## **SBML Model Report**

# Model name: "Neumann2010-\_CD95Stimulation\_NFkB\_Apoptosis"



May 6, 2016

#### 1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Vijayalakshmi Chelliah<sup>1</sup> and Leo Neumann<sup>2</sup> at March twelveth 2010 at 12:09 a.m. and last time modified at April eighth 2016 at 4:08 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	1
species types	0	species	23
events	0	constraints	0
reactions	23	function definitions	0
global parameters	17	unit definitions	2
rules	0	initial assignments	0

#### **Model Notes**

This is the reduced model (model 8) described in: **Dynamics within the CD95 death-inducing signaling complex decide life and death of cells.** 

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Lavrik and Roland Eils (German Cancer Research Center (DKFZ), http://www.dkfz.de); Mol Sys Biol 2010; 6:352. doi:10.1038/msb.2010.6;

#### Abstract:

This study explores the dilemma in cellular signaling that triggering of CD95 (Fas/APO-1) in some situations results in cell death and in others leads to the activation of NF-B. We established an integrated kinetic mathematical model for CD95-mediated apoptotic and NF-B signaling. Systematic model reduction resulted in a surprisingly simple model well approximating experimentally observed dynamics. The model postulates a new link between c-FLIP<sub>L</sub> cleavage in the death-inducing signaling complex (DISC) and the NF-B pathway. We validated experimentally that CD95 stimulation resulted in an interaction of p43-FLIP with the IKK complex followed by its activation. Furthermore, we showed that the apoptotic and NF-B pathways diverge already at the DISC. Model and experimental analysis of DISC formation showed that a subtle balance of c-FLIP<sub>L</sub> and procaspase-8 determines life/death decisions in a nonlinear manner. We present an integrated model describing the complex dynamics of CD95-mediated apoptosis and NF-B signaling.

The original was taken from the MSB article supplementary material site msb20106-s2.xml. All the species ids were changed since the model was not a valid SBML with its original ids - Lukas.

Notes added to the species [L] (the initial concentration of Anti-CD95), regarding changes to be made in the initial concentration of [L], to obtain figure 5D.

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To cite BioModels Database, please use Le Novre N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. (2006) BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems Nucleic Acids Res., 34: D689-D691.

#### 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 time

**Definition** 60 s

#### 2.2 Unit substance

**Definition** nmol

#### 2.3 Unit volume

**Notes** Litre is the predefined SBML unit for volume.

#### **Definition** 1

## 2.4 Unit area

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

 $\textbf{Definition}\ m^2$ 

## 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
default	default		3	1	litre	Ø	

## 3.1 Compartment default

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

Name default

## 4 Species

This model contains 23 species. 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
L	L	default	$nmol \cdot l^{-1}$		
L_RF	L:RF	default	$\operatorname{nmol} \cdot 1^{-1}$		$\Box$
L_RF_C8	L:RF:C8	default	$nmol \cdot l^{-1}$	$\Box$	
L_RF_FL	L:RF:FL	default	$nmol \cdot l^{-1}$	$\Box$	$\Box$
L_RF_FS	L:RF:FS	default	$nmol \cdot l^{-1}$	$\Box$	
p43_p41	p43/p41	default	$nmol \cdot l^{-1}$	$\Box$	$\Box$
C3	C3	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$	$\Box$	$\Box$
C8	C8	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$		$\Box$
C8_star	C8*	default	$\operatorname{nmol} \cdot 1^{-1}$		$\Box$
C3_star	C3*	default	$nmol \cdot l^{-1}$	$\Box$	
p43_FLIP	p43-FLIP	default	$nmol \cdot l^{-1}$	$\Box$	$\Box$
NF_kB_IkB	NF-kB:IkB	default	$nmol \cdot l^{-1}$	$\Box$	
NF_kB_IkB_P	NF-kB:IkB:P	default	$nmol \cdot l^{-1}$	$\Box$	
p43_FLIP_IKK_star	p43-FLIP:IKK*	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$	$\Box$	
NF_kB_star	NF-kB*	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$		$\Box$
RF	RF	default	$\operatorname{nmol} \cdot 1^{-1}$		$\Box$
FL	FL	default	$nmol \cdot l^{-1}$	$\Box$	$\Box$
FS	FS	default	$nmol \cdot l^{-1}$		$\Box$
IKK	IKK	default	$\operatorname{nmol} \cdot 1^{-1}$		$\Box$
L_RF_C8_FS	L:RF:C8:FS	default	$nmol \cdot l^{-1}$	$\Box$	$\Box$
L_RF_FL_FL	L:RF:FL:FL	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$	$\Box$	$\Box$
L_RF_FL_FS	L:RF:FL:FS	default	$nmol \cdot l^{-1}$		

