



Context-based generation of kinetic equations with SBMLsqueezer 1.3

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

Reversible Michaelis-Menten equation with inhibition

$$v_j = \frac{\frac{v_+^m}{K_S^M} [S] - \frac{v_-^m}{K_P^M} [P]}{1 + \frac{[I]}{K^{Ia}} + \left(\frac{[S]}{K_S^M} + \frac{[P]}{K_P^M} \right) \left(1 + \frac{[I]}{K^{Ib}} \right)}$$

$$v_j = \frac{k_{+j}^{\text{cat}} \prod_i \left(\frac{S_i}{K_{ji}^M} \right)^{n_{ij}^-} - k_{-j}^{\text{cat}} \prod_i \left(\frac{S_i}{K_{ji}^M} \right)^{n_{ij}^+}}{\prod_i \sum_{m=0}^{n_{ij}^-} \left(\frac{S_i}{K_{ji}^M} \right)^m + \prod_i \sum_{m=0}^{n_{ij}^+} \left(\frac{S_i}{K_{ji}^M} \right)^m - 1} \cdot [E_j] \cdot \prod_m h_A(S_m, K_{jm}^A)^{w_{jm}^+} h_I(S_m, K_{jm}^I)^{w_{jm}^-} \quad \text{Convenience rate law}$$

Langevin equation
$$dx_i(t) = \sum_{j=1}^M n_{ij} a_j(\mathbf{x}(t)) + \sum_{j=1}^M n_{ij} \sqrt{a_j(\mathbf{x}(t))} dW_j, \quad i = 1, \dots, N$$



Reaction context in annotated systems

What we learn from a topology:

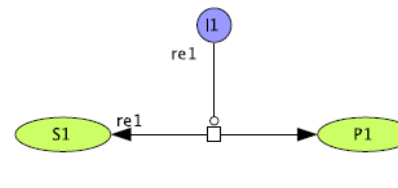
- Balance equations
- Species concentration dependencies
- Stoichiometric relationships

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

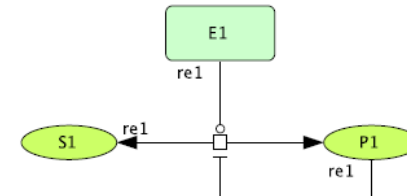
And what we cannot learn:

- Regulatory relationships
- Reaction velocity

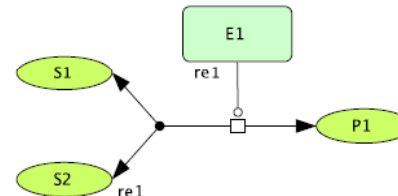
$$\nu(\mathbf{S}(t), \mathbf{p})$$



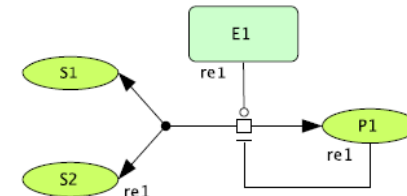
(a) Reversible ion-catalyzed reaction



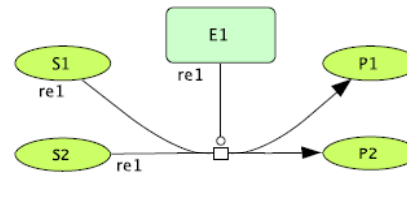
(b) Reversible uni-uni enzyme reaction with feedback inhibition



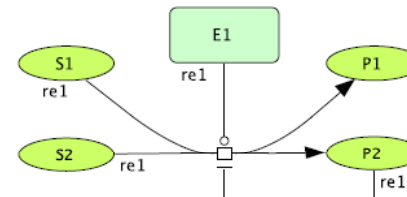
(c) Reversible bi-uni enzyme reaction



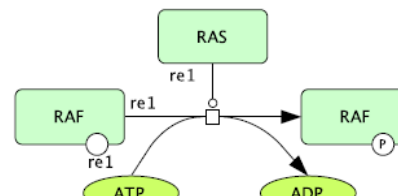
(d) Reversible bi-uni enzyme reaction with feedback inhibition



