SBML Model Report

Model name: "Ray2013 - Meiotic initiation in S. cerevisiae"



February 28, 2017

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Varun Kothamachu¹, Ray Debjit² and Hamza Umut Karakurt³ at February third 2017 at 2:41 p. m. and last time modified at February 28th 2017 at 4:47 p. m. Table 1 shows 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	6
events	0	constraints	0
reactions	6	function definitions	6
global parameters	0	unit definitions	1
rules	0	initial assignments	0

Model Notes

Ray2013 - Meiotic initiation in S. cerevisiae

A mathematical representation of early meiotic events, particularly feedback mechanisms at the system level and phosphorylation of signalling molecules for regulating protein activities, is described here

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This model is described in the article: Dynamic modeling of yeast meiotic initiation. Ray D, Su Y, Ye P.BMC Syst Biol. 2013 May 1;7:37

Abstract:

BACKGROUND: Meiosis is the sexual reproduction process common to eukaryotes. The diploid yeast Saccharomyces cerevisiae undergoes meiosis in sporulation medium to form four haploid spores. Initiation of the process is tightly controlled by intricate networks of positive and negative feedback loops. Intriguingly, expression of early meiotic proteins occurs within a narrow time window. Further, sporulation efficiency is strikingly different for yeast strains with distinct mutations or genetic backgrounds. To investigate signal transduction pathways that regulate transient protein expression and sporulation efficiency, we develop a mathematical model using ordinary differential equations. The model describes early meiotic events, particularly feedback mechanisms at the system level and phosphorylation of signaling molecules for regulating protein activities.

RESULTS: The mathematical model is capable of simulating the orderly and transient dynamics of meiotic proteins including Ime1, the master regulator of meiotic initiation, and Ime2, a kinase encoded by an early gene. The model is validated by quantitative sporulation phenotypes of single-gene knockouts. Thus, we can use the model to make novel predictions on the cooperation between proteins in the signaling pathway. Virtual perturbations on feedback loops suggest that both positive and negative feedback loops are required to terminate expression of early meiotic proteins. Bifurcation analyses on feedback loops indicate that multiple feedback loops are coordinated to modulate sporulation efficiency. In particular, positive auto-regulation of Ime2 produces a bistable system with a normal meiotic state and a more efficient meiotic state.

CONCLUSIONS: By systematically scanning through feedback loops in the mathematical model, we demonstrate that, in yeast, the decisions to terminate protein expression and to sporulate at different efficiencies stem from feedback signals toward the master regulator Ime1 and the early meiotic protein Ime2. We argue that the architecture of meiotic initiation pathway generates a robust mechanism that assures a rapid and complete transition into meiosis. This type of systems-level regulation is a commonly used mechanism controlling developmental programs in yeast and other organisms. Our mathematical model uncovers key regulations that can be manipulated to enhance sporulation efficiency, an important first step in the development of new strategies for producing gametes with high quality and quantity.

This model is hosted on BioModels Database and identifiedby: BIOMD0000000626.

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

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2 Unit Definitions

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

2.1 Unit time

Name time

Definition 3600 s

2.2 Unit substance

Notes Mole is the predefined SBML unit for substance.

Definition mol

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.

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
V	Cell	0000290	3	1	litre	✓	

3.1 Compartment V

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

Name Cell

SBO:0000290 physical compartment

4 Species

This model contains six 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
Rim11	Rim11	V	$\text{mol} \cdot l^{-1}$		
pUme6	pUme6	V	$\text{mol} \cdot l^{-1}$	\Box	
pSok2	pSok2	V	$\text{mol} \cdot 1^{-1}$	\Box	
Ime1	Ime1	V	$\text{mol} \cdot 1^{-1}$	\Box	
pIme1	pIme1	V	$\text{mol} \cdot 1^{-1}$		\Box
Ime2	Ime2	V	$\text{mol} \cdot 1^{-1}$		\Box

5 Function definitions

This is an overview of six function definitions.

