EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

MATHEMATISCH-
NATURWISSENSCHAFTLICHE FAKULTÄT

Center for Bioinformatics Tuebingen (ZBIT)

Context-based generation of kinetic equations with SBMLsqueezer 1.3

COMBINE Workshop 2010, Edinburgh

Andreas Dräger, Sandra Nitschmann, Alexander Dörr, Johannes Eichner, Michael J Ziller, and Andreas Zell

Selected rate laws for biochemical systems

$$v_j(\mathbf{S},\mathbf{p}) = F_j(\mathbf{S},\mathbf{p})\left(k_{+j}\prod_i S_i^{n_{ij}^-} - k_{-j}\prod_i S_i^{n_{ij}^+}\right)$$

Generalized mass-action equation

Reversible Michaelis-Menten equation with inhibition

$$v_j = \frac{\frac{v_+^{\mathrm{m}}}{K_{\mathrm{S}}^{\mathrm{M}}}[\mathrm{S}] - \frac{v_-^{\mathrm{m}}}{K_{\mathrm{P}}^{\mathrm{M}}}[\mathrm{P}]}{1 + \frac{[\mathrm{I}]}{K^{\mathrm{I}a}} + \left(\frac{[\mathrm{S}]}{K_{\mathrm{S}}^{\mathrm{M}}} + \frac{[\mathrm{P}]}{K_{\mathrm{P}}^{\mathrm{M}}}\right)\left(1 + \frac{[\mathrm{I}]}{K^{\mathrm{I}b}}\right)}$$

$$v_j = \frac{k_{+j}^{\mathrm{cat}}\prod_i\left(\frac{S_i}{K_{ji}^{\mathrm{M}}}\right)^{n_{ij}^-} - k_{-l}^{\mathrm{cat}}\prod_i\left(\frac{S_i}{K_{ji}^{\mathrm{M}}}\right)^{n_{ij}^+}}{\prod_i\sum_{m=0}^{n_{ij}^-}\left(\frac{S_i}{K_{ji}^{\mathrm{M}}}\right)^m + \prod_i\sum_{m=0}^{n_{ij}^+}\left(\frac{S_i}{K_{ji}^{\mathrm{M}}}\right)^m - 1} \cdot [\mathrm{E}_j]\cdot\prod_m h_{\mathrm{A}}(S_m, K_{jm}^{\mathrm{A}})^{w_{jm}^+} h_{\mathrm{I}}(S_m, K_{jm}^{\mathrm{I}})^{w_{jm}^-}$$

Convenience rate law

Langevin equation

$$\mathrm{d}x_i(t) = \sum_{j=1}^{M} n_{ij}a_j(\mathbf{x}(t)) + \sum_{j=1}^{M} n_{ij}\sqrt{a_j(\mathbf{x}(t))}\mathrm{d}W_j,\ i = 1,\ldots,N$$

© 2010 Universität Tübingen

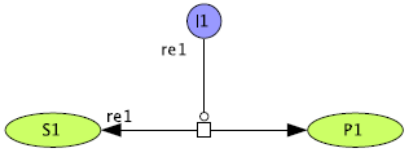
Reaction context in annotated systems

What we learn from a topology:
- Balance equations
- Species concentration dependencies
- Stoichiometric relationships

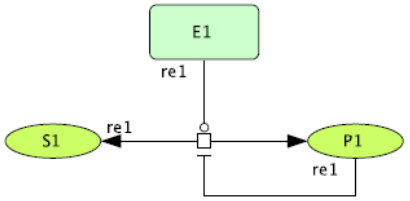
$$\frac{\mathrm{d}\mathbf{S}}{\mathrm{d}t} = \mathbf{N}\nu(\mathbf{S}(t), \mathbf{p})$$

And what we cannot learn:
- Regulatory relationships
- Reaction velocity

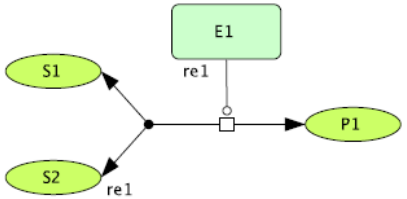
$$\nu(\mathbf{S}(t), \mathbf{p})$$



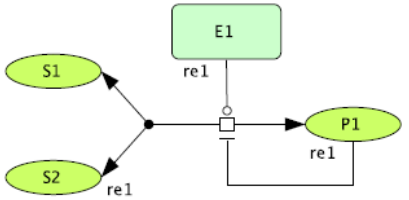
(a) Reversible ion-catalyzed reaction



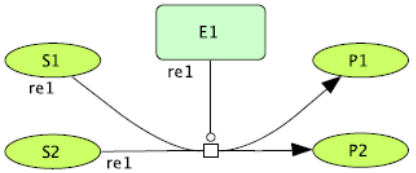
(b) Reversible uni-uni enzyme reaction with feedback inhibition



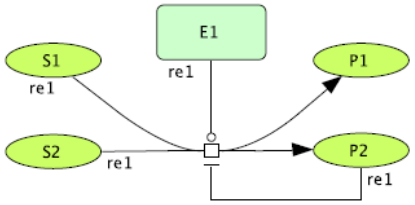
(c) Reversible bi-uni enzyme reaction



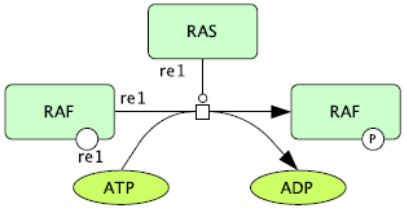
(d) Reversible bi-uni enzyme reaction with feedback inhibition