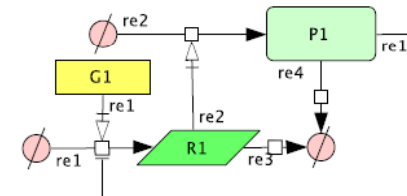
(e) Irreversible bi-bi enzyme reaction



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



(g) Irreversible signal transduction reaction



(h) Transcription and translation

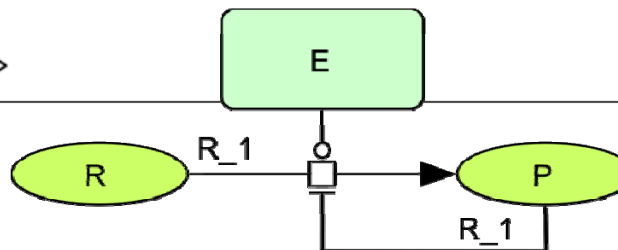


An example for a Reaction object in SBML

```

1 <listOfReactions>
2   <reaction id="R_1" reversible="false" sboTerm="SB0:0000393">
3     <!-- production -->
4     <listOfReactants>
5       <speciesReference sboTerm="SB0:0000015" species="R"/>
6       <!-- substrate -->
7     </listOfReactants>
8     <listOfProducts>
9       <speciesReference sboTerm="SB0:0000011" species="P"/>
10      <!-- product -->
11    </listOfProducts>
12    <listOfModifiers>
13      <modifierSpeciesReference sboTerm="SB0:0000460" species="E"/>
14      <!-- enzymatic catalyst -->
15      <modifierSpeciesReference sboTerm="SB0:0000020" species="P"/>
16      <!-- inhibitor -->
17    </listOfModifiers>
18    <!-- A KineticLaw object can be placed here. -->
19  </reaction>
20 </listOfReactions>

```





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)



Assignment of rate laws step by step

SBMLsqueezer

Please choose one kinetic law

- Common modular rate law (CM)
- Convenience kinetics
- Direct binding modular rate law (DM)
- Force-dependent modular rate law (FM)
- Ordered mechanism
- Power-law modular rate law (PM)
- Random order mechanism
- Simultaneous binding modular rate law (SM)

Equation Preview

$$v_{re2} = [s3] \cdot vol(c1) \cdot \frac{k_{cre2}s3 \cdot \frac{[s4] \cdot vol(c1)}{k_{mcre2}s4s3} \cdot \frac{[s5] \cdot vol(c1)}{k_{mcre2}s5}}{\left(1 + \frac{[s4] \cdot vol(c1)}{k_{mcre2}s4s3}\right) \cdot \left(1 + \frac{[s5] \cdot vol(c1)}{k_{mcre2}s5}\right)}$$

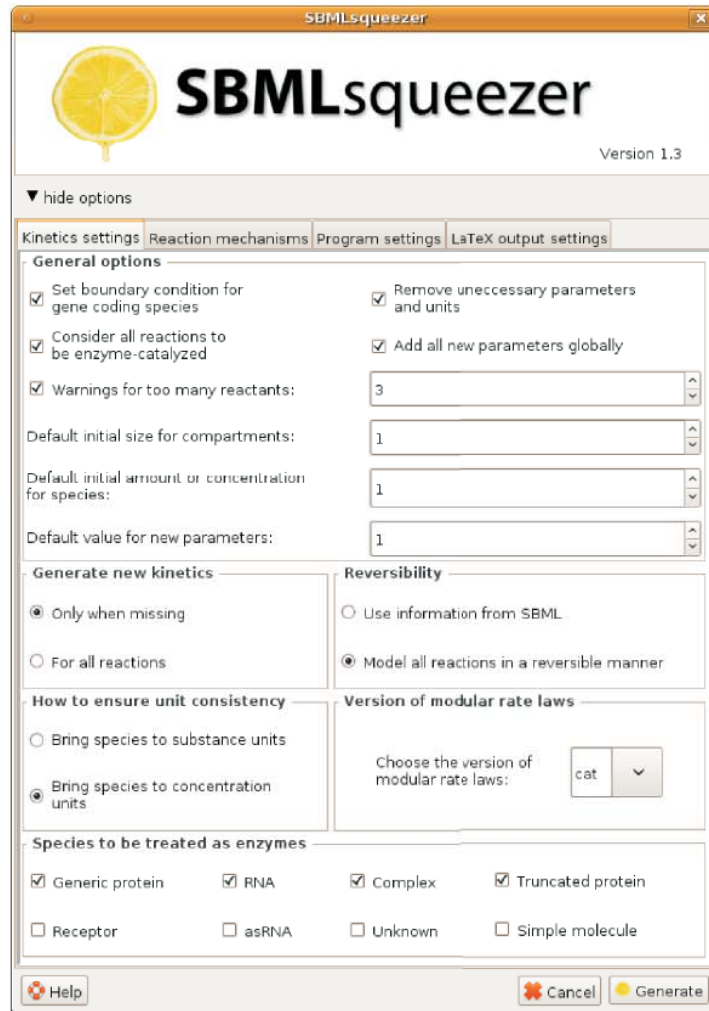
Reaction options

- Consider this reaction to be enzyme-catalyzed
- Reversible Irreversible
- Global parameters Local parameters

