Merging of systems biology models with semanticSBML

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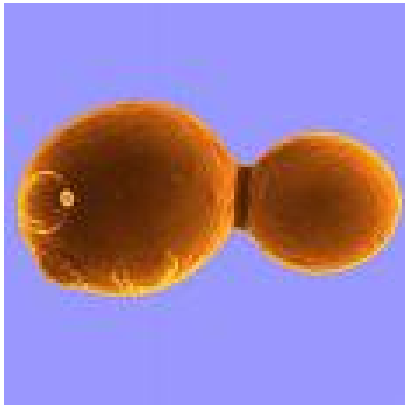
Max Planck Institute for Molecular Genetics, Berlin

5th Workshop on Computation of Biochemical Pathways and Genetic Networks

Heidelberg, September 22-23, 2008

I. Mathematical models in systems biology

Biochemical pathway models

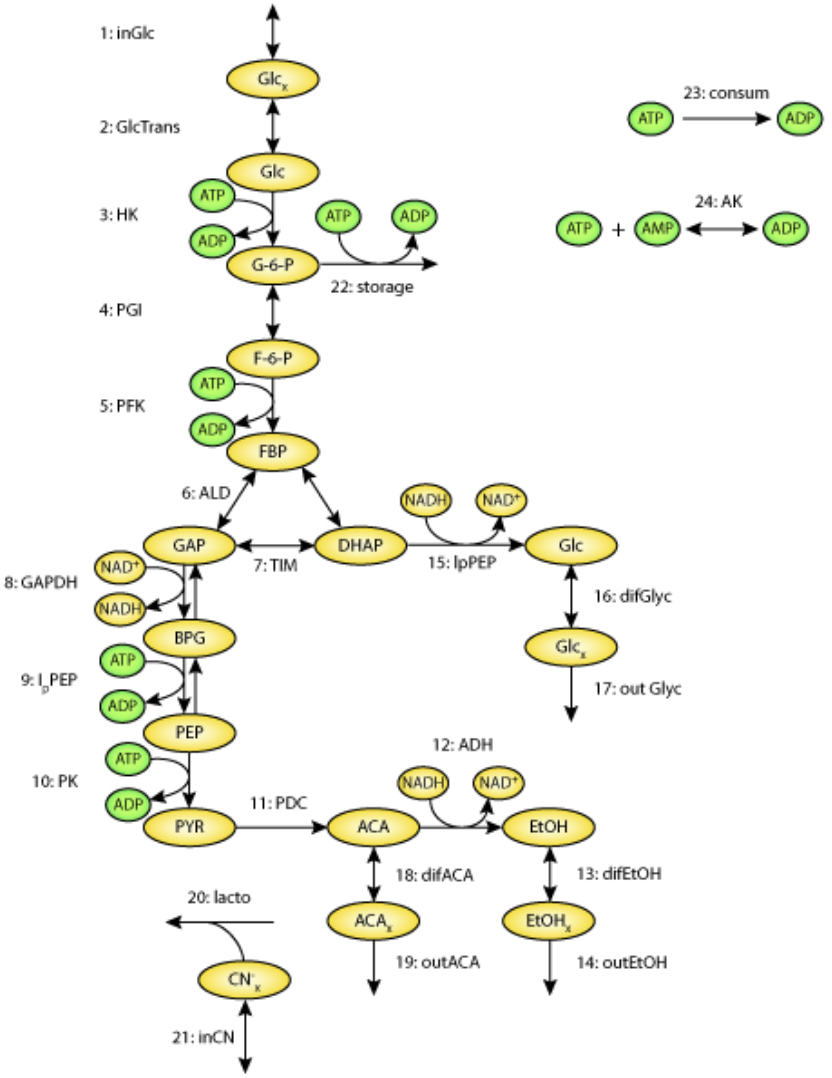


Budding yeast

Biochemical entities
Metabolites, reactions, ...

Biochemical quantities
Concentrations, velocities, ...

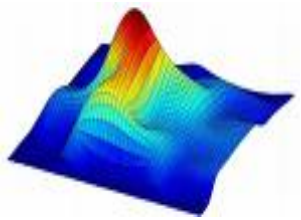
Mathematical statements
Values, equations, ...



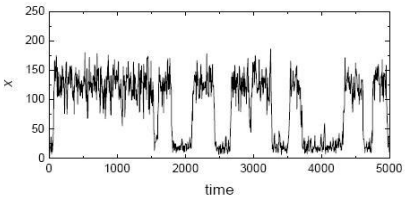
Full-scale model of glycolysis in Saccharomyces cerevisiae,
F. Hynne et al., 2001, Biophysical Chemistry (94), 121-163.

Mathematical frameworks used in systems biology

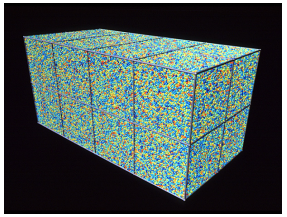
Ordinary differential equations



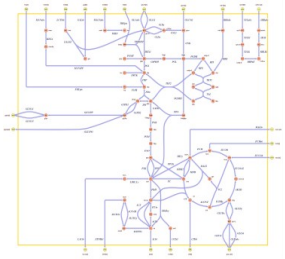
Partial differential equations



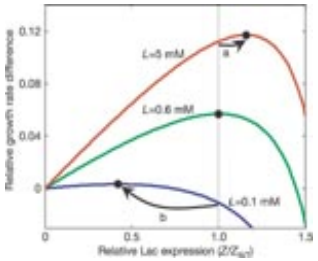
Stochastic processes



Particle-based models



Constraint-based models



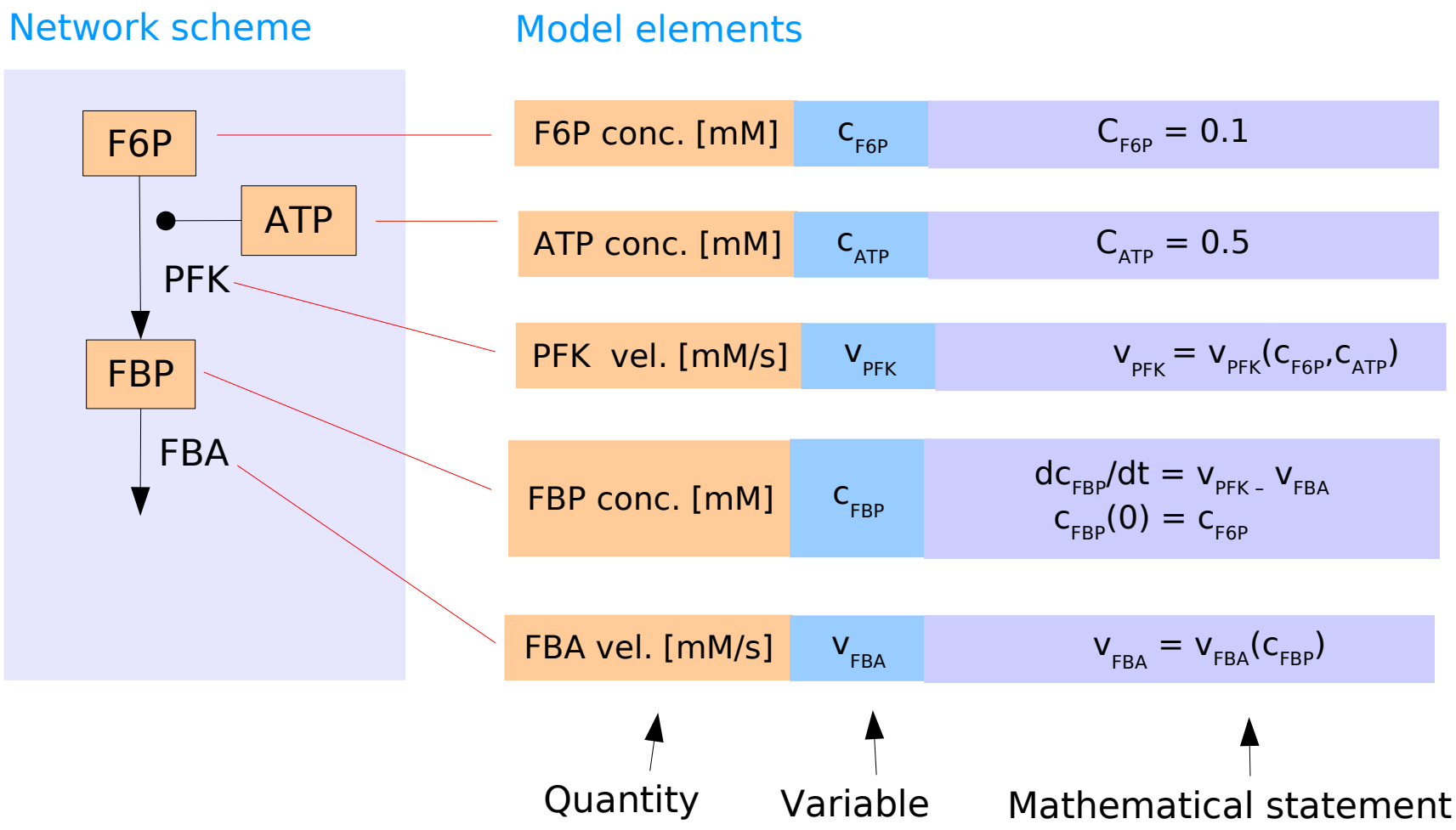
Optimality-based models

A common feature: the **semantics**

- List of mathematical objects
- Mapping to biochemical objects / quantities
- List of mathematical statements

Statements can be seen as **facts**
or **rules for computation**

Kinetic models with formal semantics



SBML/MIRIAM annotations

Species called “ATP” represents KEGG C06262 (ATP)

```
<species metaid=".." id="ATP" name="ATP concentration" compartment="cytosol">
 <annotation>
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
           xmlns:bqbiol=”http://biomodels.net/biology-qualifiers/"
           xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
   <rdf:Description rdf:about="#metaid_0000076">
    <bqbiol:is>
     <rdf:Bag>
      <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A15422"/>
      <rdf:li rdf:resource="urn:miriam:kegg.compound:C00002"/>
     </rdf:Bag>
    </bqbiol:is>
   </rdf:Description>
  </rdf:RDF>
 </annotation>
...
</species>
```

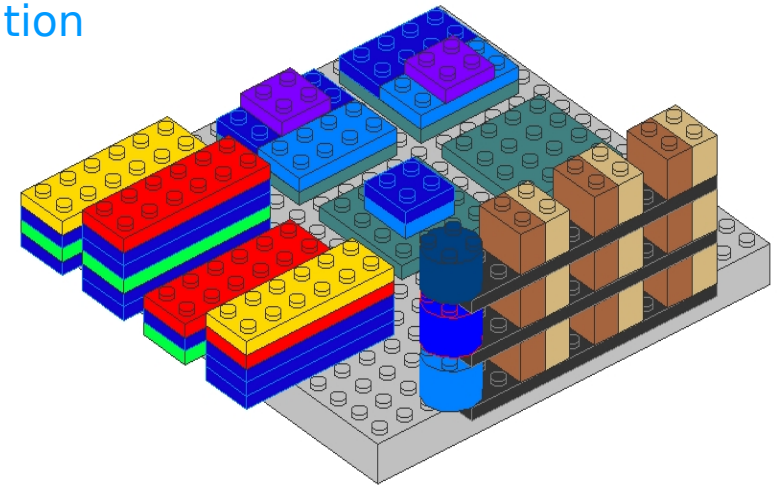
Species Qualifier Database Identifier

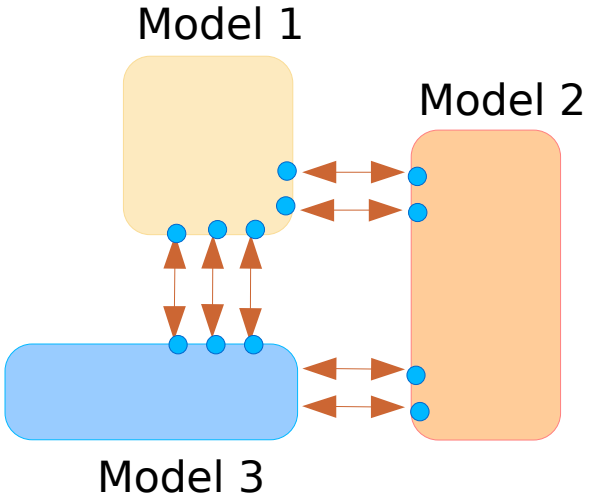
"A simple scheme for annotating SBML with references to controlled vocabularies and database entries"
Le Novere and Finney, 2005

II. Merging of biochemical models

Playing LEGO with biochemical models ?

Model composition





Playing LEGO with biochemical models ?

