SBML Model Report

Model name: "Wang2008 - Mimicking the inhibitory effect of riluzole on membrane conductance in skeletal fibres"



May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Matthew Grant Roberts¹ at March 21st 2018 at 2:33 p.m. and last time modified at March 21st 2018 at 4:32 p.m. Table 1 provides 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	1
species types	0	species	27
events	0	constraints	0
reactions	0	function definitions	0
global parameters	55	unit definitions	3
rules	36	initial assignments	0

Model Notes

Wang2008 - Mimicking the inhibitory effect of riluzole on membrane conductance in skeletal fibres

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This model is described in the article:Riluzole-induced block of voltage-gated Na+ current and activation of BKCa channels in cultured differentiated human skeletal muscle cells.Wang YJ, Lin MW, Lin AA, Wu SN.Life Sci. 2008 Jan; 82(1-2): 11-20

Abstract

Riluzole is known to be of therapeutic use in the management of amyotrophic lateral sclerosis. In this study, we investigated the effects of riluzole on ion currents in cultured differentiated human skeletal muscle cells (dHSkMCs). Western blotting revealed the protein expression of alpha-subunits for both large-conductance Ca2+-activated K+ (BK(Ca)) channel and Na+ channel (Na(v)1.5) in these cells. Riluzole could reduce the frequency of spontaneous beating in dHSkMCs. In whole-cell configuration, riluzole suppressed voltage-gated Na+ current (I(Na)) in a concentration-dependent manner with an IC50 value of 2.3 microM. Riluzole (10 microM) also effectively increased Ca2+-activated K+ current (I(K(Ca))) which could be reversed by iberiotoxin (200 nM) and paxilline (1 microM), but not by apamin (200 nM). In inside-out patches, when applied to the inside of the cell membrane, riluzole (10 microM) increased BK(Ca)-channel activity with a decrease in mean closed time. Simulation studies also unraveled that both decreased conductance of I(Na) and increased conductance of I(K(Ca)) utilized to mimic riluzole actions in skeletal muscle cells could combine to decrease the amplitude of action potentials and increase the repolarization of action potentials. Taken together, inhibition of I(Na) and stimulation of BK(Ca)-channel activity caused by this drug are partly, if not entirely, responsible for its muscle relaxant actions in clinical setting.

This model is hosted on BioModels Database and identified by: BIOMD0000000693.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

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2 Unit Definitions

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

2.1 Unit volume

Name volume

Definition ml

2.2 Unit time

Name time

Definition ms

2.3 Unit substance

Name substance

Definition mmol

2.4 Unit area

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

Definition m²

2.5 Unit length

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

Definition m

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
Skeletal_Muscle_Cells	Skeletal Muscle Cells		3	1	litre	Ø	

3.1 Compartment Skeletal_Muscle_Cells

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

Name Skeletal Muscle Cells

4 Species

This model contains 27 species. The boundary condition of 27 of these species is set to true so that these species' amount cannot be changed by any reaction. Section 7 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
Vm	Vm	Skeletal_Muscle_Cells	$\operatorname{mmol} \cdot \operatorname{ml}^{-1}$		\overline{Z}
m	m	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$\overline{\mathbf{Z}}$
h	h	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$\overline{\mathbf{Z}}$
n	n	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$\overline{\mathbf{Z}}$
Vt	Vt	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$ \overline{\checkmark} $
d	d	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
0	o	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\checkmark} $
С	c	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
cer	cer	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
INa	INa	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$ \overline{\mathbf{Z}} $
IT	IT	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$ \overline{\checkmark} $
IKCa	IKCa	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$ \overline{\mathbf{Z}} $
ICa	ICa	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
IL	IL	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
IK	IK	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\mathbf{Z}} $
Stimulus	Stimulus	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		$ \overline{\checkmark} $
beta_n	beta_n	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$ \overline{\mathbf{Z}} $
beta_m	beta_m	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$\overline{\mathbf{Z}}$
beta_h	beta_h	Skeletal_Muscle_Cells	$\mathrm{mmol}\cdot\mathrm{ml}^{-1}$		$\overline{\mathbf{Z}}$
alpha_n	alpha_n	$Skeletal_Muscle_Cells$	$\text{mmol}\cdot\text{ml}^{-1}$		$\overline{\mathbf{Z}}$

Id	Name	Compartment	Derived Unit	Constant	Boundary Condi- tion
alpha_m	alpha_m	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		\overline{Z}
alpha_h	alpha_h	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		
W	W	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$	\Box	
jmem	jmem	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		
jleak	jleak	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		
jserca	jserca	Skeletal_Muscle_Cells	$\text{mmol}\cdot\text{ml}^{-1}$		
jer	jer	${\tt Skeletal_Muscle_Cells}$	$\text{mmol}\cdot\text{ml}^{-1}$		