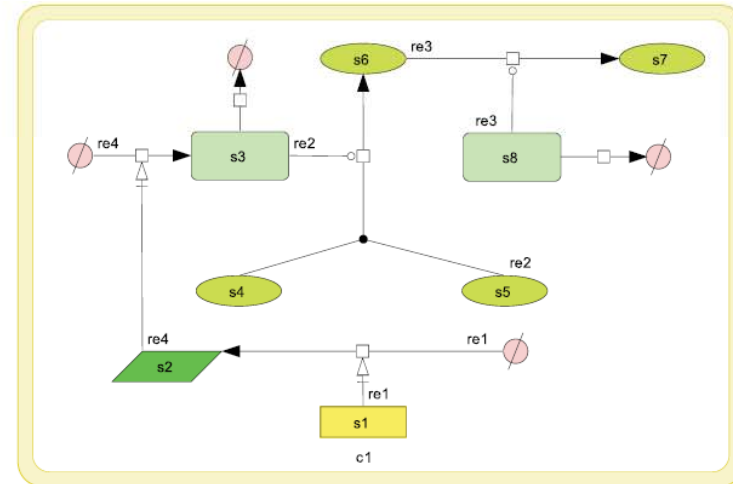
Cancel OK



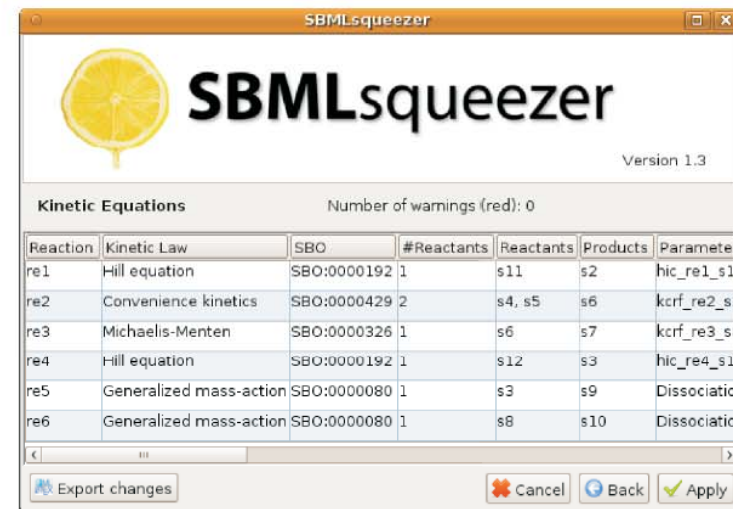
Rate law generation in one single step



1
←

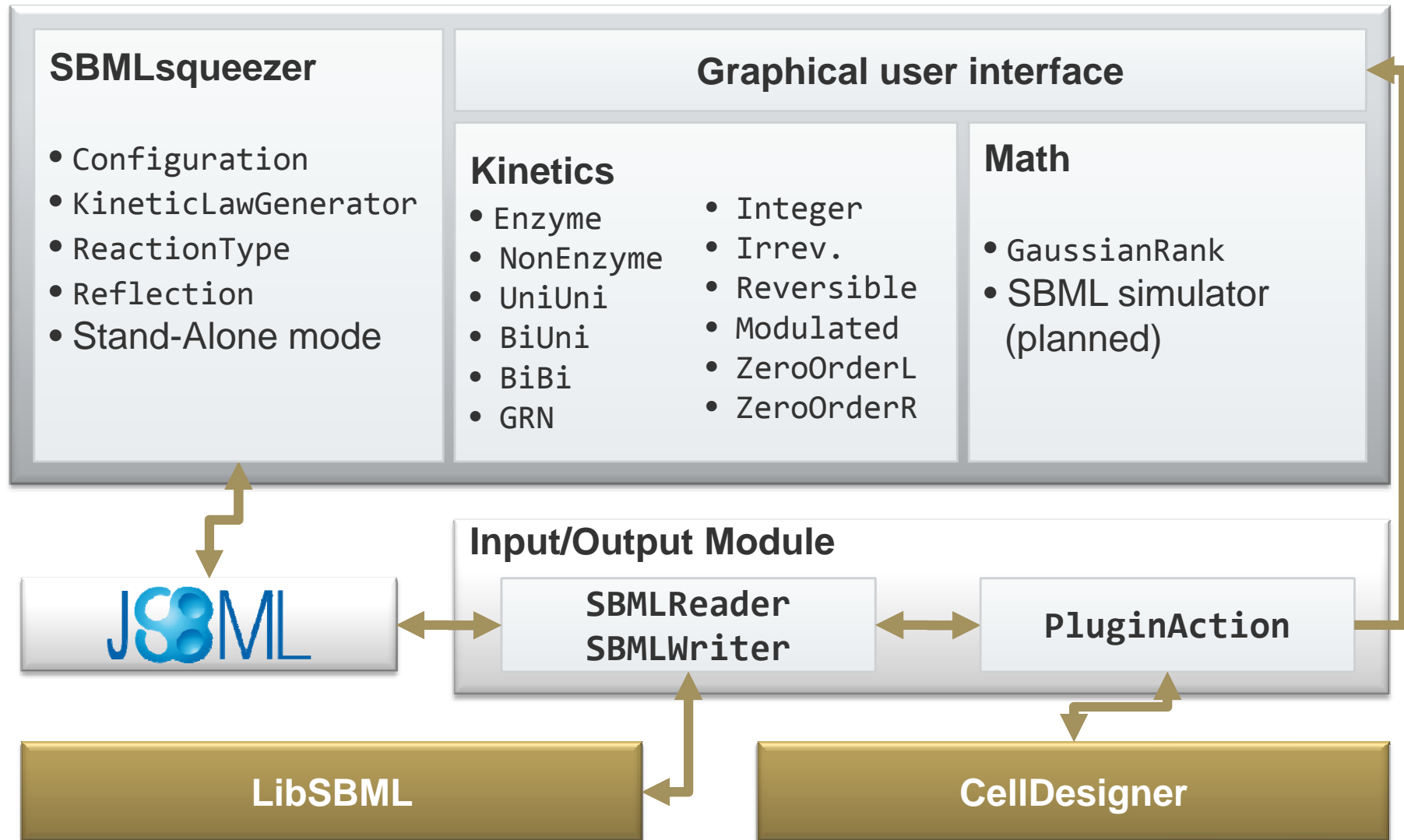


2
→





Architecture of SBMLsqueezer 1.3





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

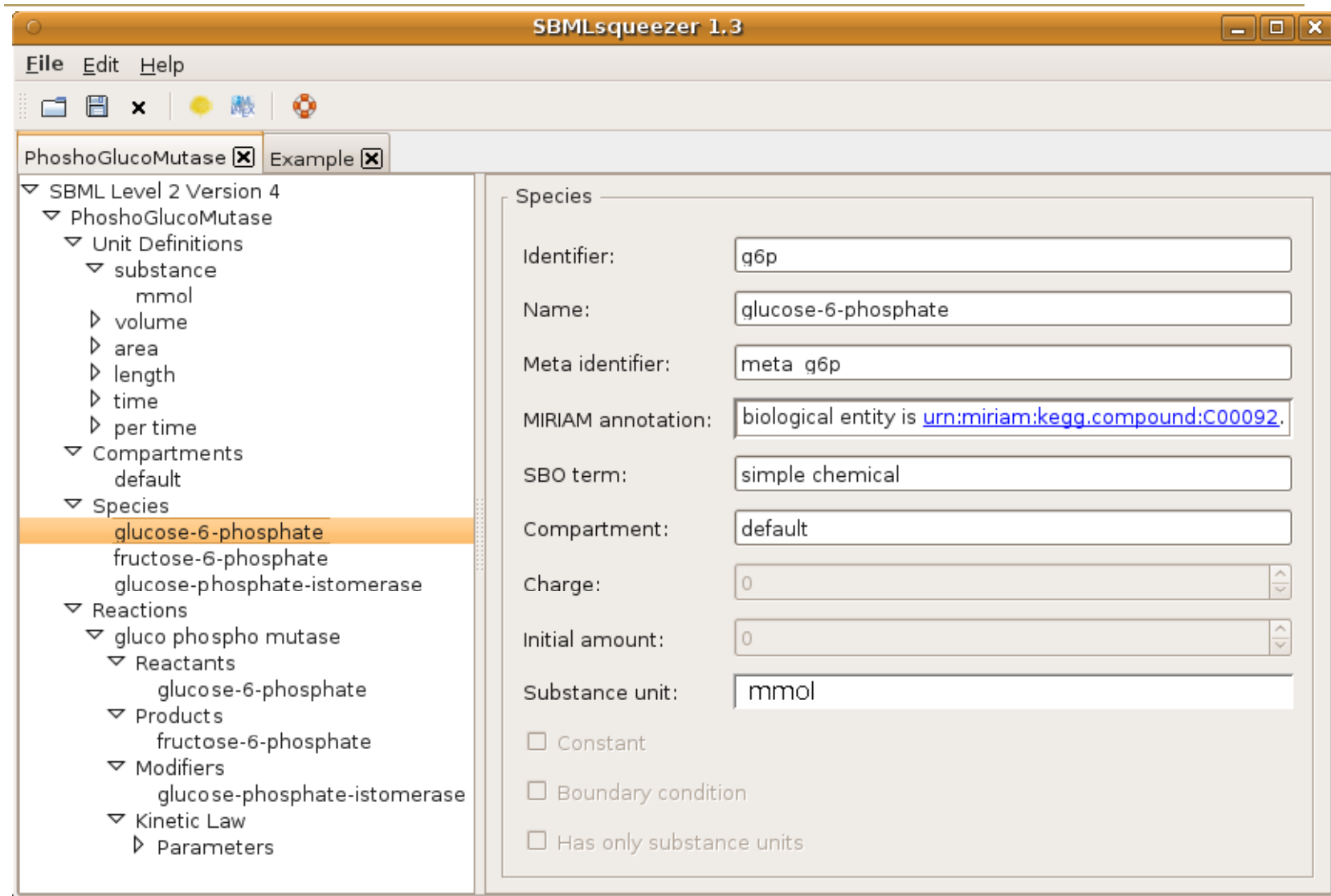
CellDesigner term	SBO term
KNOWN_TRANSITION_OMITTED	omitted process
STATE_TRANSITION	biochemical reaction
TRANSCRIPTION	transcription
TRANSLATION	translation
TRANSPORT	transport reaction
UNKNOWN_TRANSITION	uncertain process