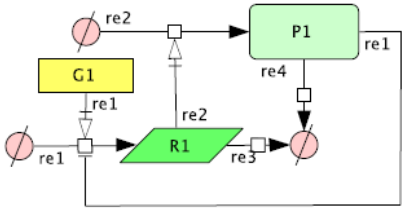
(e) Irreversible bi-bi enzyme reaction



(f) Irreversible bi-bi enzyme reaction with feedback inhibition



(g) Irreversible signal transduction reaction

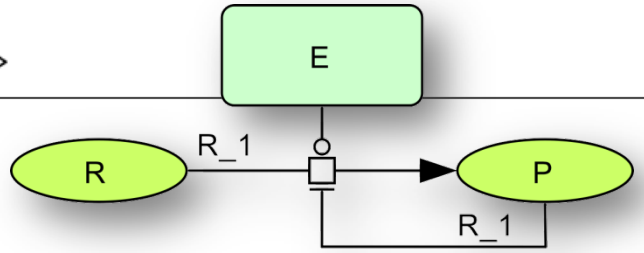


(h) Transcription and translation

© 2010 Universität Tübingen

An example for a `Reaction` object in SBML

```
1  <listOfReactions>
2    <reaction id="R_1" reversible="false" sboTerm="SBO:0000393">
       <!-- production -->
3      <listOfReactants>
4        <speciesReference sboTerm="SBO:0000015" species="R"/>
           <!-- substrate -->
5      </listOfReactants>
6      <listOfProducts>
7        <speciesReference sboTerm="SBO:0000011" species="P"/>
           <!-- product -->
8      </listOfProducts>
9      <listOfModifiers>
10       <modifierSpeciesReference sboTerm="SBO:0000460" species="E"/>
           <!-- enzymatic catalyst -->
11       <modifierSpeciesReference sboTerm="SBO:0000020" species="P"/>
           <!-- inhibitor -->
12     </listOfModifiers>
13     <!-- A KineticLaw object can be placed here. -->
14   </reaction>
15 </listOfReactions>
```



© 2010 Universität Tübingen

Example: Definition of parameters and units

Definition of parameters in SBML using SBO annotations

```
1   <!-- ... -->
2   <listOfParameters> <!-- Defined globally or locally -->
3     <parameter id="V" units="mol_per_s" sboTerm="SBO:0000025"/>
4     <parameter id="Ks" units="substance" sboTerm="SBO:0000027"/>
5     <parameter id="Kp" units="substance" sboTerm="SBO:0000027"/>
6   </listOfParameters>
7   <!-- ... -->
```

catalytic rate constant

Michaelis constant

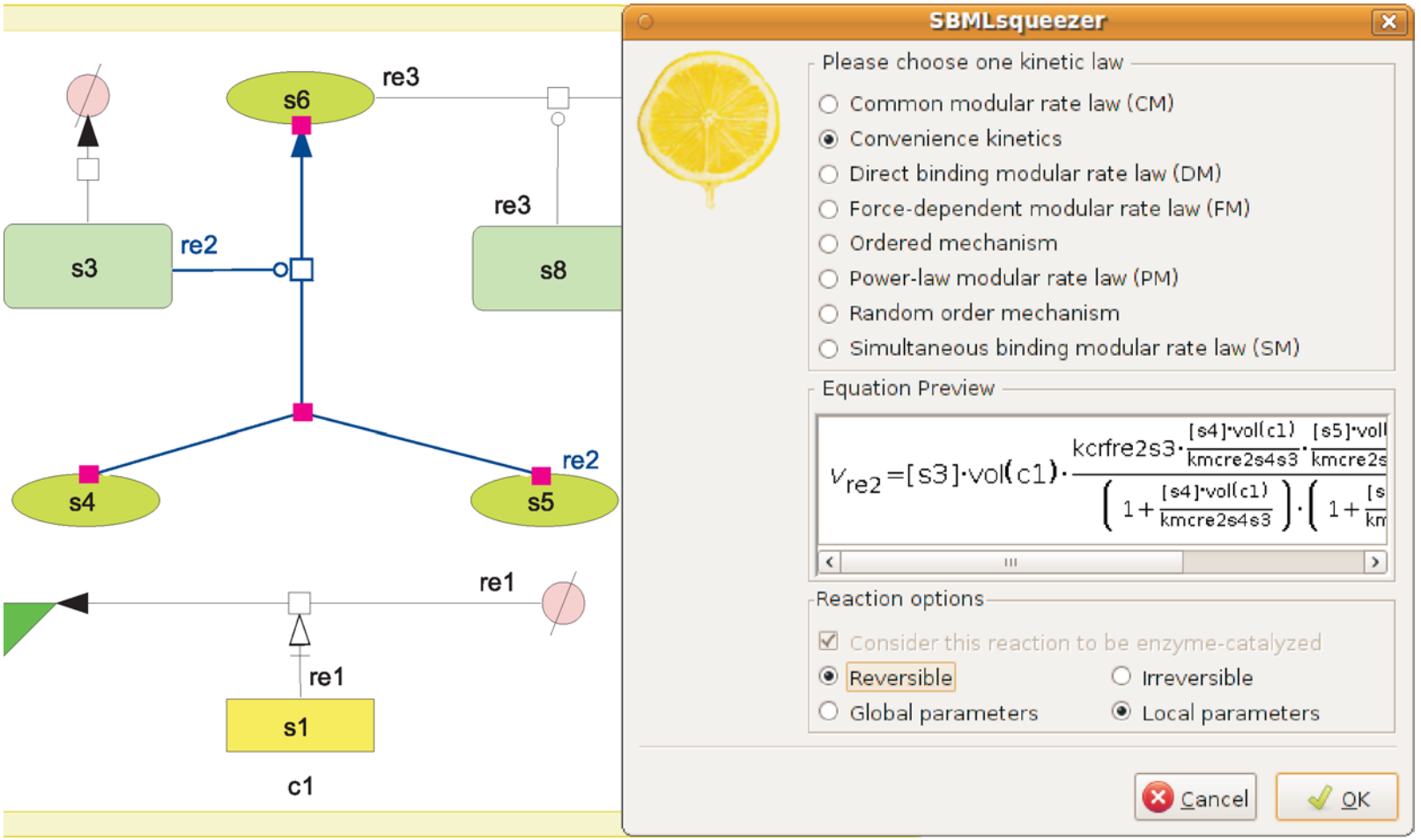
Definition of a unit in SBML

```
1   <!-- ... -->
2   <listOfUnitDefinitions>
3     <unitDefinition id="mol_per_s">
4       <listOfUnits>
5         <unit kind="mole"/>
6         <unit kind="second" exponent="-1"/>
7       </listOfUnits>
8     </unitDefinition>
9   </listOfUnitDefinitions>
10  <!-- ... -->
```