Id	Name	Compartment	Derived Unit	Constant	Boundary Condi- tion
L_RF_FS_FS	L:RF:FS:FS	default	$\mathrm{nmol}\cdot\mathrm{l}^{-1}$	$\Box$	

## **5 Parameters**

This model contains 17 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		1.000		$\overline{Z}$
k2	k2	1	$.277248 \cdot 10^{-6}$	4	$   \overline{\mathscr{L}} $
k3	k3		0.669		
k4	k4		$10^{-3}$	5	$\overline{\mathbf{Z}}$
k5	k5	5	$5.946569 \cdot 10^{-6}$	4	$\overline{\mathbf{Z}}$
k6	k6		1.000		$\overline{\mathbf{Z}}$
k7	k7		0.888		$   \overline{\mathscr{L}} $
k8	k8	8	$3.044378 \cdot 10^{-6}$	4	$\overline{\mathbf{Z}}$
k9	k9		0.002		$\overline{\mathbf{Z}}$
k10	k10		0.121		$\overline{\mathbf{Z}}$
k11	k11		0.029		$\overline{\checkmark}$
k12	k12		0.150		$\overline{\checkmark}$
k13	k13	7	7.204261 · 10-4	4	$\overline{\mathbf{Z}}$
k14	k14		0.359		$\overline{\mathbb{Z}}$
k15	k15		3.684		$\overline{\mathbb{Z}}$
k16	k16		0.022		$\overline{\mathbb{Z}}$
k17	k17		0.006		<b>Z</b>

## **6 Reactions**

This model contains 23 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

reaction_1 reaction_2 reaction_3 reaction_4 reaction_5 reaction_6 reaction_7	reaction_1 reaction_2 reaction_3 reaction_4 reaction_5 reaction_6	$L+RF \longrightarrow L\_RF$ $L\_RF+C8 \longrightarrow L\_RF\_C8$ $L\_RF+FL \longrightarrow L\_RF\_FL$ $L\_RF+FS \longrightarrow L\_RF\_FS$ $L\_RF\_C8+C8 \longrightarrow p43\_p41+p43\_p41$ $L\_RF\_C8+FL \longrightarrow p43\_FLIP$	0000526 0000526 0000526 0000526
reaction_3 reaction_4 reaction_5 reaction_6	reaction_3 reaction_4 reaction_5	$L\_RF + FL \longrightarrow L\_RF\_FL$ $L\_RF + FS \longrightarrow L\_RF\_FS$ $L\_RF\_C8 + C8 \longrightarrow p43\_p41 + p43\_p41$	0000526
reaction_4 reaction_5 reaction_6	reaction_4 reaction_5	$L\_RF+FS \longrightarrow L\_RF\_FS$ $L\_RF\_C8+C8 \longrightarrow p43\_p41+p43\_p41$	
reaction_5 reaction_6	reaction_5	$L_RF_C8 + C8 \longrightarrow p43_p41 + p43_p41$	0000526
reaction_6		1 1 1	
	reaction_6	$L_RF_C8 + FL \longrightarrow p43_FLIP$	
reaction_7		2-14-00   12   P :0-1 2-11	
	reaction_7	$L\_RF\_C8 + FS \longrightarrow L\_RF\_C8\_FS$	0000526
reaction_8	reaction_8	$L_RF_FL + C8 \longrightarrow p43_FLIP$	
${\tt reaction\_9}$	reaction_9	$L\_RF\_FL + FL \longrightarrow L\_RF\_FL\_FL$	0000526
${\tt reaction\_10}$	reaction_10	$L\_RF\_FL+FS \longrightarrow L\_RF\_FL\_FS$	0000526
reaction_11	reaction_11	$L\_RF\_FS + C8 \longrightarrow L\_RF\_C8\_FS$	0000526
reaction_12	reaction_12	$L\_RF\_FS + FL \longrightarrow L\_RF\_FL\_FS$	0000526
reaction_13	reaction_13	$L\_RF\_FS + FS \longrightarrow L\_RF\_FS\_FS$	0000526
${\tt reaction\_14}$	reaction_14	$p43_p41 + p43_p41 \longrightarrow C8_star$	
reaction_15	reaction_15	$C3 + C8\_star \longrightarrow C3\_star + C8\_star$	
${\tt reaction\_16}$	reaction_16	$C8 + C3\_star \longrightarrow p43\_p41 + C3\_star$	
$reaction_17$	reaction_17	$C8\_star \longrightarrow \emptyset$	
reaction_18	reaction_18	$C3\_star \longrightarrow \emptyset$	
reaction_19	reaction_19	p43_FLIP+IKK → p43_FLIP_IKK_star	0000526
reaction_20	reaction_20	NF_kB_IkB+p43_FLIP_IKK_star → NF_kB_IkB_P+ p43_FLIP_IKK_star	
reaction_21	reaction_21	$NF_kB_IkB_P \longrightarrow NF_kB_star$	
reaction_22	reaction_22	$p43$ _FLIP_IKK_star $\longrightarrow \emptyset$	
	reaction_8 reaction_9 reaction_10 reaction_11 reaction_12 reaction_13 reaction_14 reaction_15 reaction_16 reaction_17 reaction_19 reaction_20 reaction_20	reaction_8 reaction_9 reaction_10 reaction_11 reaction_11 reaction_12 reaction_13 reaction_14 reaction_15 reaction_15 reaction_16 reaction_17 reaction_17 reaction_18 reaction_19 reaction_19 reaction_20 reaction_21 reaction_21 reaction_21 reaction_21 reaction_20 reaction_21 reaction_21	reaction_8 reaction_8 reaction_9 reaction_9 reaction_10 reaction_10 reaction_11 reaction_11 reaction_11 reaction_12 reaction_12 reaction_12 reaction_13 reaction_13 reaction_14 reaction_14 reaction_15 reaction_15 reaction_15 reaction_16 reaction_16 reaction_17 reaction_17 reaction_18 reaction_18 reaction_19 reaction_19 reaction_19 reaction_19 reaction_19 reaction_20 reaction_20 reaction_21 reaction_22 reaction_22 reaction_21 reaction_22 reaction_