reactant	reactant
product	product

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



SBMLsqueezer 1.3 stand-alone





Equation generation for single reactions

SBML Level 2 Version 4

- Example
 - Unit Definitions
 - mmol_per_min
 - mmol
 - $(60 \cdot 1 \cdot s)^{-1}$
 - Predefined unit substance
 - $1 \cdot \text{mol}$
 - Predefined unit volume
 - Predefined unit area
 - Predefined unit length
 - Predefined unit time
 - Compartments
 - cytosol
 - Species
 - S
 - P
 - Reactions
 - Squeeze kinetic law
 - Export to LaTeX

SBMLsqueezer

Please choose one kinetic law

- Common saturable rate law
- Convenience kinetics
- Direct saturable rate law
- Force dependent rate law
- Multiplicative saturable rate law
- Ordered mechanism
- Random order mechanism
- Reversible power law

Equation Preview

$$r_{e2} = \frac{v_{maf} r_{e2} \cdot \frac{[s4]}{k_{mcre2s4}} \cdot \frac{[s5]}{k_{mcre2s5}} - v_{mar} r_{e2} \cdot \frac{[s6]}{k_{mcre2s6}}}{\left(1 + \frac{[s4]}{k_{mcre2s4}}\right) \cdot \left(1 + \frac{[s5]}{k_{mcre2s5}}\right) + \frac{[s6]}{k_{mcre2s6}}}$$