5.1 Function definition ODE_pIme1_1_1_1

Name ODE pIme1_1_1 [1]

Arguments [Ime1], [Rim11], dpime_1, [pIme1], pime_1

Mathematical Expression

$$pime_{-1} \cdot [Ime1] \cdot [Rim11] - dpime_{-1} \cdot [pIme1]$$
 (1)

5.2 Function definition ODE_pUme6_1_1_1_1

Name ODE pUme6_1_1 [1]

Arguments [Rim11], [pUme6], pume_6, uume_6

Mathematical Expression

$$(1 - [pUme6]) \cdot pume_6 \cdot [Rim11] - uume_6 \cdot [pUme6]$$
 (2)

5.3 Function definition ODE_Ime2_1_1_1_1

Name ODE Ime2_1_1_1 [1]

Arguments [Ime2], c_2, c_3, dime_2, [pIme1], [pUme6], sime_2, sprimeime_2

Mathematical Expression

$$sime_2 \cdot [pUme6] \cdot [pIme1] + \frac{sprimeime_2 \cdot [Ime2]^5}{c_2^5 + [Ime2]^5} - \frac{dime_2 \cdot [Ime2]}{c_3 + [Ime2]} \quad (3)$$

5.4 Function definition ODE_pSok2_1_1_1_1

Name ODE pSok2_1_1 [1]

Arguments [Ime1], csok_2, [pSok2], psok_2, usok_2

Mathematical Expression

$$\frac{csok_2}{csok_2 + [Ime1]} \cdot (1 - [pSok2]) \cdot psok_2 - usok_2 \cdot [pSok2] \tag{4}$$

5.5 Function definition ODE_Ime1_1_1_1

Name ODE Ime1_1_1 [1]

Arguments [Ime1], [Ime2], [Rim11], c_1, cime_1, dime_1, dprimeime_1, [pSok2], pime_1, sime_1

Mathematical Expression

$$\begin{split} &\frac{\text{cime_1}}{\text{cime_1} + [pSok2]} \cdot \text{sime_1} - \left(\text{pime_1} \cdot [Ime1] \cdot [Rim11] \right. \\ &+ \text{dime_1} \cdot [Ime1] + \text{dprimeime_1} \cdot [Ime2] \cdot \frac{[Ime1]}{c_1 + [Ime1]} \right) \end{split} \tag{5}$$

5.6 Function definition ODE_Rim11_1_1

Name ODE Rim11_1_1

Arguments [Rim11], prim_11, urim_11

Mathematical Expression

$$urim_{-}11 \cdot (1 - [Rim11]) - prim_{-}11 \cdot [Rim11]$$

$$(6)$$

6 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 4: Overview of all reactions

No	Id	Name	Reaction Equation	SBO
1	rim11_1	Rim11 Dephosphorylation	$\emptyset \stackrel{\underline{\text{Rim}}11}{\longleftarrow} \text{Rim}11$	0000330
2	$pume6_{-}1$	Ume6 Phosphorylation	$\emptyset \xrightarrow{\text{Rim} 11} \text{pUme6}$	0000216
3	sok2_1	Production of Phosphorylated Sok2	$\emptyset \xrightarrow{\text{Ime1, pSok2}} \text{pSok2}$	0000216
4	${\tt ime1_1}$	Ime1 Protein Production	$\emptyset \xrightarrow{pSok2, Rim11, Ime2} Ime1$	0000393
5	$pime1_{-}1$	Phosphorylation of Ime1	$\emptyset \xrightarrow{\text{Ime1}, \text{Rim11}, \text{pIme1}} \text{pIme1}$	0000216
6	${\tt ime2_1}$	Ime2 Protein Production	$\emptyset \stackrel{\text{pUme6, pIme1}}{\longleftarrow} \text{Ime2}$	0000393

6.1 Reaction rim11_1

This is a reversible reaction of no reactant forming one product influenced by one modifier.

Name Rim11 Dephosphorylation

SBO:0000330 dephosphorylation

Notes Rim11 Dephosphorylation

Reaction equation

$$\emptyset \stackrel{\underline{Rim11}}{\longleftarrow} Rim11 \tag{7}$$

Modifier

Table 5: Properties of each modifier.

Id	Name	SBO
Rim11	Rim11	

Product

Table 6: Properties of each product.

