

# Merging of systems biology models with semanticSBML

Wolfram Liebermeister, Falko Krause, Edda Klipp

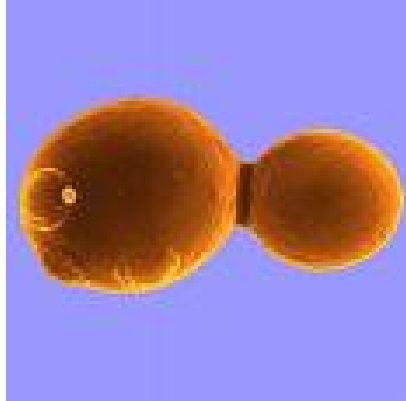
Max Planck Institute for Molecular Genetics, Berlin

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

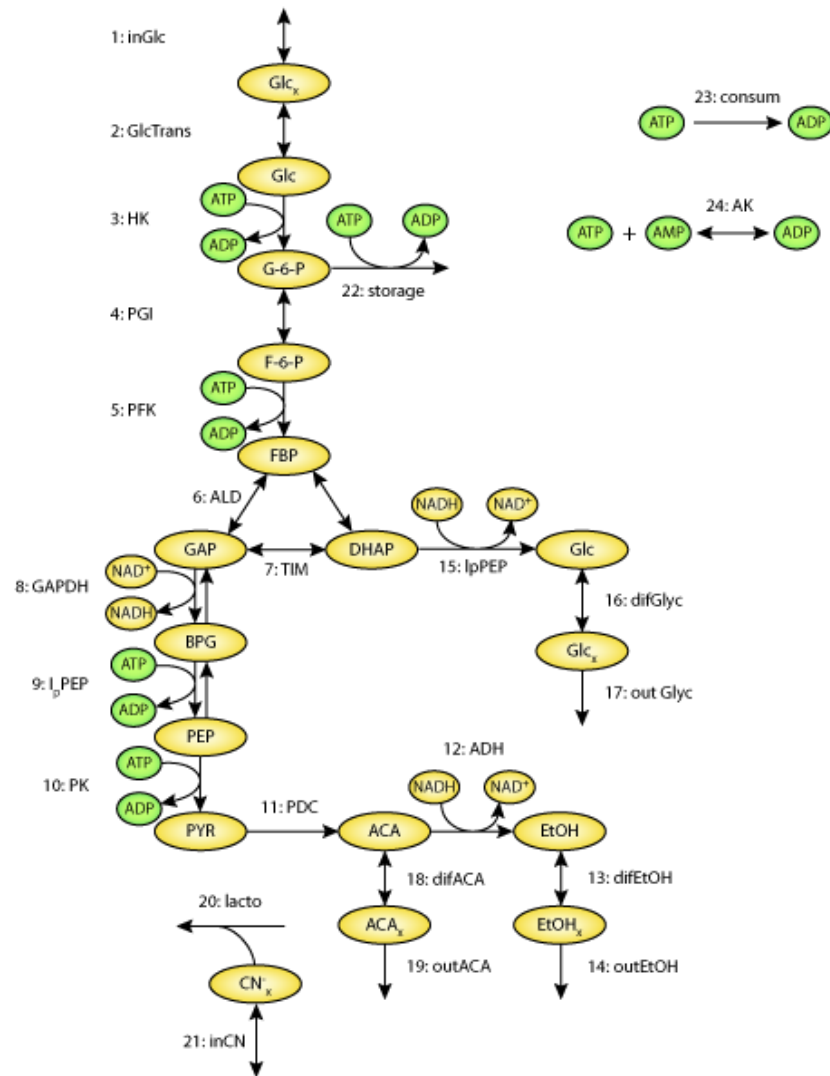
Metabolites, reactions, ...

## Biochemical quantities

Concentrations, velocities, ...

## Mathematical statements

Values, equations, ...

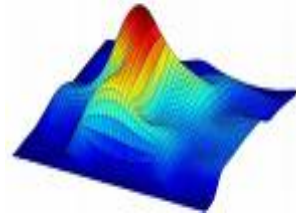


Full-scale model of glycolysis in *Saccharomyces cerevisiae*,  
F. Hynne et al., 2001, *Biophysical Chemistry* (94), 121-163.

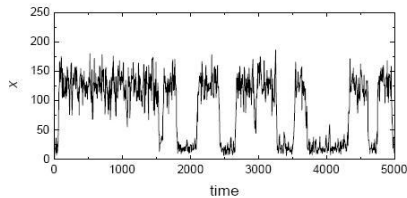
# Mathematical frameworks used in systems biology



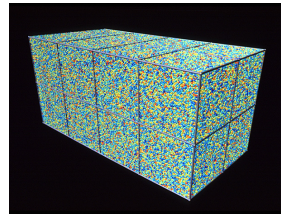
Ordinary differential equations



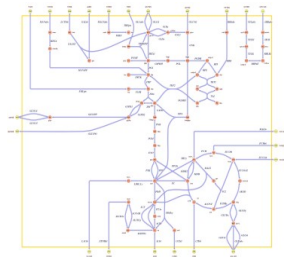
Partial differential equations



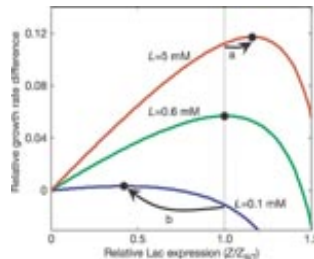
Stochastic processes



Particle-based models



Constraint-based models



Optimality-based models

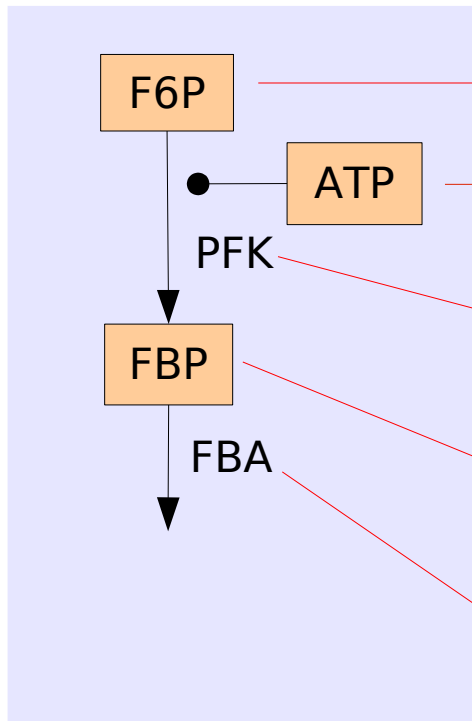
A common feature: the **semantics**

- 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

Network scheme



Model elements

F6P conc. [mM]	$c_{F6P}$	$c_{F6P} = 0.1$
ATP conc. [mM]	$c_{ATP}$	$c_{ATP} = 0.5$
PFK vel. [mM/s]	$v_{PFK}$	$v_{PFK} = v_{PFK}(c_{F6P}, c_{ATP})$
FBP conc. [mM]	$c_{FBP}$	$\frac{dc_{FBP}}{dt} = v_{PFK} - v_{FBA}$ $c_{FBP}(0) = c_{F6P}$
FBA vel. [mM/s]	$v_{FBA}$	$v_{FBA} = v_{FBA}(c_{FBP})$