No	Id	Name	Reaction Equation	SBO
23	reaction_23	reaction_23	$NF_kB_star \longrightarrow \emptyset$	

#### **6.1 Reaction** reaction\_1

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

Name reaction\_1

SBO:0000526 protein complex formation

## **Reaction equation**

$$L + RF \longrightarrow L_{-}RF \tag{1}$$

#### **Reactants**

Table 6: Properties of each reactant.

Id	Name	SBO
L	L	
RF	RF	

#### **Product**

Table 7: Properties of each product.

Id	Name	SBO
$L\_RF$	L:RF	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_1 = \text{vol}(\text{default}) \cdot \text{k1} \cdot [\text{L}] \cdot [\text{RF}]$$
 (2)

#### **6.2 Reaction** reaction\_2

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

Name reaction\_2

SBO:0000526 protein complex formation

## **Reaction equation**

$$L\_RF + C8 \longrightarrow L\_RF\_C8 \tag{3}$$

#### **Reactants**

Table 8: Properties of each reactant.

Id	Name	SBO
L_RF C8	L:RF C8	

#### **Product**

Table 9: Properties of each product.

Id	Name	SBO
L_RF_C8	L:RF:C8	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_2 = vol(default) \cdot k2 \cdot [L\_RF] \cdot [C8]$$
(4)

## **6.3 Reaction** reaction\_3

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

Name reaction\_3

SBO:0000526 protein complex formation

## **Reaction equation**

$$L\_RF + FL \longrightarrow L\_RF\_FL \tag{5}$$

## **Reactants**

Table 10: Properties of each reactant.

Id	Name	SBO
L_RF	L:RF	
FL	FL	

#### **Product**

Table 11: Properties of each product.

Id	Name	SBO
L_RF_FL	L:RF:FL	

**Derived unit** contains undeclared units

$$v_3 = \text{vol}(\text{default}) \cdot \text{k3} \cdot [\text{L\_RF}] \cdot [\text{FL}]$$
 (6)

#### **6.4 Reaction** reaction\_4

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

Name reaction\_4

SBO:0000526 protein complex formation

## **Reaction equation**

$$L_RF + FS \longrightarrow L_RF_FS \tag{7}$$

#### **Reactants**

Table 12: Properties of each reactant.