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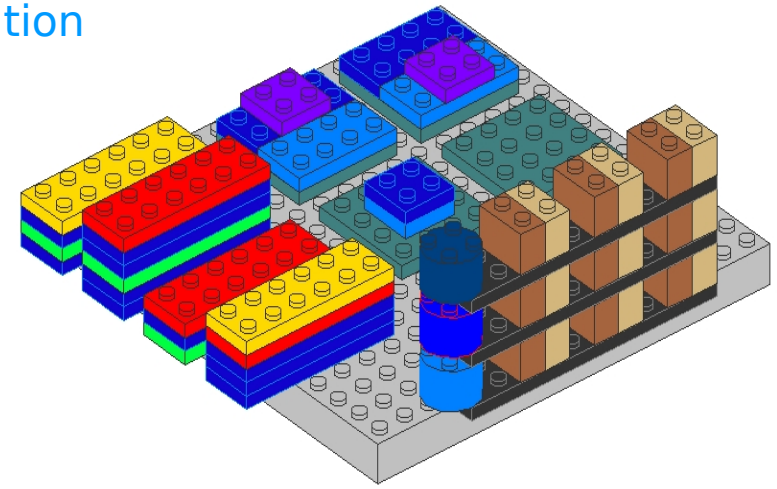
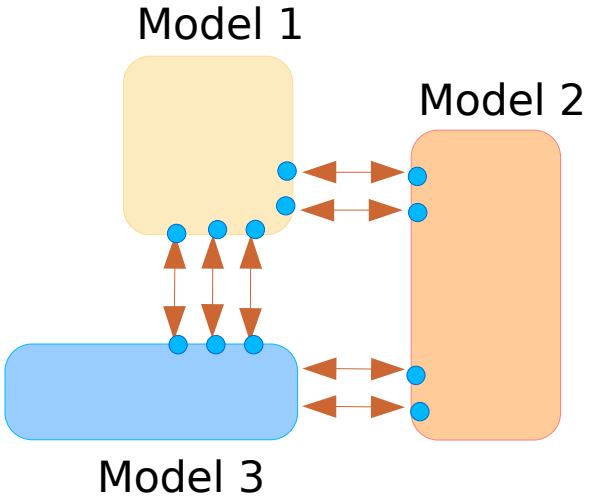
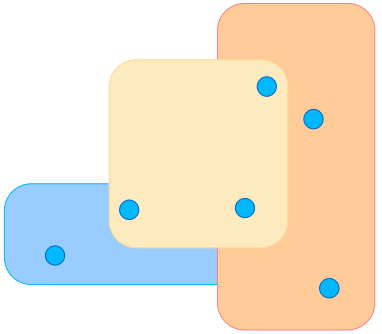
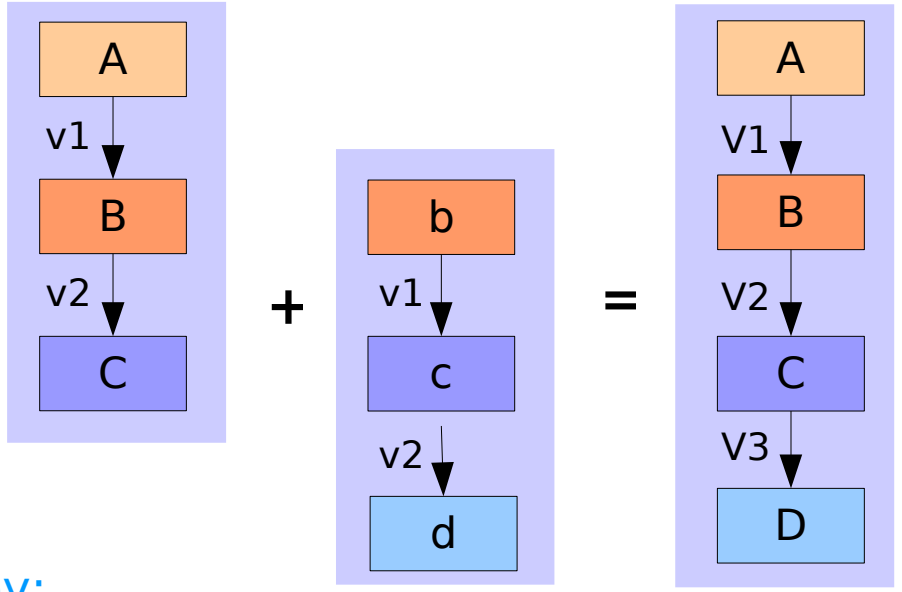




Model merging



Merging of graphical models



Elements are characterised by:

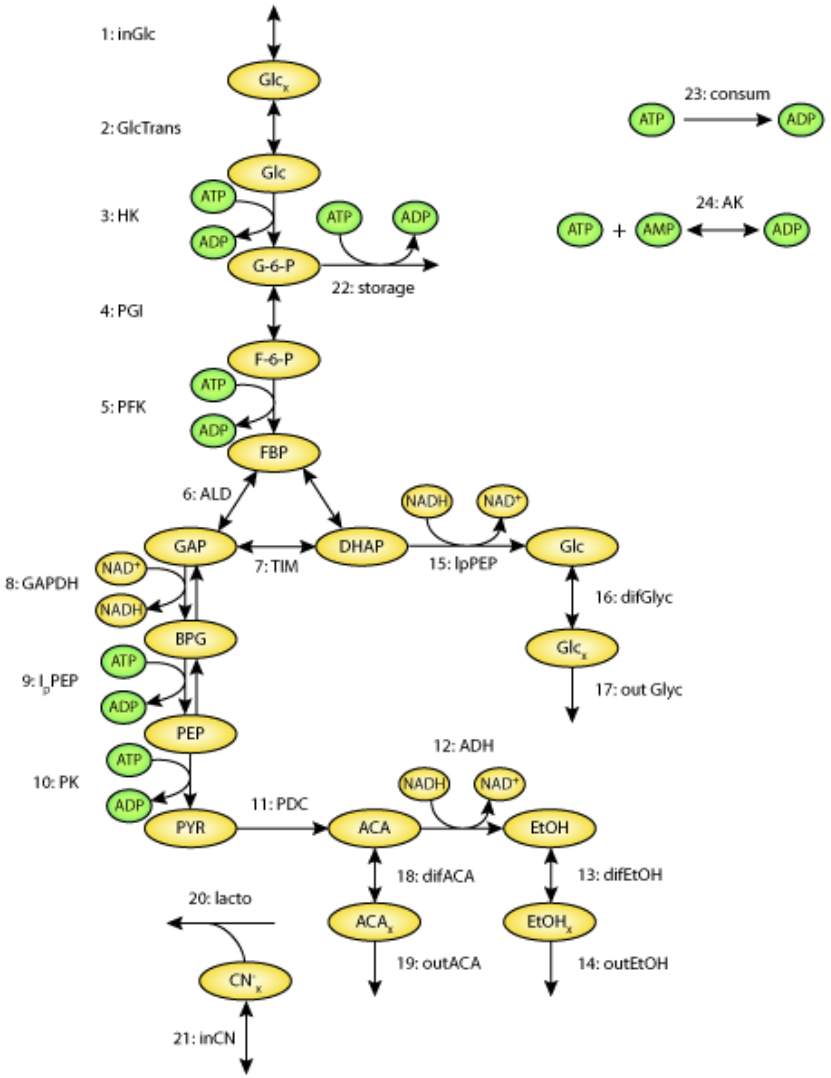
Name: "*How is the element called?*"
(need not be compatible between models)

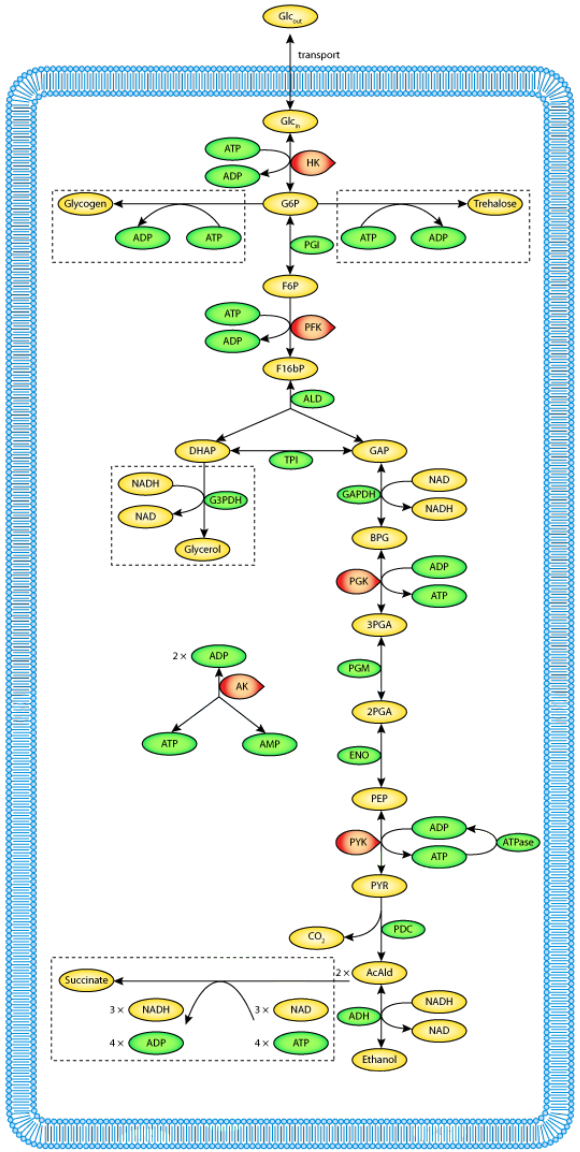
Semantics ("annotation"): "*What does the element represent?*"
(used for matching the elements between models)

Statements: "*What is stated about the element?*"
(can lead to conflicts between models / have to be chosen)

Additional information
(e.g., icon, position in graphics etc)

Matching elements between models





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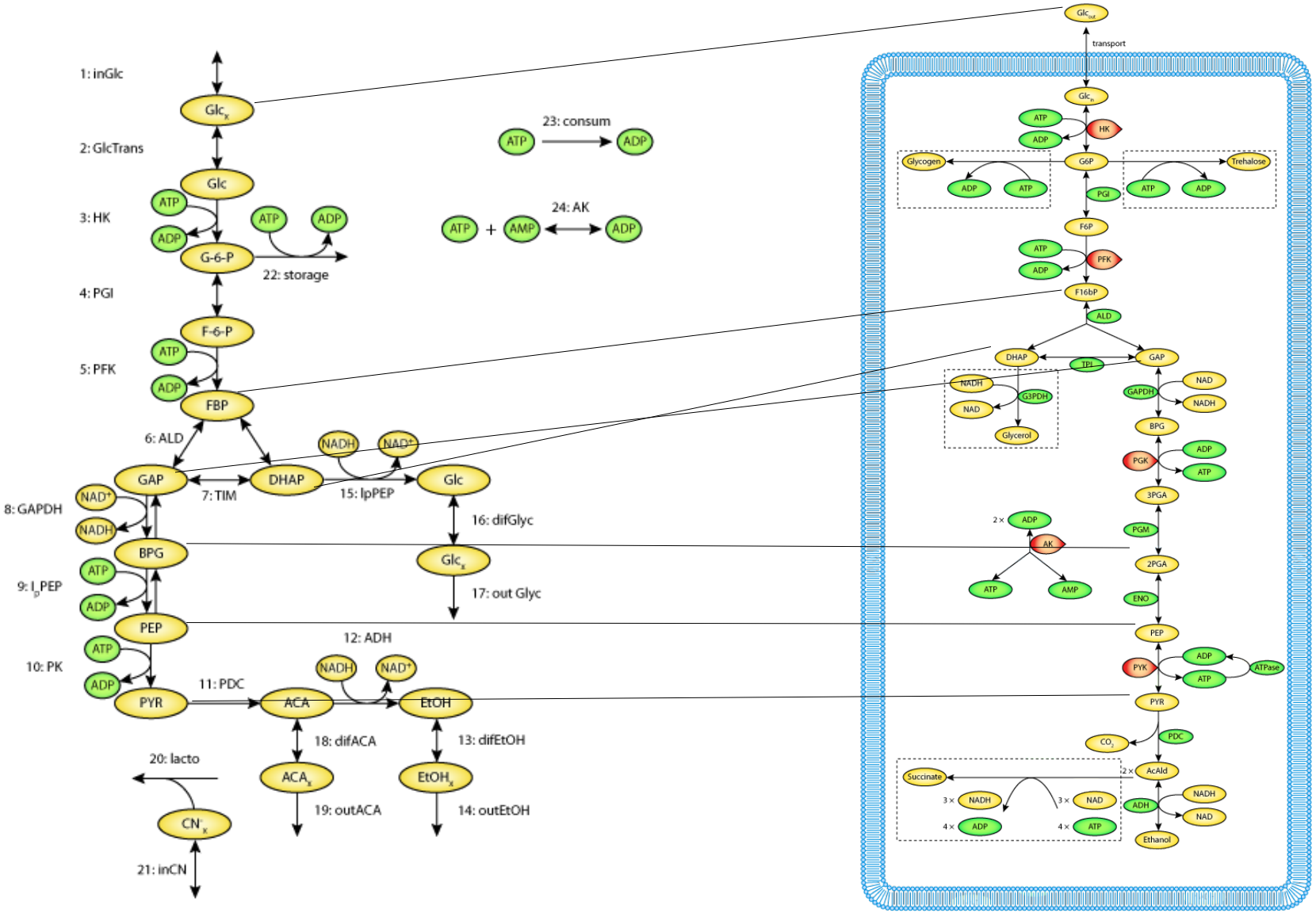
Matching elements between models



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Semantic relations between quantities

1. Independent: nothing in common, no constraints, no conflict

Model 1

ATP concentration

Model 2

ADP concentration

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ATP concentration ⟷ **ATP** concentration

Semantic relations between quantities

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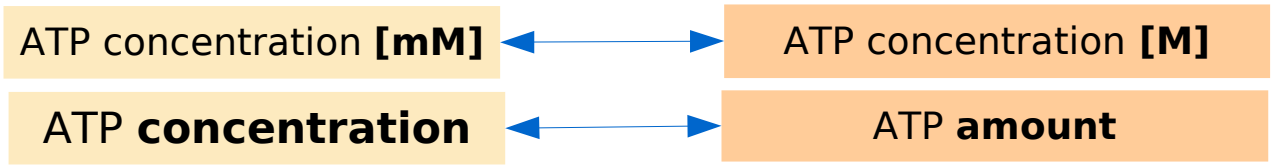
3. Interconvertible: need to be converted in advance (afterwards, see “identical”)