Quantity

Variable

Mathematical statement

# SBML/MIRIAM annotations

Species called "ATP" represents **KEGG C06262 (ATP)**

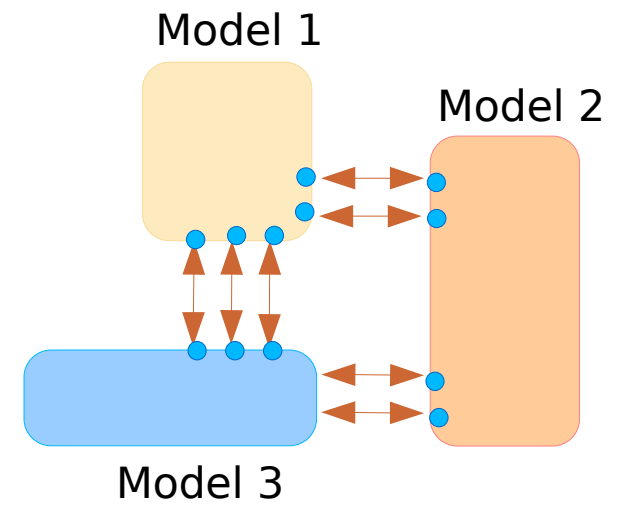
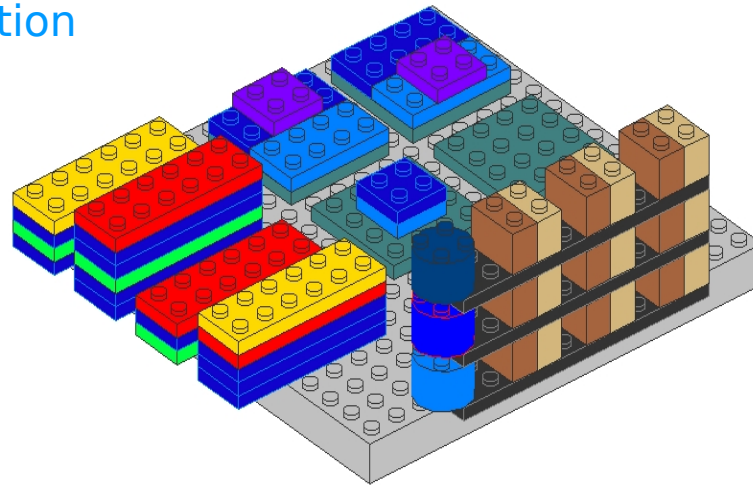
```
<species metaid=".." id="ATP" name="ATP concentration" compartment="cytosol">
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
             xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
             xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
      <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

## II. Merging of biochemical models

# Playing with biochemical models ?

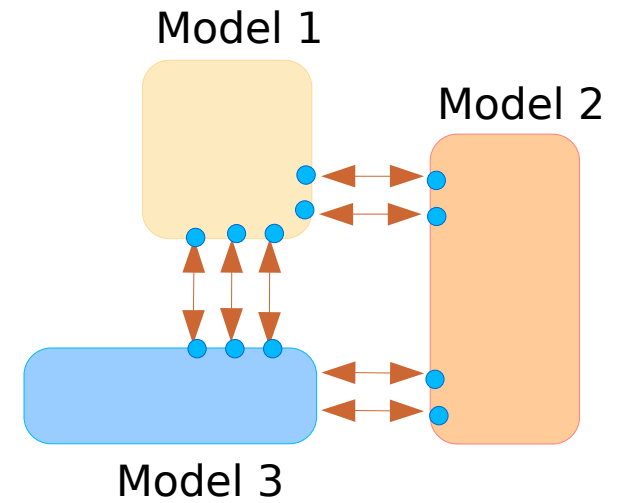
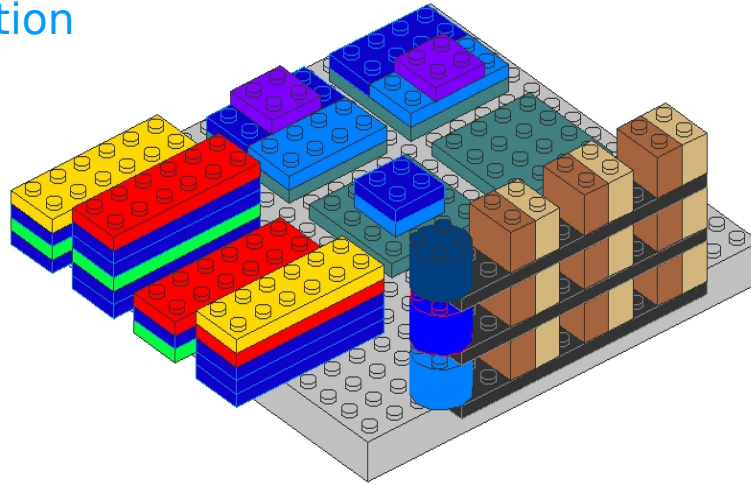
Model composition



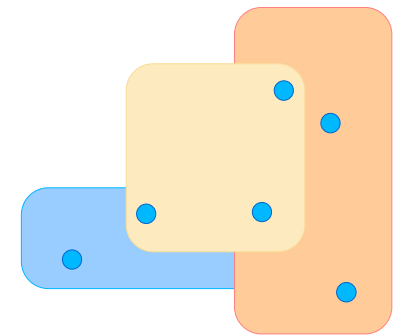


# Playing with biochemical models ?

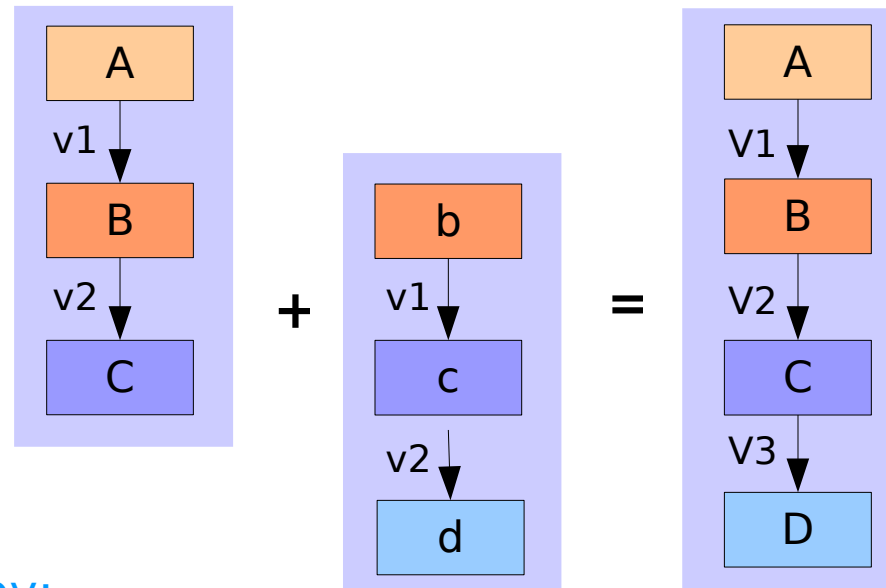
## Model composition



## 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)





# Semantic relations between quantities

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

Model 1

**ATP** concentration

Model 2

**ADP** concentration

# Semantic relations between quantities

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

Model 1

**ATP** concentration

Model 2

**ADP** concentration

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

**ATP** concentration



**ATP** concentration

# Semantic relations between quantities

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

Model 1

**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**

# Semantic relations between quantities

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

Model 1

**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

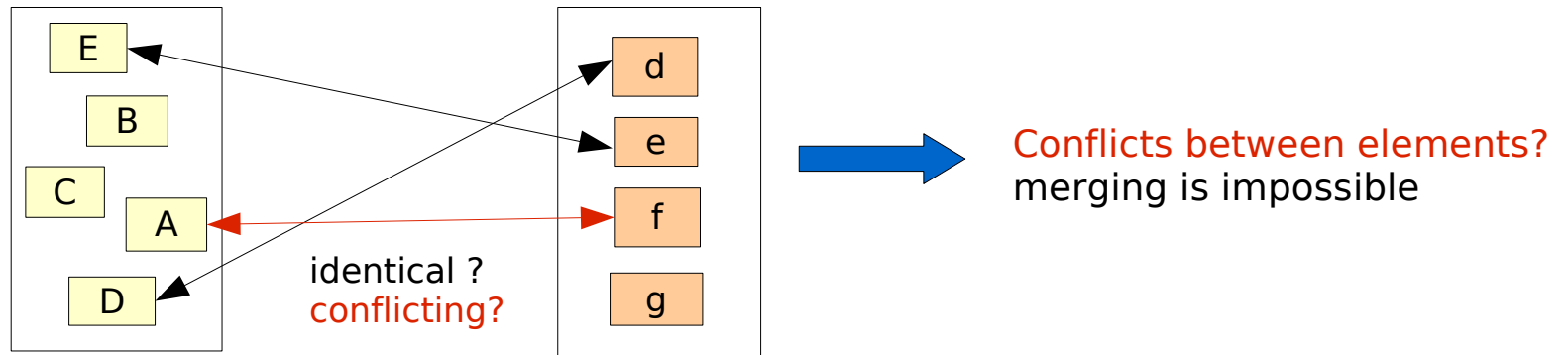


# A merging algorithm for semantic models with explicit equations

1. Convert all quantities to standard units

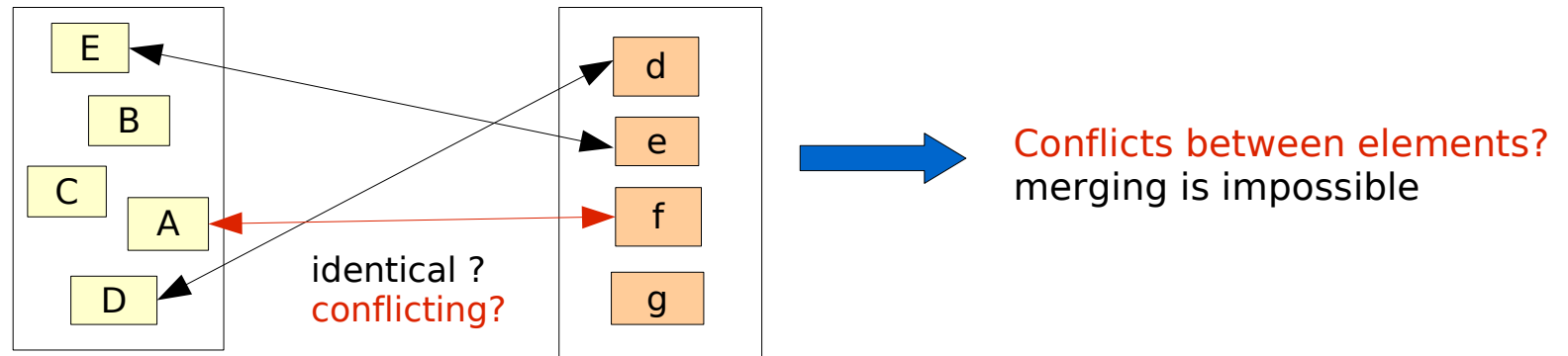
# A merging algorithm for semantic models with explicit equations

1. Convert all quantities to standard units
2. Match redundant / conflicting elements

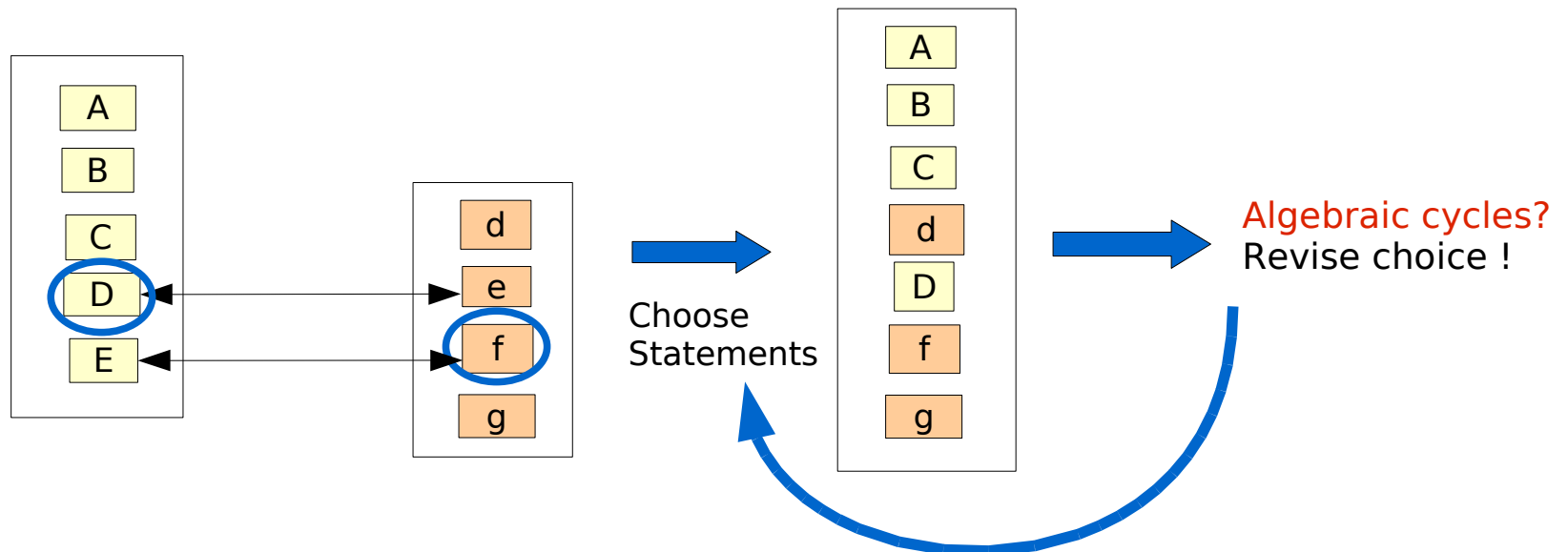


# A merging algorithm for semantic models with explicit equations

1. Convert all quantities to standard units
2. Match redundant / conflicting elements



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

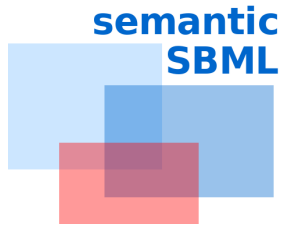
- realistic numerical values
- correct thermodynamics
- correct reaction balances, ...

### 5. Context

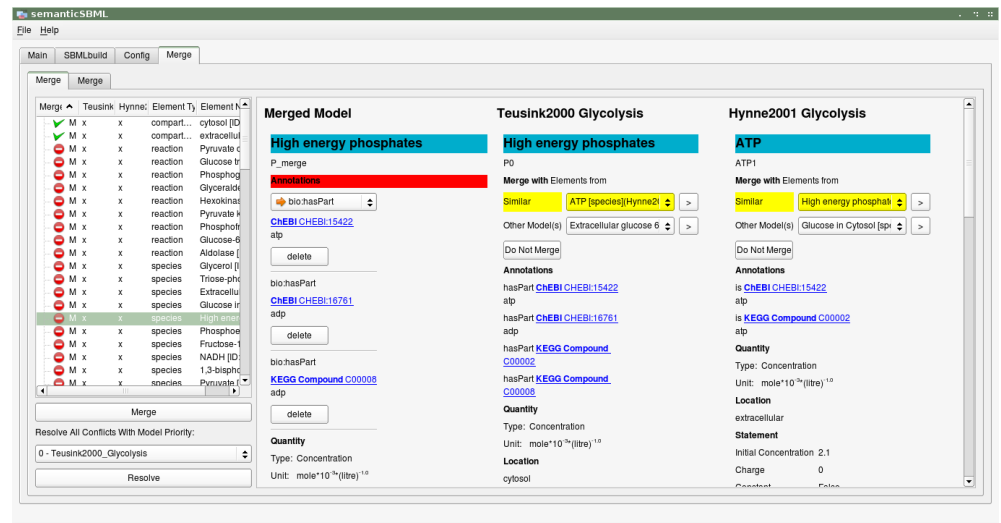
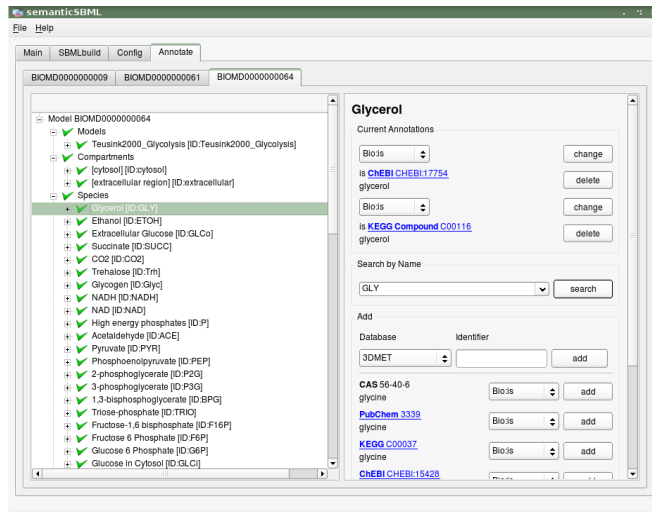
Model performs well and suits its purpose

- agreement with data
- plausible assumptions
- no irrelevant parts, ...

### 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)

# Annotation GUI

The screenshot displays the semanticSBML software interface. The window title is "semanticSBML" and it has a menu bar with "File" and "Help". Below the menu bar are tabs for "Main", "SBMLbuild", "Config", and "Annotate", with "Annotate" being the active tab. The interface shows three model tabs: "BIOMD000000009", "BIOMD000000061", and "BIOMD000000064".

The left sidebar shows a tree view of the model structure for "Model BIOMD000000064":

- Models
  - Teusink2000\_Glycolysis [ID:Teusink2000\_Glycolysis]
- Compartments
  - [cytosol] [ID:cytosol]
  - [extracellular region] [ID:extracellular]
- Species
  - Glycerol [ID:GLY]** (highlighted)
  - Ethanol [ID:ETOH]
  - Extracellular Glucose [ID:GLCo]
  - Succinate [ID:SUCC]
  - CO2 [ID:CO2]
  - Trehalose [ID:Trh]
  - Glycogen [ID:Glyc]
  - NADH [ID:NADH]
  - NAD [ID:NAD]
  - High energy phosphates [ID:P]
  - Acetaldehyde [ID:ACE]
  - Pyruvate [ID:PYP]
  - Phosphoenolpyruvate [ID:PEP]
  - 2-phosphoglycerate [ID:P2G]
  - 3-phosphoglycerate [ID:P3G]
  - 1,3-bisphosphoglycerate [ID:BPG]
  - Triose-phosphate [ID:TRIO]
  - Fructose-1,6 bisphosphate [ID:F16P]
  - Fructose 6 Phosphate [ID:F6P]
  - Glucose 6 Phosphate [ID:G6P]
  - Glucose in Cytosol [ID:GLCi]