Id	Name	SBO
L_RF	L:RF	
FS	FS	

#### **Product**

Table 13: Properties of each product.

Id	Name	SBO
L_RF_FS	L:RF:FS	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_4 = \text{vol}\left(\text{default}\right) \cdot \text{k4} \cdot [\text{L\_RF}] \cdot [\text{FS}] \tag{8}$$

#### **6.5 Reaction** reaction\_5

This is an irreversible reaction of two reactants forming two products.

Name reaction\_5

## **Reaction equation**

$$L\_RF\_C8 + C8 \longrightarrow p43\_p41 + p43\_p41 \tag{9}$$

#### **Reactants**

Table 14: Properties of each reactant.

Id	Name	SBO
L_RF_C8	L:RF:C8	
C8	C8	

#### **Products**

Table 15: Properties of each product.

Id	Name	SBO
p43_p41	p43/p41	
p43_p41	p43/p41	

## **Kinetic Law**

**Derived unit** contains undeclared units

$$v_5 = \text{vol}(\text{default}) \cdot \text{k5} \cdot [\text{L\_RF\_C8}] \cdot [\text{C8}]$$
(10)

## **6.6 Reaction** reaction\_6

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

Name reaction\_6

## **Reaction equation**

$$L_RF_C8 + FL \longrightarrow p43\_FLIP$$
 (11)

#### **Reactants**

Table 16: Properties of each reactant.

Id	Name	SBO
L_RF_C8	L:RF:C8	
FL	FL	

#### **Product**

Table 17: Properties of each product.

Id	Name	SBO
p43_FLIP	p43-FLIP	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_6 = \text{vol}(\text{default}) \cdot \text{k6} \cdot [\text{L\_RF\_C8}] \cdot [\text{FL}]$$
 (12)

## **6.7 Reaction** reaction\_7

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

Name reaction\_7

SBO:0000526 protein complex formation

## **Reaction equation**

$$L_RF_C8 + FS \longrightarrow L_RF_C8_FS$$
 (13)

#### **Reactants**

Table 18: Properties of each reactant.

Id	Name	SBO
L_RF_C8 FS	L:RF:C8 FS	

#### **Product**

Table 19: Properties of each product

Id	Name	SBO
L_RF_C8_FS	L:RF:C8:FS	

**Derived unit** contains undeclared units

$$v_7 = \text{vol}(\text{default}) \cdot \text{k7} \cdot [\text{L\_RF\_C8}] \cdot [\text{FS}]$$
 (14)

#### **6.8 Reaction** reaction\_8

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

Name reaction\_8

## **Reaction equation**

$$L\_RF\_FL + C8 \longrightarrow p43\_FLIP \tag{15}$$

#### **Reactants**

Table 20: Properties of each reactant.

Id	Name	SBO
L_RF_FL C8	L:RF:FL C8	

#### **Product**

Table 21: Properties of each product.

Id	Name	SBO
p43_FLIP	p43-FLIP	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_8 = \text{vol}(\text{default}) \cdot \text{k5} \cdot [\text{L\_RF\_FL}] \cdot [\text{C8}]$$
 (16)

#### **6.9 Reaction** reaction\_9

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

Name reaction\_9

SBO:0000526 protein complex formation

## **Reaction equation**

$$L_RF_FL + FL \longrightarrow L_RF_FL_FL$$
 (17)

#### **Reactants**

Table 22: Properties of each reactant.

Id	Name	SBO
L_RF_FL	L:RF:FL	
FL	FL	

#### **Product**

Table 23: Properties of each product.

Id	Name	SBO
L_RF_FL_FL	L:RF:FL:FL	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_9 = \text{vol}(\text{default}) \cdot \text{k6} \cdot [\text{L\_RF\_FL}] \cdot [\text{FL}]$$
(18)

#### **6.10 Reaction** reaction\_10

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

Name reaction\_10

SBO:0000526 protein complex formation

#### **Reaction equation**

$$L\_RF\_FL + FS \longrightarrow L\_RF\_FL\_FS$$
 (19)

#### **Reactants**

Table 24: Properties of each reactant.