5 Parameters

This model contains 55 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
gNa_max	gNa_max		0.900		
gcabar	gcabar		0.050		$ \overline{\mathscr{A}} $
$\mathtt{gk}\mathtt{_max}$	gk_max		0.420		\square
$\mathtt{gL}\mathtt{_max}$	gL_max		0.002		
gKca	gKca		0.500		
ENa	ENa		50.000		
EK	EK		-70.000		
EL	EL		-75.000		
ECa	ECa		50.000		
En	En		-40.000		\square
Em	Em		-42.000		
Eh	Eh		-41.000		
Ct	Ct		0.040		
Cm	Cm		0.009		
Rs	Rs		15.000		
Am	Am		200.000		
$alpha_n_max$	alpha_n_max		0.023		
beta_n_max	beta_n_max		0.096		
v_alpha_m	v_alpha_m		10.000		
v_alpha_n	v_alpha_n		7.000		
v_alpha_h	v_alpha_h		14.700		
${\tt alpha_m_max}$	alpha_m_max		0.208		
beta_m_max	beta_m_max		2.081		\square
v_beta_n	v_beta_n		40.000		
${\tt v_beta_m}$	v_beta_m		18.000		
v_beta_h	v_beta_h		7.600		\square
$alpha_h_max$	alpha_h_max		0.016		\square
beta_h_max	beta_h_max		3.382		\square
kd	kd		0.180		\square
alpha	alpha		4.5 · 10	0^{-6}	\square
kpmca	kpmca		0.200		\square
pleak	pleak		5 · 10	0^{-4}	\square
kserca	kserca		0.400		\checkmark
d1	d1		0.840		\checkmark
d2	d2		1.000		\checkmark
k1	k1		0.180		

Id	Name	SBO	Value	Unit	Constant
k2	k2		0.011		\overline{Z}
bbar	bbar		0.280		$ \overline{\mathscr{A}} $
abar	abar		0.480		
fer	fer		0.010		
vcytver	vcytver		5.000		\mathbf{Z}
fcyt	fcyt		0.010		
Stimulus-	Stimulus_Period		50.000		
_Period	C4:1		2 000		
Stimulus-	Stimulus-		2.000		\square
Magnitude	_Magnitude		<i>5</i> ,000		
Stimulus-	Stimulus_Start		5.000		\square
_Start	ar i b r		1 000		
Stimulus-	Stimulus_Duration		1.000		\square
_Duration	1		0.004		_
alp	alp		0.004		
beta	beta		0.267		\Box
tau	tau		3.699		\Box
ooinf	ooinf		0.013		\Box
dinf	dinf		0.011		
taud	taud		141.867		
alphad	alphad		8.05558916679958 · 10-	5	
betad	betad		0.007		\Box
gca	gca		-3.751		

6 Rules

This is an overview of 36 rules.

6.1 Rule IK

Rule IK is an assignment rule for species IK:

$$IK = gk_{max} \cdot [n]^4 \cdot ([Vm] - EK)$$
 (1)

6.2 Rule INa

Rule INa is an assignment rule for species INa:

$$INa = gNa_max \cdot [m]^3 \cdot [h] \cdot ([Vm] - ENa)$$
 (2)

6.3 Rule Stimulus

Rule Stimulus is an assignment rule for species Stimulus:

 $Stimulus \\ = \begin{cases} Stimulus_Magnitude & if (time \geq Stimulus_Start) \land \left(time - Stimulus_Start - \left\lfloor \frac{time - Stimulus_Start}{Stimulus_Period} \right\rfloor \cdot Stimulus_Period \end{cases}$

6.4 Rule IL

Rule IL is an assignment rule for species IL:

$$IL = gL_{max} \cdot ([Vm] - EL) \tag{4}$$

6.5 Rule IT

Rule IT is an assignment rule for species IT:

$$IT = \frac{[Vm] - [Vt]}{Rs} \tag{5}$$

6.6 Rule beta_n

Rule beta_n is an assignment rule for species beta_n:

$$beta_n = beta_n \max \cdot exp\left(\frac{En - [Vm]}{v_beta_n}\right)$$
 (6)

6.7 Rule alpha_n

Rule alpha_n is an assignment rule for species alpha_n:

$$alpha_n = \frac{alpha_n_max \cdot ([Vm] - En)}{1 - exp\left(\frac{En - [Vm]}{v_alpha_n}\right)}$$
(7)

6.8 Rule beta_h

Rule beta_h is an assignment rule for species beta_h:

$$beta_h = \frac{beta_h max}{1 + exp\left(\frac{Eh - [Vm]}{v_beta_h}\right)}$$
(8)