Predefined units in SBML:
- `substance` (in mole)
- `volume` (in litre)
- `area` (in square metres)
- `length` (in metre)
- `time` (in seconds)

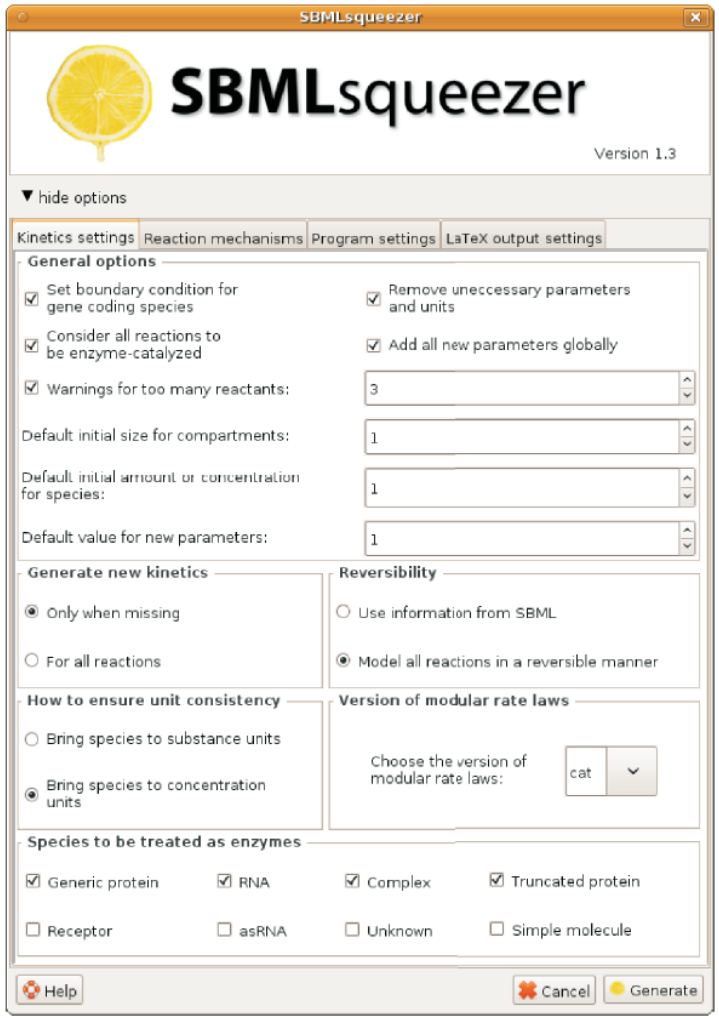
© 2010 Universität Tübingen

Assignment of rate laws step by step

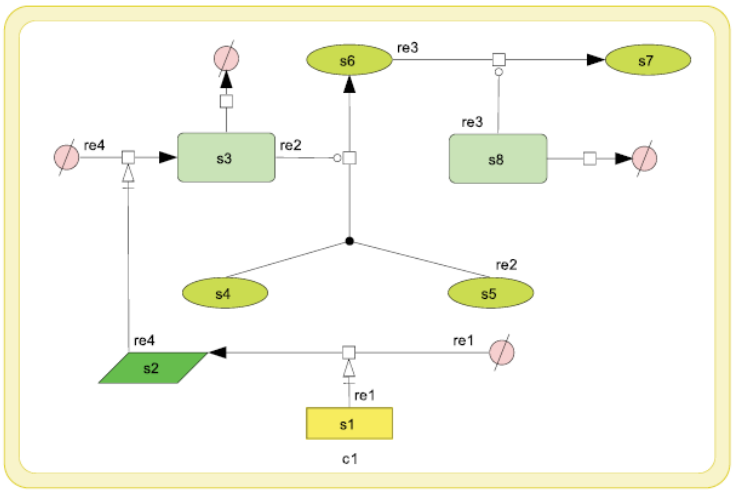


© 2010 Universität Tübingen