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ATP concentration

Model 2

ADP concentration

2. Identical: *statement conflict possible;* choose between statements

ATP concentration ⟷ **ATP** concentration

3. Interconvertible: need to be converted in advance (afterwards, see “identical”)

ATP concentration **[mM]** ⟷ ATP concentration **[M]**

ATP **concentration** ⟷ ATP **amount**

4. Semantic overlap: *uncontrollable conflicts;*
models cannot be merged automatically

lumped reaction ⟷ **individual** reaction steps

ribosome concentration ⟷ **total RNA** concentration

A merging algorithm for semantic models with explicit equations

1. Convert all quantities to standard units

A merging algorithm for semantic models with explicit equations

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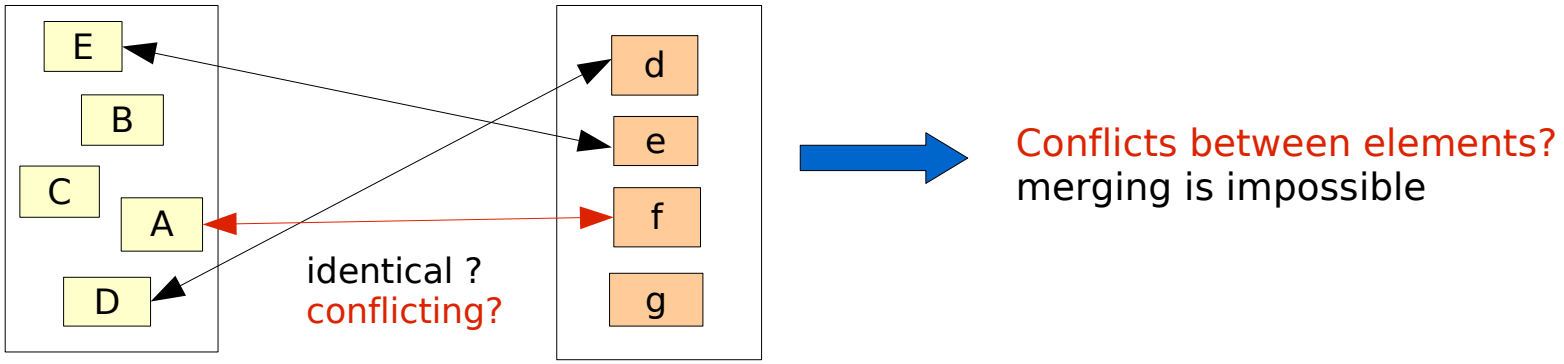
2. Match redundant / conflicting elements



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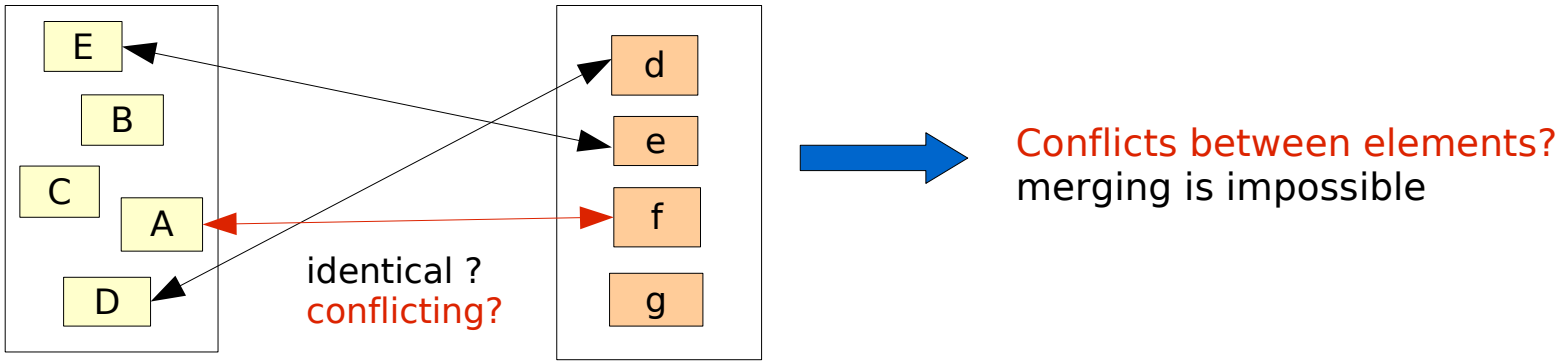
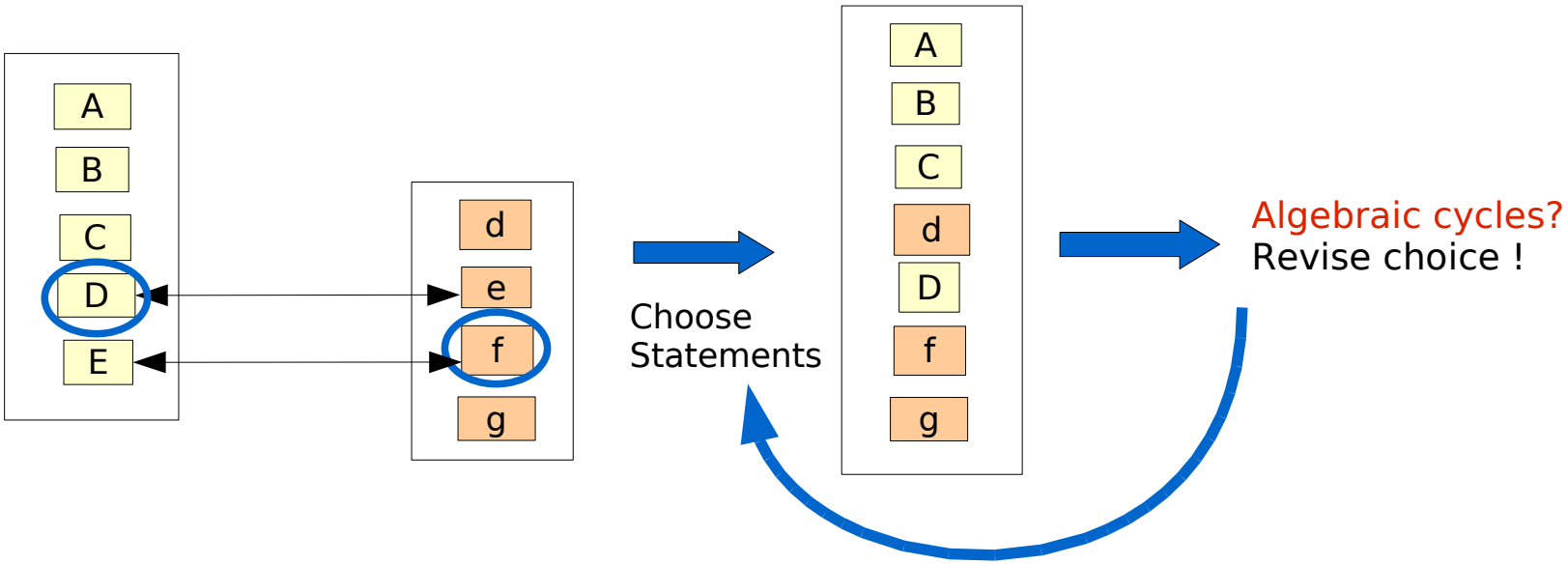


3. Choose between statements



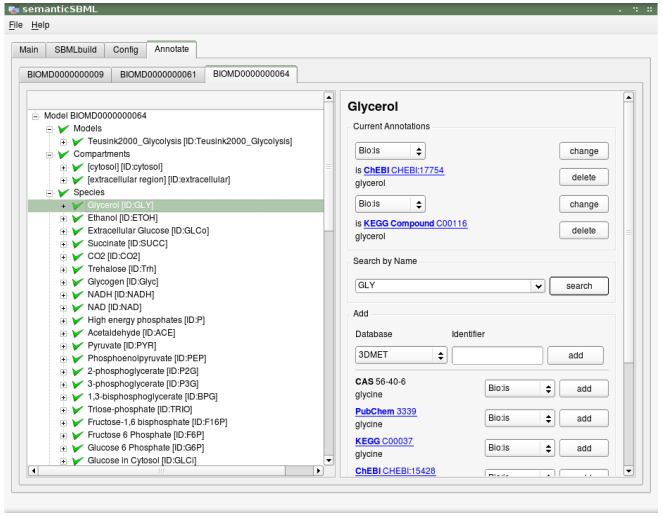
Validity criteria for systems biology models

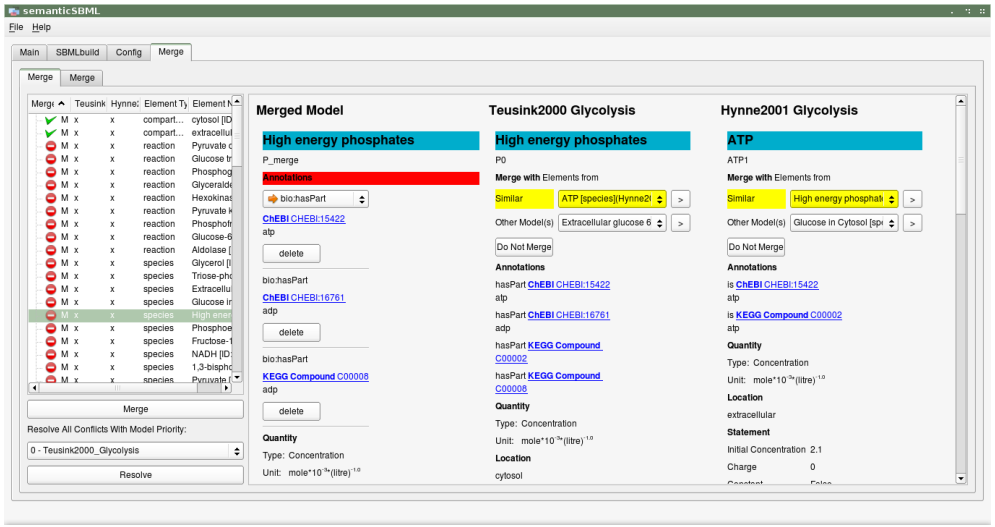
Aspects of validity	Example validity criteria
1. Syntax Model can be read and processed	• correct file format ...
2. Computation Model can be used for predictive simulations	• statements unique + complete • sequential evaluation possible ...
3. Semantic correctness Model statements agree with the model semantics	• valid statements • no semantic dependencies ...
4. Empirical correctness Model agrees with physical and biochemical facts	• realistic numerical values • correct thermodynamics • correct reaction balances, ...
5. Context Model performs well and suits its purpose	• agreement with data • plausible assumptions • no irrelevant parts, ...

Liebermeister W. (2008), Validity and combination of biochemical models, To appear in "Proceedings of 3rd International ESCEC Workshop on Experimental Standard Conditions on Enzyme Characterizations".

III. Model annotation and merging with semanticSBML

SemanticSBML: an interactive tool for model annotation and merging





Functions in semanticSBML

- Annotate
- Check
- Merge
- Build
- Display

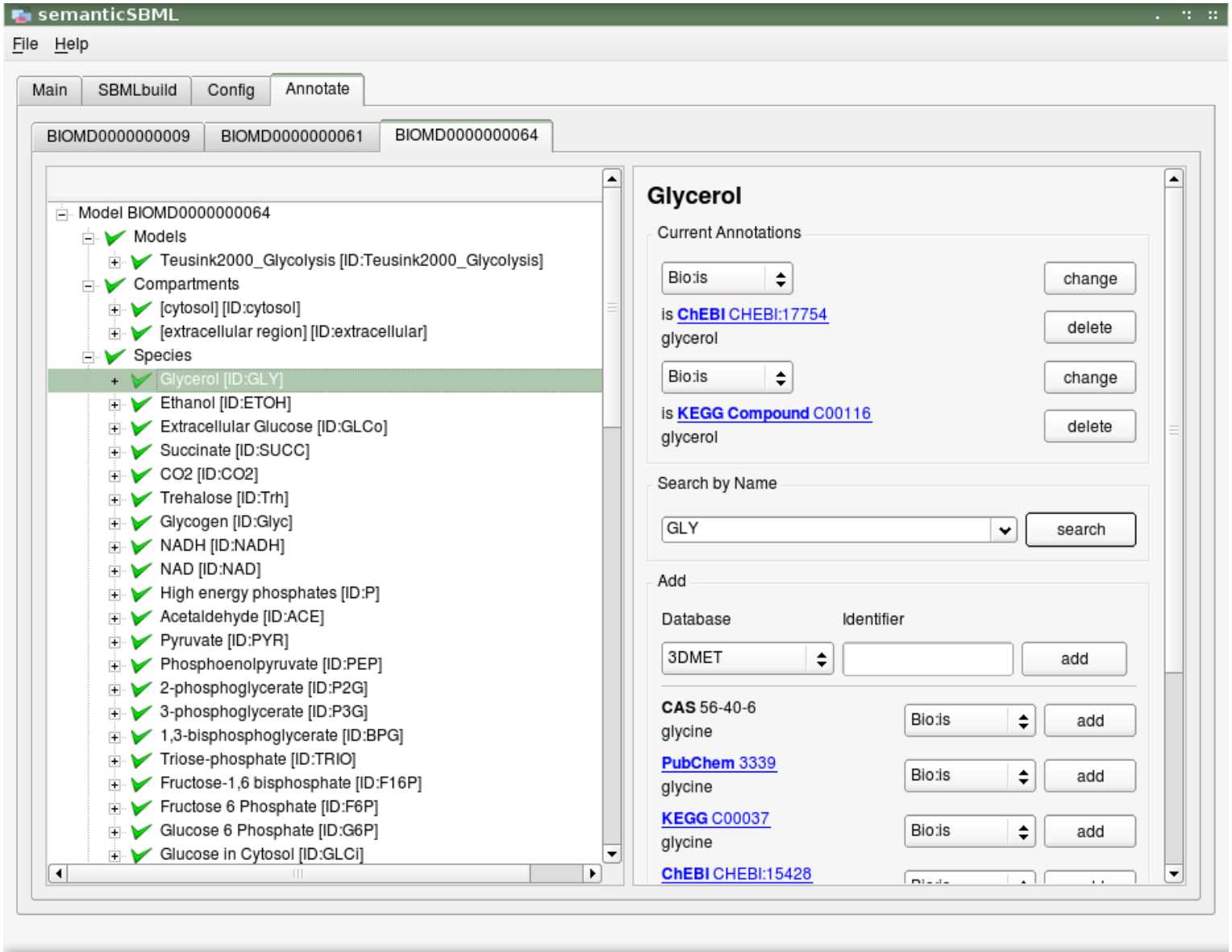
Versions of semanticSBML

- Stand-alone version with GUI
- Web version (merging still under development)
- API (programming interface)

