SBML Model Report

Model name: “Ibrahim2008 - Mitotic Spindle Assembly Checkpoint - Convey variant”

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1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following five authors: Lukas Endler[1], Eberhard Schmitt[2], Peter Dittrich[3], Stephan Diekmann[4] and Bashar Ibrahim[5] at September first 2008 at 2:18 p. m. and last time modified at June third 2014 at 2:50 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	11
events	1	constraints	0
reactions	9	function definitions	0
global parameters	17	unit definitions	2
rules	0	initial assignments	0

Model Notes

Ibrahim2008 - Mitotic Spindle Assembly Checkpoint - Convey variant

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The Mitotic Spindle Assembly Checkpoint ((M)SAC) is an evolutionary conserved mechanism. This model incorporates the perspectives of three central control pathways, namely Mad1/Mad2 induced Cdc20 sequestering based on the Template Model, MCC formation, and APC inhibition. MCC:APC dissociation is described by two alternatives models, namely the „Dissociation„ and the „Convey„ model variants. Both these model are available in BioModels Database. This model corresponds to the „Convey„ variant.

This model is described in the article:In-silico modeling of the mitotic spindle assembly checkpoint.Ibrahim B, Diekmann S, Schmitt E, Dittrich PPLoS One. 2008 Feb 6;3(2):e1555.

Abstract:

BACKGROUND: The Mitotic Spindle Assembly Checkpoint ((M)SAC) is an evolutionary conserved mechanism that ensures the correct segregation of chromosomes by restraining cell cycle progression from entering anaphase until all chromosomes have made proper bipolar attachments to the mitotic spindle. Its malfunction can lead to cancer.

PRINCIPLE FINDINGS: We have constructed and validated for the human (M)SAC mechanism an in silico dynamical model, integrating 11 proteins and complexes. The model incorporates the perspectives of three central control pathways, namely Mad1/Mad2 induced Cdc20 sequestering based on the Template Model, MCC formation, and APC inhibition. Originating from the biochemical reactions for the underlying molecular processes, non-linear ordinary differential equations for the concentrations of 11 proteins and complexes of the (M)SAC are derived. Most of the kinetic constants are taken from literature, the remaining four unknown parameters are derived by an evolutionary optimization procedure for an objective function describing the dynamics of the APC:Cdc20 complex. MCC:APC dissociation is described by two alternatives, namely the „Dissociation„ and the „Convey„ model variants. The attachment of the kinetochore to microtubuli is simulated by a switching parameter silencing those reactions which are stopped by the attachment. For both, the Dissociation and the Convey variants, we compare two different scenarios concerning the microtubule attachment dependent control of the dissociation reaction. Our model is validated by simulation of ten perturbation experiments.

CONCLUSION: Only in the controlled case, our models show (M)SAC behaviour at meta- to anaphase transition in agreement with experimental observations. Our simulations revealed that for (M)SAC activation, Cdc20 is not fully sequestered; instead APC is inhibited by MCC binding.

This model describes the controlled dissociation variant of the mitotic spindle assembly checkpoint. If the tool you use has problems with events, you can uncomment the assignment rules for u and u_prime and comment out the list of events.

In accordance with the authors due to typos in the original publication some initial conditions and parameters were slightly changed in the model:

	article	**model**
[O-Mad2]	1.5e-7 M	1.3e-7 M
[BubR1:Bub3]	1.30e-7 M	1.27e-7 M
k_{-4}	0.01 M^{-1} s^{-1}	0.02 M^{-1} s^{-1}
k_{-5}	0.1 M^{-1} s^{-1}	0.2 M^{-1} s^{-1}

This model is hosted on BioModels Database and identified by: MODEL6655578762 .

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models .

2 Unit Definitions

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

2.1 Unit ps

Name per second

Definition s^{-1}

2.2 Unit pMps

Name liter per mole per second

Definition $l \cdot mol^{-1} \cdot s^{-1}$

2.3 Unit substance

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.4 Unit volume

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

Definition l

2.5 Unit area

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

Definition m^2

2.6 Unit length

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

Definition m

2.7 Unit time

Notes Second is the predefined SBML unit for time.

Definition s

3 Compartment

This model contains one compartment.