Id	Name	SBO
L_RF_FL	L:RF:FL	
FS	FS	

#### **Product**

Table 25: Properties of each product.

Id	Name	SBO
L_RF_FL_FS	L:RF:FL:FS	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{10} = \text{vol}(\text{default}) \cdot \text{k7} \cdot [\text{L\_RF\_FL}] \cdot [\text{FS}]$$
 (20)

## **6.11 Reaction** reaction\_11

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

Name reaction\_11

SBO:0000526 protein complex formation

## **Reaction equation**

$$L\_RF\_FS + C8 \longrightarrow L\_RF\_C8\_FS$$
 (21)

#### **Reactants**

Table 26: Properties of each reactant.

Id	Name	SBO
L_RF_FS	L:RF:FS	
C8	C8	

#### **Product**

Table 27: Properties of each product.
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Table 27. Properties of each product.		
Id	Name	SBO
L_RF_C8_FS	L:RF:C8:FS	

**Derived unit** contains undeclared units

$$v_{11} = \text{vol}(\text{default}) \cdot \text{k5} \cdot [\text{L\_RF\_FS}] \cdot [\text{C8}]$$
 (22)

#### **6.12 Reaction** reaction\_12

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

Name reaction\_12

SBO:0000526 protein complex formation

## **Reaction equation**

$$L\_RF\_FS + FL \longrightarrow L\_RF\_FL\_FS$$
 (23)

#### **Reactants**

Table 28: Properties of each reactant.

Id	Name	SBO
L_RF_FS	L:RF:FS	
FL	FL	

## **Product**

Table 29: Properties of each product.

Id	Name	SBO
L_RF_FL_FS	L:RF:FL:FS	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{12} = \text{vol}(\text{default}) \cdot \text{k6} \cdot [\text{L\_RF\_FS}] \cdot [\text{FL}]$$
 (24)

#### **6.13 Reaction** reaction\_13

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

Name reaction\_13

SBO:0000526 protein complex formation

## **Reaction equation**

$$L_RF_FS + FS \longrightarrow L_RF_FS_FS$$
 (25)

#### **Reactants**

Table 30: Properties of each reactant.

Id	Name	SBO
L_RF_FS	L:RF:FS	
FS	FS	

#### **Product**

Table 31: Properties of each product.

Id	Name	SBO
L_RF_FS_FS	L:RF:FS:FS	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{13} = \text{vol}(\text{default}) \cdot \text{k7} \cdot [\text{L\_RF\_FS}] \cdot [\text{FS}]$$
 (26)

#### **6.14 Reaction** reaction\_14

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

Name reaction\_14

## **Reaction equation**

$$p43-p41+p43-p41 \longrightarrow C8-star$$
 (27)

#### **Reactants**

Table 32: Properties of each reactant.

Id	Name	SBO
p43_p41 p43_p41	p43/p41 p43/p41	

#### **Product**

Table 33: Properties of each product.

Id	Name	SBO
C8_star	C8*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{14} = \text{vol}(\text{default}) \cdot \text{k8} \cdot [\text{p43\_p41}] \cdot [\text{p43\_p41}]$$
 (28)

## **6.15 Reaction** reaction\_15

This is an irreversible reaction of two reactants forming two products.

Name reaction\_15

## **Reaction equation**

$$C3 + C8\_star \longrightarrow C3\_star + C8\_star$$
 (29)

#### **Reactants**

Table 34: Properties of each reactant.

Id	Name	SBO
C3	C3	
C8_star	C8*	

#### **Products**

Table 35: Properties of each product.

Id	Name	SBO
C3_star	C3*	
C8_star	C8*	

**Derived unit** contains undeclared units

$$v_{15} = \text{vol}\left(\text{default}\right) \cdot \text{k9} \cdot [\text{C3}] \cdot [\text{C8\_star}]$$
 (30)

#### **6.16 Reaction** reaction\_16

This is an irreversible reaction of two reactants forming two products.

Name reaction\_16

#### **Reaction equation**

$$C8 + C3\_star \longrightarrow p43\_p41 + C3\_star$$
 (31)

#### **Reactants**

Table 36: Properties of each reactant.

Id	Name	SBO
C8	C8	
${\tt C3\_star}$	C3*	

#### **Products**

Table 37: Properties of each product.