http://semanticSBML.sf.net

http://www.semanticsbml.org

Annotation GUI



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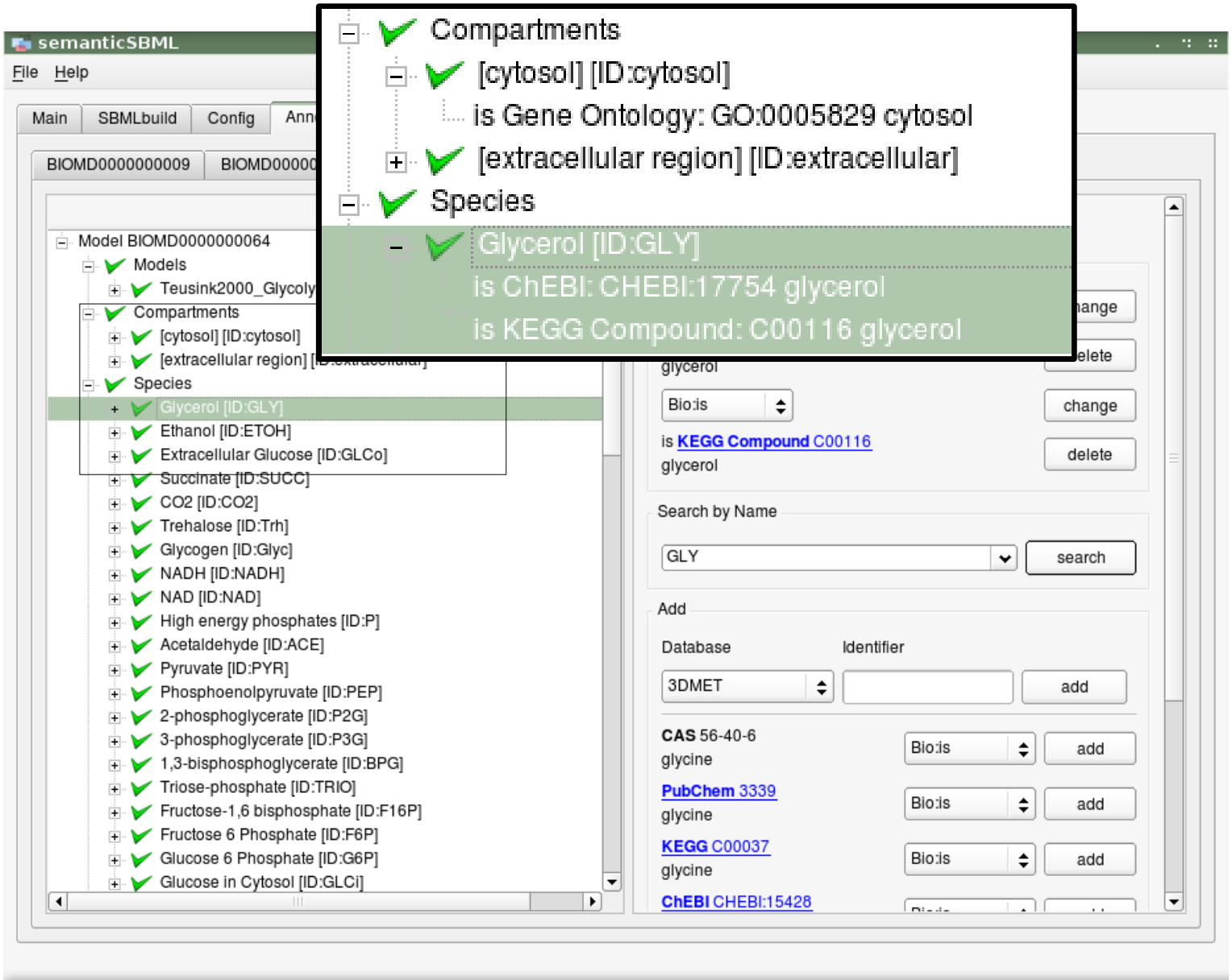

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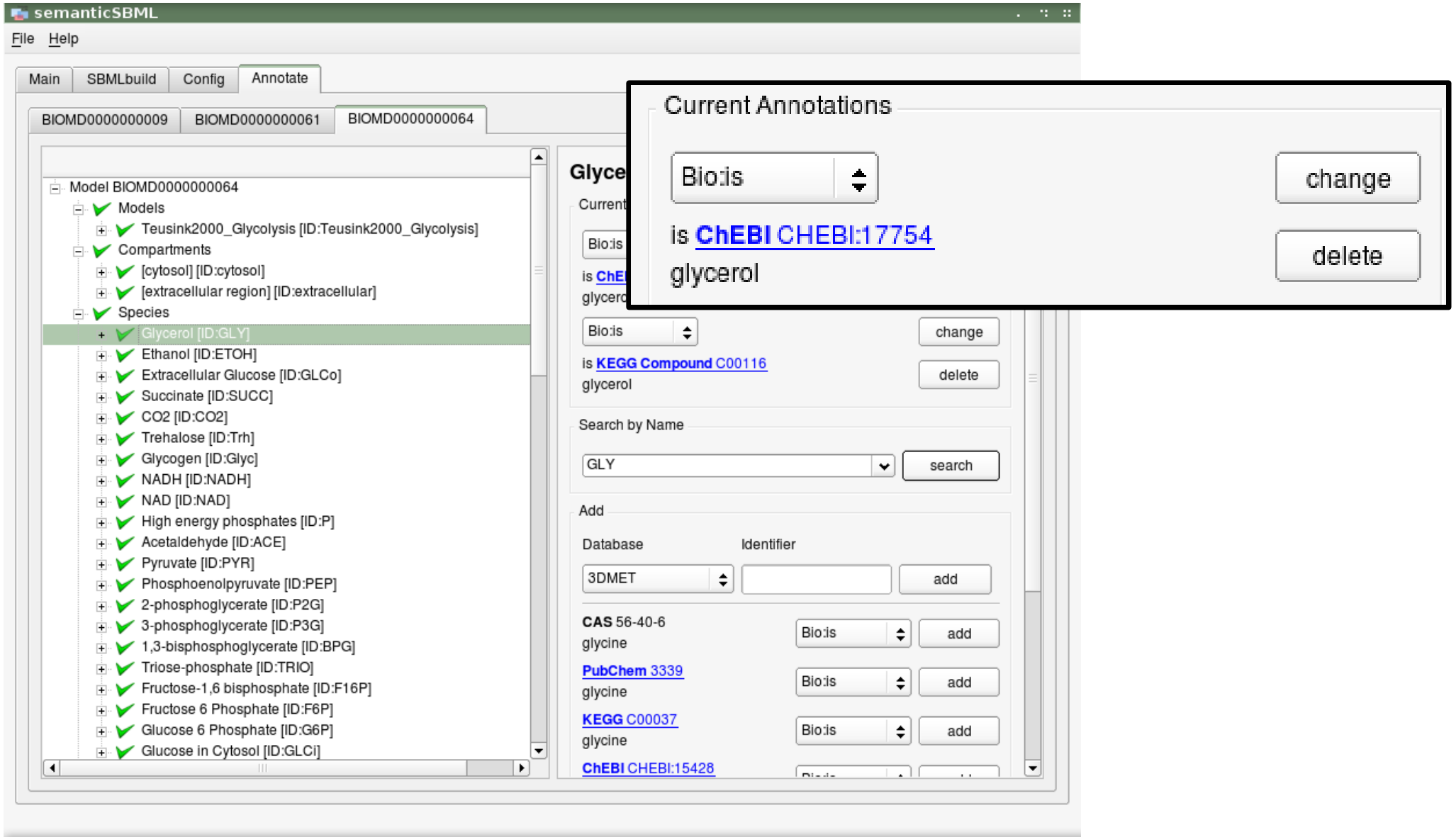

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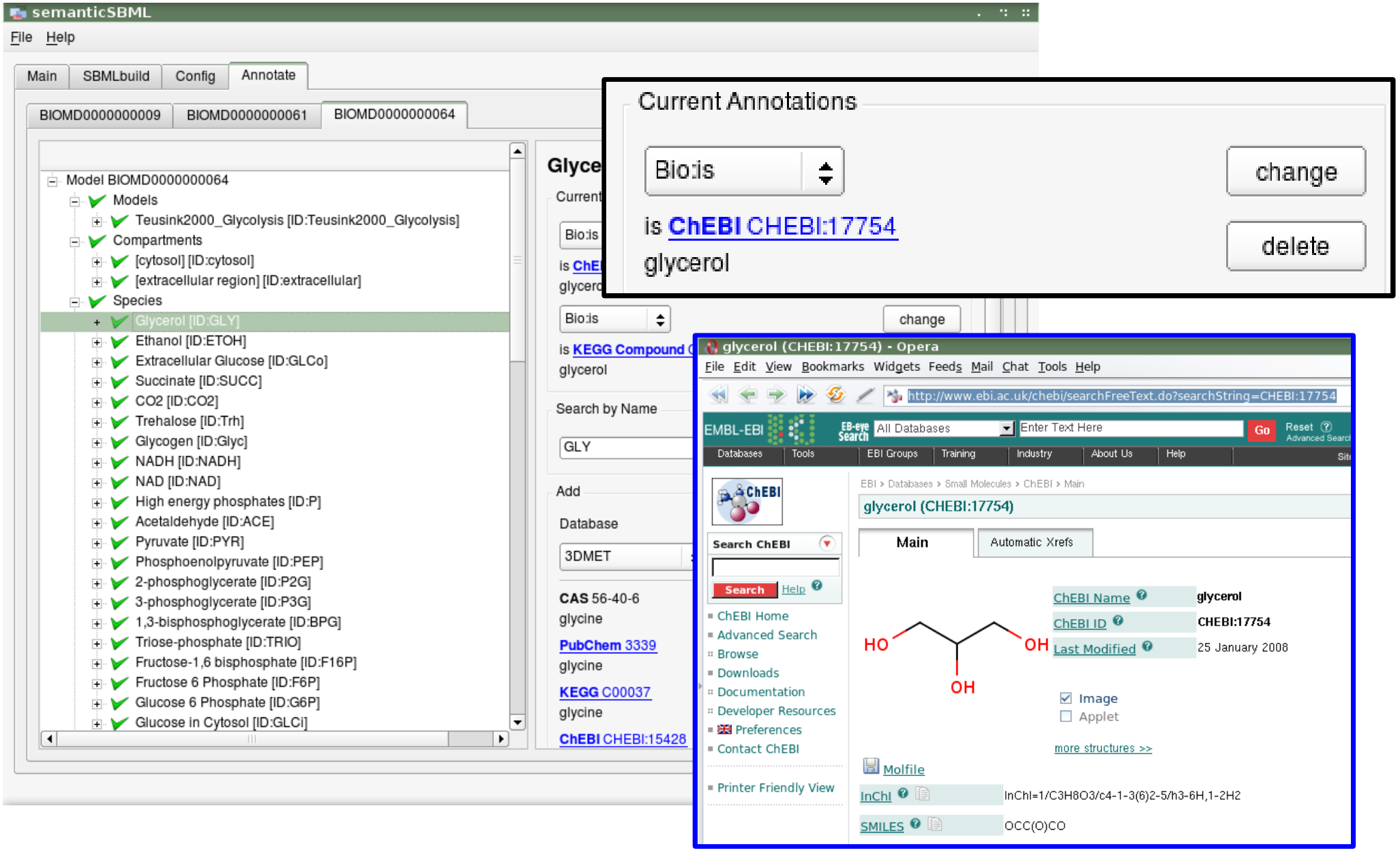

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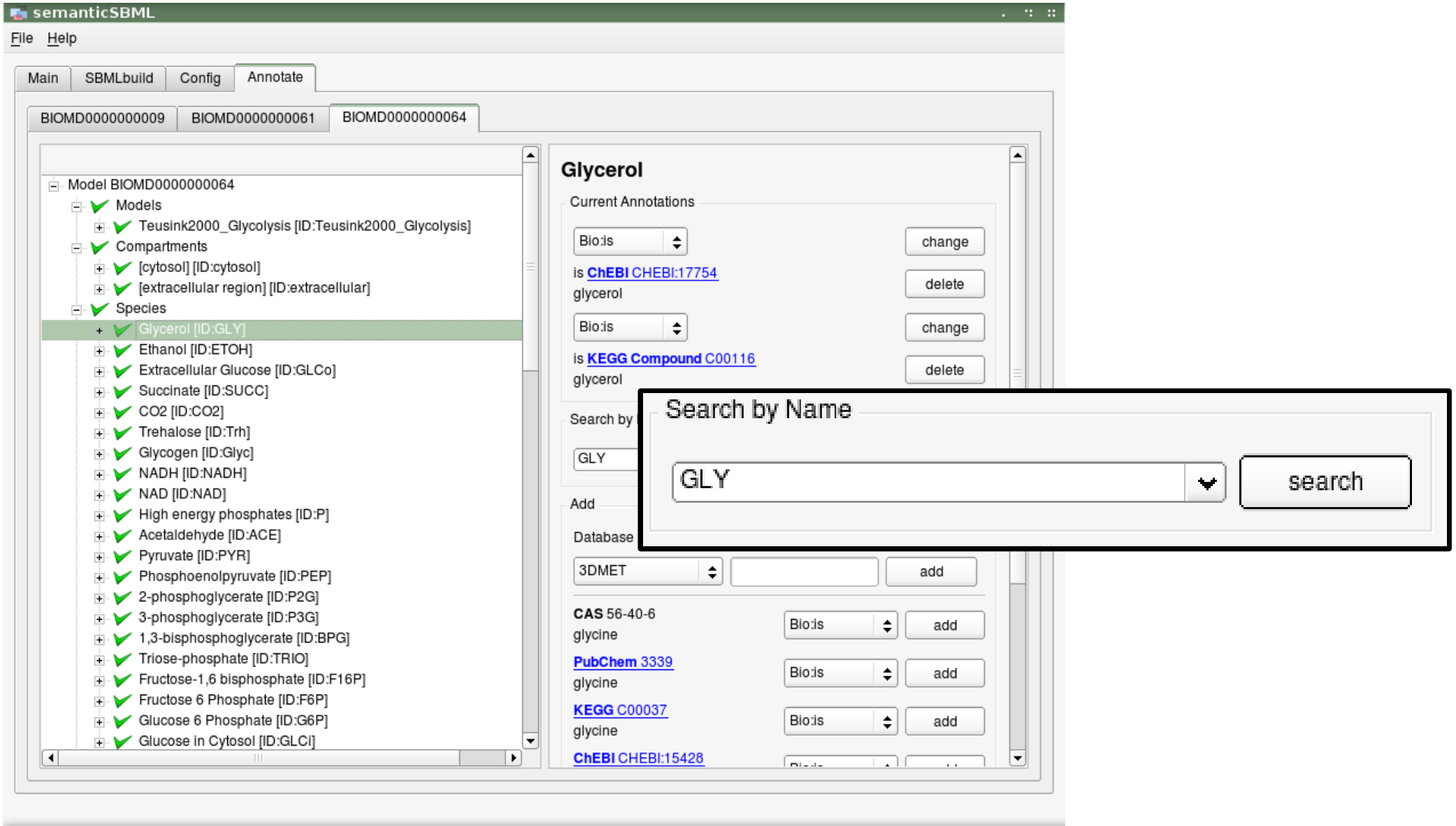

