



## Context-based generation of kinetic equations with SBMLsqueezer 1.3

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

Generalized mass-action equation

Reversible Michaelis-Menten equation with inhibition

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

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

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:

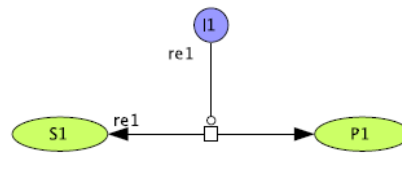
- Balance equations
- Species concentration dependencies
- Stoichiometric relationships

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

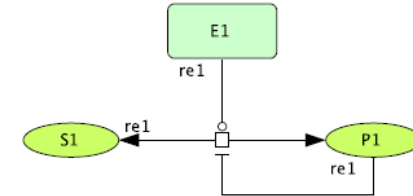
And what we cannot learn:

- Regulatory relationships
- Reaction velocity

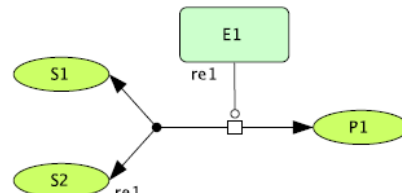
$$\nu(\mathbf{S}(t), \mathbf{p})$$



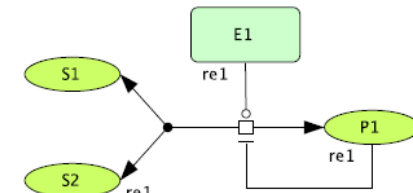
(a) Reversible ion-catalyzed reaction



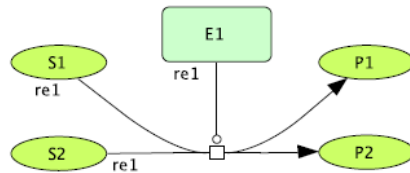
(b) Reversible uni-uni enzyme reaction with feedback inhibition



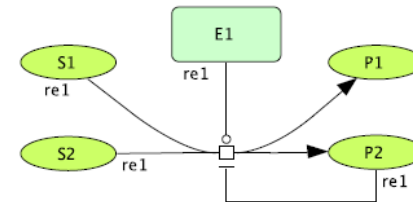
(c) Reversible bi-uni enzyme reaction



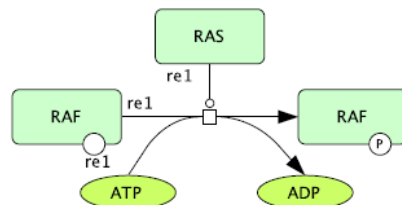
(d) Reversible bi-uni enzyme reaction with feedback inhibition