Table 3: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
Cytoplasm	Cytoplasm		3	1	litre	☑	

3.1 Compartment Cytoplasm

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

Name Cytoplasm

4 Species

This model contains eleven species. Section 8 provides further details and the derived rates of change of each species.

Table 4: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
Mad1_CMad2	Mad1:C-Mad2	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
OMad2	O-Mad2	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Mad1_CMad2_OMad2	Mad1:C-Mad2:O-Mad2*	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Cdc20	Cdc20	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Cdc20_CMad2	Cdc20:C-Mad2	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Bub3_BubR1	Bub3:BubR1	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
MCC	MCC	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Bub3_BubR1_Cdc20	Bub3:BubR1:Cdc20	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
APC	APC	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
MCC_APC	MCC:APC	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
APC_Cdc20	APC:Cdc20	Cytoplasm	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains 17 global parameters.

Table 5: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k3f			0.010	s^{-1}	☑
kf6			1000.000	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k5f			10000.000	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k5r			0.200	s^{-1}	☑
k2f			10^8	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k1f			200000.000	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k1r			0.200	s^{-1}	☑
k4f			10^7	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k4r			0.020	s^{-1}	☑
k7f			10^8	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k7bf			0.080	s^{-1}	☑
k8f			5000000.000	$l \cdot mol^{-1} \cdot s^{-1}$	☑
k8r			0.080	s^{-1}	☑
u			1.000	dimensionless	⊟
u_prime			0.000	dimensionless	⊟
const_val_0			0.000	dimensionless	☑
const_val_1			1.000	dimensionless	☑

6 Event

This is an overview of one event. Each event is initiated whenever its trigger condition switches from `false` to `true`. A delay function postpones the effects of an event to a later time point. At the time of execution, an event can assign values to species, parameters or compartments if these are not set to constant.

6.1 Event `mt_attachment`

Name Microtubule attachment

Trigger condition

$$\text{time} > 2000 \tag{1}$$

Assignments

$$\text{u} = \text{const\_val\_0} \tag{2}$$

$$\text{u\_prime} = \text{const\_val\_1} \tag{3}$$

7 Reactions

This model contains nine 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 6: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	R1		Mad1_CMad2 + OMad2 $\rightleftharpoons$ Mad1_CMad2_OMad2	
2	R2		Mad1_CMad2_OMad2 + Cdc20 $\longrightarrow$ Mad1_CMad2 + Cdc20_CMad2	
3	R3		Cdc20_CMad2 $\longrightarrow$ Cdc20 + OMad2	
4	R4		Cdc20_CMad2 + Bub3_BubR1 $\rightleftharpoons$ MCC	
5	R5		Bub3_BubR1 + Cdc20 $\rightleftharpoons$ Bub3_BubR1_Cdc20	
6	R6		OMad2 + Cdc20 $\longrightarrow$ Cdc20_CMad2	
7	R7		MCC + APC $\longrightarrow$ MCC_APC	
8	R7b		MCC_APC $\longrightarrow$ OMad2 + Bub3_BubR1 + APC_Cdc20	
9	R8		APC + Cdc20 $\rightleftharpoons$ APC_Cdc20	

7.1 Reaction R1

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$\text{Mad1\_CMad2} + \text{OMad2} \rightleftharpoons \text{Mad1\_CMad2\_OMad2} \tag{4}$$

Reactants

Table 7: Properties of each reactant.

Id	Name	SBO
Mad1_CMad2	Mad1:C-Mad2	
OMad2	O-Mad2	

Product

Table 8: Properties of each product.

Id	Name	SBO
Mad1_CMad2_OMad2	Mad1:C-Mad2:O-Mad2*	

Kinetic Law

Derived unit $\text{s}^{-1} \cdot \text{mol}$

$$v_1 = \text{vol}\,(\text{Cytoplasm}) \cdot (\text{u} \cdot \text{k1f} \cdot [\text{Mad1\_CMad2}] \cdot [\text{OMad2}] - \text{k1r} \cdot [\text{Mad1\_CMad2\_OMad2}]) \tag{5}$$

7.2 Reaction R2

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

Reaction equation

$$\text{Mad1\_CMad2\_OMad2} + \text{Cdc20} \longrightarrow \text{Mad1\_CMad2} + \text{Cdc20\_CMad2} \tag{6}$$

Reactants

Table 9: Properties of each reactant.