The right pane is titled "Glycerol" and shows "Current Annotations":

- Annotation 1: Bio:is glycerol (change), is [ChEBI CHEBI:17754](#) glycerol (delete)
- Annotation 2: Bio:is glycerol (change), is [KEGG Compound C00116](#) glycerol (delete)

Below the annotations is a "Search by Name" section with a text input containing "GLY" and a "search" button.

The "Add" section has a table for adding new annotations:

Database	Identifier	
3DMET		add
CAS 56-40-6		Bio:is add
glycine		Bio:is add
<a href="#">PubChem 3339</a>		Bio:is add
glycine		Bio:is add
<a href="#">KEGG C00037</a>		Bio:is add
glycine		Bio:is add
<a href="#">ChEBI CHEBI:15428</a>		Bio:is add

# Annotation GUI

The screenshot displays the semanticSBML Annotation GUI. The left sidebar shows a tree view of the model structure:

- Model BIOMD0000000064
  - Models
    - Teusink2000\_Glycoly
  - Compartments
    - [cytosol] [ID:cytosol]
    - [extracellular region] [ID:extracellular]
  - Species
    - Glycerol [ID:GLY] (highlighted)
    - Ethanol [ID:ETOH]
    - Extracellular Glucose [ID:GLCo]
    - Succinate [ID:SUCC]
    - CO2 [ID:CO2]
    - Trehalose [ID:Trh]
    - Glycogen [ID:Glyc]
    - NADH [ID:NADH]
    - NAD [ID:NAD]
    - High energy phosphates [ID:P]
    - Acetaldehyde [ID:ACE]
    - Pyruvate [ID:PYP]
    - Phosphoenolpyruvate [ID:PEP]
    - 2-phosphoglycerate [ID:P2G]
    - 3-phosphoglycerate [ID:P3G]
    - 1,3-bisphosphoglycerate [ID:BPG]
    - Triose-phosphate [ID:TRIO]
    - Fructose-1,6 bisphosphate [ID:F16P]
    - Fructose 6 Phosphate [ID:F6P]
    - Glucose 6 Phosphate [ID:G6P]
    - Glucose in Cytosol [ID:GLCi]

The main panel shows the detailed view for the selected Glycerol species:

- glycerol
- Bio:is
- is [KEGG Compound C00116](#) glycerol
- glycerol
- change
- delete
- Search by Name
- GLY
- search
- Add
- Database Identifier
- 3DMET
- add
- CAS 56-40-6
- glycine
- Bio:is
- add
- PubChem 3339
- glycine
- Bio:is
- add
- KEGG C00037
- glycine
- Bio:is
- add
- ChEBI CHEBI:15428

A callout box highlights the following annotations for Glycerol:

- ✓ Compartments
- ✓ [cytosol] [ID:cytosol]
- is Gene Ontology: GO:0005829 cytosol
- ✓ [extracellular region] [ID:extracellular]
- ✓ Species
- ✓ Glycerol [ID:GLY]
- is ChEBI: CHEBI:17754 glycerol
- is KEGG Compound: C00116 glycerol



# Annotation GUI

The screenshot displays the semanticSBML software interface. On the left, a tree view shows the model structure for BIOMD0000000064, with 'Glycerol [ID:GLY]' selected under the 'Species' category. The right panel shows the 'Glycerol' species details, including its current annotations and search options.

**Current Annotations**

Database	Identifier	Change	Delete
Bio:is	is <a href="#">ChEBI CHEBI:17754</a>	change	delete
Bio:is	is <a href="#">KEGG Compound C00116</a>	change	delete

**Search by Name**

GLY

**Add**

Database	Identifier	Add
3DMET	<input type="text"/>	add
CAS 56-40-6	glycine	add
<a href="#">PubChem 3339</a>	glycine	add
<a href="#">KEGG C00037</a>	glycine	add
<a href="#">ChEBI CHEBI:15428</a>	glycine	add

# Annotation GUI

The screenshot displays the semanticSBML software interface. On the left, a tree view shows a model structure with various components like Models, Compartments, and Species. The 'Species' section is expanded, listing various molecules such as Ethanol, Glucose, and Glycerol. The 'Glycerol' species is highlighted. On the right, a 'Current Annotations' dialog box is open, showing a dropdown menu with 'Bio:is' selected, followed by the text 'is ChEBI CHEBI:17754 glycerol'. Below this, there are 'change' and 'delete' buttons. In the background, a web browser window shows the ChEBI entry for glycerol (CHEBI:17754), including its chemical structure and various identifiers like CAS, PubChem, and KEGG.

**semanticSBML**

File Help

Main SBMLbuild Config **Annotate**

BIOMD000000009 BIOMD000000061 BIOMD000000064

Model BIOMD000000064

- Models
