

## SBML Model Report

**Model name:**  
**“Arnold2011\_Giersch1990\_CalvinCycle”**



May 6, 2016

### 1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Vijayalakshmi Chelliah<sup>1</sup>, Anne Arnold<sup>2</sup> and Zoran Nikoloski<sup>3</sup> at October 19<sup>th</sup> 2011 at 2:53 p. m. and last time modified at April eighth 2016 at 5:10 p. m. Table 1 gives an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	2
species types	0	species	11
events	0	constraints	0
reactions	6	function definitions	6
global parameters	2	unit definitions	2
rules	1	initial assignments	0

### Model Notes

This model is from the article:

**A quantitative comparison of CalvinBenson cycle models**

---

<sup>1</sup>EMBL-EBI, [viji@ebi.ac.uk](mailto:viji@ebi.ac.uk)

<sup>2</sup>Max-Planck-Institute of Molecular Plant Physiology, [arnold@mpimp-golm.mpg.de](mailto:arnold@mpimp-golm.mpg.de)

<sup>3</sup>Institute of Biochemistry and Biology, University of Potsdam, 14476 Potsdam, Germany, [nikoloski@mpimp-golm.mpg.de](mailto:nikoloski@mpimp-golm.mpg.de)

Anne Arnold, Zoran Nikoloski Trends in Plant Science 2011 Oct 14. [22001849](#),

**Abstract:**

The Calvin-Benson cycle (CBC) provides the precursors for biomass synthesis necessary for plant growth. The dynamic behavior and yield of the CBC depend on the environmental conditions and regulation of the cellular state. Accurate quantitative models hold the promise of identifying the key determinants of the tightly regulated CBC function and their effects on the responses in future climates. We provide an integrative analysis of the largest compendium of existing models for photosynthetic processes. Based on the proposed ranking, our framework facilitates the discovery of best-performing models with regard to metabolomics data and of candidates for metabolic engineering.

**Note:** Model of the Calvin cycle by Giersch et al. (1990, [DOI:10.1007/BF00032595](#)). The parameter values are taken from Figure 4 and 5. The initial metabolite values are chosen from the data set of Zhu et al. (2007, [DOI:10.1104/pp.107.103713](#)). A detailed description of all modifications is given in the model described by Arnold and Nikoloski (2011, [PMID:22001849](#)).

This model originates from BioModels Database: A Database of Annotated Published Models (<http://www.ebi.ac.uk/biomodels/>). It is copyright (c) 2005-2012 The BioModels.net Team.

For more information see the [terms of use](#).

To cite BioModels Database, please use: Li C, Donizelli M, Rodriguez N, Dharuri H, Endler L, Chelliah V, Li L, He E, Henry A, Stefan MI, Snoep JL, Hucka M, Le Novre N, Laibe C (2010) BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC Syst Biol.*, 4:92.

## 2 Unit Definitions

This is an overview of five unit definitions of which three are predefined by SBML and not mentioned in the model.

### 2.1 Unit volume

**Definition** l

### 2.2 Unit substance

**Definition** mmol

### 2.3 Unit area

**Notes** Square metre is the predefined SBML unit for area since SBML Level 2 Version 1.

**Definition** m<sup>2</sup>

### 2.4 Unit length

**Notes** Metre is the predefined SBML unit for length since SBML Level 2 Version 1.

**Definition** m

## 2.5 Unit time

**Notes** Second is the predefined SBML unit for time.

**Definition** s

## 3 Compartments

This model contains two compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
chloroplast	chloroplast		3	1	litre	<input checked="" type="checkbox"/>	
cytosol	cytosol		3	1	litre	<input checked="" type="checkbox"/>	

### 3.1 Compartment chloroplast

This is a three dimensional compartment with a constant size of one litre.

**Name** chloroplast

### 3.2 Compartment cytosol

This is a three dimensional compartment with a constant size of one litre.

**Name** cytosol

## 4 Species

This model contains eleven species. The boundary condition of four of these species is set to `true` so that these species' amount cannot be changed by any reaction. Section 9 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condi- tion
RuBP	RuBP	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
PGA	PGA	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
TP	TP	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Ru5P	Ru5P	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Pi	Pi	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
ATP	ATP	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
ADP	ADP	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
E_RuBisCO	RuBisCo	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
totRuBP	totRuBP	chloroplast	$\text{mmol} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
TPc	TPc	cytosol	$\text{mmol} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Pic	Pic	cytosol	$\text{mmol} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

## 5 Parameters

This model contains two global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V6	V6	0000009	5.880		<input checked="" type="checkbox"/>
P_0	P_0	0000009	16.000		<input checked="" type="checkbox"/>

## 6 Function definitions

This is an overview of six function definitions.