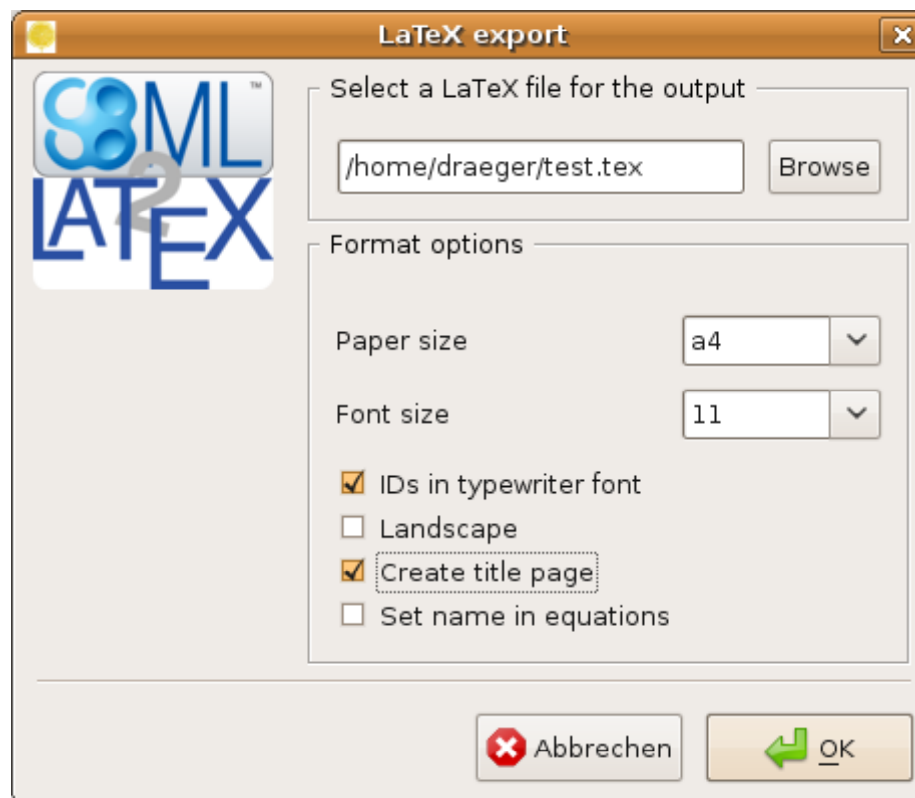
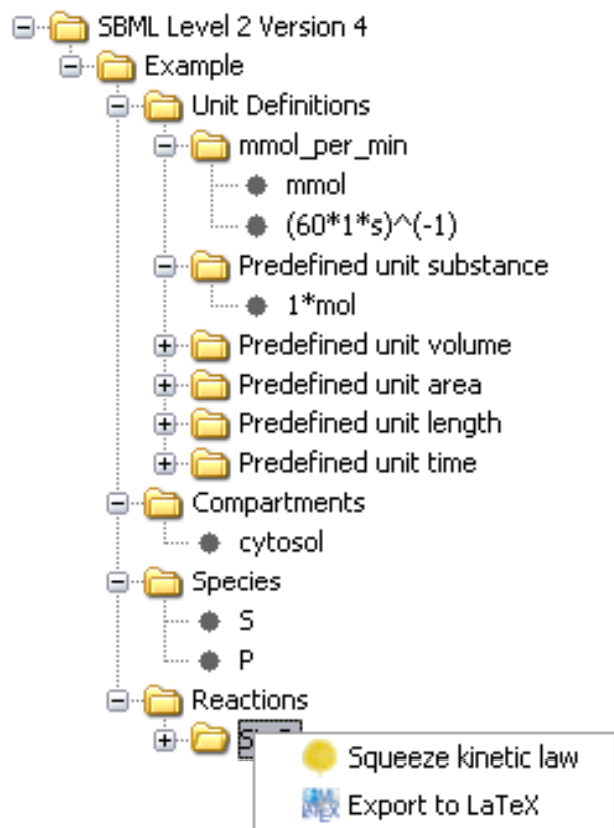
Reaction options

- Consider this reaction to be enzyme-catalyzed
- Reversible Irreversible
- Global parameters Local parameters

Abbrechen OK



Equation generation for single reactions





```

1 public static void main(String[] args) {
2     // Initialize SBMLsqueezer with appropriate SBML readers/writers
3     SBMLsqueezer sq = new SBMLsqueezer(new LibSBMLReader(), new
4         LibSBMLWriter());
5     // Configure SBMLsqueezer
6     sq.set(CfgKeys.OPT_ALL_REACTIONS_ARE_ENZYME_CATALYZED, true);
7     sq.set(CfgKeys.OPT_DEFAULT_COMPARTMENT_INITIAL_SIZE, 1d);
8     sq.set(CfgKeys.POSSIBLE_ENZYME_RNA, true);
9     sq.set(CfgKeys.KINETICS_UNI_UNI_TYPE, "MichaelisMenten");
10    sq.set(CfgKeys.KINETICS_OTHER_ENZYME_REACTIONS,
11        "ConvenienceKinetics");
12    try {
13        // Create kinetic equations, parameters, units etc. and save
14        // the result; args contains infile and outfile path
15        sq.squeeze(args[0], args[1]);
16    } catch (Throwable e) {
17        e.printStackTrace();
18    }
19 }

```

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





Thank you!

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