Comparison of Metabolic Networks

Thomas Gatter

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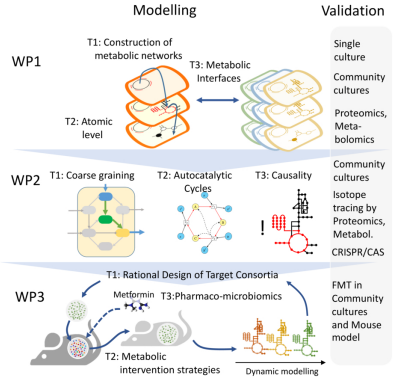
Leipzig University

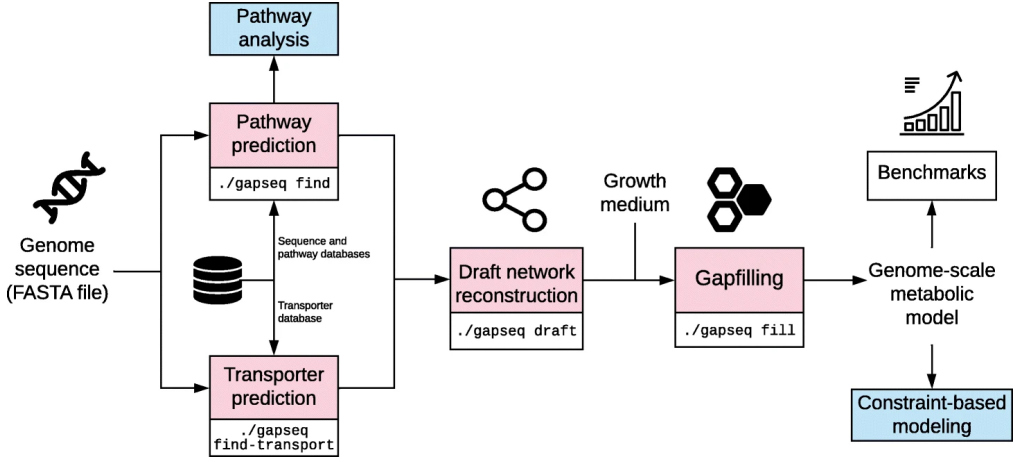
The Ultimate Goal



Model the interactions of **SIHUMix** organisms:

A. cacae L1-92 (DSM 14662), B. thetaiotaomicron (DSM 2079), B. longum (NCC2705), B. producta (DSM 2950), C. butyricum (DSM 10702), C. ramosum (DSM 1402), E. coli (K-12 MG1655), L. plantarum (DSM 20174)

Reconstruction Pipeline of GapSeq



[1] Zimmermann et al. (2021)

SBML Reaction Parsing

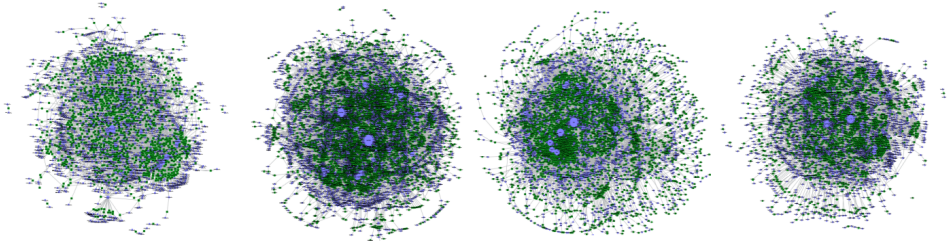
We want to compare the following networks (for each species):

- CarveMe[2] prediction (gapfilled by medium)
- GapSeq[3] prediction (gapfilled by medium)
- AGORA2 (hand-curated) [4] based on KBase prediction[5]

Question: How different are they?

[1] Machado et al. (2018), [2] Zimmermann et al. (2021), [3] Heinken et al. (2023), [4] Arkin et al. (2018)

Option A: Manual Comparison



Networks of different reconstructions of the same organism (E. coli)

[1]SAMMI (https://bioinformatics.mdanderson.org/Software/SAMMI/)

Option B: Experimental Validation

Compare how well models fit to lab measurements:

- Growth rates
- Compound uptake and secretion rates
- Isotope tracing
- ...