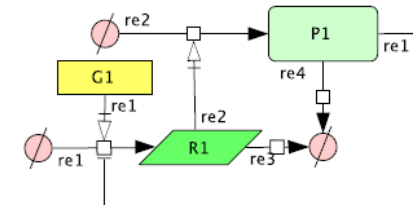
(e) Irreversible bi-bi enzyme reaction



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



(g) Irreversible signal transduction reaction



(h) Transcription and translation

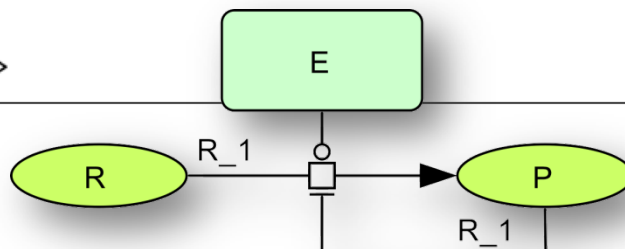


## An example for a Reaction object in SBML

```

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

The diagram shows a metabolic pathway with species s1, s3, s4, s5, s6, and s8, and reactions re1, re2, and re3. Species s1 is a yellow rectangle, s3 and s8 are green rectangles, and s4, s5, and s6 are green ovals. Reactions re1, re2, and re3 are indicated by arrows. A green triangle and a pink circle with a slash are also present.

The SBMLsqueezer window is open, showing the following options:

- 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:
 
$$v_{re2} = [s3] \cdot vol(c1) \cdot \frac{k_{cr} f_{re2} s_3 \cdot \frac{[s4] \cdot vol(c1)}{k_{mcr} e_2 s_4 s_3} \cdot \frac{[s5] \cdot vol(c1)}{k_{mcr} e_2 s_5}}{\left(1 + \frac{[s4] \cdot vol(c1)}{k_{mcr} e_2 s_4 s_3}\right) \cdot \left(1 + \frac{[s5] \cdot vol(c1)}{k_{mcr} e_2 s_5}\right)}$$
- Reaction options:
  - Consider this reaction to be enzyme-catalyzed
  - Reversible  Irreversible
  - Global parameters  Local parameters

Buttons: Cancel, OK



# Rate law generation in one single step

**SBMLsqueezer** Version 1.3

▼ hide options

Kinetics settings | Reaction mechanisms | Program settings | LaTeX output settings

**General options**

- Set boundary condition for gene coding species
- Consider all reactions to be enzyme-catalyzed
- Warnings for too many reactants: 3
- Default initial size for compartments: 1
- Default initial amount or concentration for species: 1
- Default value for new parameters: 1
- Remove unnecessary parameters and units
- Add all new parameters globally

**Generate new kinetics**

- Only when missing
- For all reactions
- Bring species to substance units
- Bring species to concentration units

**Reversibility**

- Use information from SBML
- Model all reactions in a reversible manner

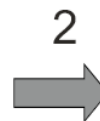
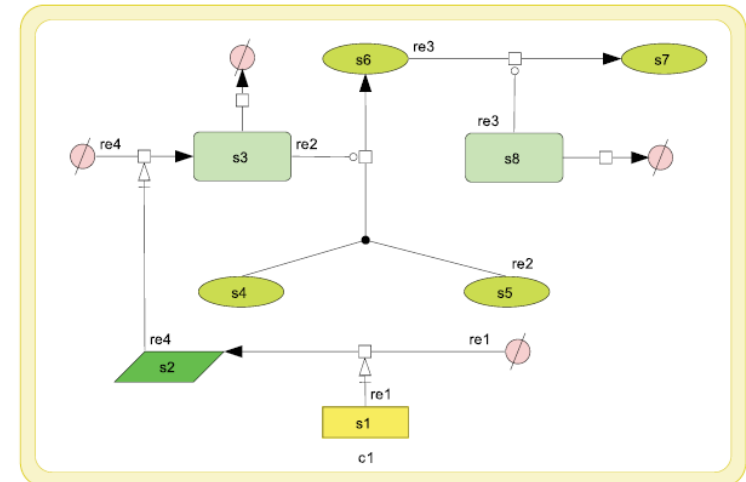
**Version of modular rate laws**

Choose the version of modular rate laws: cat

**Species to be treated as enzymes**

- Generic protein
- RNA
- Complex
- Truncated protein
- Receptor
- asRNA
- Unknown
- Simple molecule

Help | Cancel | Generate



**SBMLsqueezer** Version 1.3

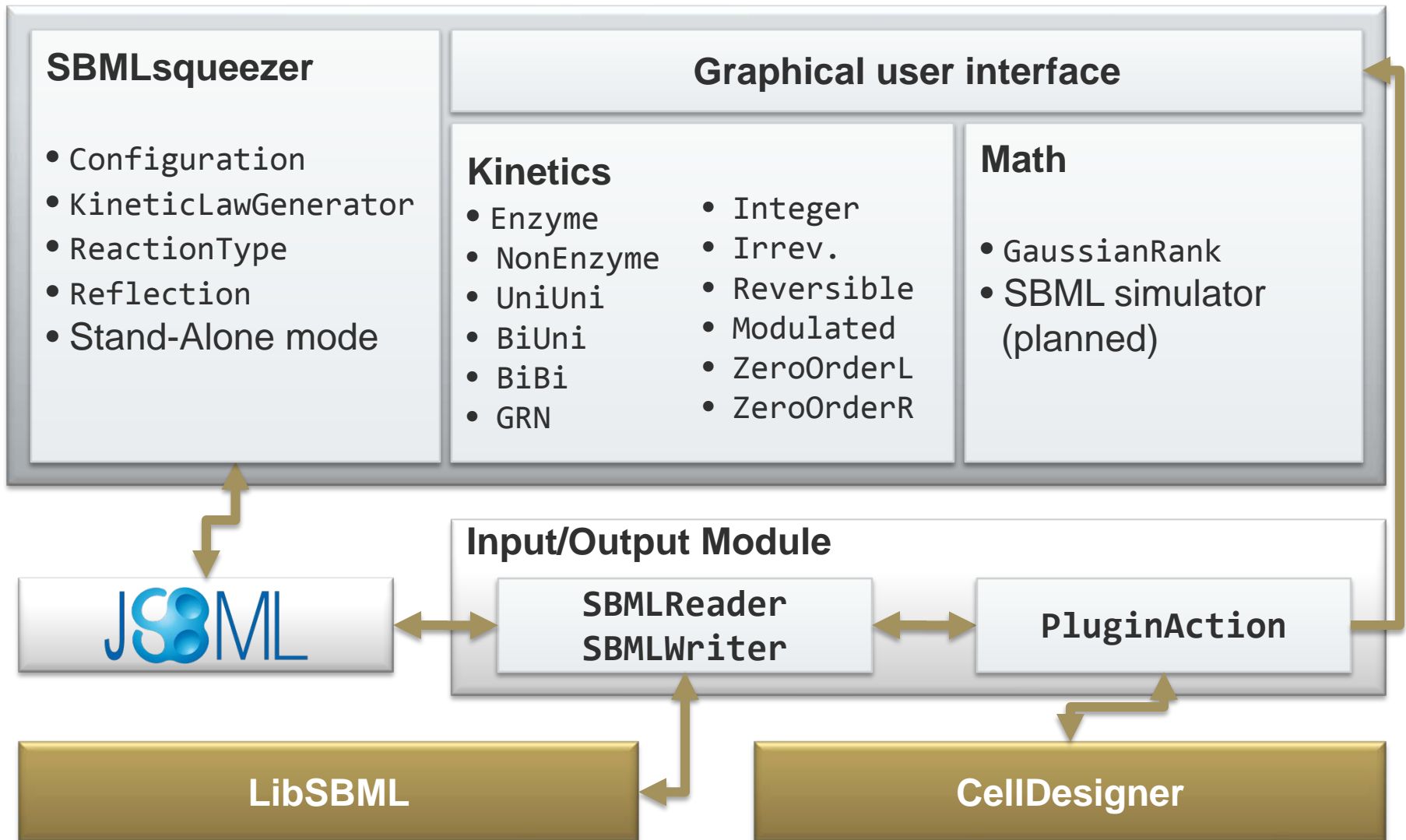
**Kinetic Equations** Number of warnings (red): 0

Reaction	Kinetic Law	SBO	#Reactants	Reactants	Products	Parameter