Id	Name	SBO
p43_p41 C3_star	p43/p41 C3*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{16} = \text{vol}(\text{default}) \cdot \text{k10} \cdot [\text{C8}] \cdot [\text{C3\_star}]$$
 (32)

#### **6.17 Reaction** reaction\_17

This is an irreversible reaction of one reactant forming no product.

Name reaction\_17

## **Reaction equation**

$$C8\_star \longrightarrow \emptyset \tag{33}$$

#### Reactant

Table 38: Properties of each reactant.

Id	Name	SBO
C8_star	C8*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{17} = \text{vol}(\text{default}) \cdot \text{k11} \cdot [\text{C8\_star}]$$
 (34)

#### 6.18 Reaction reaction\_18

This is an irreversible reaction of one reactant forming no product.

Name reaction\_18

#### **Reaction equation**

$$C3\_star \longrightarrow \emptyset$$
 (35)

#### Reactant

Table 39: Properties of each reactant.

Id	Name	SBO
C3_star	C3*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{18} = \text{vol}\left(\text{default}\right) \cdot \text{k12} \cdot [\text{C3\_star}]$$
 (36)

#### **6.19 Reaction** reaction\_19

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

Name reaction\_19

SBO:0000526 protein complex formation

## **Reaction equation**

$$p43\_FLIP + IKK \longrightarrow p43\_FLIP\_IKK\_star$$
 (37)

#### **Reactants**

Table 40: Properties of each reactant.

Id	Name	SBO
p43_FLIP IKK	p43-FLIP IKK	

#### **Product**

Table 41: Properties of each product.

Id	Name	SBO
p43_FLIP_IKK_star	p43-FLIP:IKK*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{19} = \text{vol}(\text{default}) \cdot \text{k13} \cdot [\text{p43\_FLIP}] \cdot [\text{IKK}]$$
 (38)

#### **6.20 Reaction** reaction\_20

This is an irreversible reaction of two reactants forming two products.

Name reaction\_20

#### **Reaction equation**

$$NF_kB_IkB + p43_FLIP_IKK_star \longrightarrow NF_kB_IkB_P + p43_FLIP_IKK_star$$
 (39)

#### **Reactants**

Table 42: Properties of each reactant.

Id	Name	SBO
NF_kB_IkB	NF-kB:IkB	
p43_FLIP_IKK_star	p43-FLIP:IKK*	

#### **Products**

Table 43: Properties of each product.

Id	Name	SBO
NF_kB_IkB_P	NF-kB:IkB:P	
p43_FLIP_IKK_star	p43-FLIP:IKK*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{20} = \text{vol}(\text{default}) \cdot \text{k14} \cdot [\text{NF\_kB\_lkB}] \cdot [\text{p43\_FLIP\_IKK\_star}]$$
 (40)

## **6.21 Reaction** reaction\_21

This is an irreversible reaction of one reactant forming one product.

Name reaction\_21

## **Reaction equation**

$$NF_kB_IkB_P \longrightarrow NF_kB_star$$
 (41)

#### Reactant

Table 44: Properties of each reactant.

Id	Name	SBO
NF_kB_IkB_P	NF-kB:IkB:P	

#### **Product**

Table 45: Properties of each product.

Id	Name	SBO
NF_kB_star	NF-kB*	

**Derived unit** contains undeclared units

$$v_{21} = \text{vol}(\text{default}) \cdot \text{k15} \cdot [\text{NF\_kB\_IkB\_P}]$$
 (42)

#### **6.22 Reaction** reaction\_22

This is an irreversible reaction of one reactant forming no product.

Name reaction\_22

#### **Reaction equation**

$$p43\_FLIP\_IKK\_star \longrightarrow \emptyset$$
 (43)

#### Reactant

Table 46: Properties of each reactant.

Id	Name	SBO
p43_FLIP_IKK_star	p43-FLIP:IKK*	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{22} = \text{vol}(\text{default}) \cdot \text{k16} \cdot [\text{p43\_FLIP\_IKK\_star}]$$
 (44)

## 6.23 Reaction reaction\_23

This is an irreversible reaction of one reactant forming no product.

Name reaction\_23

#### **Reaction equation**

$$NF_kB_star \longrightarrow \emptyset$$
 (45)

## Reactant

Table 47: Properties of each reactant.