  - Teusink2000\_Glycolysis [ID:Teusink2000\_Glycolysis]
- Compartments
  - [cytosol] [ID:cytosol]
  - [extracellular region] [ID:extracellular]
- Species
  - Glycerol [ID:GLY]**
  - Ethanol [ID:ETOH]
  - Extracellular Glucose [ID:GLCo]
  - Succinate [ID:SUCC]
  - CO2 [ID:CO2]
  - Trehalose [ID:Trh]
  - Glycogen [ID:Glyc]
  - NADH [ID:NADH]
  - NAD [ID:NAD]
  - High energy phosphates [ID:P]
  - Acetaldehyde [ID:ACE]
  - Pyruvate [ID:PYR]
  - Phosphoenolpyruvate [ID:PEP]
  - 2-phosphoglycerate [ID:P2G]
  - 3-phosphoglycerate [ID:P3G]
  - 1,3-bisphosphoglycerate [ID:BPG]
  - Triose-phosphate [ID:TRIO]
  - Fructose-1,6 biphosphate [ID:F16P]
  - Fructose 6 Phosphate [ID:F6P]
  - Glucose 6 Phosphate [ID:G6P]
  - Glucose in Cytosol [ID:GLCi]

**Glycerol**

Current

Bio:is

is **ChEBI CHEBI:17754**  
glycerol

change

delete

glycerol (CHEBI:17754) - Opera

File Edit View Bookmarks Widgets Feeds Mail Chat Tools Help

<http://www.ebi.ac.uk/chebi/searchFreeText.do?searchString=CHEBI:17754>

EMBL-EBI EB-eye Search All Databases Enter Text Here Go Reset Advanced Search

Databases Tools EBI Groups Training Industry About Us Help Site

EBI > Databases > Small Molecules > ChEBI > Main

**glycerol (CHEBI:17754)**

Main Automatic Xrefs

ChEBI Name glycerol

ChEBI ID CHEBI:17754

Last Modified 25 January 2008

Image  
 Applet

[more structures >>](#)

Molfile

InChI InChI=1/C3H8O3/c4-1-3(6)2-5/h3-6H,1-2H2

SMILES OCC(O)CO

Search ChEBI

Search Help

ChEBI Home

Advanced Search

Browse

Downloads

Documentation

Developer Resources

Preferences

Contact ChEBI

Printer Friendly View

CAS 56-40-6  
glycine

PubChem 3339  
glycine

KEGG C00037  
glycine

ChEBI CHEBI:15428

# Annotation GUI

The screenshot displays the semanticSBML software interface. The main window is titled "semanticSBML" and has a menu bar with "File" and "Help". Below the menu bar are tabs for "Main", "SBMLbuild", "Config", and "Annotate". The "Annotate" tab is active, showing a list of models: "BIOMD000000009", "BIOMD000000061", and "BIOMD000000064". The "BIOMD000000064" model is selected, and its contents are shown in a tree view on the left. The tree view includes "Models", "Compartments", and "Species". Under "Species", "Glycerol [ID:GLY]" is selected and highlighted in green. Below the tree view, a list of species is shown, including Ethanol, Extracellular Glucose, Succinate, CO2, Trehalose, Glycogen, NADH, NAD, High energy phosphates, Acetaldehyde, Pyruvate, Phosphoenolpyruvate, 2-phosphoglycerate, 3-phosphoglycerate, 1,3-bisphosphoglycerate, Triose-phosphate, Fructose-1,6 bisphosphate, Fructose 6 Phosphate, Glucose 6 Phosphate, and Glucose in Cytosol.

The right panel shows the "Glycerol" annotation details. It has a title "Glycerol" and a section "Current Annotations". The first annotation is "Bio:is" with a dropdown menu and a "change" button. Below it, the text "is [ChEBI CHEBI:17754](#)" is shown, followed by "glycerol" and a "delete" button. The second annotation is "Bio:is" with a dropdown menu and a "change" button. Below it, the text "is [KEGG Compound C00116](#)" is shown, followed by "glycerol" and a "delete" button.

Below the "Current Annotations" section, there is a "Search by" section with a dropdown menu set to "GLY" and a "search" button. Below that, there is an "Add" section with a "Database" dropdown menu set to "3DMET" and an "add" button. Below the "Add" section, there are several rows of annotations, each with a "Bio:is" dropdown menu and an "add" button. The first row is "CAS 56-40-6" followed by "glycine". The second row is "[PubChem 3339](#)" followed by "glycine". The third row is "[KEGG C00037](#)" followed by "glycine". The fourth row is "[ChEBI CHEBI:15428](#)" followed by "glycine".

A search dialog box is overlaid on the right panel, titled "Search by Name". It has a text input field containing "GLY" and a "search" button.