Id	Name	SBO
Rim11	Rim11	

Kinetic Law

$$v_1 = \text{vol}(V) \cdot \text{ODE_Rim}11_{-1}1([\text{Rim}11], \text{prim}_{-1}1, \text{urim}_{-1}1)$$
 (8)

$$ODE_Rim11_1_1([Rim11], prim_11, urim_11) = urim_11 \cdot (1 - [Rim11]) - prim_11 \cdot [Rim11]$$
 (9)

$$ODE_Rim11_1_1\left([Rim11],prim_11,urim_11\right) = urim_11 \cdot \left(1 - [Rim11]\right) - prim_11 \cdot [Rim11] \quad (10)$$

Table 7: Properties of each parameter.

Id	Name	SBO Value Unit	Constant
prim_11	prim_11	0.01	
$urim_{-}11$	urim_11	0.10	

6.2 Reaction pume6_1

This is a reversible reaction of no reactant forming one product influenced by one modifier.

Name Ume6 Phosphorylation

SBO:0000216 phosphorylation

Notes Ume6 Phosphorylation

Reaction equation

$$\emptyset \xrightarrow{\text{Rim11}} \text{pUme6} \tag{11}$$

Modifier

Table 8: Properties of each modifier.

Id	Name	SBO
Rim11	Rim11	

Product

Table 9: Properties of each product.

Id	Name	SBO
pUme6	pUme6	

Kinetic Law

$$v_2 = \text{vol}(V) \cdot \text{ODE_pUme6_1_1_1}([\text{Rim11}], [\text{pUme6}], \text{pume_6}, \text{uume_6})$$
 (12)

ODE_pUme6_1_1_1 ([Rim11], [pUme6], pume_6, uume_6)
=
$$(1 - [pUme6]) \cdot pume_6 \cdot [Rim11] - uume_6 \cdot [pUme6]$$
 (13)

ODE_pUme6_1_1_1 ([Rim11], [pUme6], pume_6, uume_6)
=
$$(1 - [pUme6]) \cdot pume_6 \cdot [Rim11] - uume_6 \cdot [pUme6]$$
 (14)

Table 10: Properties of each parameter.

Id	Name	SBO Value Unit	Constant
pume_6	pume_6	0.30	
$\mathtt{uume}_{-}6$	uume_6	0.01	

6.3 Reaction sok2_1

This is a reversible reaction of no reactant forming one product influenced by two modifiers.

Name Production of Phosphorylated Sok2

SBO:0000216 phosphorylation

Notes Production of phosphorylated Sok2

Reaction equation

$$\emptyset \xrightarrow{\text{Ime1, pSok2}} \text{pSok2} \tag{15}$$

Modifiers

Table 11: Properties of each modifier.

Id	Name	SBO
Ime1	Ime1	
pSok2	pSok2	

Product

Table 12: Properties of each product.

Id	Name	SBO
pSok2	pSok2	

Kinetic Law

$$v_3 = \text{vol}(V) \cdot \text{ODE_pSok2_1_1_1}([\text{Ime1}], \text{csok_2}, [\text{pSok2}], \text{psok_2}, \text{usok_2})$$
 (16)

$$\begin{aligned} & ODE_pSok2_1_1_1 \left([Ime1], csok_2, [pSok2], psok_2, usok_2 \right) \\ &= \frac{csok_2}{csok_2 + [Ime1]} \cdot (1 - [pSok2]) \cdot psok_2 - usok_2 \cdot [pSok2] \end{aligned} \tag{17}$$

ODE_pSok2_1_1_1 ([Ime1], csok_2, [pSok2], psok_2, usok_2)

$$= \frac{\text{csok}_2}{\text{csok}_2 + [Ime1]} \cdot (1 - [pSok2]) \cdot \text{psok}_2 - \text{usok}_2 \cdot [pSok2]$$
(18)

Table 13: Properties of each parameter.

Id	Name	SBO Value Unit	Constant
csok_2	csok_2	0.05	\square
psok_2	psok_2	0.70	
$usok_{-}2$	$usok_{-}2$	1.00	

6.4 Reaction ime1_1

This is an irreversible reaction of no reactant forming one product influenced by three modifiers.