re1	Hill equation	SBO:0000192	1	s11	s2	hic_re1_s1
re2	Convenience kinetics	SBO:0000429	2	s4, s5	s6	kcrf_re2_s3
re3	Michaelis-Menten	SBO:0000326	1	s6	s7	kcrf_re3_s6
re4	Hill equation	SBO:0000192	1	s12	s3	hic_re4_s1
re5	Generalized mass-action	SBO:0000080	1	s3	s9	Dissociatio
re6	Generalized mass-action	SBO:0000080	1	s8	s10	Dissociatio

Export changes | Cancel | Back | Apply



# 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

File Edit Help

PhoshoGlucoMutase Example

- SBML Level 2 Version 4
  - PhoshoGlucoMutase
    - Unit Definitions
      - substance
        - mmol
        - volume
        - area
        - length
        - time
        - per time
      - Compartments
        - default
      - Species
        - glucose-6-phosphate**
        - fructose-6-phosphate
        - glucose-phosphate-istomerase
      - Reactions
        - gluco phospho mutase
          - Reactants
            - glucose-6-phosphate
          - Products
            - fructose-6-phosphate
          - Modifiers
            - glucose-phosphate-istomerase
          - Kinetic Law
            - Parameters

Species

Identifier: g6p

Name: glucose-6-phosphate

Meta identifier: meta g6p

MIRIAM annotation: biological entity is [urn:miriam:kegg.compound:C00092](http://www.ebi.ac.uk/kegg/compound/C00092).

SBO term: simple chemical

Compartment: default

Charge: 0

Initial amount: 0

Substance unit: mmol

Constant

Boundary condition

Has only substance units



# Equation generation for single reactions

SBML Level 2 Version 4

- Example
  - Unit Definitions
    - mmol\_per\_min
      - mmol
      - (60\*1\*s)^(-1)
    - Predefined unit substance
      - 1\*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

$$r_{e2} = \frac{v_{mafre2} \cdot \frac{[s4]}{k_{mcre2s4}} \cdot \frac{[s5]}{k_{mcre2s5}} - v_{marre2} \cdot \frac{[s6]}{k_{mcre2s6}}}{\left(1 + \frac{[s4]}{k_{mcre2s4}}\right) \cdot \left(1 + \frac{[s5]}{k_{mcre2s5}}\right) + \frac{[s6]}{k_{mcre2s6}}}$$

Reaction options

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

Abbrechen OK



SBML Level 2 Version 4

- Example
  - Unit Definitions
    - mmol\_per\_min
      - mmol
      - $(60*1*s)^{-1}$
    - Predefined unit substance
      - 1\*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

LaTeX export

Select a LaTeX file for the output

Format options

Paper size:

Font size:

IDs in typewriter font

Landscape

Create title page

Set name in equations



```

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





# Thank you!

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