Utilizing the semantic web for kinetic modeling of metabolic disease pathways

Denise Slenter[1], **Egon L Willighagen**[1]

[1] Dept of Bioinformatics - BiGCaT, NUTRIM, Maastricht University, The Netherlands

Introduction, Discussion, Conclusion

Currently, a vast amount of biomedical data is captured in various databases, which have limited capabilities to interact with each other. The knowledge in these databases could be used to explore if existing **drugs** can be **repurposed** for (rare) metabolic diseases, or if the **synergies of drug combinations** could lead to fewer side effects for patients [1]. Both of these use cases could be modeled in silico with the appropriate **kinetic data**, by applying semantic web technologies (e.g. RDF).

Here, we present our approach to create pharmacologically compatible pathway for metabolic disorders. First, **machine-readable pathway** models were created [2] (Fig. 1), which were uploaded to WikiPathways [3] converting the pathway data to the RDF format [4]. Second, we visited four **kinetics databases** and literature to identify relevant kinetic parameters, for which we **created an RDF model** (Fig. 2 and 3), compatible with the pathway models. Third, three drug-target databases with existing RDF schema where queried to find corresponding inhibitors (Fig. 4).

Our approach led to five new pathways relevant for metabolic disorders, which are supported by kinetic and drug-target information (Fig. 5). Unfortunately, kinetic data could not be obtained for all metabolic interactions. However, **when relevant data is captured in a semantic model**, researchers can easily assess which interactions are missing data, shortening wet-lab time. Furthermore, adding data for other pathways is user-friendly, allowing others to extend and utilize our method.

Step 1: Pathways

WikiPathways
PathVisio

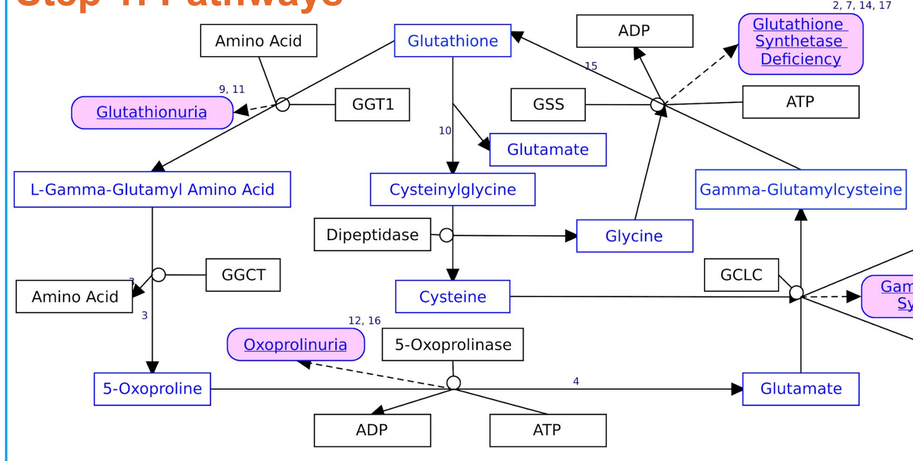
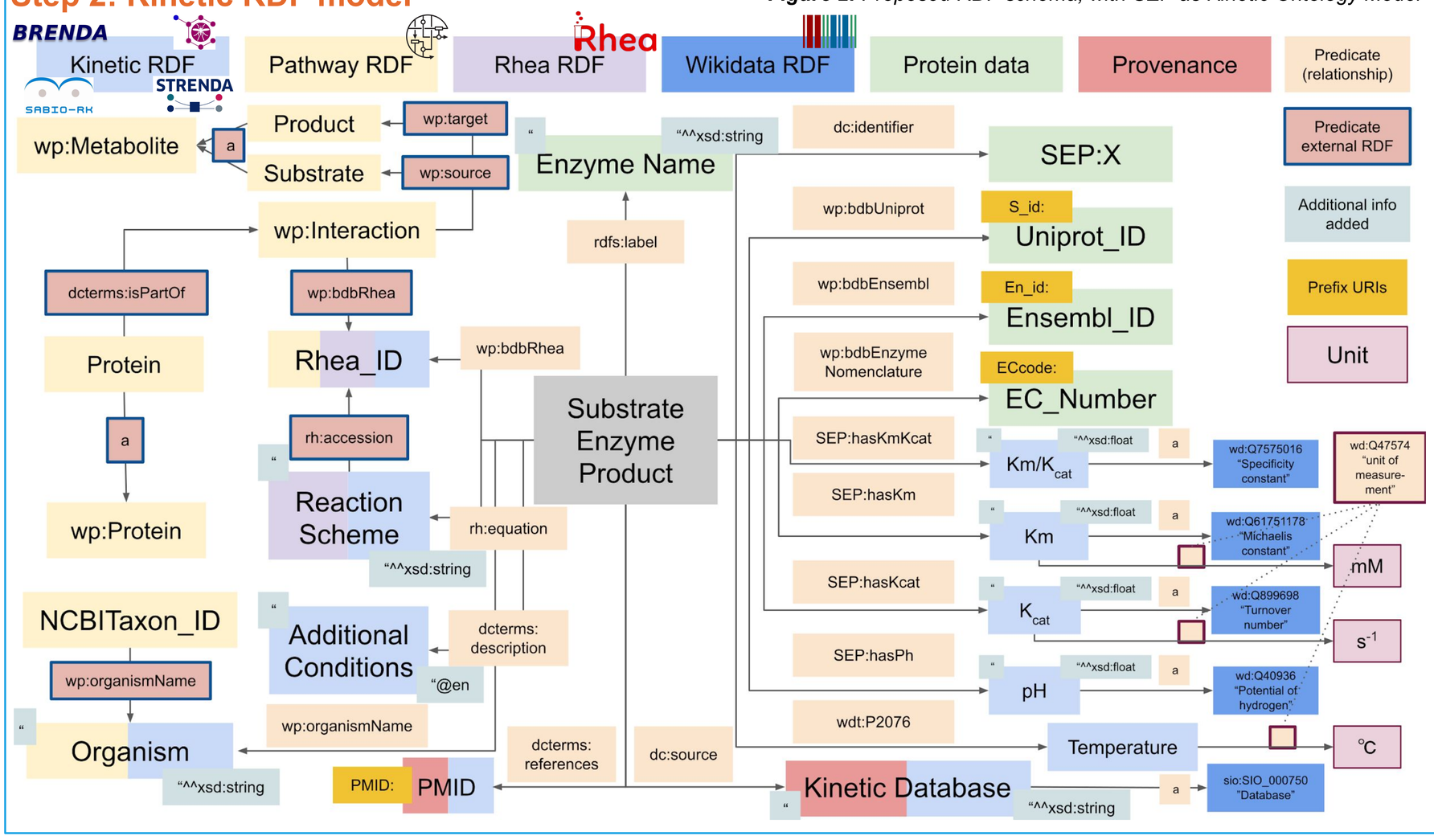