### 6.1 Function definition [function\\_6](#)

**Name** PGA reduction

**Arguments**  $V_m$ ,  $S_1$ ,  $S_2$ ,  $P_1$ ,  $P_2$ ,  $P_3$ ,  $k$ ,  $K_1$ ,  $K_2$

**Mathematical Expression**

$$\frac{V_m \cdot \left( S_1 \cdot S_2 - \frac{P_1 \cdot P_2 \cdot P_3}{k} \right)}{K_1 + \frac{S_1 \cdot S_2 \cdot K_1}{K_2} + \frac{P_1 \cdot P_2 \cdot P_3}{k}} \quad (1)$$

### 6.2 Function definition [function\\_5](#)

**Name** High Substrate MM - RuBisCO

**Arguments**  $k$ ,  $E$ ,  $S$ ,  $K$

**Mathematical Expression**

$$\frac{k}{2} \cdot \left( E + S + K - \sqrt{2} \right) \quad (2)$$

### 6.3 Function definition [function\\_7](#)

**Name** MM s1 - reg (TP reduction)

**Arguments**  $V_m$ ,  $S$ ,  $K$

**Mathematical Expression**

$$\frac{V_m \cdot S}{S + K} \quad (3)$$

## 6.4 Function definition [function\\_8](#)

**Name** RuBP regeneration

**Arguments**  $V_m$ ,  $S_1$ ,  $S_2$ ,  $K_1$ ,  $K_2$ ,  $K_3$ ,  $R$

**Mathematical Expression**

$$\frac{V_m \cdot S_1 \cdot S_2}{K_1 \cdot K_2 + K_2 \cdot S_2 + S_1 \cdot S_2 + K_3 \cdot R} \quad (4)$$

## 6.5 Function definition [function\\_10](#)

**Name** MM s2 - reg (ATP synthesis)

**Arguments**  $V_m$ ,  $s_1$ ,  $s_2$ ,  $K_1$ ,  $K_2$

**Mathematical Expression**

$$\frac{V_m \cdot s_1 \cdot s_2}{(s_1 + K_1) \cdot (s_2 + K_2)} \quad (5)$$

## 6.6 Function definition [function\\_9](#)

**Name** TP translocator

**Arguments**  $S_1$ ,  $S_2$ ,  $P_1$ ,  $P_2$ ,  $K_2$ ,  $K_1$ ,  $V_m$

**Mathematical Expression**

$$\frac{V_m \cdot (S_1 \cdot S_2 - P_1 \cdot P_2)}{(S_1 + P_1) \cdot K_2 + (S_2 + P_2) \cdot K_1 + K_1 \cdot K_2 \cdot \left(\frac{S_1}{K_1} + \frac{P_2}{K_2}\right) \cdot \left(\frac{S_2}{K_2} + \frac{P_1}{K_1}\right)} \quad (6)$$

# 7 Rule

This is an overview of one rule.

## 7.1 Rule [totRuBP](#)

Rule `totRuBP` is an assignment rule for species `totRuBP`:

$$\text{totRuBP} = \frac{1}{2} \cdot (P_0 - ([\text{PGA}] + [\text{TP}] + [\text{Ru5P}] + [\text{Pi}] + [\text{ATP}])) \quad (7)$$

## 8 Reactions

This model contains six reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by a modifier, the identifier of this species is written above the reaction arrow.

Table 5: Overview of all reactions

Nº	Id	Name	Reaction Equation	SBO
1	RuBisCO	RuBisCO	$\text{totRuBP} + \text{RuBP} \xrightarrow{\text{E\_RuBisCO}} 2 \text{PGA}$	
2	PGA_red	PGA reduction	$\text{PGA} + \text{ATP} \rightleftharpoons \text{ADP} + \text{TP} + \text{Pi}$	
3	TP_red	TP reduction	$5 \text{TP} \longrightarrow 3 \text{Ru5P} + 2 \text{Pi}$	
4	RuBP_reg	RuBP regeneration	$\text{Ru5P} + \text{ATP} \xrightarrow{\text{Pi}} \text{RuBP} + \text{ADP}$	
5	TPT	TP translocator	$\text{TP} + \text{Pic} \rightleftharpoons \text{TPc} + \text{Pi}$	
6	ATP_S	ATP synthesis	$\text{ADP} + \text{Pi} \longrightarrow \text{ATP}$	

## 8.1 Reaction RuBisCO

This is an irreversible reaction of two reactants forming one product influenced by one modifier.