# Annotation GUI

The screenshot displays the semanticSBML software interface. The main window is titled "semanticSBML" and has a menu bar with "File" and "Help". Below the menu bar are tabs for "Main", "SBMLbuild", "Config", and "Annotate". The "Annotate" tab is active, showing a list of models: "BIOMD0000000009", "BIOMD0000000061", and "BIOMD0000000064". The "BIOMD0000000064" model is selected, and its structure is shown in a tree view on the left. The tree view includes "Models", "Compartments", and "Species". The "Species" section is expanded, showing a list of species including "Glycerol [ID:GLY]", "Ethanol [ID:ETOH]", "Extracellular Glucose [ID:GLCo]", "Succinate [ID:SUCC]", "CO2 [ID:CO2]", "Trehalose [ID:Trh]", "Glycogen [ID:Glyc]", "NADH [ID:NADH]", "NAD [ID:NAD]", "High energy phosphates [ID:P]", "Acetaldehyde [ID:ACE]", "Pyruvate [ID:PYP]", "Phosphoenolpyruvate [ID:PEP]", "2-phosphoglycerate [ID:P2G]", "3-phosphoglycerate [ID:P3G]", "1,3-bisphosphoglycerate [ID:BPG]", "Triose-phosphate [ID:TRIO]", "Fructose-1,6 bisphosphate [ID:F16P]", "Fructose 6 Phosphate [ID:F6P]", "Glucose 6 Phosphate [ID:G6P]", and "Glucose in Cytosol [ID:GLCi]".

The "Glycerol" species is selected, and its details are shown in the right-hand panel. The panel is titled "Glycerol" and contains a "Current Annotations" section. This section lists two annotations: "Bio:is" and "is CHEBI CHEBI:17754 glycerol". Each annotation has a "change" button and a "delete" button. Below the "Current Annotations" section is a "Search by Name" section with a text input field containing "GLY" and a "search" button. At the bottom of the panel is an "Add" section with a "Database" dropdown menu and an "Identifier" input field. The "Database" dropdown is currently set to "3DMET".

A modal dialog box is overlaid on the bottom right of the screen, titled "Add". It contains a "Database" dropdown menu and an "Identifier" input field. The "Database" dropdown is currently set to "3DMET". Below the input fields are two "add" buttons. The first "add" button is positioned to the right of the "Identifier" input field. The second "add" button is positioned to the right of the "Bio:is" dropdown menu.

Database	Identifier
3DMET	
CAS 56-40-6	glycine

# Annotation GUI

The screenshot displays the semanticSBML software interface. The main window shows a hierarchical tree of a model named "Model BIOMD0000000064". The tree includes a "Compartment" named "[cytosol] [ID:cytosol]" which is annotated with the Gene Ontology term "GO:0005829 cytosol". Below the tree, a list of metabolites is shown, including Ethanol, Extracellular Glucose, Succinate, CO2, Trehalose, Glycogen, NADH, NAD, High energy phosphates, Acetaldehyde, Pyruvate, Phosphoenolpyruvate, 2-phosphoglycerate, 3-phosphoglycerate, 1,3-bisphosphoglycerate, Triose-phosphate, Fructose-1,6 biphosphate, Fructose 6 Phosphate, Glucose 6 Phosphate, and Glucose in Cytosol.

On the right side, a "Compartment" panel is visible, containing the text: "Automatic annotation: Annotate all elements in the Compartments with the first search hit found" and a button labeled "annotate now".

Below the compartment panel, a search interface is shown. It includes a "Search by Name" field with the text "GLY" and a "search" button. Below this, there is an "Add" section with a table for adding identifiers from various databases:

Database	Identifier	Action
3DMET		add
CAS 56-40-6	glycine	Bio:is add
PubChem 3339	glycine	Bio:is add
KEGG C00037	glycine	Bio:is add
ChEBI CHEBI:15428		

# Merge GUI

The screenshot displays the Merge GUI in semanticSBML. The interface is divided into several sections:

- Left Panel (Merge Table):** A table with columns for Merge status, Teusink2000, Hynne2001, Element type, and Element Name. The first row, 'cytosol [ID:cytosol\_m]', is highlighted in green and has a checkmark in the Merge column. Other rows have red minus signs.