Figure 1: *Gamma-Glutamyl Cycle for the biosynthesis and degradation of glutathione, including diseases (Homo sapiens). https://www.wikipathways.org/instance/WP4518*

Pathway Name	PW ID	Proteins	Metabolites	Reactions
Gamma-Glutamyl Cycle related to glutathione	WP4518	6	11	6
Cerebral Organic Acidurias	WP4519	8	28	6
Glycosylation Pathway	WP4521	25	29	16
Classical pathway of steroidogenesis	WP4523	15	19	14
Alternative pathway of fetal androgen synthesis	WP4524	13	18	14

Step 2: Kinetic RDF model

Figure 2: *Proposed RDF schema, with SEP as Kinetic Ontology Model*



Step 2: Example Kinetic RDF model

```
SEP:238
    dc:identifier SEP:238 ;
    rdfs:label "GSS"^^xsd:string ;
    wp:bdbEnzymeNomenclature ECcode:6.3.2.3 ;
    wp:bdbUniprot S_id:P48637 ;
    wp:bdbRhea RHEA:13558 ;
    SEP:hasKm "16"^^xsd:float ;
    SEP:hasPh "8,2"^^xsd:float ;
    dcterms:description "D458N"@en ;
    wp:organismName "Homo sapiens"^^xsd:string ;
    dc:source "BRENDA"^^xsd:string .

SEP:239
    dc:identifier SEP:239 ;
    rdfs:label "GSS"^^xsd:string ;
    wp:bdbEnzymeNomenclature ECcode:6.3.2.3 ;
    wp:bdbUniprot S_id:P48637 ;
```