**Name** RuBisCO

### Reaction equation



### Reactants

Table 6: Properties of each reactant.

Id	Name	SBO
totRuBP	totRuBP	
RuBP	RuBP	

### Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
E_RuBisCO	RuBisCo	

### Product

Table 8: Properties of each product.

Id	Name	SBO
PGA	PGA	

### Kinetic Law

**Derived unit** contains undeclared units

$$v_1 = \text{vol}(\text{chloroplast}) \cdot \text{function\_5}(k, [\text{E\_RuBisCO}], [\text{totRuBP}], K) \quad (9)$$

$$\text{function\_5}(k, E, S, K) = \frac{k}{2} \cdot (E + S + K - \sqrt{2}) \quad (10)$$

$$\text{function\_5}(k, E, S, K) = \frac{k}{2} \cdot (E + S + K - \sqrt{2}) \quad (11)$$



Table 9: Properties of each parameter.

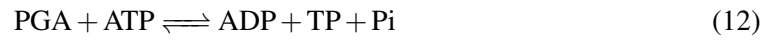
Id	Name	SBO	Value	Unit	Constant
k	k	0000009	0.504		<input checked="" type="checkbox"/>
K	K	0000009	0.040		<input checked="" type="checkbox"/>

## 8.2 Reaction `PGA_red`

This is a reversible reaction of two reactants forming three products.

**Name** PGA reduction

### Reaction equation



### Reactants

Table 10: Properties of each reactant.

Id	Name	SBO
PGA	PGA	
ATP	ATP	

### Products

Table 11: Properties of each product.

Id	Name	SBO
ADP	ADP	
TP	TP	
Pi	Pi	

### Kinetic Law

**Derived unit** contains undeclared units

$$v_2 = \text{vol}(\text{chloroplast}) \cdot \text{function\_6}(V_m, [\text{PGA}], [\text{ATP}], [\text{ADP}], [\text{TP}], [\text{Pi}], k, K_1, K_2) \quad (13)$$

$$\text{function\_6}(V_m, S_1, S_2, P_1, P_2, P_3, k, K_1, K_2) = \frac{V_m \cdot \left( S_1 \cdot S_2 - \frac{P_1 \cdot P_2 \cdot P_3}{k} \right)}{K_1 + \frac{S_1 \cdot S_2 \cdot K_1}{K_2} + \frac{P_1 \cdot P_2 \cdot P_3}{k}} \quad (14)$$

$$\text{function\_6}(V_m, S_1, S_2, P_1, P_2, P_3, k, K_1, K_2) = \frac{V_m \cdot \left( S_1 \cdot S_2 - \frac{P_1 \cdot P_2 \cdot P_3}{k} \right)}{K_1 + \frac{S_1 \cdot S_2 \cdot K_1}{K_2} + \frac{P_1 \cdot P_2 \cdot P_3}{k}} \quad (15)$$

Table 12: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V <sub>m</sub>	V <sub>m</sub>	0000009	3.49		<input checked="" type="checkbox"/>
k	k	0000009	14.00		<input checked="" type="checkbox"/>
K <sub>1</sub>	K <sub>1</sub>	0000009	1.00		<input checked="" type="checkbox"/>
K <sub>2</sub>	K <sub>2</sub>	0000009	1.00		<input checked="" type="checkbox"/>

### 8.3 Reaction TP<sub>red</sub>

This is an irreversible reaction of one reactant forming two products.

**Name** TP reduction

#### Reaction equation



#### Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
TP	TP	

#### Products

Table 14: Properties of each product.

Id	Name	SBO
Ru5P	Ru5P	
Pi	Pi	

#### Kinetic Law

**Derived unit** contains undeclared units

$$v_3 = \text{vol}(\text{chloroplast}) \cdot \text{function\_7}(V_m, [\text{TP}], K) \quad (17)$$

$$\text{function\_7}(V_m, S, K) = \frac{V_m \cdot S}{S + K} \quad (18)$$

$$\text{function\_7}(V_m, S, K) = \frac{V_m \cdot S}{S + K} \quad (19)$$

Table 15: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V <sub>m</sub>	V <sub>m</sub>	0000009	1.06		<input checked="" type="checkbox"/>
K	K	0000009	0.40		<input checked="" type="checkbox"/>

## 8.4 Reaction RuBP<sub>reg</sub>

This is an irreversible reaction of two reactants forming two products influenced by one modifier.