- Merged Model:** Shows the 'cytosol' element with ID 'cytosol\_merge'. It includes annotations like 'bio:is' and 'Gene Ontology GO:0005829'. It also shows quantity (Type: volume, Unit: litre) and location (no outside specified) information.
- Teusink2000 Glycolysis:** Shows the 'cytosol' element with ID 'cytosol0'. It includes a 'Merge with Elements from' dropdown set to 'extracellular [compartn]' and a 'Do Not Merge' button. It also shows quantity and location information.
- Hynne2001 Glycolysis:** Shows the 'cytosol' element with ID 'cytosol1'. It includes a 'Merge with Elements from' dropdown set to 'extracellular [compartn]' and a 'Do Not Merge' button. It also shows quantity and location information.

At the bottom, there are buttons for 'Merge', 'Resolve All Conflicts With Model Priority:' (with a dropdown set to '0 - Teusink2000\_Glycolysis'), and 'Resolve'.

# Merge GUI

Overview

Merged Model

Models 1...n

semanticSBML

File Help

Main SBMLbuild Merge Merge

Merge

Merge	Te	Hj	Elem	Element Name
<input checked="" type="checkbox"/>	M	x	x	comp... cytosol [ID:cytosol_m]
<input checked="" type="checkbox"/>	M	x	x	comp... extracellular [ID:extr...
<input checked="" type="checkbox"/>	M	x	x	reaction Pyruvate decarboxyl...
<input checked="" type="checkbox"/>	M	x	x	reaction Glucose transport [I...
<input checked="" type="checkbox"/>	M	x	x	reaction Phosphoglycerate ki...
<input checked="" type="checkbox"/>	M	x	x	reaction Glyceraldehyde 3-p...
<input checked="" type="checkbox"/>	M	x	x	reaction Hexokinase [ID:vGL...
<input checked="" type="checkbox"/>	M	x	x	reaction Pyruvate kinase [ID:...
<input checked="" type="checkbox"/>	M	x	x	reaction Phosphofructokinas...
<input checked="" type="checkbox"/>	M	x	x	reaction Glucose-6-phosphat...
<input checked="" type="checkbox"/>	M	x	x	reaction Aldolase [ID:vALD_m]
<input checked="" type="checkbox"/>	M	x	x	species Glycerol [ID:GLY_m]
<input checked="" type="checkbox"/>	M	x	x	species Triose-phosphate [I...
<input checked="" type="checkbox"/>	M	x	x	species Extracellular Glucos...
<input checked="" type="checkbox"/>	M	x	x	species Glucose in Cytosol [I...
<input checked="" type="checkbox"/>	M	x	x	species High energy phosph...
<input checked="" type="checkbox"/>	M	x	x	species Phosphoenolpyruva...
<input checked="" type="checkbox"/>	M	x	x	species Fructose-1,6 bispho...
<input checked="" type="checkbox"/>	M	x	x	species NADH [ID:NADH_m]
<input checked="" type="checkbox"/>	M	x	x	species 1,3-bisphosphoglyc...
<input checked="" type="checkbox"/>	M	x	x	species Pyruvate [ID:PYR_m]
<input checked="" type="checkbox"/>	M	x	x	species NAD [ID:NAD_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

### 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**

no outside 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 outside specified

**Statement**

Constant True

Size 1.0

Volume 1.0

**Dependencies**

This Element Is Depending On

Elements Depending On This Element

# Merge GUI

The screenshot displays the Merge GUI in semanticSBML. A central table compares elements from two models: Teusink and Hynne2001. The table includes columns for Merge status, model names, element types, and element names. A red minus sign indicates a conflict, while a green checkmark indicates a match.

Merge	Teusink	Hynne2001	Element Type	Element Name
⊖	M	x	species	NAD [ID:NAD_m]
⊖	M	x	species	Acetaldehyde [ID:ACETALD_m]
⊖	M	x	species	Ethanol [ID:ETHANOL_m]
✓	x	x	parameter	CPFKATP [ID:CPFKATP_m]
✓	x	x	parameter	KPFKF16 [ID:KPFKF16_m]
✓	x	x	parameter	CPFKF16 [ID:CPFKF16_m]

Below the table, the properties for the 'cytosol' element are shown for both models. The Teusink2000\_Glycolysis model shows 'cytosol' with a Gene Ontology annotation of GO:0005829, a quantity of 1.0, and a volume of 1.0. The Hynne2001\_Glycolysis model shows 'cytosol1' with the same Gene Ontology annotation, quantity, and volume. Both models have a 'Do Not Merge' button and a 'Resolve Conflicts' button.