Figure 3: *Kinetic data captured in RDF*

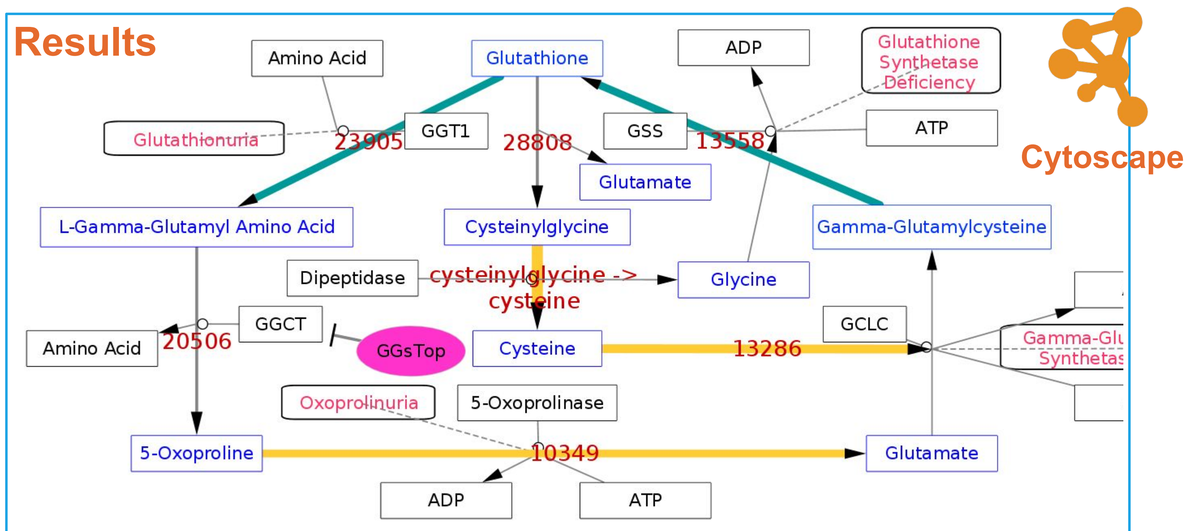
Step 3: Querying RDF drug-target databases

Guide to PHARMACOLOGY

ChEMBL

DRUGBANK

Results



Cytoscape

Figure 5: *Combining pathways through Rhea identifiers (red) with Km values (edge thickness) for two species: Homo sapiens (green) and Rattus norvegicus (yellow) and inhibitor (pink).*

Step3:

Example query on Guide to PHARMA-COLOGY RDF

```
SELECT ?ligand ?name ?Uniprot ?MOA ?lowAffinity
WHERE {
?ligand gtpo:ligandName ?name .      #1.Find drugs
?ligand gtpo:iupacName ?iupacName . #1.Obtain IUPAC-name

?interaction gtpo:hasLigand ?ligand.#2.Ligand->interaction
?interaction gtpo:hasTarget ?target.#2.Target->interaction
?target      gtpo:hasRef ?ref.      #3.GTP protein ID
?ref    gtpo:xref ?Uniprot .        #3.Uniprot ID protein
?ref    gtpo:hasTaxonomy taxon:9606.#3.Only Hs proteins
?interaction gtpo:hasAction ?MOA .  #4.Mode of Action (MOA)
?interaction gtpo:hasTaxonomy taxon:9606.#4.Only Hs MOA

?interaction gtpo:hasAffinity ?affinity1.#5.Find affinity
?affinity1   gtpo:hasLowValue ?lowAffinity.#5.Obtain value
?affinity1   gtpo:hasUnits bao:0190004.#5.filter pKi
}
```

Figure 4: *SPARQL query for proteins-drugs interactions affinity (pKi).*

Correspondence to:
Denise Slenter

denise.slenter@maastrichtuniversity.nl

@SMaLLCaT4Sci

0000-0001-8449-1318

Department of Bioinformatics - BiGCaT, NUTRIM

Maastricht University, The Netherlands

[1] **Benson** et al. 2017. Br. J. Pharmacol. 174(23), 4362-4382. DOI: 10.1111/bph.14037

[2] **Kutmon** et al. 2015. PLoS Comput. Biol. 11(2), e1004085. DOI: 10.1371/journal.pcbi.1004085

[3] **Slenter** et al. 2018. Nucleic Acids Res., 46(D1), D661-D667. DOI: 10.1093/nar/gkx1064

[4] **Waagmeester** et al. 2016. PLoS Comput. Biol. 12(6), e1004989. DOI: 10.1371/journal.pcbi.1004989