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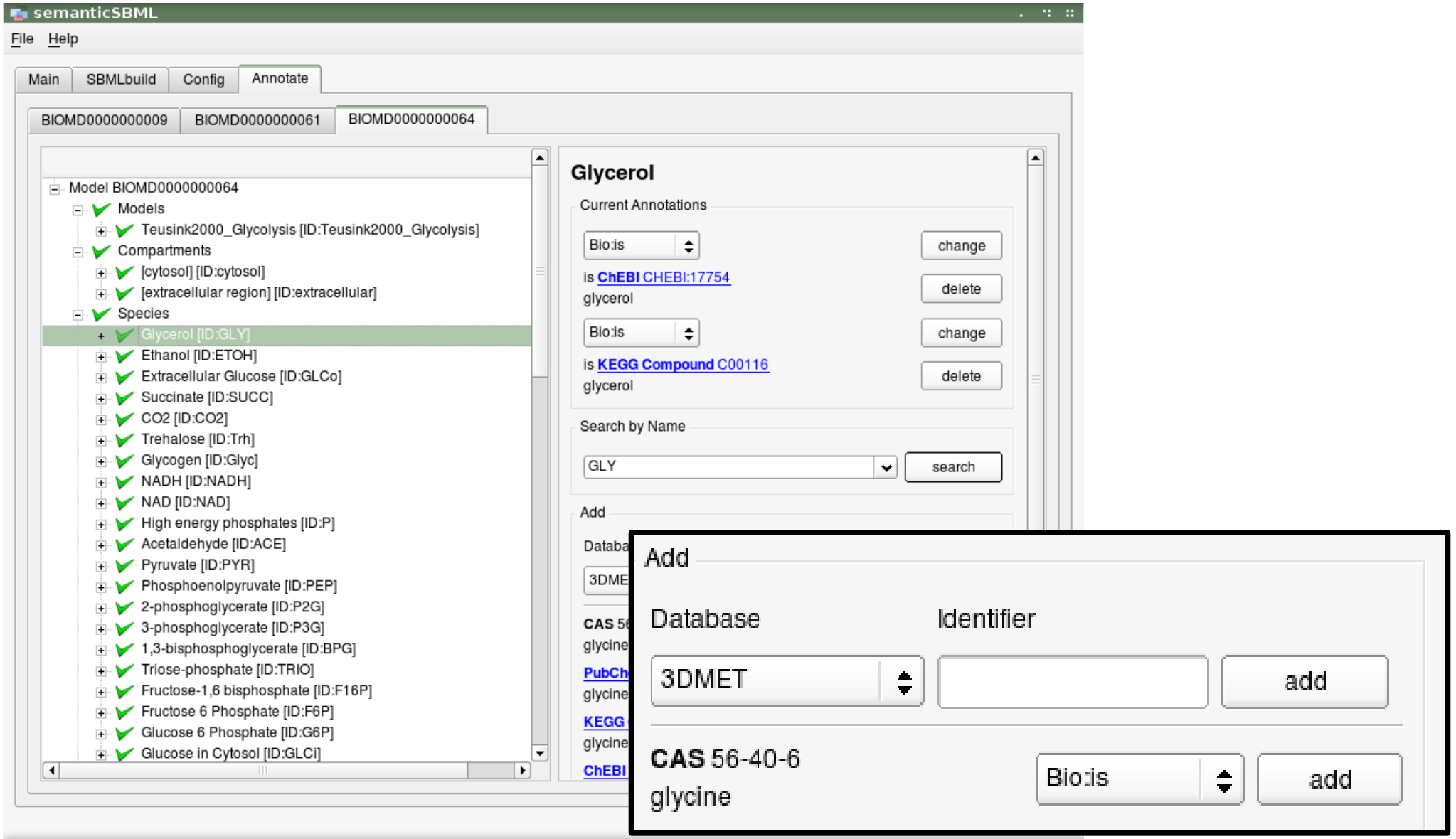

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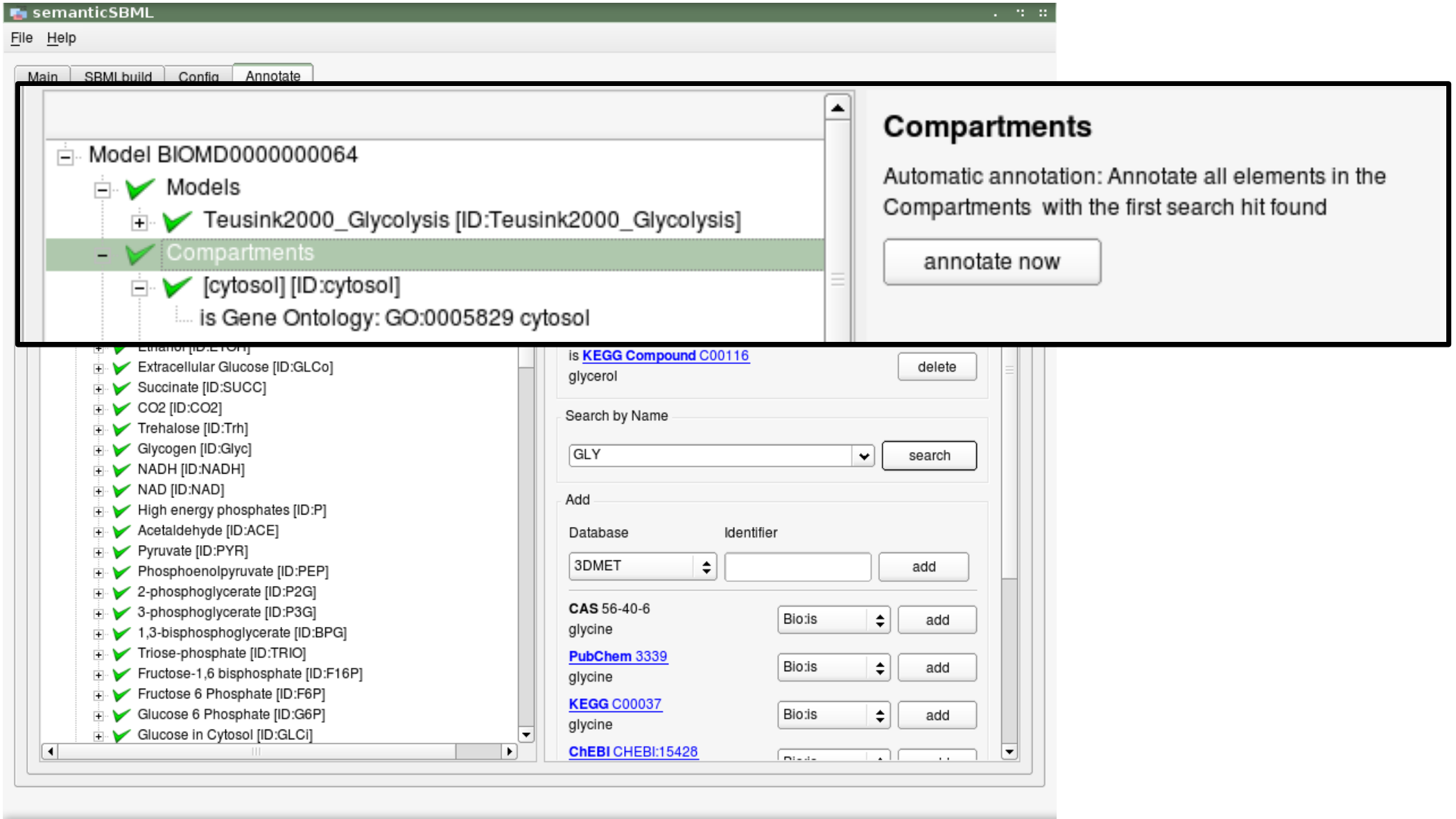
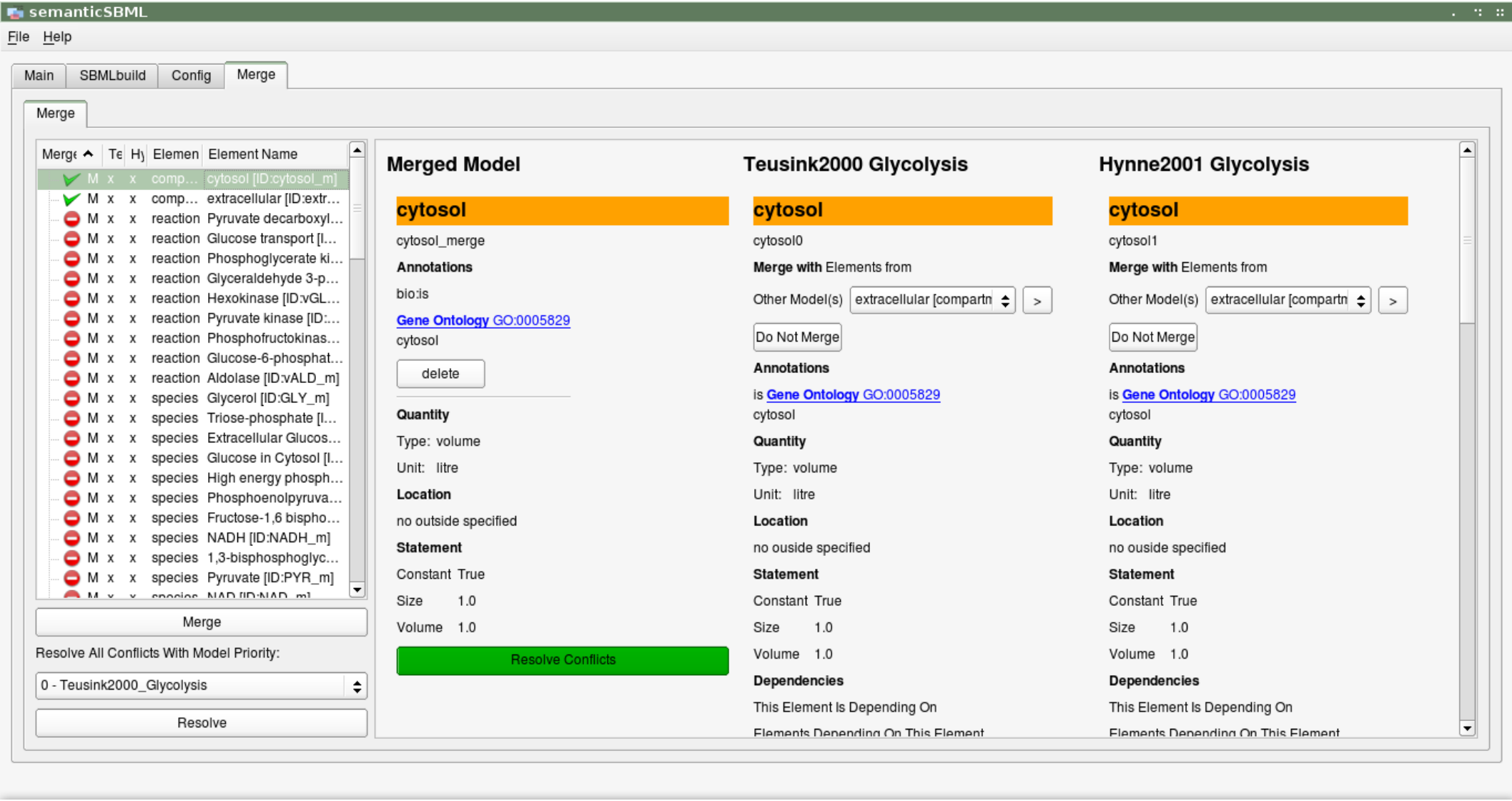