# Merge GUI

The screenshot displays the 'Merge' window of the semanticSBML application. On the left, a table lists elements from three models for comparison:

Merge	Te	Hy	Element	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 Phosphofructokin...
✗	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
✗	M	x	x	species
✗	M	x	x	species
✗	M	x	x	species

The main area shows three panels for the 'cytosol' element:

- Merged Model:** cytosol\_merge. Annotations: bio:is [Gene Ontology GO:0005829](#). Location: cytosol. A 'delete' button is present.
- Teusink2000 Glycolysis:** cytosol0. Merge with Elements from: extracellular [compartn]. Annotations: is [Gene Ontology GO:0005829](#). Location: no outside specified.
- Hynne2001 Glycolysis:** cytosol1. Merge with Elements from: extracellular [compartn]. Annotations: is [Gene Ontology GO:0005829](#). Location: no outside specified.

A dialog box is open for resolving conflicts, with the following content:

Merge

Resolve All Conflicts With Model Priority:

0 - Teusink2000\_Glycolysis

Resolve

# Merge GUI

The screenshot shows the semanticSBML Merge GUI. A dialog box titled "Merging not Possible" is open, listing various elements with conflicting values. The dialog text is as follows:

**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 Phosphoglucosomerase 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.

Buttons: Resolve All Conflicts With, 0 - Teusink2000\_Glycolysis, Ok

The background window shows the Merge tab with a table of elements and their names, and a detailed view of the "cytosol" element on the right.

Merge	Te	Hy	Element	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_n...
✗	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 ...
✗	M	x	x	species ...
✗	M	x	x	species ...
✗	M	x	x	species ...
✗	M	x	x	species ...

**Merged Model** Teusink2000 Glycolysis

**Hynne2001 Glycolysis**

**cytosol**

cytosol1

Merge with Elements from

Other Model(s) extracellular [compartm] >

Do Not Merge

**Annotations**

is [Gene Ontology GO:0005829](#)

cytosol

**Quantity**

Type: volume

Unit: litre

**Location**

no outside specified

**Statement**

Constant True

Size 1.0

Volume 1.0

**Dependencies**

This Element Is Depending On

Elements Depending On This Element

# Merge GUI

The screenshot displays the semanticSBML Merge GUI. The main window is titled "semanticSBML" and has a menu bar with "File" and "Help". Below the menu bar are tabs for "Main", "SBMLbuild", "Config", and "Merge". The "Merge" tab is active, showing a list of elements to be merged. The list has columns for "Merge", "Te", "H", and "Element Name". The first element, "cytosol [ID:cytosol\_m]", is selected and highlighted in green. Below the list are buttons for "Merge" and "Resolve". The "Resolve" button is disabled, and a dropdown menu shows "0 - Teusink2000\_Glycolysis".

The "Merged Model" section shows the details for the selected element, "cytosol". It includes a "delete" button, "Annotations" (bio:is, Gene Ontology GO:0005829), "Quantity" (Type: volume, Unit: litre), "Location" (no outside specified), and "Statement" (Constant True, Size 1.0, Volume 1.0). A green "Resolve Conflicts" button is visible at the bottom of this section.

An "Annotations" panel is overlaid on the right side of the window. It has a red header and contains the following information:

- Annotation: **bio:hasPart**
- Entity: [ChEBI CHEBI:15422](#)
- Entity Name: **atp**
- Action: **delete**
- Entity: **bio:is**
- Entity Name: [Reactome 243599](#)
- Action: **delete**
- Entity: **bio:is**
- Entity Name: [Reactome 70102](#)
- Action: **delete**

# Merge GUI

The screenshot shows the semanticSBML Merge GUI. The main window displays a list of elements in a 'Merged Model' table. A dialog box titled 'Merging of Annotation Not Possible' is overlaid on the screen, indicating an error: 'You are trying to merge two MIRIAM annotations with qualifier 'is' pointing to the database EC code. Merging is not possible.' The dialog includes an 'OK' button.