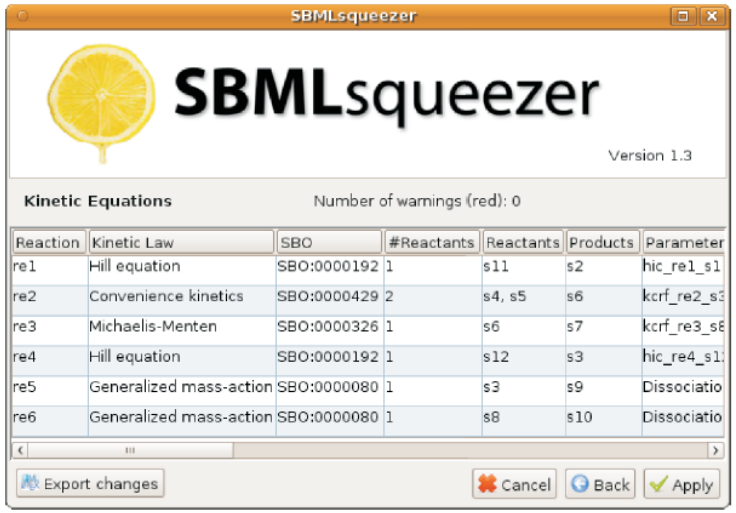
Rate law generation in one single step



1

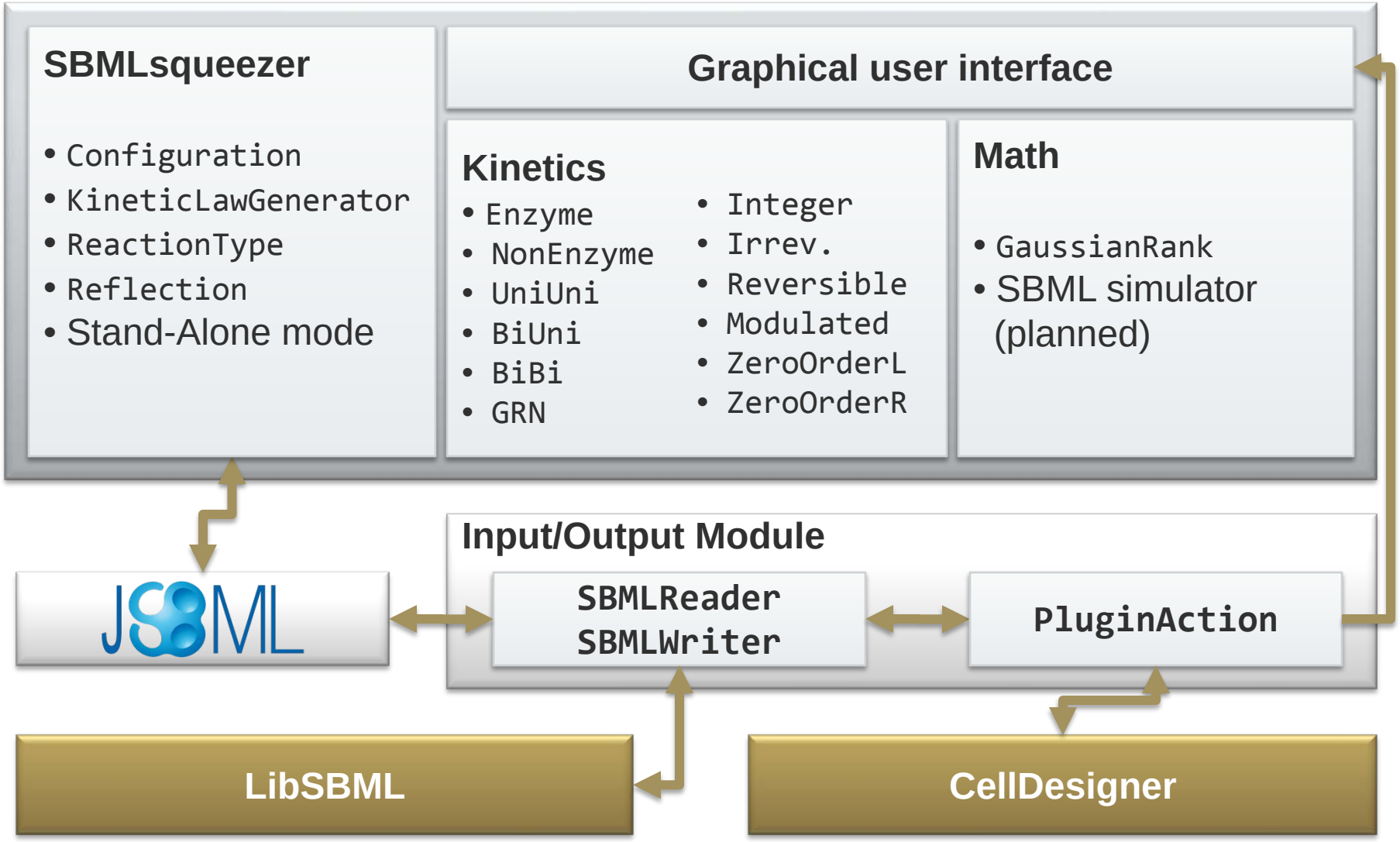


2



© 2010 Universität Tübingen

Architecture of SBMLsqueezer 1.3



© 2010 Universität Tübingen

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Translating from CellDesigner to SBO

