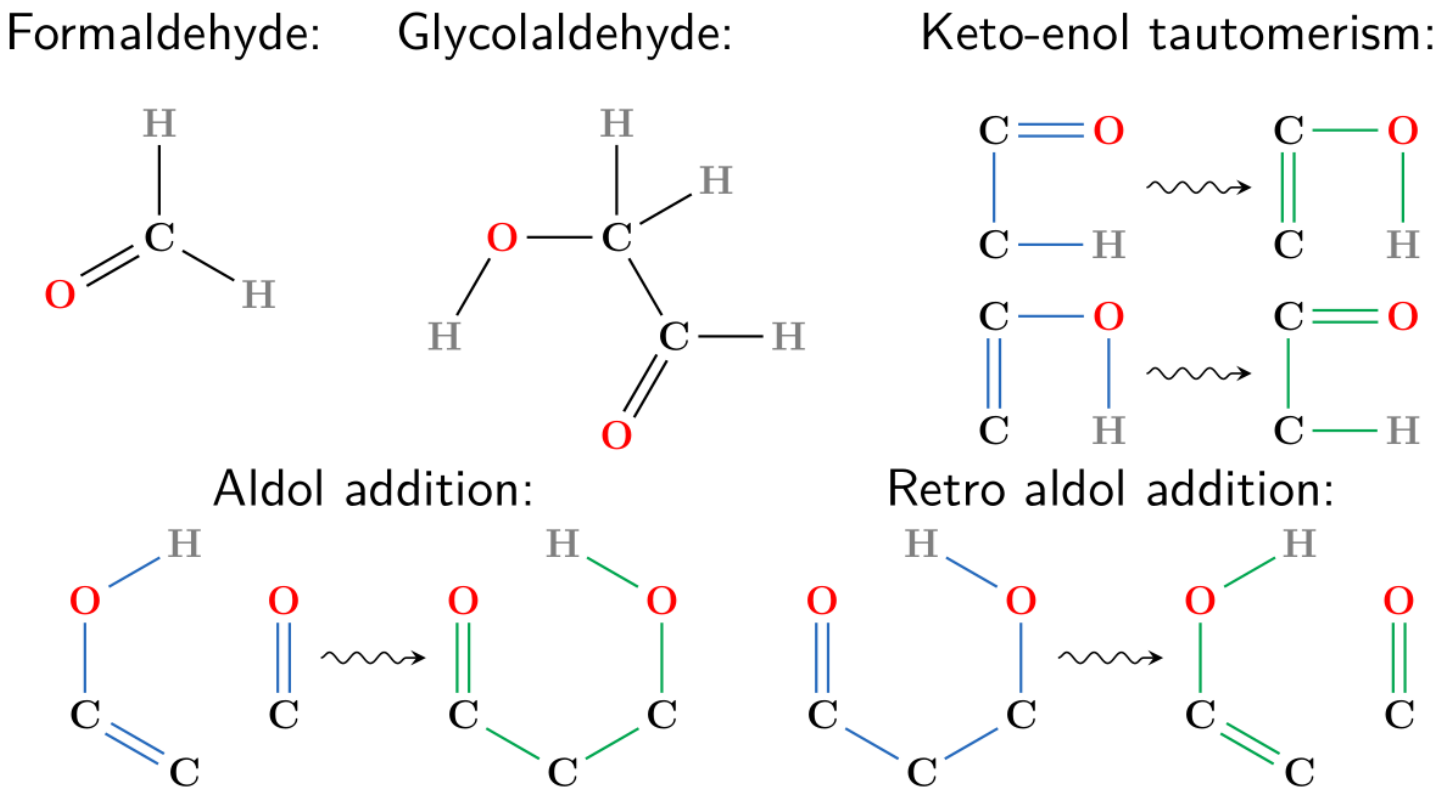
Network-free Gillespie-like simulations

- Reaction rates are needed

Can potentially be used to verify one-pot systems

Stoch-sims are in development for MØD

Reaction Network



Example: Formose

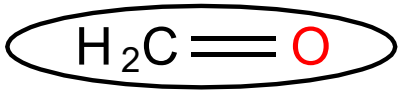
Starting graphs:

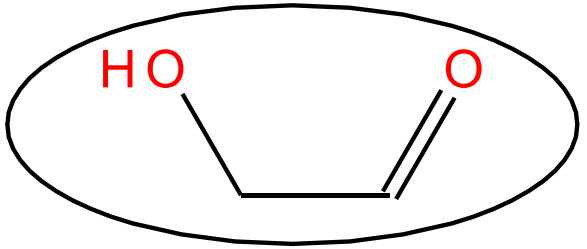
- Formaldehyde
- Glycolaldehyde

Transformation rules:

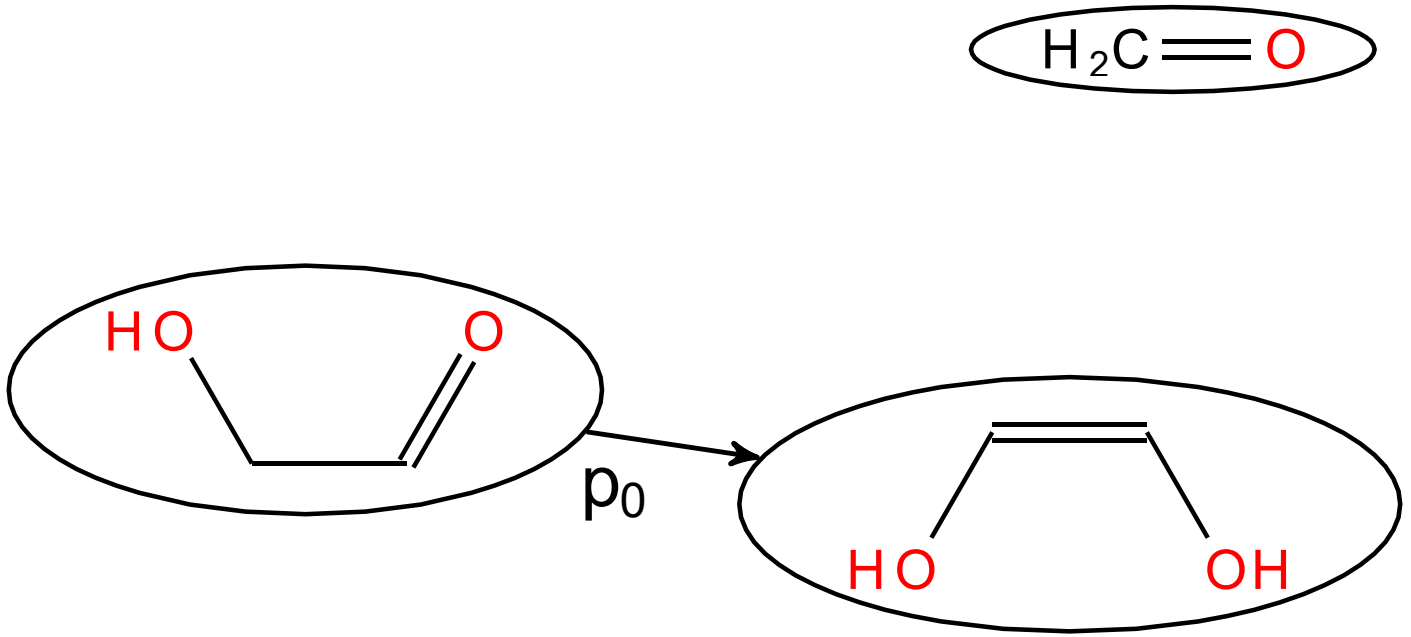
- $\mathbf{p_0}$: keto-enol-tautomerism, one direction
- $\mathbf{p_1}$: keto-enol-tautomerism, the other direction
- $\mathbf{p_2}$: aldol addition, one direction
- $\mathbf{p_3}$: aldol addition, the other direction