**Name** RuBP regeneration

### Reaction equation



### Reactants

Table 16: Properties of each reactant.

Id	Name	SBO
Ru5P	Ru5P	
ATP	ATP	

### Modifier

Table 17: Properties of each modifier.

Id	Name	SBO
Pi	Pi	

### Products

Table 18: Properties of each product.

Id	Name	SBO
RuBP	RuBP	
ADP	ADP	

### Kinetic Law

**Derived unit** contains undeclared units

$$v_4 = \text{vol}(\text{chloroplast}) \cdot \text{function\_8}(V_m, [\text{Ru5P}], [\text{ATP}], K_1, K_2, K_3, [\text{Pi}]) \quad (21)$$

$$\text{function\_8}(V_m, S_1, S_2, K_1, K_2, K_3, R) = \frac{V_m \cdot S_1 \cdot S_2}{K_1 \cdot K_2 + K_2 \cdot S_2 + S_1 \cdot S_2 + K_3 \cdot R} \quad (22)$$

$$\text{function\_8}(V_m, S_1, S_2, K_1, K_2, K_3, R) = \frac{V_m \cdot S_1 \cdot S_2}{K_1 \cdot K_2 + K_2 \cdot S_2 + S_1 \cdot S_2 + K_3 \cdot R} \quad (23)$$

Table 19: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V <sub>m</sub>	V <sub>m</sub>	0000009	4.81		✓
K <sub>1</sub>	K <sub>1</sub>	0000009	0.05		✓
K <sub>2</sub>	K <sub>2</sub>	0000009	0.50		✓
K <sub>3</sub>	K <sub>3</sub>	0000009	0.05		✓

### 8.5 Reaction TPT

This is a reversible reaction of two reactants forming two products.

**Name** TP translocator

### Reaction equation



### Reactants

Table 20: Properties of each reactant.

Id	Name	SBO
TP	TP	
Pic	Pic	

## Products

Table 21: Properties of each product.

Id	Name	SBO
TPc	TPc	
Pi	Pi	

## Kinetic Law

**Derived unit** contains undeclared units

$$v_5 = \text{function\_9}([TP], [Pic], [TPc], [Pi], K2, K1, Vm) \quad (25)$$

$$\begin{aligned} & \text{function\_9}(S1, S2, P1, P2, K2, K1, Vm) \\ &= \frac{Vm \cdot (S1 \cdot S2 - P1 \cdot P2)}{(S1 + P1) \cdot K2 + (S2 + P2) \cdot K1 + K1 \cdot K2 \cdot \left(\frac{S1}{K1} + \frac{P2}{K2}\right) \cdot \left(\frac{S2}{K2} + \frac{P1}{K1}\right)} \end{aligned} \quad (26)$$

Table 22: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K2	K2	0000009	0.25		<input checked="" type="checkbox"/>
K1	K1	0000009	0.08		<input checked="" type="checkbox"/>
Vm	Vm	0000009	3.30		<input checked="" type="checkbox"/>

## 8.6 Reaction ATP\_S

This is an irreversible reaction of two reactants forming one product.

**Name** ATP synthesis

## Reaction equation



## Reactants

Table 23: Properties of each reactant.

Id	Name	SBO
ADP	ADP	
Pi	Pi	

## Product

Table 24: Properties of each product.

Id	Name	SBO
ATP	ATP	

## Kinetic Law

**Derived unit** contains undeclared units

$$v_6 = \text{vol}(\text{chloroplast}) \cdot \text{function\_10}(V_6, [\text{ADP}], [\text{Pi}], K_1, K_2) \quad (28)$$

$$\text{function\_10}(V_m, s_1, s_2, K_1, K_2) = \frac{V_m \cdot s_1 \cdot s_2}{(s_1 + K_1) \cdot (s_2 + K_2)} \quad (29)$$

$$\text{function\_10}(V_m, s_1, s_2, K_1, K_2) = \frac{V_m \cdot s_1 \cdot s_2}{(s_1 + K_1) \cdot (s_2 + K_2)} \quad (30)$$

Table 25: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K1	K1	0000009	0.08		<input checked="" type="checkbox"/>
K2	K2	0000009	0.50		<input checked="" type="checkbox"/>

## 9 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

Identifiers for kinetic laws highlighted in gray cannot be verified to evaluate to units of SBML substance per time. As a result, some SBML interpreters may not be able to verify the

consistency of the units on quantities in the model. Please check if

- parameters without an unit definition are involved or
- volume correction is necessary because the `hasOnlySubstanceUnits` flag may be set to `false` and `spacialDimensions`  $> 0$  for certain species.