Id	Name	SBO
NF_kB_star	NF-kB*	

**Derived unit** contains undeclared units

$$v_{23} = \text{vol}(\text{default}) \cdot \text{k17} \cdot [\text{NF\_kB\_star}]$$
 (46)

## 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.

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.

#### 7.1 Species L

#### Name L

#### SBO:0000245 macromolecule

**Notes** Initial concentration of anti-CD95 = 113.22nM is equivalent to 1500ng/ml. The model as such reproduces the figure 5D (black plot: i.e. anti-CD95=1500ng/ml).

To obtain the blue (anti-CD95=500ng/ml) and red (250ng/ml) plot of figure 5D, the model parameter [L] (initial concentration of anti-CD95 [L]) should be set as 37.74nM and 18.87nM respectively.

#### Initial concentration 113.22 nmol·1<sup>-1</sup>

This species takes part in one reaction (as a reactant in reaction\_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{L} = -v_1 \tag{47}$$

#### 7.2 Species L\_RF

Name L:RF

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_2, reaction\_3, reaction\_4 and as a product in reaction\_1).

$$\frac{d}{dt}L_{RF} = |v_1| - |v_2| - |v_3| - |v_4| \tag{48}$$

### 7.3 Species L\_RF\_C8

Name L:RF:C8

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_5, reaction\_6, reaction\_7 and as a product in reaction\_2).

$$\frac{d}{dt}L_RF_C8 = |v_2| - |v_5| - |v_6| - |v_7|$$
 (49)

#### 7.4 Species L\_RF\_FL

Name L:RF:FL

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_8, reaction\_9, reaction\_10 and as a product in reaction\_3).

$$\frac{d}{dt}L_RF_FL = |v_3| - |v_8| - |v_9| - |v_{10}|$$
 (50)

#### 7.5 Species L\_RF\_FS

Name L:RF:FS

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_11, reaction\_12, reaction\_13 and as a product in reaction\_4).

$$\frac{d}{dt}L_RF_FS = v_4 - |v_{11}| - |v_{12}| - |v_{13}|$$
 (51)

## **7.6 Species** p43\_p41

**Name** p43/p41

SBO:0000245 macromolecule

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in five reactions (as a reactant in reaction\_14, reaction\_14 and as a product in reaction\_5, reaction\_5, reaction\_16).

$$\frac{\mathrm{d}}{\mathrm{d}t} p43 - p41 = |v_5| + |v_5| + |v_{16}| - |v_{14}| - |v_{14}|$$
(52)

#### 7.7 Species C3

Name C3

SBO:0000245 macromolecule

Initial concentration  $1.443404 \text{ nmol} \cdot l^{-1}$ 

This species takes part in one reaction (as a reactant in reaction\_15).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C}3 = -v_{15} \tag{53}$$

#### 7.8 Species C8

Name C8

SBO:0000245 macromolecule

Initial concentration 64.47652 nmol·l<sup>-1</sup>

This species takes part in five reactions (as a reactant in reaction\_2, reaction\_5, reaction\_8, reaction\_11, reaction\_16).

$$\frac{\mathrm{d}}{\mathrm{d}t}C8 = -v_2 - v_5 - v_8 - v_{11} - v_{16} \tag{54}$$

#### 7.9 Species C8\_star

Name C8\*

SBO:0000245 macromolecule

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_15, reaction\_17 and as a product in reaction\_14, reaction\_15).

$$\frac{\mathrm{d}}{\mathrm{d}t} C8 \cdot \mathrm{star} = |v_{14}| + |v_{15}| - |v_{15}| - |v_{17}| \tag{55}$$

#### 7.10 Species C3\_star

Name C3\*

SBO:0000245 macromolecule

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_16, reaction\_18 and as a product in reaction\_15, reaction\_16).

$$\frac{d}{dt}C3_{star} = |v_{15}| + |v_{16}| - |v_{16}| - |v_{18}|$$
 (56)

#### 7.11 Species p43\_FLIP

Name p43-FLIP

SBO:0000245 macromolecule

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in three reactions (as a reactant in reaction\_19 and as a product in reaction\_6, reaction\_8).

$$\frac{d}{dt}p43\_FLIP = |v_6| + |v_8| - |v_{19}|$$
 (57)

#### 7.12 Species NF\_kB\_IkB

Name NF-kB:IkB

SBO:0000296 macromolecular complex

Initial concentration  $4.739546 \text{ nmol} \cdot 1^{-1}$ 

This species takes part in one reaction (as a reactant in reaction\_20).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NF}_{-}\mathrm{kB}_{-}\mathrm{IkB} = -v_{20} \tag{58}$$