Option C: ID Matching/Matching of Chemical Structure

```
<species metaid="meta_M_h2o_e" sboTerm="SBO:0000247" id="M_h2o_e"
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      boundaryCondition="false" constant="false" fbc:charge="0"
      fbc:chemicalFormula="H2O">
  <notes>
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      <p>FORMULA: H2O</p>
      <p>CHARGE: 0</p>
      <p>SBOTerm: SBO:0000247</p>
    </html>
  </notes>
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dcterms="
      <rdf:Description rdf:about="#meta_M_h2o_e">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="https://identifiers.org/reactome/R-ALL-109276"/>
            <rdf:li rdf:resource="https://identifiers.org/reactome/R-ALL-113518"/>
            <rdf:li rdf:resource="https://identifiers.org/reactome/R-ALL-113519"/>
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            <rdf:li rdf:resource="https://identifiers.org/reactome/R-ALL-141343"/>
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            <rdf:li rdf:resource="https://identifiers.org/kegg.compound/C00001"/>
            <rdf:li rdf:resource="https://identifiers.org/kegg.compound/C01328"/>
```
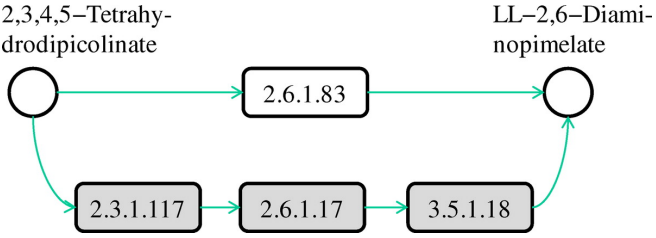

SBML provides no common ID scheme and no chemical structures!

Tools use different databases / versions!

Option C: ID Matching/Matching of Chemical Structure



Most existing software relies purely on KEGG, e.g. Chen and Hofestädt (2004), Hatzimanikatis et al. (2005), Li et al. (2008), Ay et al. (2011), Abaka et al. (2013), Alberich et al. (2014), Cocco et al. (2021)

Idea: translate to chemical structures whatever we can → abstract → compare

Image: Ay et al. (2011))

How to parse an SBML?

Supported Paths:

- SMBL Compounds → StructRecon → Best InChI * → SBML Reactions
- Seed Reaction → Seed Compounds → InChIKey → PubChem → InChI
- Rhea Reaction → CHEBI Compounds → InChI
- MetaNetX Reaction * → MetaNetX Compounds * → InChI
- KEGG Reaction → KEGG Compounds → Mol → RDK to InChI
- reactome Reaction → reactome Compounds * → CHEBI Compounds → InChI
- BiGG Reaction * → BiGG Compounds * → InChIKey → PubChem → InChI
  or → MetaNetX Compounds * → InChI

* = potential ID links to other databases/structures

For each sbml reaction entry we get list of structurally resolved reactions.

How to process?

Problems...

- directions inconsistent $\rightarrow$ educt, product sides inconsistent
- missing structures (for some databases)
- variation in charges, tautomers, steorechemistry etc
- long query times (10+ online DB requests per reaction)
- networking errors with APIs

Two metrics for equality...

How to process?

When are two reactions identical?

Full Identity

- number of compounds without structure identical
- structures identical
- either direction matches

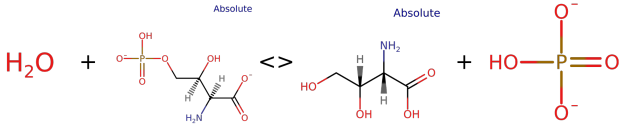
Simplified and Unified

- compounds without structure ignored
- presence of water and protons ignored
- all structures simplified by FICTS [2]
- either direction matches
- subsets matched $\rightarrow$ represented by larger

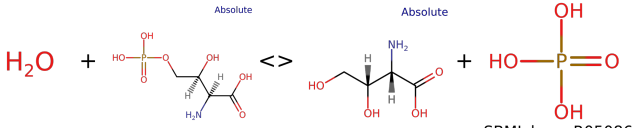
[2] Eriksen et al. (2023)

Example

Fully Identical

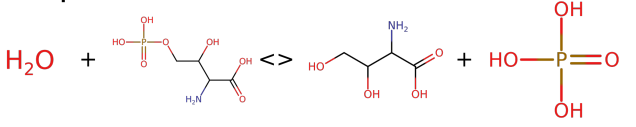


bigg:4HTHRS,rhea:30659,metanetx:MNXR95024,seed:rxn03446



SBML,kegg:R05086

Simplified



SBML,kegg:R05086,bigg:4HTHRS,rhea:30659,
metanetx:MNXR95024,seed:rxn03446

Some example stats

CarveMe reconstruction E. coli with cimIV.