6.9 Rule beta_m

Rule beta_m is an assignment rule for species beta_m:

$$beta_m = beta_m_max \cdot exp\left(\frac{Em - [Vm]}{v_beta_m}\right) \tag{9}$$

6.10 Rule alpha_m

Rule alpha m is an assignment rule for species alpha m:

$$alpha_m = \frac{alpha_m_max \cdot ([Vm] - Em)}{1 - exp\left(\frac{Em - [Vm]}{v_alpha_m}\right)}$$
(10)

6.11 Rule alpha_h

Rule alpha_h is an assignment rule for species alpha_h:

$$alpha_h = alpha_h_max \cdot exp\left(\frac{Eh - [Vm]}{v_alpha_m}\right) \tag{11}$$

6.12 Rule w

Rule w is an assignment rule for species w:

$$w = \frac{[c]^5}{[c]^5 + kd^5}$$
 (12)

6.13 Rule IKCa

Rule IKCa is an assignment rule for species IKCa:

$$IKCa = gKca \cdot [o] \cdot [w] \cdot ([Vm] - EK)$$
(13)

6.14 Rule jleak

Rule jleak is an assignment rule for species jleak:

$$jleak = pleak \cdot ([cer] - [c])$$
 (14)

6.15 Rule jserca

Rule jserca is an assignment rule for species jserca:

$$jserca = kserca \cdot [c]$$
 (15)

6.16 Rule jer

Rule jer is an assignment rule for species jer:

$$ier = [ileak] - [iserca]$$
 (16)

Derived unit $mmol \cdot ml^{-1}$

6.17 Rule alp

Rule alp is an assignment rule for parameter alp:

$$alp = \frac{abar}{\frac{k1 \cdot exp\left(\frac{2 \cdot d1 \cdot 96 \cdot 485 \cdot [Vm]}{8 \cdot 313424}\right)}{[c]}}$$

$$1 + \frac{[c]}{[c]}$$
(17)

6.18 Rule beta

Rule beta is an assignment rule for parameter beta:

beta =
$$\frac{\text{bbar}}{1 + \frac{[c]}{k2 \cdot \exp\left(\frac{2 \cdot d2 \cdot 96 \cdot 485 \cdot [Vm]}{310}\right)}}$$
 (18)

6.19 Rule tau

Rule tau is an assignment rule for parameter tau:

$$tau = \frac{1}{alp + beta} \tag{19}$$

6.20 Rule ooinf

Rule ooinf is an assignment rule for parameter ooinf:

$$ooinf = alp \cdot tau \tag{20}$$

6.21 Rule dinf

Rule dinf is an assignment rule for parameter dinf:

$$dinf = \frac{1}{1 + \exp\left(\frac{24.6 - [Vm]}{11.3}\right)}$$
 (21)

6.22 Rule taud

Rule taud is an assignment rule for parameter taud:

taud =
$$\frac{80}{\frac{1}{\cosh(0.031 \cdot ([Vm] + 37.1))}}$$
 (22)

6.23 Rule alphad

Rule alphad is an assignment rule for parameter alphad:

$$alphad = \frac{dinf}{taud}$$
 (23)

6.24 Rule betad

Rule betad is an assignment rule for parameter betad:

$$betad = \frac{1 - dinf}{taud}$$
 (24)

6.25 Rule gca

Rule gca is an assignment rule for parameter gca:

$$gca = \frac{gcabar \cdot [Vm]}{exp(0.117 \cdot [Vm]) - 1}$$
(25)

6.26 Rule ICa

Rule ICa is an assignment rule for species ICa:

$$ICa = gca \cdot [d]^2 \tag{26}$$

6.27 Rule jmem

Rule jmem is an assignment rule for species jmem:

$$jmem = (alpha \cdot [ICa] + kpmca \cdot [c])$$
 (27)

Derived unit $mmol \cdot ml^{-1}$

6.28 Rule Vm

Rule Vm is a rate rule for species Vm:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Vm} = \frac{[\mathrm{Stimulus}] - ([\mathrm{INa}] + [\mathrm{ICa}] + [\mathrm{IK}] + [\mathrm{II}] + [\mathrm{IT}] + [\mathrm{IKCa}])}{\mathrm{Cm}} \tag{28}$$

6.29 Rule m

Rule m is a rate rule for species m:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{m} = [\mathrm{alpha}_{-}\mathbf{m}] \cdot (1 - [\mathbf{m}]) - [\mathrm{beta}_{-}\mathbf{m}] \cdot [\mathbf{m}]$$
 (29)

6.30 Rule h

Rule h is a rate rule for species h:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{h} = [\mathbf{alpha}_{-}\mathbf{h}] \cdot (1 - [\mathbf{h}]) - [\mathbf{beta}_{-}\mathbf{h}] \cdot [\mathbf{h}]$$
(30)