#### 7.13 Species NF\_kB\_IkB\_P

Name NF-kB:IkB:P

SBO:0000296 macromolecular complex

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

This species takes part in two reactions (as a reactant in reaction\_21 and as a product in reaction\_20).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NF}_{-}\mathrm{kB}_{-}\mathrm{IkB}_{-}\mathrm{P} = v_{20} - v_{21} \tag{59}$$

#### 7.14 Species p43\_FLIP\_IKK\_star

Name p43-FLIP:IKK\*

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_20, reaction\_22 and as a product in reaction\_19, reaction\_20).

$$\frac{d}{dt}p43\_FLIP\_IKK\_star = |v_{19}| + |v_{20}| - |v_{20}| - |v_{22}|$$
(60)

#### 7.15 Species NF\_kB\_star

Name NF-kB\*

SBO:0000245 macromolecule

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in two reactions (as a reactant in reaction\_23 and as a product in reaction\_21).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{NF}_{\mathbf{k}} \mathrm{B}_{\mathbf{s}} \mathrm{tar} = |v_{21}| - |v_{23}| \tag{61}$$

#### 7.16 Species RF

Name RF

SBO:0000296 macromolecular complex

Initial concentration  $91.26592 \text{ nmol} \cdot l^{-1}$ 

This species takes part in one reaction (as a reactant in reaction\_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RF} = -\nu_1 \tag{62}$$

#### 7.17 Species FL

Name FL

SBO:0000245 macromolecule

Initial concentration  $7.398562 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_3, reaction\_6, reaction\_9, reaction\_12).

$$\frac{d}{dt}FL = -|v_3| - |v_6| - |v_9| - |v_{12}| \tag{63}$$

## 7.18 Species FS

Name FS

SBO:0000245 macromolecule

Initial concentration  $5.083923 \text{ nmol} \cdot l^{-1}$ 

This species takes part in four reactions (as a reactant in reaction\_4, reaction\_7, reaction\_10, reaction\_13).

$$\frac{d}{dt}FS = -|v_4| - |v_7| - |v_{10}| - |v_{13}| \tag{64}$$

### 7.19 Species IKK

Name IKK

SBO:0000245 macromolecule

Initial concentration  $5.772825 \text{ nmol} \cdot l^{-1}$ 

This species takes part in one reaction (as a reactant in reaction\_19).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IKK} = -v_{19} \tag{65}$$

### 7.20 Species L\_RF\_C8\_FS

Name L:RF:C8:FS

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in two reactions (as a product in reaction\_7, reaction\_11).

$$\frac{\mathrm{d}}{\mathrm{d}t} L_{RF}C8_{FS} = v_7 + v_{11} \tag{66}$$

#### 7.21 Species L\_RF\_FL\_FL

Name L:RF:FL:FL

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in one reaction (as a product in reaction\_9).

$$\frac{\mathrm{d}}{\mathrm{d}t} L RF F L F L = v_9 \tag{67}$$

#### 7.22 Species L\_RF\_FL\_FS

Name L:RF:FL:FS

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in two reactions (as a product in reaction\_10, reaction\_12).

$$\frac{\mathrm{d}}{\mathrm{d}t} L_{\mathrm{RF}} = v_{10} + v_{12} \tag{68}$$

#### 7.23 Species L\_RF\_FS\_FS

Name L:RF:FS:FS

SBO:0000296 macromolecular complex

Initial concentration  $0 \text{ nmol} \cdot l^{-1}$ 

This species takes part in one reaction (as a product in reaction\_13).

$$\frac{\mathrm{d}}{\mathrm{d}t} L_{\mathrm{RF}} F_{\mathrm{S}} F_{\mathrm{S}} = v_{13} \tag{69}$$

## A Glossary of Systems Biology Ontology Terms

**SBO:0000245** macromolecule: Molecular entity mainly built-up by the repetition of pseudo-identical units. CHEBI:3383

**SBO:0000296** macromolecular complex: Non-covalent complex of one or more macromolecules and zero or more simple chemicals

**SBO:0000526 protein complex formation:** The process by which two or more proteins interact non-covalently to form a protein complex (SBO:0000297)

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