**Annotations**

bio:hasPart

[ChEBI CHEBI:15422](#)

atp

**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

**bio:is**

[Reactome 70102](#)

delete

Merge	Te	Hj	Elemen	Element Name
✓	M	x	x	comp... cytosol [ID:cyt...
✓	M	x	x	comp... extracellular [ID:...
✗	M	x	x	reaction Pyruvate deca...
✗	M	x	x	reaction Glucose transp...
✗	M	x	x	reaction Phosphoglyce...
✗	M	x	x	reaction Glyceraldehyd...
✗	M	x	x	reaction Hexokinase [ID:...
✗	M	x	x	reaction Pyruvate kinas...
✗	M	x	x	reaction Phosphofructo...
✗	M	x	x	reaction Glucose-6-pho...
✗	M	x	x	reaction Aldolase [ID:va...
✗	M	x	x	species Glycerol [ID:GL...
✗	M	x	x	species Triose-phosph...
✗	M	x	x	species Extracellular G...
✗	M	x	x	species Glucose in Cytosol [ID:...
✗	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:PYP_m]
✗	M	x	x	species NAD [ID:NAD_m]

Unit: litre

**Location**

no outside specified

**Statement**

Constant True

Size 1.0

Volume 1.0

Resolve Conflicts

# Merge GUI

The screenshot displays the Merge GUI in semanticSBML. A modal dialog box is open, titled "Glycerol", with the identifier "GLY0". The dialog prompts the user to "Merge with Elements from" and offers three options: "Similar", "Other Model(s)", and "Do Not Merge".

The "Similar" option is selected, and the element "Extracellular glycerol [s]" is chosen from the "2001 Glycolysis" model. The "Other Model(s)" option is also visible, with "Extracellular glucose 6" selected from the "Teusink2000\_Glycolysis" model.

The background interface shows a list of elements to be merged, including "cytosol [ID:cytosol\_m]", "extracellular [ID:extr...]", and "Glycerol [ID:GLY\_m]". The "Glycerol" element is highlighted in orange. Below the list, there are buttons for "Merge" and "Resolve All Conflicts With Model Priority:", with "0 - Teusink2000\_Glycolysis" selected in the dropdown menu.

The "Merged Model" section shows the details for the selected "cytosol" element, including its annotations (bio:is, Gene Ontology GO:0005829), quantity (Type: volume, Unit: litre), location (no outside specified), and statement (Constant True, Size 1.0, Volume 1.0). A green "Resolve Conflicts" button is visible at the bottom of this section.

# Merge GUI

semanticSBML

File Help

Main SBMLbuild Config Merge

Merge

Merge	T	H	Element	Element Name
✓	M	x	species	Glucose 6 Phosphat...
✓	M	x	reaction	Glucose transport [L...
✓	M	x	reaction	Hexokinase [ID:vGLK]
✓	M	x	reaction	Glucose-6-phosphat...
✓	M	x	reaction	Glyceraldehyde 3-p...
✓	M	x	reaction	Pyruvate decarboxyl...
✓	M	x	reaction	Pyruvate kinase [ID:...
✓	M	x	reaction	Phosphofruktokinas...
✓	M	x	reaction	Aldolase [ID:vALD]
✓	M	x	reaction	Phosphoglycerate ki...
✓	M	x	species	Glycerol [ID:GLY]
✓	M	x	species	Ethanol [ID:ETOH]
✓	M	x	species	Pyruvate [ID:PYR]
✓	M	x	species	Phosphoenolpyruva...
✓	M	x	species	Glucose in Cytosol [L...
✓	M	x	species	Triose-phosphate [L...
✓	M	x	species	Acetaldehyde [ID:ACE]
✓	M	x	species	High energy phosph...
✓	M	x	species	Extracellular Glucos...
✓	M	x	species	NAD [ID:NAD]
✓	M	x	species	NADH [ID:NADH]
✓	M	x	species	Fructose 1,6 bispho...

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<sup>-3</sup>\*(60.0\*second)<sup>-1.0</sup>

Reactant Glucose in Cytosol [ID:GLC],High energy phosphates [ID:P]

Product

**Location**

Reactant(s) cytosol

Modifier(s)

Product(s) cytosol

**Statement**

Reversible True

### Teusink2000 Glycolysis

**Hexokinase**

vGLK0

Merge with Elements from

Other Model(s)  >

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<sup>-3</sup>\*(60.0\*second)<sup>-1.0</sup>

Reactant Glucose in Cytosol [ID:GLC],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)  >

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<sup>-3</sup>\*(60.0\*second)<sup>-1.0</sup>

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)

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