### 9.1 Species RuBP

**Name** RuBP

**Initial concentration**  $2 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in [RuBisCO](#) and as a product in [RuBP\\_reg](#)).

$$\frac{d}{dt}\text{RuBP} = v_4 - v_1 \quad (31)$$

### 9.2 Species PGA

**Name** PGA

**Initial concentration**  $2.4 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in [PGA\\_red](#) and as a product in [RuBisCO](#)).

$$\frac{d}{dt}\text{PGA} = 2 v_1 - v_2 \quad (32)$$

### 9.3 Species TP

**Name** TP

**Initial concentration**  $0.5 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in [TP\\_red](#), [TPT](#) and as a product in [PGA\\_red](#)).

$$\frac{d}{dt}\text{TP} = v_2 - 5 v_3 - v_5 \quad (33)$$

### 9.4 Species Ru5P

**Name** Ru5P

**Initial concentration**  $0.0500747384155456 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in [RuBP\\_reg](#) and as a product in [TP\\_red](#)).

$$\frac{d}{dt}\text{Ru5P} = 3 v_3 - v_4 \quad (34)$$

## 9.5 Species Pi

**Name** Pi

**Initial concentration** 5 mmol · l<sup>-1</sup>

This species takes part in five reactions (as a reactant in [ATP\\_S](#) and as a product in [PGA\\_red](#), [TP\\_red](#), [TPT](#) and as a modifier in [RuBP\\_reg](#)).

$$\frac{d}{dt}\text{Pi} = v_2 + 2 v_3 + v_5 - v_6 \quad (35)$$

## 9.6 Species ATP

**Name** ATP

**Initial concentration** 0.68 mmol · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in [PGA\\_red](#), [RuBP\\_reg](#) and as a product in [ATP\\_S](#)).

$$\frac{d}{dt}\text{ATP} = v_6 - v_2 - v_4 \quad (36)$$

## 9.7 Species ADP

**Name** ADP

**Initial concentration** 0.82 mmol · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in [ATP\\_S](#) and as a product in [PGA\\_red](#), [RuBP\\_reg](#)).

$$\frac{d}{dt}\text{ADP} = v_2 + v_4 - v_6 \quad (37)$$

## 9.8 Species E\_RuBisCO

**Name** RuBisCo

**Initial concentration** 3.56 mmol · l<sup>-1</sup>

This species takes part in one reaction (as a modifier in [RuBisCO](#)), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{E\_RuBisCO} = 0 \quad (38)$$



## 9.9 Species `totRuBP`

**Name** `totRuBP`

**Initial concentration**  $3.68496263079223 \text{ mmol} \cdot \text{l}^{-1}$

**Involved in rule** `totRuBP`

This species takes part in one reaction (as a reactant in `RuBisCO`). Not this but one rule determines the species' quantity because this species is on the boundary of the reaction system.

## 9.10 Species `TPc`

**Name** `TPc`

**Initial concentration**  $0.2 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a product in `TPT`), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt} \text{TPc} = 0 \quad (39)$$

## 9.11 Species `Pic`

**Name** `Pic`

**Initial concentration**  $1.4 \text{ mmol} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a reactant in `TPT`), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt} \text{Pic} = 0 \quad (40)$$

# A Glossary of Systems Biology Ontology Terms

**SBO:0000009 kinetic constant:** Numerical parameter that quantifies the velocity of a chemical reaction

SBML<sup>2</sup>TeX was developed by Andreas Dräger<sup>a</sup>, Hannes Planatscher<sup>a</sup>, Dieudonné M Wouamba<sup>a</sup>, Adrian Schröder<sup>a</sup>, Michael Hucka<sup>b</sup>, Lukas Endler<sup>c</sup>, Martin Golebiewski<sup>d</sup> and Andreas Zell<sup>a</sup>. Please see <http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX> for more information.

<sup>a</sup>Center for Bioinformatics Tübingen (ZBIT), Germany

<sup>b</sup>California Institute of Technology, Beckman Institute BNMC, Pasadena, United States

<sup>c</sup>European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom

<sup>d</sup>EML Research gGmbH, Heidelberg, Germany