Merge GUI


semanticSBML
File Help
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M x x comp... extracellular [ID:extr...
M x x reaction Pyruvate decarboxyl...
M x x reaction Glucose transport [I...
M x x reaction Phosphoglycerate ki...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Hexokinase [ID:vGL...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Glucose-6-phosphat...
M x x reaction Aldolase [ID:vALD_m]
M x x species Glycerol [ID:GLY_m]
M x x species Triose-phosphate [I...
M x x species Extracellular Glucos...
M x x species Glucose in Cytosol [I...
M x x species High energy phosph...
M x x species Phosphoenolpyruva...
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M x x species NADH [ID:NADH_m]
M x x species 1,3-bisphosphoglyc...
M x x species Pyruvate [ID:PYR_m]
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve
Merged Model
cytosol
cytosol_merge
Annotations
bio:is
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cytosol
delete
Quantity
Type: volume
Unit: litre
Location
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Statement
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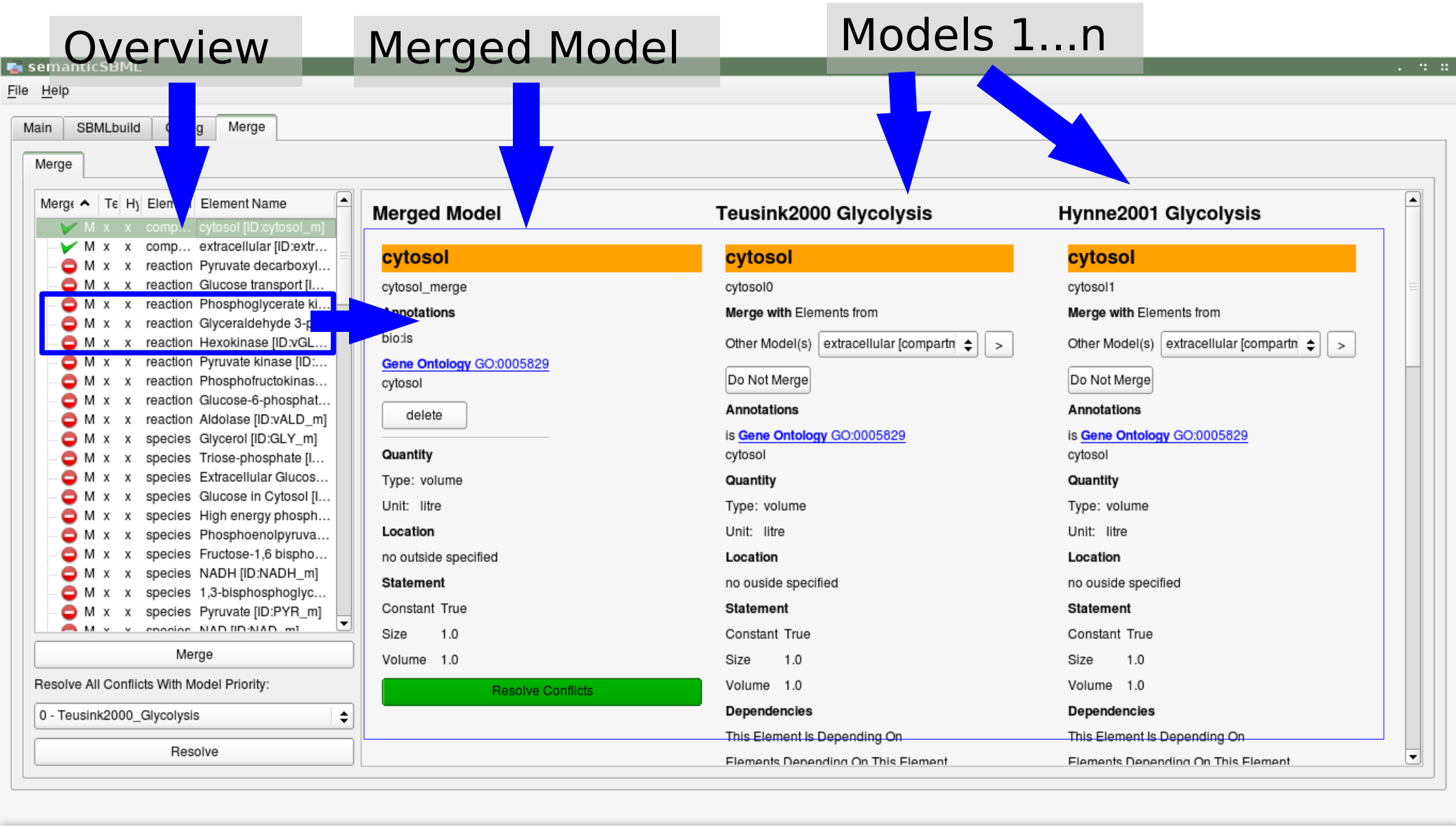
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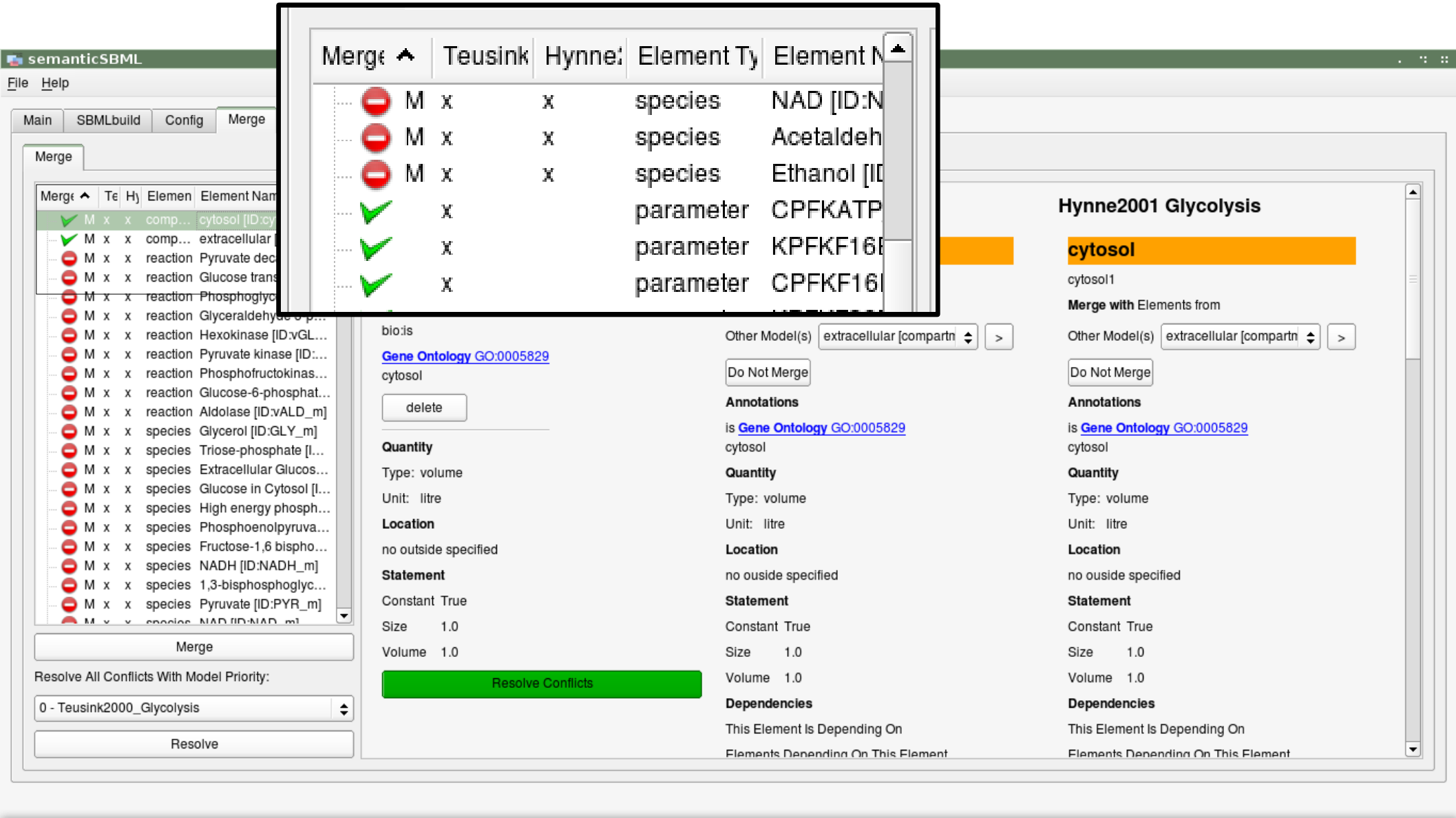
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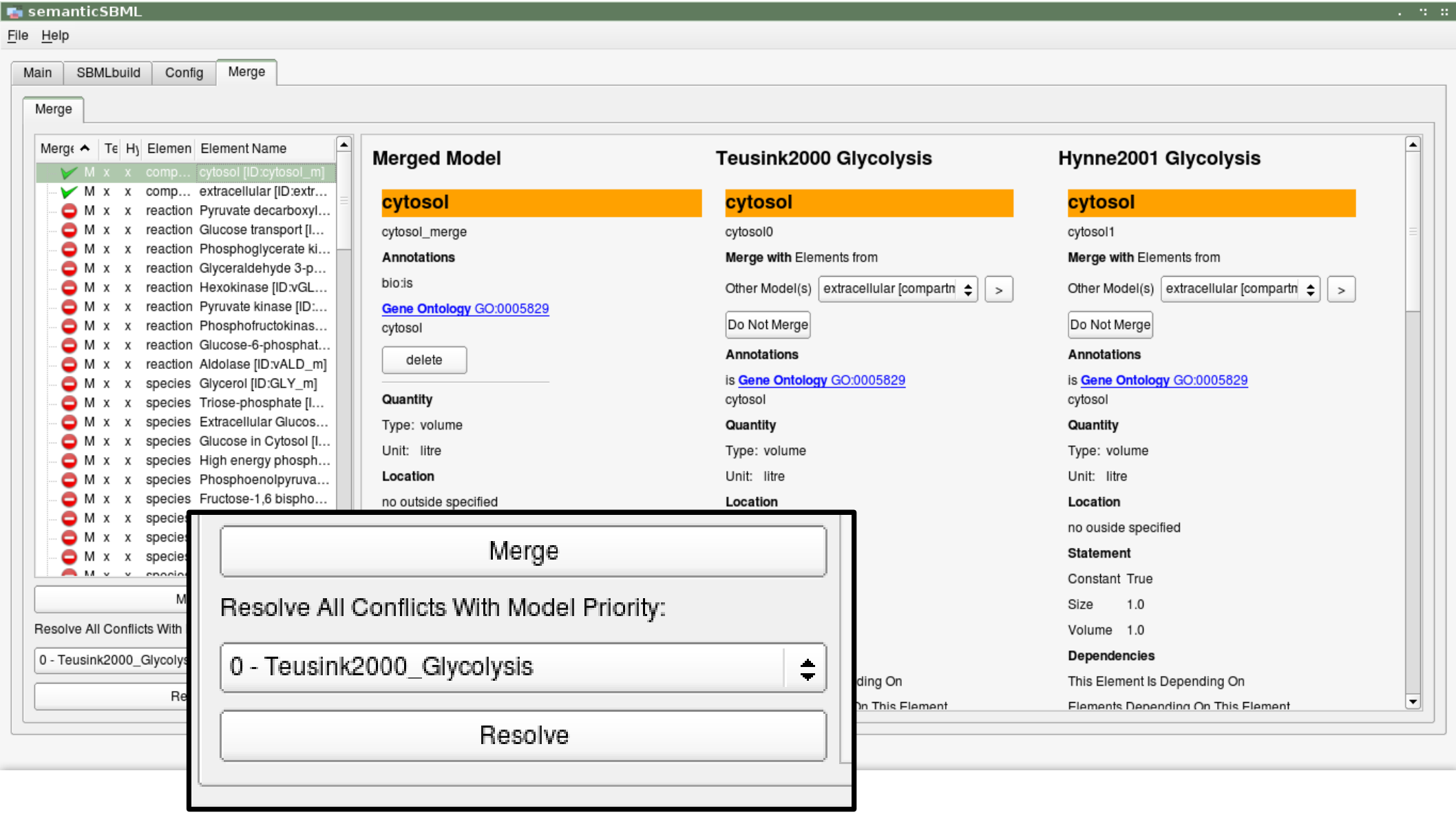
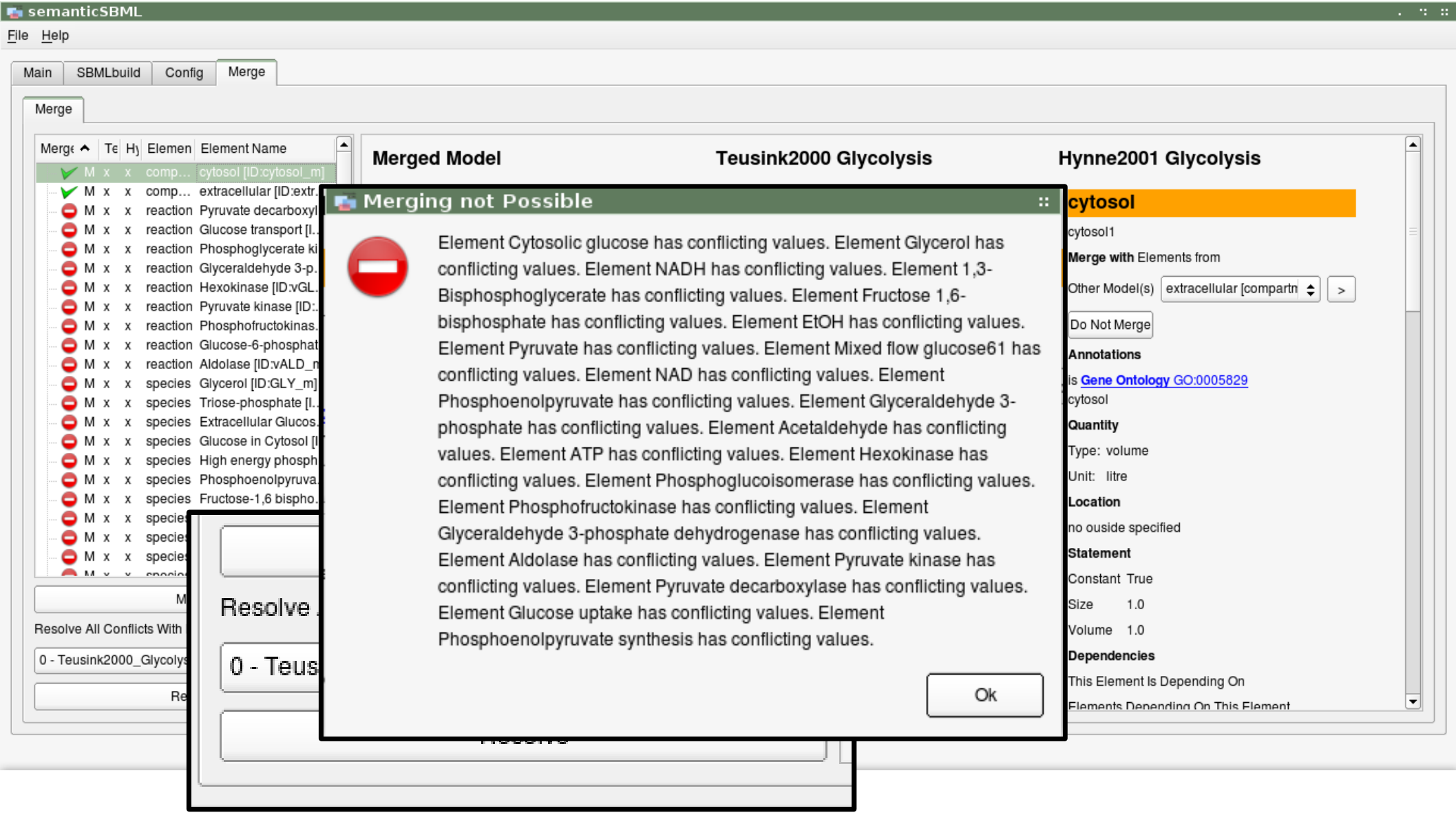
0 - Teusink2000_Glycolysis
Resolve
Merge Teusink Hynne: Element Ty Element N
M x x species NAD [ID:N
M x x species Acetaldeh
M x x species Ethanol [ID
x parameter CPFKATP
x parameter KPFKF16
x parameter CPFKF16
bio:is
Gene Ontology GO:0005829
cytosol
delete
Quantity
Type: volume
Unit: litre
Location
no outside specified
Statement
Constant True
Size 1.0
Volume 1.0
Resolve Conflicts
Other Model(s) extracellular [compartn >
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element
Hynne2001 Glycolysis
cytosol
cytosol1
Merge with Elements from
Other Model(s) extracellular [compartn >
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element