Species Aliases

CellDesigner term	SBO term
ANTISENSE_RNA	small interfering RNA
COMPLEX	non-covalent complex
DEGRADED	empty set
DRUG	synthetic chemical compound
GENE	gene
GENERIC	polypeptide chain
ION	non-macromolecular ion
PHENOTYPE	phenotype
PROTEIN	protein complex
RECEPTOR	receptor
RNA	ribonucleic acid
ION_CHANNEL	channel
SIMPLE_MOLECULE	simple chemical
TRUNCATED	chemical macromolecule
UNKNOWN	material entity of unspecified nature

- Unique translation important
- Sometimes no exactly matching term available

Reaction Aliases

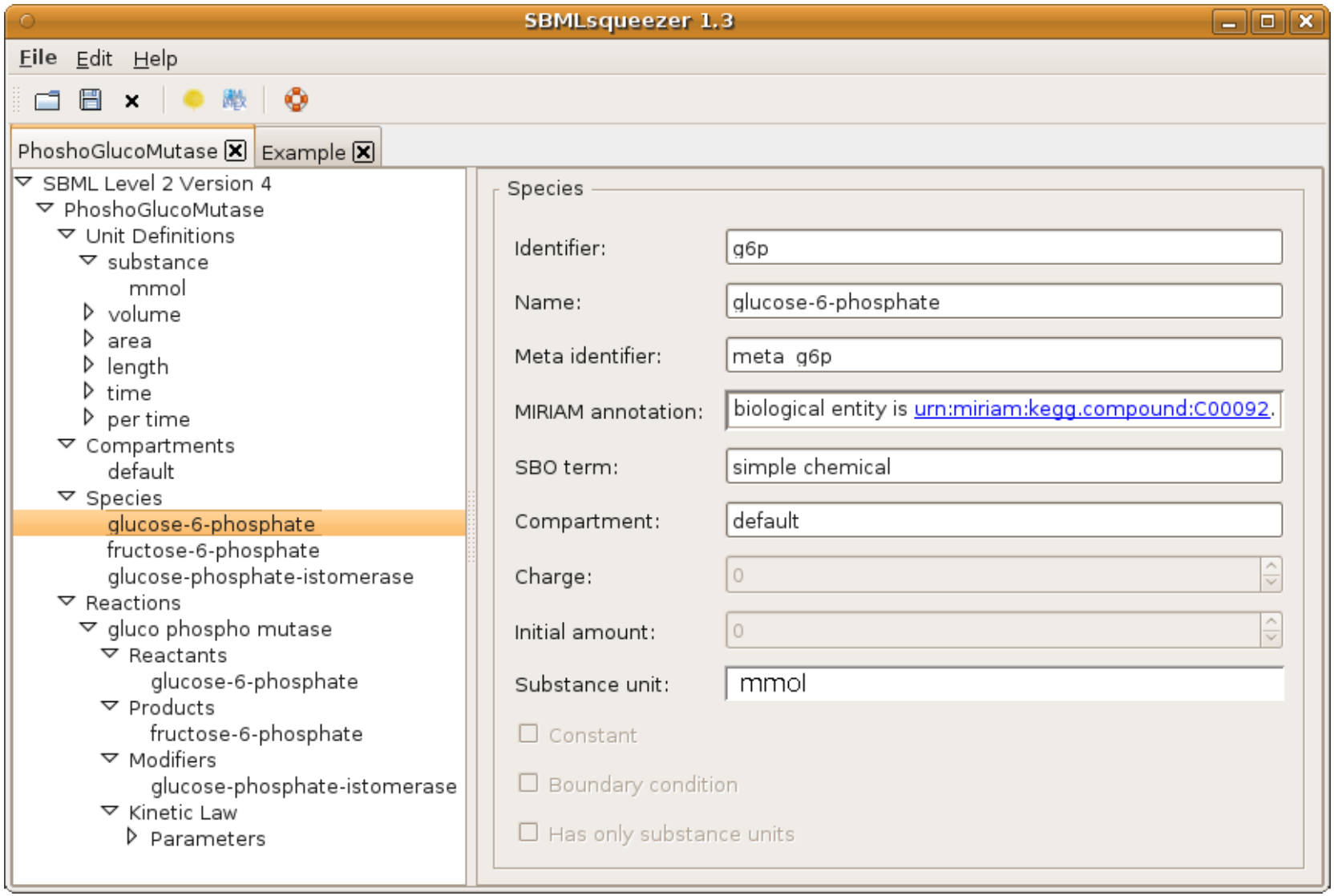
CellDesigner term	SBO term
KNOWN_TRANSITION_OMITTED	omitted process
STATE_TRANSITION	biochemical reaction
TRANSCRIPTION	transcription
TRANSLATION	translation
TRANSPORT	transport reaction
UNKNOWN_TRANSITION	uncertain process
reactant	reactant
product	product