Id	Name	SBO
Mad1_CMad2_OMad2	Mad1:C-Mad2:O-Mad2*	

Id	Name	SBO
Cdc20	Cdc20	

Products

Table 10: Properties of each product.

Id	Name	SBO
Mad1_CMad2	Mad1:C-Mad2	
Cdc20_CMad2	Cdc20:C-Mad2	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_2 = \mathrm{u} \cdot \mathrm{k2f} \cdot [\mathrm{Mad1\_CMad2\_OMad2}] \cdot [\mathrm{Cdc20}] \cdot \mathrm{vol}\,(\mathrm{Cytoplasm}) \tag{7}$$

7.3 Reaction R3

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

Reaction equation

$$\mathrm{Cdc20\_CMad2} \longrightarrow \mathrm{Cdc20} + \mathrm{OMad2} \tag{8}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
Cdc20_CMad2	Cdc20:C-Mad2	

Products

Table 12: Properties of each product.

Id	Name	SBO
Cdc20	Cdc20	
OMad2	O-Mad2	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_3 = \mathrm{k3f} \cdot [\mathrm{Cdc20\_CMad2}] \cdot \mathrm{vol}\,(\mathrm{Cytoplasm}) \tag{9}$$

7.4 Reaction R4

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$\mathrm{Cdc20\_CMad2} + \mathrm{Bub3\_BubR1} \rightleftharpoons \mathrm{MCC} \tag{10}$$

Reactants

Table 13: Properties of each reactant.

Id	Name	SBO
Cdc20_CMad2	Cdc20:C-Mad2	
Bub3_BubR1	Bub3:BubR1	

Product

Table 14: Properties of each product.

Id	Name	SBO
MCC	MCC	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_4 = \mathrm{vol}\,(\mathrm{Cytoplasm}) \cdot (\mathrm{u} \cdot \mathrm{k4f} \cdot [\mathrm{Cdc20\_CMad2}] \cdot [\mathrm{Bub3\_BubR1}] - \mathrm{k4r} \cdot [\mathrm{MCC}]) \tag{11}$$

7.5 Reaction R5

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$\mathrm{Bub3\_BubR1} + \mathrm{Cdc20} \rightleftharpoons \mathrm{Bub3\_BubR1\_Cdc20} \tag{12}$$

Reactants

Table 15: Properties of each reactant.

Id	Name	SBO
Bub3_BubR1	Bub3:BubR1	
Cdc20	Cdc20	

Product

Table 16: Properties of each product.

Id	Name	SBO
Bub3_BubR1_Cdc20	Bub3:BubR1:Cdc20	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_5 = \mathrm{vol}\,(\mathrm{Cytoplasm}) \cdot (\mathrm{u} \cdot \mathrm{k5f} \cdot [\mathrm{Bub3\_BubR1}] \cdot [\mathrm{Cdc20}] - \mathrm{k5r} \cdot [\mathrm{Bub3\_BubR1\_Cdc20}]) \quad (13)$$

7.6 Reaction R6

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

Reaction equation

$$\mathrm{OMad2} + \mathrm{Cdc20} \longrightarrow \mathrm{Cdc20\_CMad2} \quad (14)$$

Reactants

Table 17: Properties of each reactant.

Id	Name	SBO
OMad2	O-Mad2	
Cdc20	Cdc20	

Product

Table 18: Properties of each product.

Id	Name	SBO
Cdc20_CMad2	Cdc20:C-Mad2	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_6 = \mathrm{kf6} \cdot [\mathrm{OMad2}] \cdot [\mathrm{Cdc20}] \cdot \mathrm{vol}\,(\mathrm{Cytoplasm}) \tag{15}$$

7.7 Reaction R7

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

Reaction equation

$$\mathrm{MCC} + \mathrm{APC} \longrightarrow \mathrm{MCC\_APC} \tag{16}$$

Reactants

Table 19: Properties of each reactant.

Id	Name	SBO
MCC	MCC	
APC	APC	

Product

Table 20: Properties of each product.