6.31 Rule n

Rule n is a rate rule for species n:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{n} = [\mathrm{alpha_n}] \cdot (1 - [\mathrm{n}]) - [\mathrm{beta_n}] \cdot [\mathrm{n}]$$
(31)

6.32 Rule Vt

Rule Vt is a rate rule for species Vt:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Vt} = \frac{[\mathrm{Vm}] - [\mathrm{Vt}]}{\mathrm{Rs} \cdot \mathrm{Ct}} \tag{32}$$

6.33 Rule d

Rule d is a rate rule for species d:

$$\frac{d}{dt}d = (1 - [d]) \cdot alphad - [d] \cdot betad$$
(33)

6.34 Rule o

Rule o is a rate rule for species o:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{o} = \frac{\mathrm{ooinf} - [\mathrm{o}]}{\mathrm{tau}} \tag{34}$$

6.35 Rule c

Rule c is a rate rule for species c:

$$\frac{\mathrm{d}}{\mathrm{d}t}c = \mathrm{fcyt} \cdot ([\mathrm{jmem}] + [\mathrm{jer}]) \tag{35}$$

6.36 Rule cer

Rule cer is a rate rule for species cer:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{cer} = \mathrm{fer} \cdot \mathrm{vcytver} \cdot [\mathrm{jer}] \tag{36}$$

7 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.

7.1 Species Vm

Name Vm

Initial concentration $-75 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule Vm

One rule determines the species' quantity.

7.2 Species m

Name m

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule m

One rule determines the species' quantity.

7.3 Species h

Name h

Initial concentration $1 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule h

One rule determines the species' quantity.

7.4 Species n

Name n

Initial concentration $0.1 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule n

One rule determines the species' quantity.

7.5 Species Vt

Name Vt

Initial concentration $-70 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule Vt

7.6 Species d

Name d

Initial concentration $0 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule d

One rule determines the species' quantity.

7.7 Species o

Name o

Initial concentration $0.1 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule o

One rule determines the species' quantity.

7.8 Species c

Name c

Initial concentration $0.15 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule c

One rule determines the species' quantity.

7.9 Species cer

Name cer

Initial concentration $200 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule cer

One rule determines the species' quantity.

7.10 Species INa

Name INa

Initial concentration $0 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule INa

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7.11 Species IT
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Name IT

Involved in rule IT

One rule determines the species' quantity.

7.12 Species IKCa

Name IKCa

Initial concentration $-0.0716677369048711 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule IKCa

One rule determines the species' quantity.

7.13 Species ICa

Name ICa

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule ICa

One rule determines the species' quantity.

7.14 Species IL

Name IL

Initial concentration $0 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule IL

One rule determines the species' quantity.

7.15 Species IK

Name IK

Initial concentration $-2.1 \cdot 10^{-4} \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule IK

7.16 Species Stimulus

Name Stimulus

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule Stimulus

One rule determines the species' quantity.

7.17 Species beta_n

Name beta_n

Initial concentration $0.230675848267876 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule beta_n

One rule determines the species' quantity.

7.18 Species beta_m

Name beta_m

Initial concentration $13.0160326809795 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule beta_m

One rule determines the species' quantity.

7.19 Species beta_h

Name beta_h

Initial concentration $0.038137484704699 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule betah

One rule determines the species' quantity.

7.20 Species alpha_n

Name alpha_n

Initial concentration $0.00543709940740284 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule alpha_n

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7.21 Species alpha_m
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Name alpha_m

Initial concentration $0.262861215247374 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule alpha_m

One rule determines the species' quantity.

7.22 Species alpha_h

Name alpha_h

Initial concentration $0.467439960739393 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule alpha_h

One rule determines the species' quantity.

7.23 Species w

Name w

Initial concentration $0.286670947619484 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule w

One rule determines the species' quantity.

7.24 Species jmem

Name jmem

Initial concentration $-0.03 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule jmem

One rule determines the species' quantity.

7.25 Species jleak

Name jleak

Initial concentration $0.099925 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule jleak

7.26 Species jserca

Name jserca

Initial concentration $0.06 \text{ } \text{mmol} \cdot \text{ml}^{-1}$

Involved in rule jserca

One rule determines the species' quantity.

7.27 Species jer

Name jer

Initial concentration $0.039925 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule jer

One rule determines the species' quantity.

 $\mathfrak{BML2}^{\mathsf{ATEX}}$ was developed by Andreas Dräger^a, Hannes Planatscher^a, Dieudonné M Wouamba^a, Adrian Schröder^a, Michael Hucka^b, Lukas Endler^c, Martin Golebiewski^d and Andreas Zell^a. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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