Modifier Aliases

CellDesigner term	SBO term
CATALYSIS	catalyst
INHIBITION	inhibitor
MODULATION	modifier
PHYSICAL_STIMULATION	potentiator
TRANSCRIPTIONAL_ACTIVATION	stimulator
TRANSCRIPTIONAL_INHIBITION	inhibitor
TRANSLATIONAL_ACTIVATION	stimulator
TRANSLATIONAL_INHIBITION	inhibitor
TRIGGER	essential activator
UNKNOWN_CATALYSIS	catalyst
UNKNOWN_INHIBITION	inhibitor

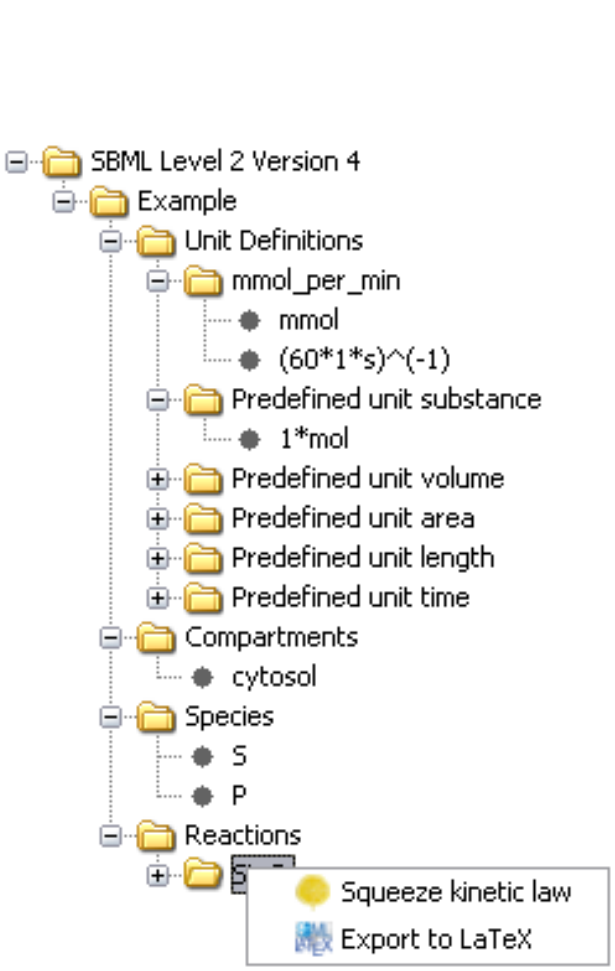
© 2010 Universität Tübingen

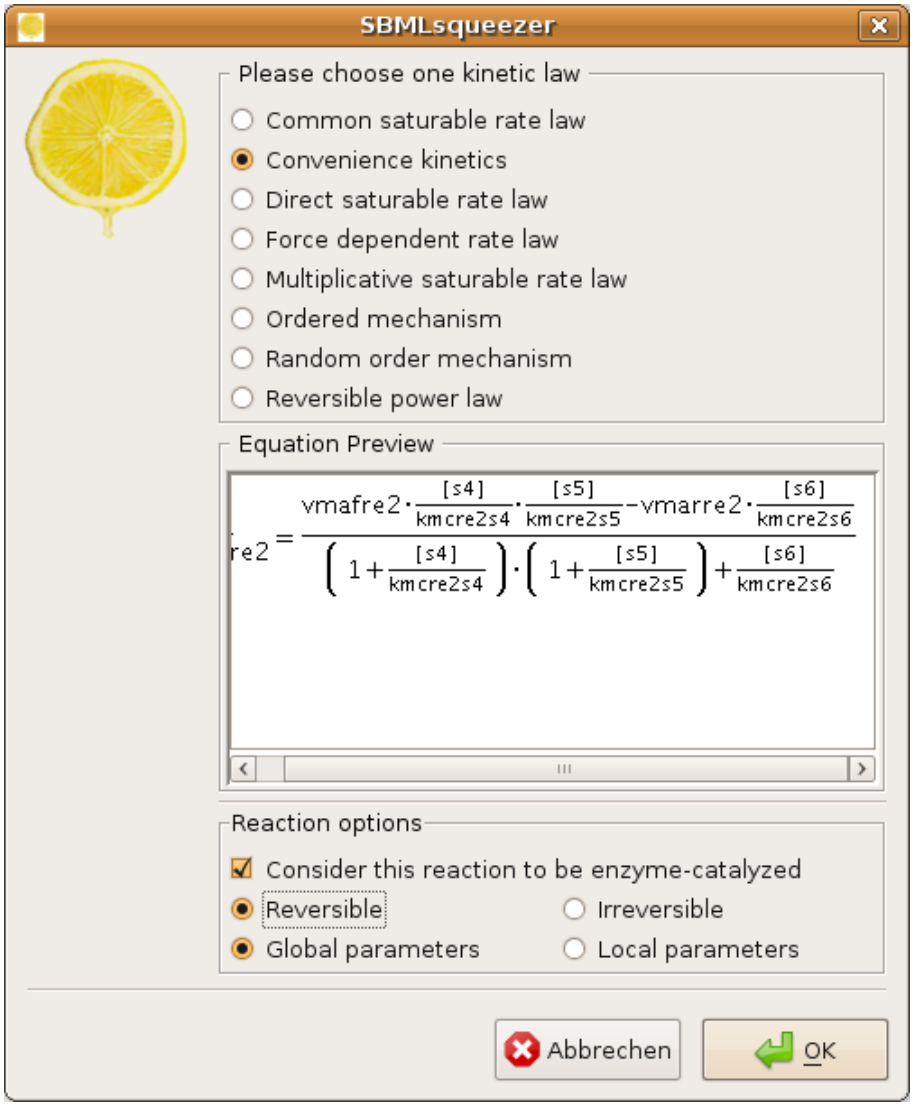
SBMLsqueezer 1.3 stand-alone



© 2010 Universität Tübingen

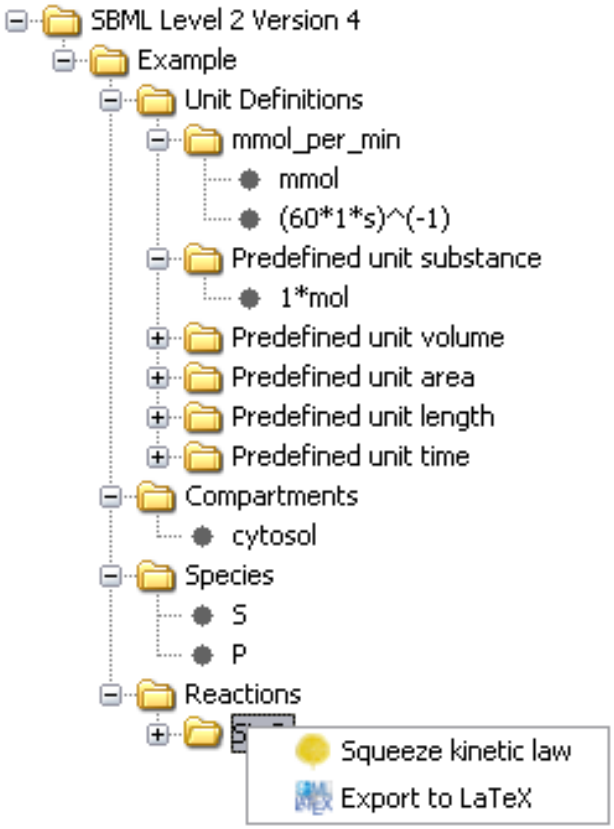
Equation generation for single reactions