Generation 0

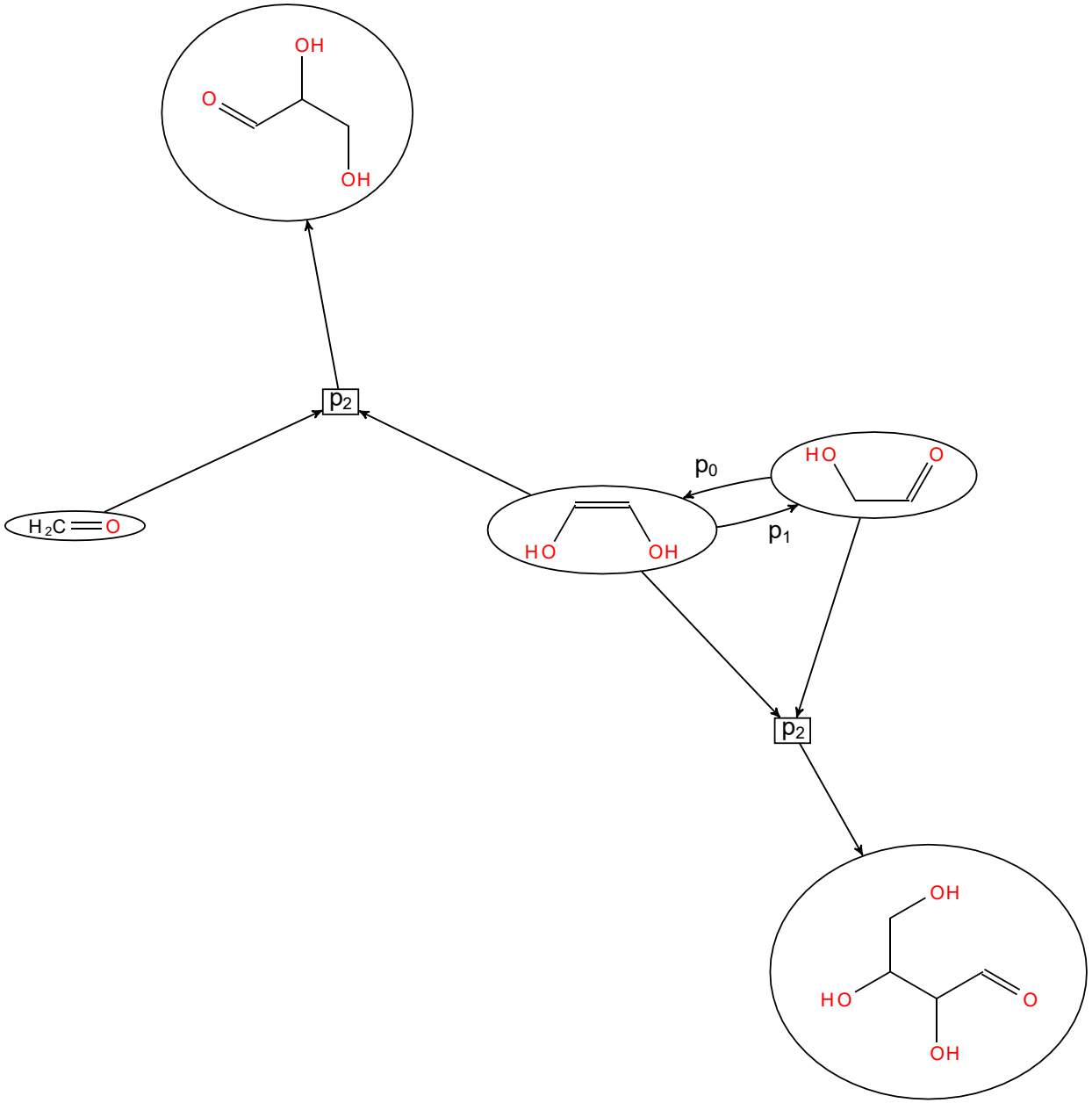




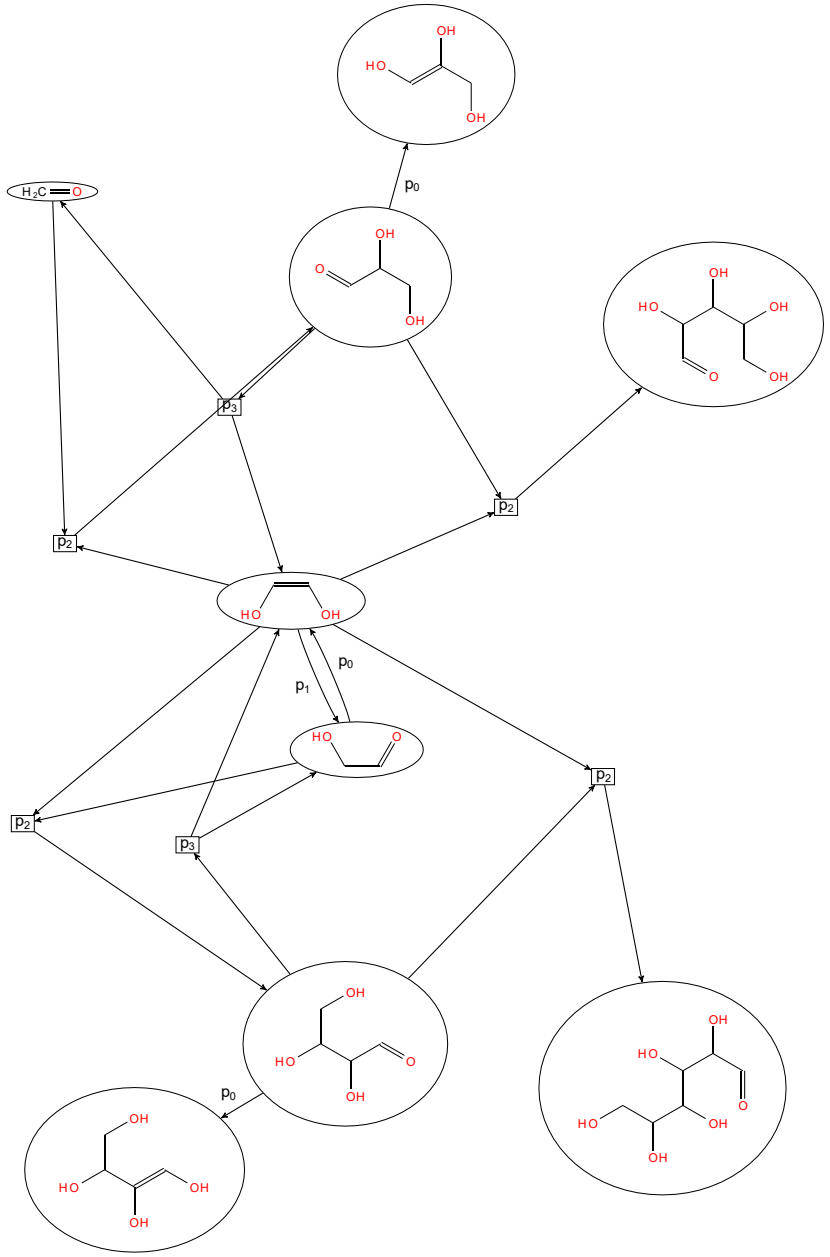
Generation 1



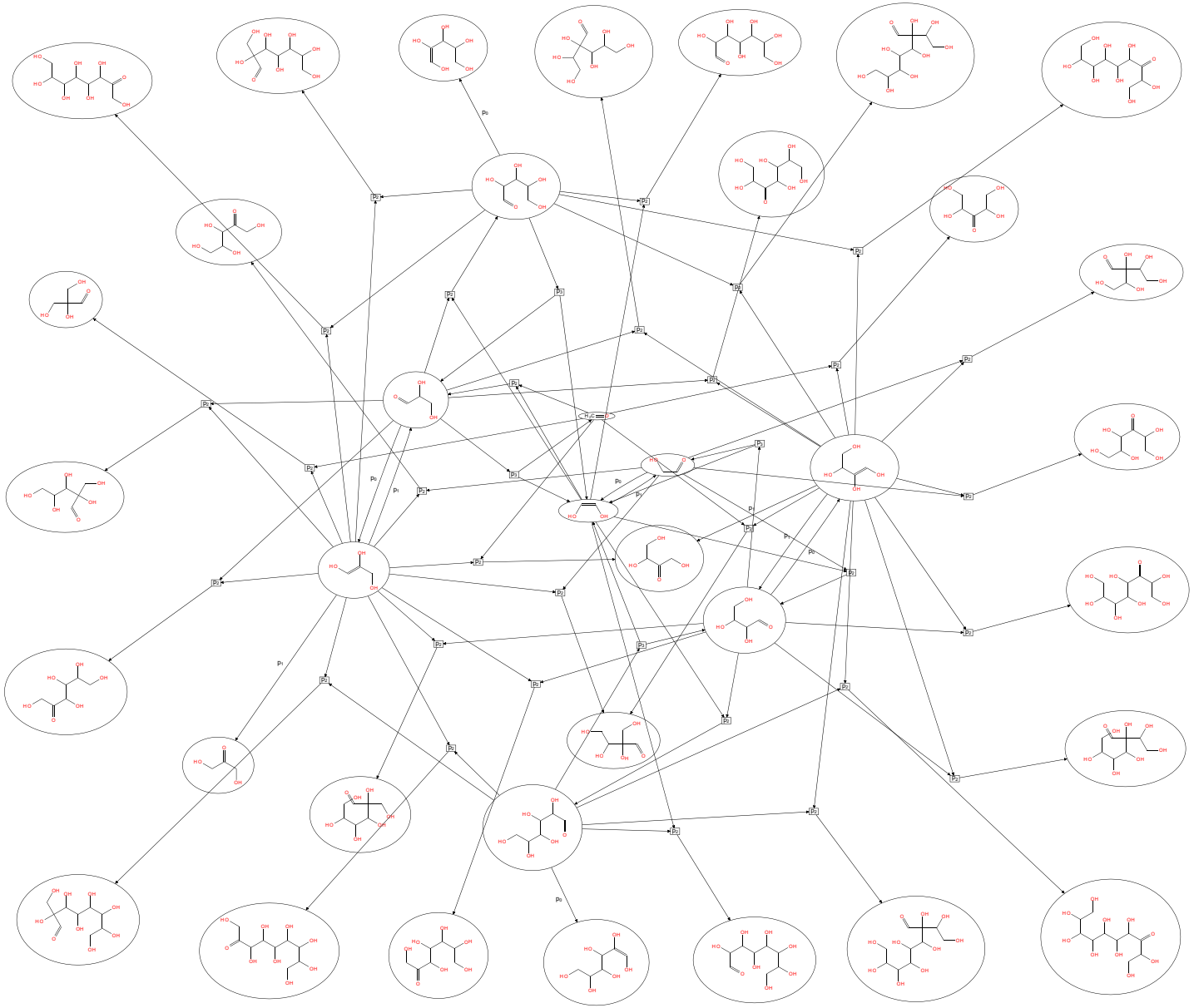
Generation 2

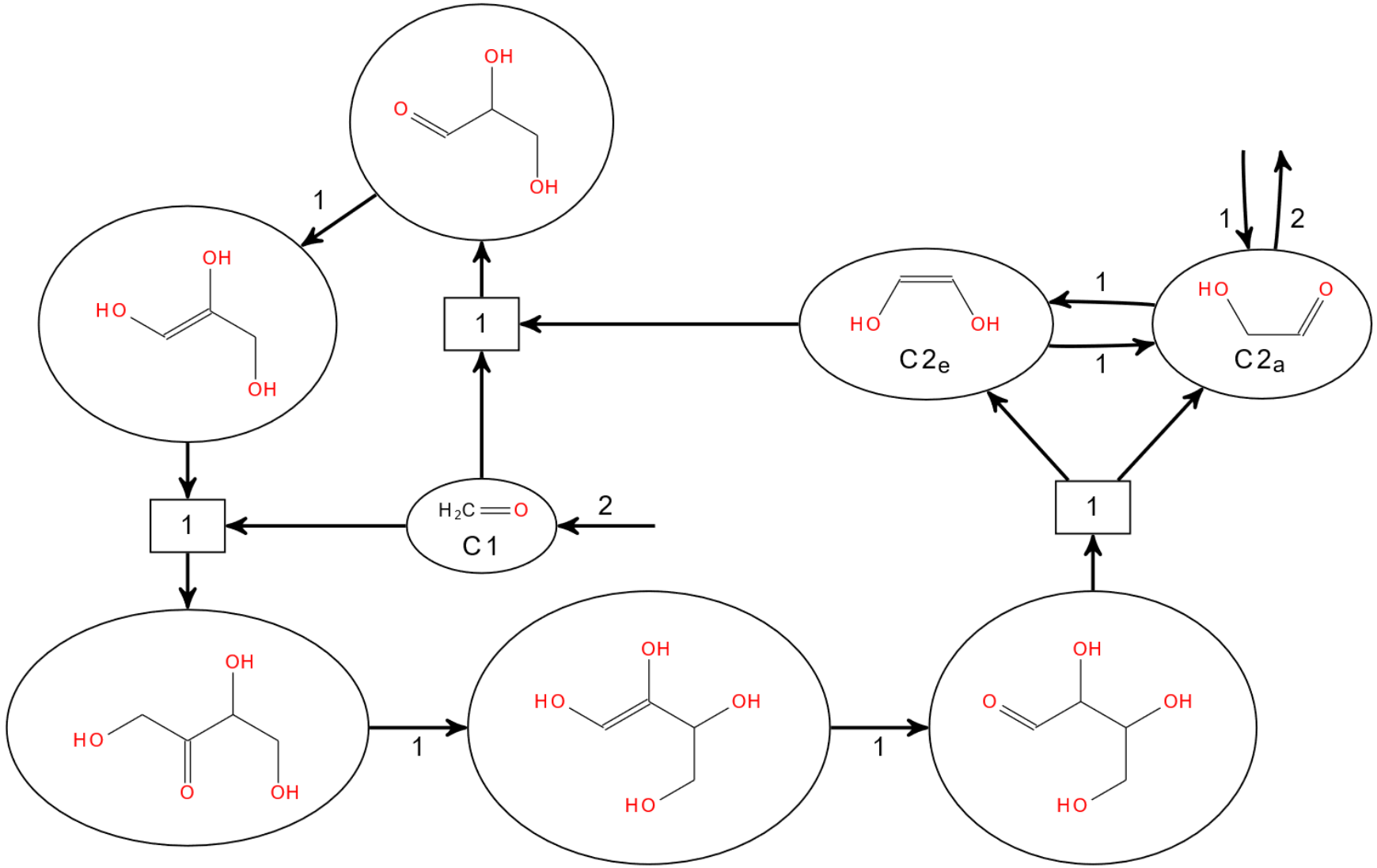


Generation 3



Generation 4




OH
O
OH
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OH
HO
OH
1
1
2
1
HO
OH
C2e
1
HO
O
C2a
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H2C O
C1
2
1
1
OH
HO
OH
O
OH
1
OH
HO
OH
HO
1
OH
O
OH
HO

Catalytic Mechanisms

From networks we find catalytic reactions

- What is a rigorous definition of catalysis? Is it useful?

Essential for enzyme-like action

From base rule set, compute super-set of likely amino-acid catalyzed reactions

- Can hopefully suggest amino acids in active site based on educt and product
- Will represent the non-3D embedded active site in beginning

Summary

What is already there:

- Modelling formalisms for chemical reactions
- Tools for computing reaction networks
- Drive to push the methods forward

Next steps:

- Building of “base” rule set
- Explore the nuances of enzyme mechanisms

Come talk to me about what is hard in enzymatic design!

Thanks!