Id	Name	SBO
MCC_APC	MCC:APC	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_7 = \mathrm{u} \cdot \mathrm{k7f} \cdot [\mathrm{MCC}] \cdot [\mathrm{APC}] \cdot \mathrm{vol}\,(\mathrm{Cytoplasm}) \tag{17}$$

7.8 Reaction R7b

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

Reaction equation

$$\text{MCC\_APC} \longrightarrow \text{OMad2} + \text{Bub3\_BubR1} + \text{APC\_Cdc20} \tag{18}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
MCC_APC	MCC:APC	

Products

Table 22: Properties of each product.

Id	Name	SBO
OMad2	O-Mad2	
Bub3_BubR1	Bub3:BubR1	
APC_Cdc20	APC:Cdc20	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_8 = \text{u\_prime} \cdot \text{k7bf} \cdot [\text{MCC\_APC}] \cdot \text{vol}\,(\text{Cytoplasm}) \tag{19}$$

7.9 Reaction R8

This is a reversible reaction of two reactants forming one product.

Reaction equation

$$\text{APC} + \text{Cdc20} \rightleftharpoons \text{APC\_Cdc20} \tag{20}$$

Reactants

Table 23: Properties of each reactant.

Id	Name	SBO
APC	APC	
Cdc20	Cdc20	

Product

Table 24: Properties of each product.

Id	Name	SBO
APC_Cdc20	APC:Cdc20	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_9 = \mathrm{vol}\,(\mathrm{Cytoplasm}) \cdot (\mathrm{k8f} \cdot [\mathrm{APC}] \cdot [\mathrm{Cdc20}] - \mathrm{k8r} \cdot [\mathrm{APC\_Cdc20}]) \tag{21}$$

8 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.

8.1 Species Mad1_CMad2

Name Mad1:C-Mad2

Initial concentration $5 \cdot 10^{-8}\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in R1 and as a product in R2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mad1\_CMad2} = v_2 - v_1 \tag{22}$$

8.2 Species OMad2

Name O-Mad2

Notes Open conformation of Mad2

Initial concentration $1.3 \cdot 10^{-7}\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in R1, R6 and as a product in R3, R7b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{OMad2} = v_3 + v_8 - v_1 - v_6 \tag{23}$$

8.3 Species Mad1_CMad2_OMad2

Name Mad1:C-Mad2:O-Mad2*

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in R2 and as a product in R1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mad1\_CMad2\_OMad2} = v_1 - v_2 \tag{24}$$

8.4 Species Cdc20

Name Cdc20

Initial concentration $2.2\cdot 10^{-7}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in five reactions (as a reactant in R2, R5, R6, R8 and as a product in R3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Cdc20} = v_3 - v_2 - v_5 - v_6 - v_9 \tag{25}$$

8.5 Species Cdc20_CMad2

Name Cdc20:C-Mad2

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in R3, R4 and as a product in R2, R6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Cdc20\_CMad2} = v_2 + v_6 - v_3 - v_4 \tag{26}$$

8.6 Species Bub3_BubR1

Name Bub3:BubR1

Initial concentration $1.27\cdot 10^{-7}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in R4, R5 and as a product in R7b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Bub3\_BubR1} = v_8 - v_4 - v_5 \tag{27}$$

8.7 Species MCC

Name MCC

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in R7 and as a product in R4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MCC} = v_4 - v_7 \tag{28}$$

8.8 Species Bub3_BubR1_Cdc20

Name Bub3:BubR1:Cdc20

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in one reaction (as a product in R5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Bub3\_BubR1\_Cdc20} = v_5 \tag{29}$$

8.9 Species APC

Name APC

Initial concentration $9\cdot 10^{-8}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in R7, R8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{APC} = -v_7 - v_9 \tag{30}$$

8.10 Species MCC_APC

Name MCC:APC

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in R7b and as a product in R7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MCC\_APC} = v_7 - v_8 \tag{31}$$

8.11 Species APC_Cdc20

Name APC:Cdc20

Initial concentration $0\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a product in R7b, R8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{APC\_Cdc20} = v_8 + v_9 \tag{32}$$

SBML2LaTeX 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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