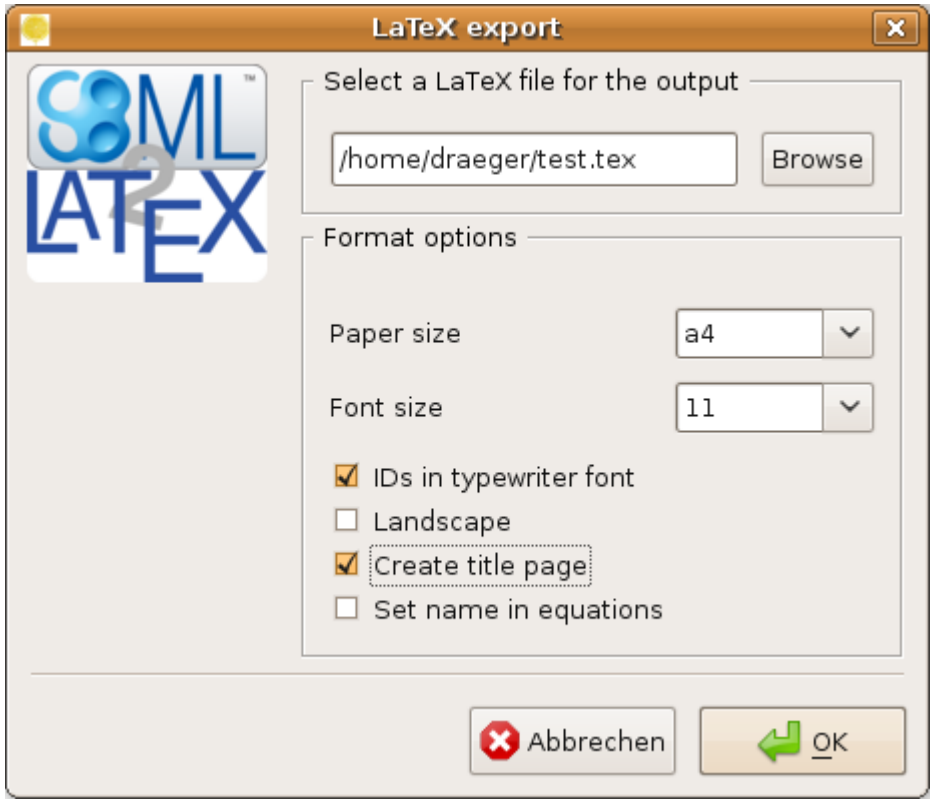




© 2010 Universität Tübingen

Equation generation for single reactions





© 2010 Universität Tübingen

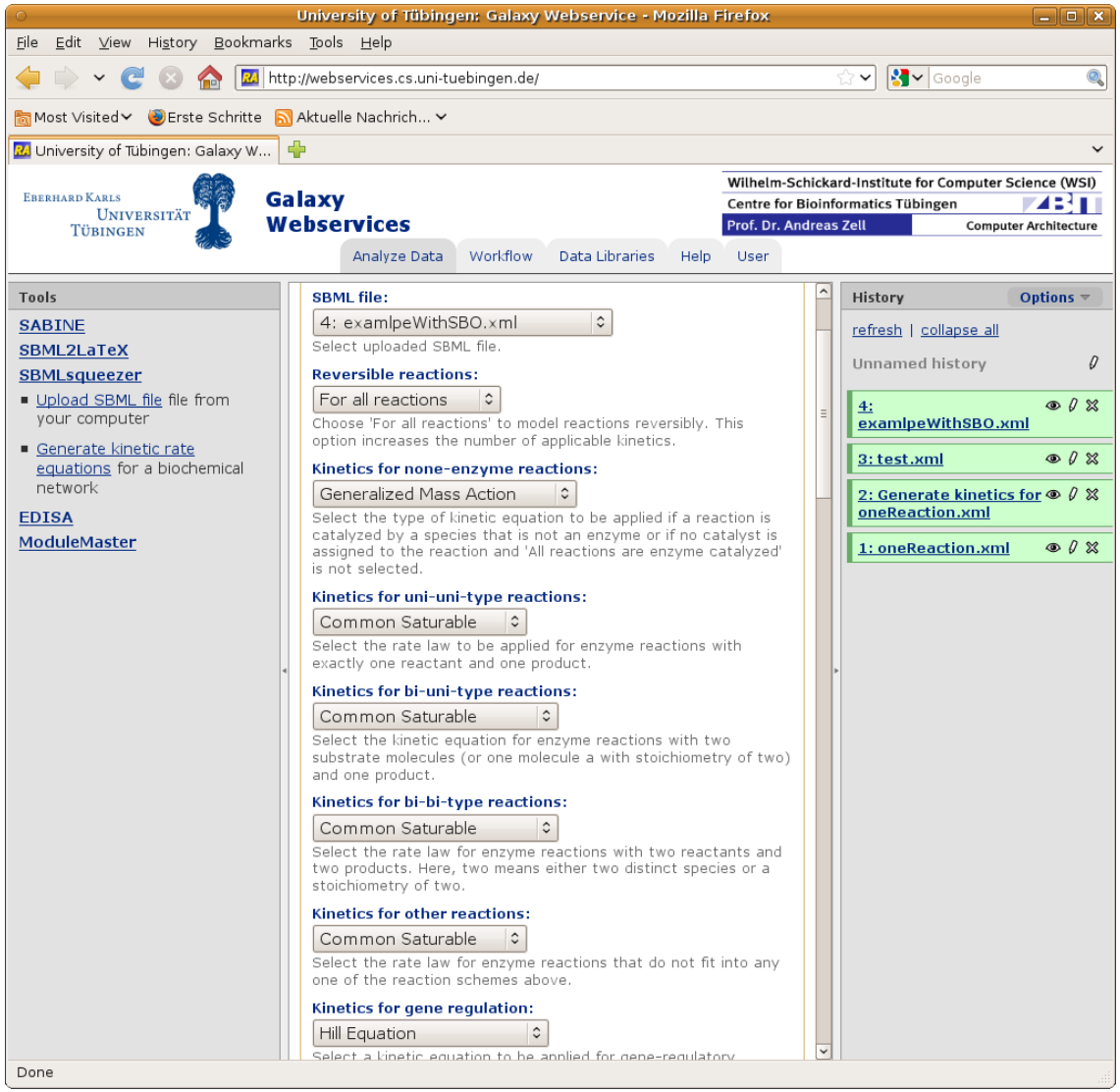
Using SBMLsqueezer via ist API

```
1  public static void main(String[] args) {
2    // Initialize SBMLsqueezer with appropriate SBML readers/writers
3    SBMLsqueezer sq = new SBMLsqueezer(new LibSBMLReader(), new
         LibSBMLWriter());
4    // Configure SBMLsqueezer
5    sq.set(CfgKeys.OPT_ALL_REACTIONS_ARE_ENZYME_CATALYZED, true);
6    sq.set(CfgKeys.OPT_DEFAULT_COMPARTMENT_INITIAL_SIZE, 1d);
7    sq.set(CfgKeys.POSSIBLE_ENZYME_RNA, true);
8    sq.set(CfgKeys.KINETICS_UNI_UNI_TYPE, "MichaelisMenten");
9    sq.set(CfgKeys.KINETICS_OTHER_ENZYME_REACTIONS,
         "ConvenienceKinetics");
10   try {
11     // Create kinetic equations, parameters, units etc. and save
12     // the result; args contains infile and outfile path
13     sq.squeeze(args[0], args[1]);
14   } catch (Throwable e) {
15     e.printStackTrace();
16   }
17 }
```

- Command-line mode: shell or batch scripts possible
- Just one central method: `squeeze`
- Easy adjustment of all settings through dedicated methods

© 2010 Universität Tübingen

Online version of SBMLsqueezer 1.3



© 2010 Universität Tübingen

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Thank you!

Contact:
Andreas Dräger
Center for Bioinformatics Tuebingen
Sand 1, 72076 Tuebingen
Phone: +49 7071 29-70436
Fax: +49 7071 29-5091
andreas.draeger@uni-tuebingen.de

Thanks to the team:
Sandra Nitschmann[1],
Alexander Dörr[1],
Johannes Eichner[1],
Michael J Ziller[2],
Andreas Zell[1]

[1]Center for Bioinformatics Tuebingen (ZBIT), Germany
[2]Harvard University, Camebridge, MA, USA

© 2010 Universität Tübingen