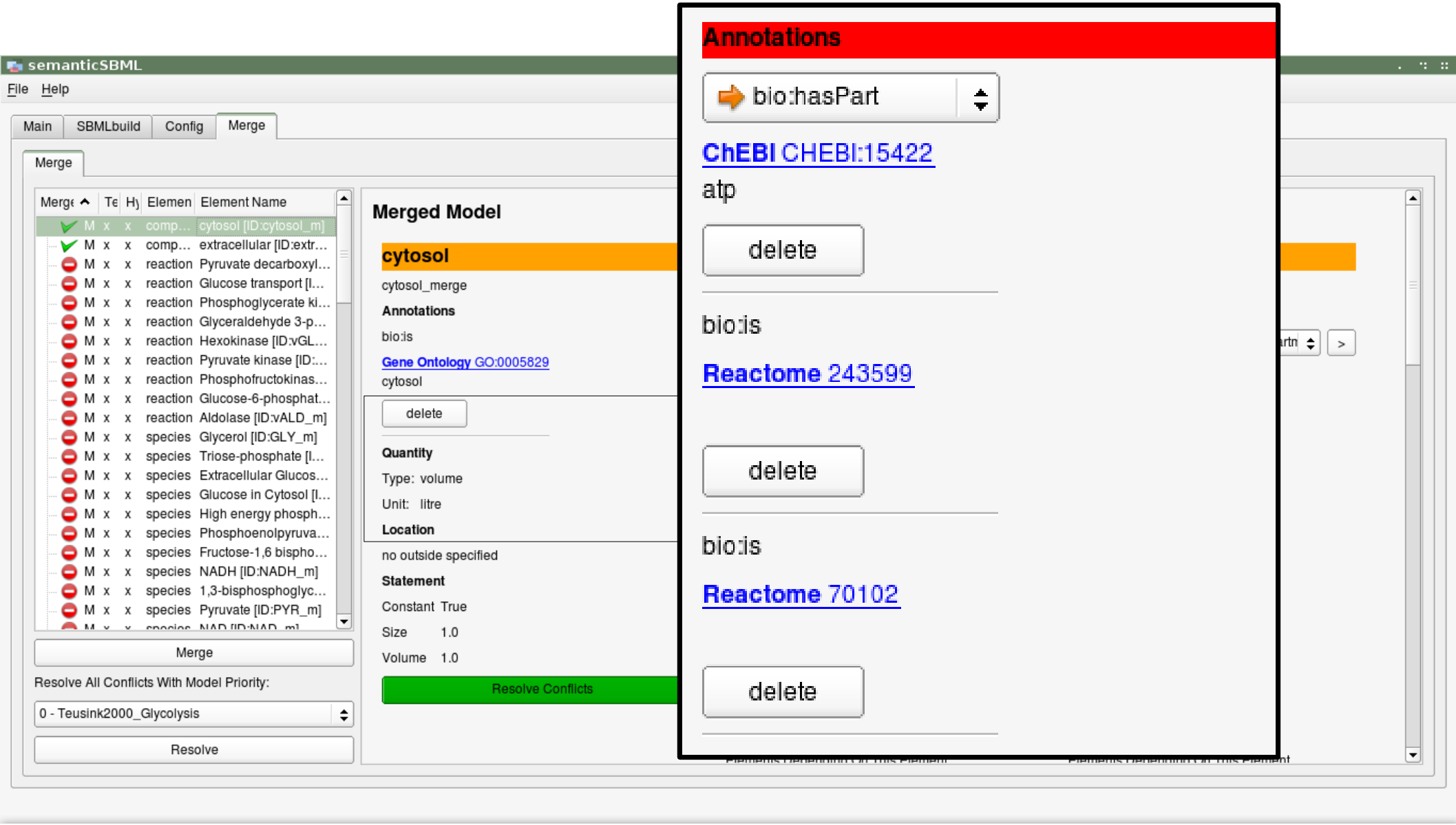
Merge GUI


semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
M x x comp... cytosol [ID:cytosol_m]
M x x comp... extracellular [ID:extr...
M x x reaction Pyruvate decarboxyl...
M x x reaction Glucose transport [I...
M x x reaction Phosphoglycerate ki...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Hexokinase [ID:vGL...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Glucose-6-phosphat...
M x x reaction Aldolase [ID:vALD_m]
M x x species Glycerol [ID:GLY_m]
M x x species Triose-phosphate [I...
M x x species Extracellular Glucos...
M x x species Glucose in Cytosol [I...
M x x species High energy phosph...
M x x species Phosphoenolpyruva...
M x x species Fructose-1,6 bispho...
Resolve All Conflicts With
0 - Teusink2000_Glycolys
Merged Model
cytosol
cytosol_merge
Annotations
bio:is
Gene Ontology GO:0005829
cytosol
delete
Quantity
Type: volume
Unit: litre
Location
no outside specified
Teusink2000 Glycolysis
cytosol
cytosol0
Merge with Elements from
Other Model(s) extracellular [compartn
>
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
Hynne2001 Glycolysis
cytosol
cytosol1
Merge with Elements from
Other Model(s) extracellular [compartn
>
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve

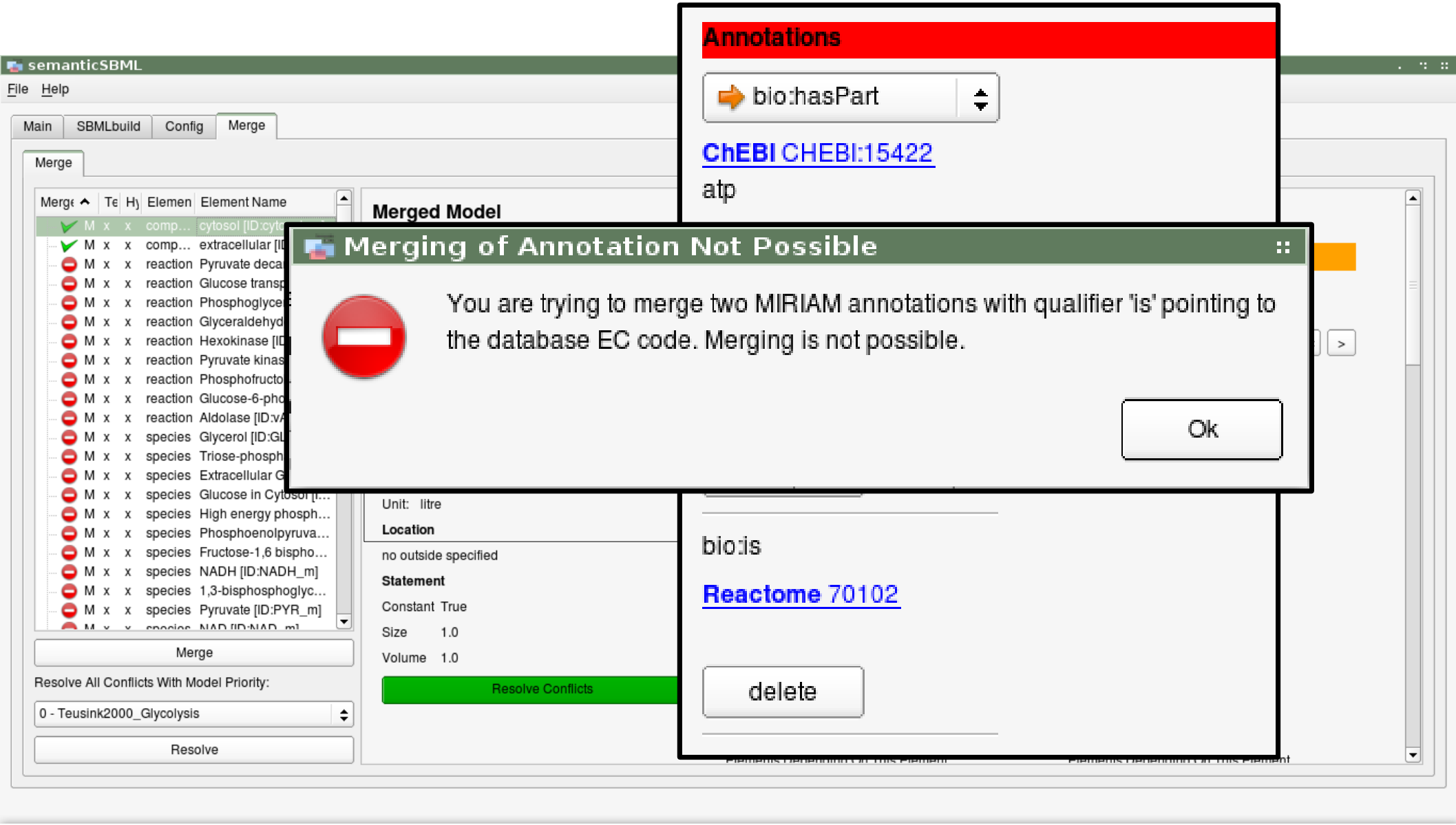
Merge GUI


semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
M x x comp... cytosol [ID:cytosol_m]
M x x comp... extracellular [ID:extr...
M x x reaction Pyruvate decarboxyl...
M x x reaction Glucose transport [I...
M x x reaction Phosphoglycerate ki...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Hexokinase [ID:vGL...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Glucose-6-phosphat...
M x x reaction Aldolase [ID:vALD_m...
M x x species Glycerol [ID:GLY_m]
M x x species Triose-phosphate [I...
M x x species Extracellular Glucos...
M x x species Glucose in Cytosol [I...
M x x species High energy phosph...
M x x species Phosphoenolpyruva...
M x x species Fructose-1,6 bispho...
Resolve All Conflicts With
0 - Teusink2000_Glycolys
Merged Model
Teusink2000 Glycolysis
Hynne2001 Glycolysis
Merging not Possible
Element Cytosolic glucose has conflicting values. Element Glycerol has conflicting values. Element NADH has conflicting values. Element 1,3-Bisphosphoglycerate has conflicting values. Element Fructose 1,6-bisphosphate has conflicting values. Element EtOH has conflicting values. Element Pyruvate has conflicting values. Element Mixed flow glucose61 has conflicting values. Element NAD has conflicting values. Element Phosphoenolpyruvate has conflicting values. Element Glyceraldehyde 3-phosphate has conflicting values. Element Acetaldehyde has conflicting values. Element ATP has conflicting values. Element Hexokinase has conflicting values. Element Phosphoglucoisomerase has conflicting values. Element Phosphofructokinase has conflicting values. Element Glyceraldehyde 3-phosphate dehydrogenase has conflicting values. Element Aldolase has conflicting values. Element Pyruvate kinase has conflicting values. Element Pyruvate decarboxylase has conflicting values. Element Glucose uptake has conflicting values. Element Phosphoenolpyruvate synthesis has conflicting values.
Ok
cytosol
cytosol1
Merge with Elements from
Other Model(s) extracellular [compartn
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element