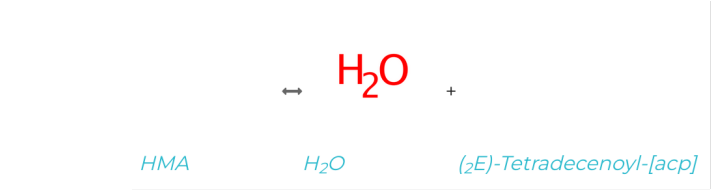
Different reactions per SBML reaction

	Full	Simplified
# Reactions	901	901
mean	3.36	1.2
min	1	1
25%	3	1
50%	3	1
75%	4	1
max	7	3

Database IDs per compacted reaction

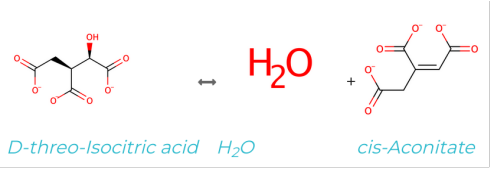
	Full	Simplified
# Reactions	901	901
mean	2.26	7.22
min	1	1
25%	1.2	3
50%	1.5	6
75%	2	6
max	42	126

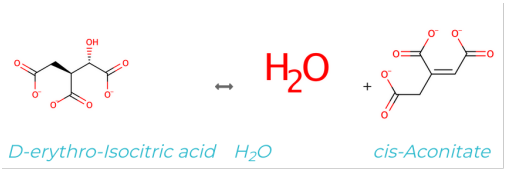
The old annotation problem...

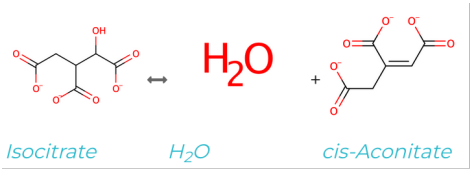


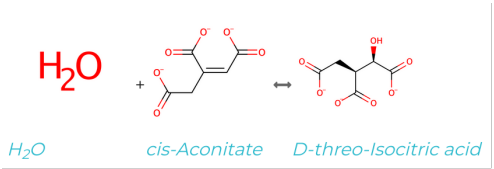
“Duplicates” within same SBML…

e.g. stereochemistry, direction



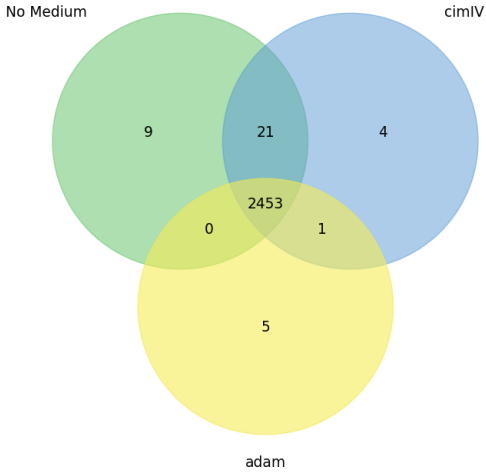






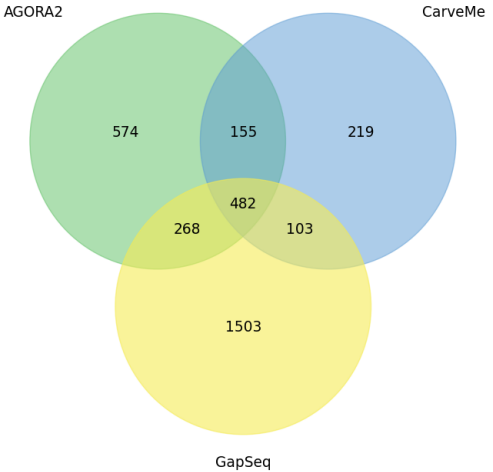
Now how similar are our reconstructions?

E. coli GapSeq reconstructions using no medium, cimIV and adam

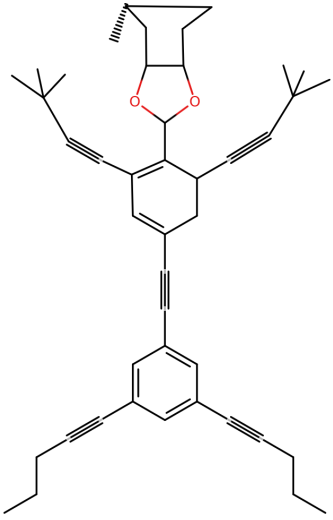


Now how similar are our reconstructions?

E. coli reconstructions of CarveMe, GapSeq and AGORA2 using cimIV



Oh well...



Thank You!

Peter Stadler

Natasha Jorge

Jobs Jobs Jobs!

We have 4 PhD positions available!

- *"RNA-seq-based screening for active self-cleaving ribozymes and transcriptome-wide assessment of their regulatory functions"* (Now!)
- for SPP 2363 *"Utilization and Development of Machine Learning for Molecular Applications"* (Summer/Autumn)
- *"Learning to Explain: Inference of Chemical Reaction Mechanisms"* (Autumn/Winter)
- *"Improving integration of multimodal omics data for precision metabolic health"* (Likely soon)

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