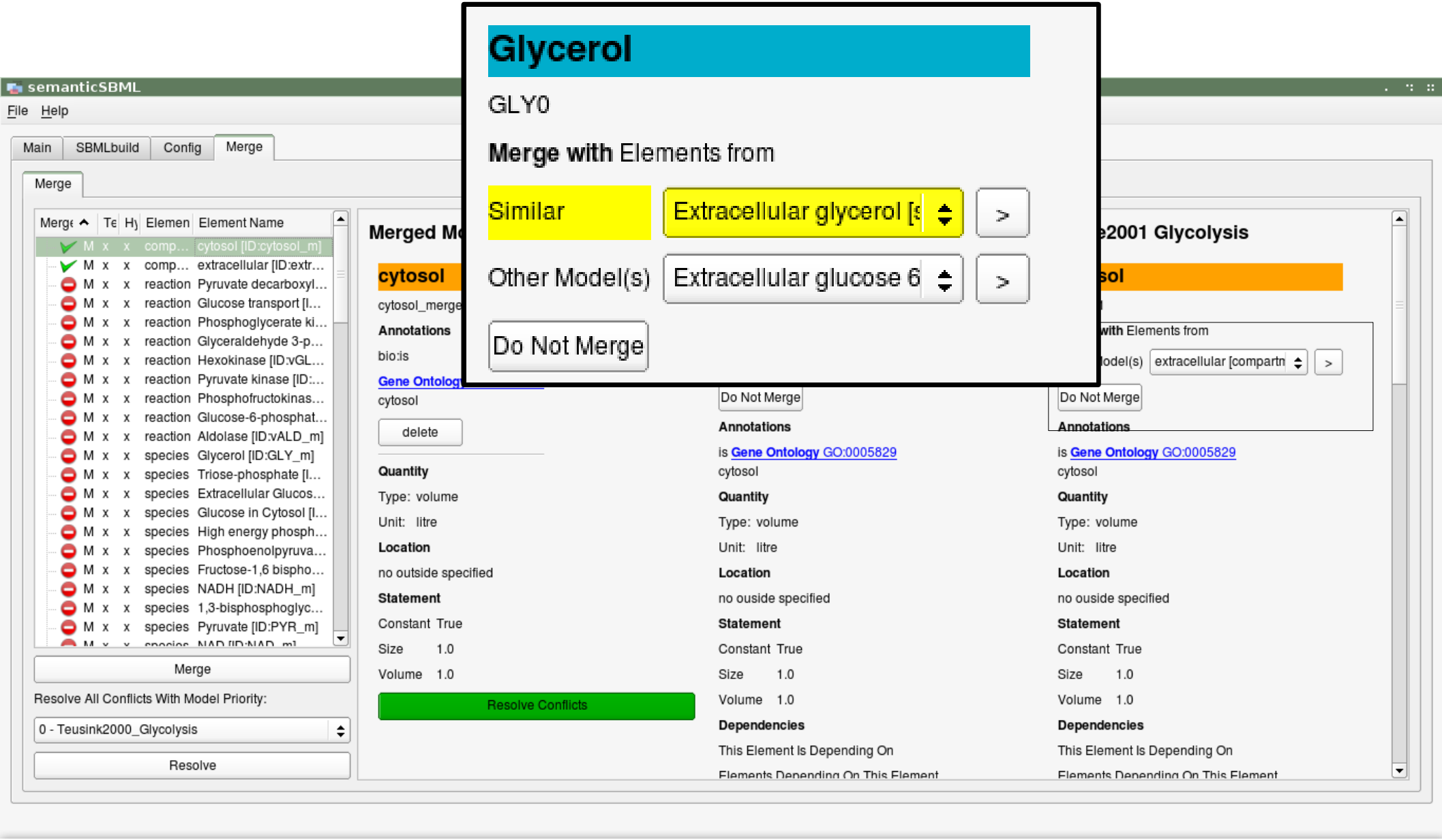
Merge GUI


semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
M x x comp... cytosol [ID:cytosol_m]
M x x comp... extracellular [ID:extr...
M x x reaction Pyruvate decarboxyl...
M x x reaction Glucose transport [I...
M x x reaction Phosphoglycerate ki...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Hexokinase [ID:vGL...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Glucose-6-phosphat...
M x x reaction Aldolase [ID:vALD_m]
M x x species Glycerol [ID:GLY_m]
M x x species Triose-phosphate [I...
M x x species Extracellular Glucos...
M x x species Glucose in Cytosol [I...
M x x species High energy phosph...
M x x species Phosphoenolpyruva...
M x x species Fructose-1,6 bispho...
M x x species NADH [ID:NADH_m]
M x x species 1,3-bisphosphoglyc...
M x x species Pyruvate [ID:PYR_m]
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve
Merged Model
cytosol
cytosol_merge
Annotations
bio:is
Gene Ontology GO:0005829
cytosol
delete
Quantity
Type: volume
Unit: litre
Location
no outside specified
Statement
Constant True
Size 1.0
Volume 1.0
Resolve Conflicts
Annotations
bio:hasPart
ChEBI CHEBI:15422
atp
delete
bio:is
Reactome 243599
delete
bio:is
Reactome 70102
delete

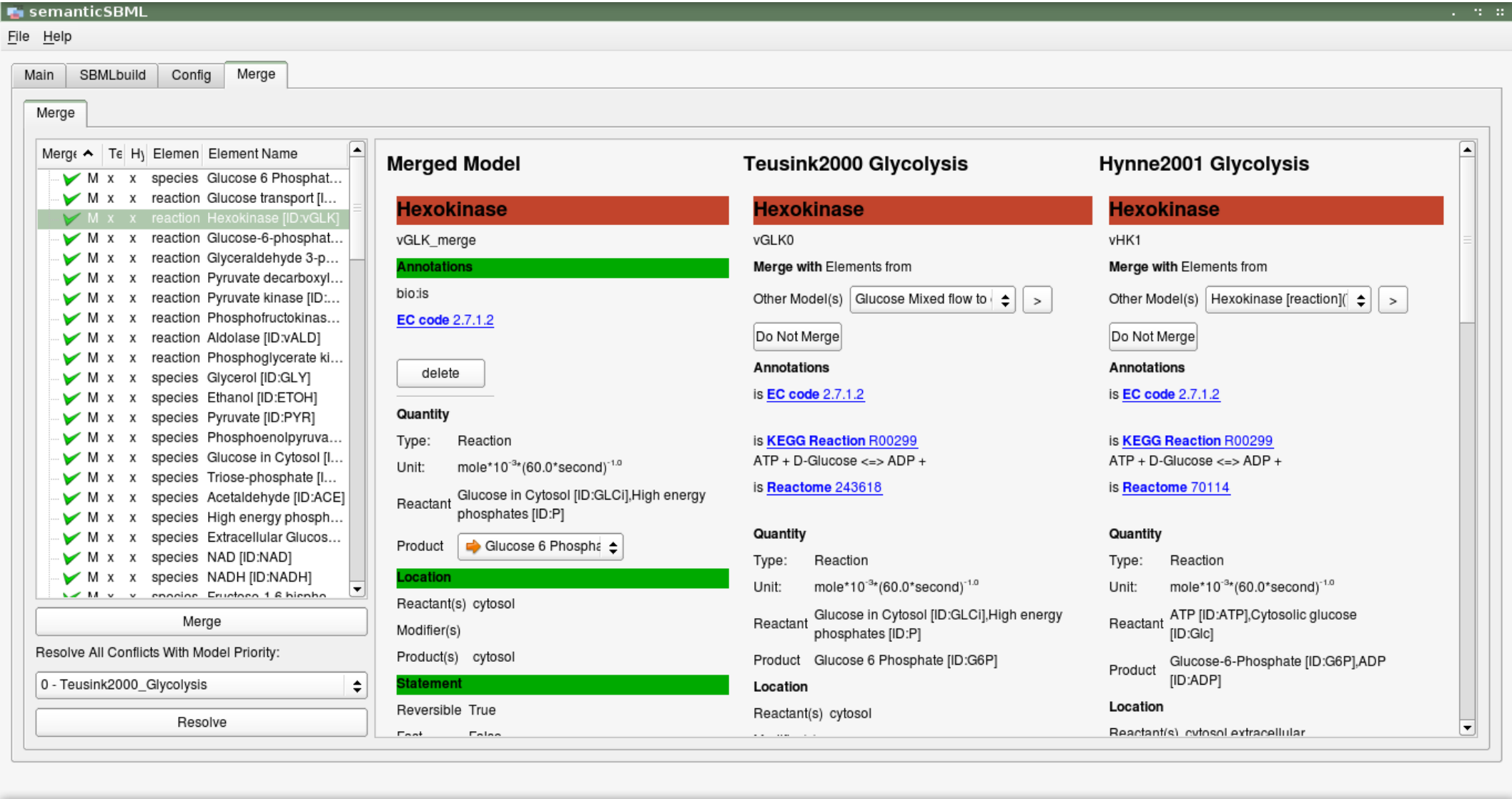
Merge GUI


semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
Merged Model
Unit: litre
Location
no outside specified
Statement
Constant True
Size 1.0
Volume 1.0
Resolve Conflicts
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve
Annotations
bio:hasPart
ChEBI CHEBI:15422
atp
bio:is
Reactome 70102
delete
Merging of Annotation Not Possible
You are trying to merge two MIRIAM annotations with qualifier 'is' pointing to the database EC code. Merging is not possible.
Ok

Merge GUI


Glycerol
GLY0
Merge with Elements from
Similar
Extracellular glycerol [s
>
Other Model(s)
Extracellular glucose 6
>
Do Not Merge
semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
M x x comp... cytosol [ID:cytosol_m]
M x x comp... extracellular [ID:extr...
M x x reaction Pyruvate decarboxyl...
M x x reaction Glucose transport [I...
M x x reaction Phosphoglycerate ki...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Hexokinase [ID:vGL...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Glucose-6-phosphat...
M x x reaction Aldolase [ID:vALD_m]
M x x species Glycerol [ID:GLY_m]
M x x species Triose-phosphate [I...
M x x species Extracellular Glucos...
M x x species Glucose in Cytosol [I...
M x x species High energy phosph...
M x x species Phosphoenolpyruva...
M x x species Fructose-1,6 bispho...
M x x species NADH [ID:NADH_m]
M x x species 1,3-bisphosphoglyc...
M x x species Pyruvate [ID:PYR_m]
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve
Merged Mo
cytosol
cytosol_merge
Annotations
bio:is
Gene Ontolog
cytosol
delete
Quantity
Type: volume
Unit: litre
Location
no outside specified
Statement
Constant True
Size 1.0
Volume 1.0
Resolve Conflicts
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element
e2001 Glycolysis
sol
with Elements from
odel(s) extracellular [compartn
>
Do Not Merge
Annotations
is Gene Ontology GO:0005829
cytosol
Quantity
Type: volume
Unit: litre
Location
no ouside specified
Statement
Constant True
Size 1.0
Volume 1.0
Dependencies
This Element Is Depending On
Elements Depending On This Element

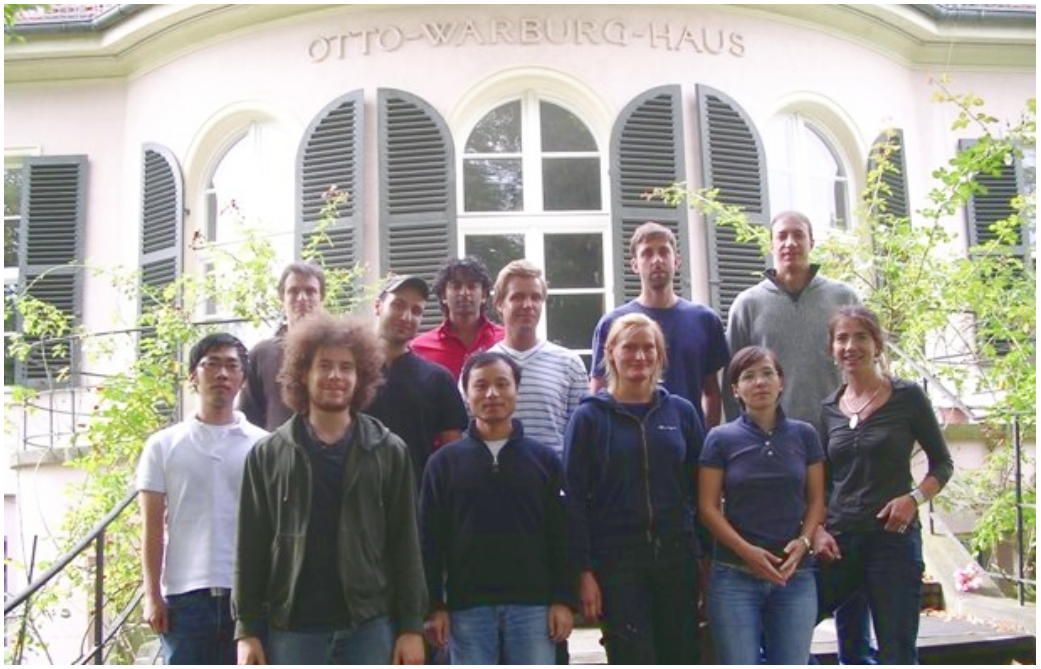
Merge GUI


semanticSBML
File Help
Main SBMLbuild Config Merge
Merge
Merge Te Hy Elemen Element Name
M x x species Glucose 6 Phosphat...
M x x reaction Glucose transport [I...
M x x reaction Hexokinase [ID:vGLK]
M x x reaction Glucose-6-phosphat...
M x x reaction Glyceraldehyde 3-p...
M x x reaction Pyruvate decarboxyl...
M x x reaction Pyruvate kinase [ID:...
M x x reaction Phosphofructokinas...
M x x reaction Aldolase [ID:vALD]
M x x reaction Phosphoglycerate ki...
M x x species Glycerol [ID:GLY]
M x x species Ethanol [ID:ETOH]
M x x species Pyruvate [ID:PYR]
M x x species Phosphoenolpyruva...
M x x species Glucose in Cytosol [I...
M x x species Triose-phosphate [I...
M x x species Acetaldehyde [ID:ACE]
M x x species High energy phosph...
M x x species Extracellular Glucos...
M x x species NAD [ID:NAD]
M x x species NADH [ID:NADH]
Merge
Resolve All Conflicts With Model Priority:
0 - Teusink2000_Glycolysis
Resolve
Merged Model
Hexokinase
vGLK_merge
Annotations
bio:is
EC code 2.7.1.2
delete
Quantity
Type: Reaction
Unit: mole*10-3*(60.0*second)-1.0
Reactant Glucose in Cytosol [ID:GLCi],High energy phosphates [ID:P]
Product Glucose 6 Phospha
Location
Reactant(s) cytosol
Modifier(s)
Product(s) cytosol
Statement
Reversible True
Teusink2000 Glycolysis
Hexokinase
vGLK0
Merge with Elements from
Other Model(s) Glucose Mixed flow to
>
Do Not Merge
Annotations
is EC code 2.7.1.2
is KEGG Reaction R00299
ATP + D-Glucose <=> ADP +
is Reactome 243618
Quantity
Type: Reaction
Unit: mole*10-3*(60.0*second)-1.0
Reactant Glucose in Cytosol [ID:GLCi],High energy phosphates [ID:P]
Product Glucose 6 Phosphate [ID:G6P]
Location
Reactant(s) cytosol
Hynne2001 Glycolysis
Hexokinase
vHK1
Merge with Elements from
Other Model(s) Hexokinase [reaction](
>
Do Not Merge
Annotations
is EC code 2.7.1.2
is KEGG Reaction R00299
ATP + D-Glucose <=> ADP +
is Reactome 70114
Quantity
Type: Reaction
Unit: mole*10-3*(60.0*second)-1.0
Reactant ATP [ID:ATP],Cytosolic glucose [ID:Glc]
Product Glucose-6-Phosphate [ID:G6P],ADP [ID:ADP]
Location
Reactant(s) cytosol extracellular

Future issues in merging of SBML models

- How to annotate models
  - Be explicit
  - Avoid lumped substances and reactions or annotate them carefully
- Our "to do" list for semanticSBML
  - Support for SBO terms
  - Improved internal database for element matching
  - Automatic recognition and annotation of kinetic rate laws
  - Smarter ways to handle biological qualifiers
- Community efforts needed
  - Agreement about annotation of protein complexes and modifications
  - Standard format for graphical representation (support by software)

Acknowledgements



Computational Systems Biology

MPI for Molecular Genetics

Edda Klipp
Falko Krause
Jannis Uhlendorf
Timo Lubitz
Marvin Schulz
Anselm Helbig
Firdevs Topcu-Alici
Anna Krivchanskaya
Hatice Celik

BaSysBio

SysMO
Systems Biology of Microorganisms