Name Imel Protein Production

SBO:0000393 production

Notes Ime1 Protein Production

Reaction equation

$$\emptyset \xrightarrow{\text{pSok2, Rim11, Ime2}} \text{Ime1}$$
 (19)

Modifiers

Table 14: Properties of each modifier.

Id	Name	SBO
pSok2	pSok2	
Rim11	Rim11	
Ime2	Ime2	

Product

Table 15: Properties of each product.

Id	Name	SBO
Ime1	Ime1	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = vol(V) \cdot ODE_Ime1_1_1_1 ([Ime1], [Ime2], [Rim11], c_1, cime_1, dime_1, \\ dprimeime_1, [pSok2], pime_1, sime_1)$$
 (20)

$$\begin{aligned} \text{ODE_Ime1_1_1_1} & ([\text{Ime1}], [\text{Ime2}], [\text{Rim11}], c_{-1}, \text{cime_1}, \text{dime_1}, \text{dprimeime_1}, [pSok2], \\ \text{pime_1}, \text{sime_1}) &= \frac{\text{cime_1}}{\text{cime_1} + [pSok2]} \cdot \text{sime_1} - \left(\text{pime_1} \cdot [\text{Ime1}] \cdot [\text{Rim11}] + \text{dime_1} \right. \\ & \cdot [\text{Ime1}] + \text{dprimeime_1} \cdot [\text{Ime2}] \cdot \frac{[\text{Ime1}]}{c_{-1} + [\text{Ime1}]} \right) \end{aligned} \tag{21}$$

$$\begin{aligned} \text{ODE_Ime1_1_1_([Ime1], [Ime2], [Rim11], c_1, cime_1, dime_1, dprimeime_1, [pSok2],} \\ \text{pime_1, sime_1}) &= \frac{\text{cime_1}}{\text{cime_1} + [pSok2]} \cdot \text{sime_1} - \left(\text{pime_1} \cdot [Ime1] \cdot [Rim11] + \text{dime_1} \right) \\ &\quad \cdot [Ime1] + \text{dprimeime_1} \cdot [Ime2] \cdot \frac{[Ime1]}{\text{c_1} + [Ime1]} \end{aligned} \tag{22}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
c_1	c_1		0.01		
$\mathtt{cime}_{-}1$	cime_1		0.01		
$\mathtt{dime}_{-}1$	dime_1		1.00		
${\tt dprimeime_1}$	dprimeime_1		1.00		
$\mathtt{pime}_{-}1$	pime_1		2.00		\square
${\tt sime_1}$	sime_1		10.00		

6.5 Reaction pime1_1

This is an irreversible reaction of no reactant forming one product influenced by three modifiers.

Name Phosphorylation of Ime1

SBO:0000216 phosphorylation

Notes Phosphorylation of Ime1

Reaction equation

$$\emptyset \xrightarrow{\text{Ime1}, \text{Rim11}, \text{pIme1}} \text{pIme1}$$
 (23)

Modifiers

Table 17: Properties of each modifier.

Id	Name	SBO
Ime1 Rim11	Ime1 Rim11	
pIme1	pIme1	

Product

Table 18: Properties of each product.

Id	Name	SBO
pIme1	pIme1	

Kinetic Law

$$v_5 = \text{vol}(V) \cdot \text{ODE_pIme1_1_1}([\text{Ime1}], [\text{Rim11}], \text{dpime_1}, [\text{pIme1}], \text{pime_1})$$
 (24)

Table 19: Properties of each parameter.

Id	Name	SBO Value Unit	Constant
dpime_1	dpime_1 pime_1	1.0 2.0	

6.6 Reaction ime2_1

This is a reversible reaction of no reactant forming one product influenced by two modifiers.

Name Ime2 Protein Production

SBO:0000393 production

Notes Ime2 Protein Production

Reaction equation

$$\emptyset \xleftarrow{\text{pUme6, pIme1}} \text{Ime2}$$
 (27)

Modifiers

Table 20: Properties of each modifier.

Id	Name	SBO
pUme6	pUme6	
pIme1	pIme1	

Product

Table 21: Properties of each product.

Id	Name	SBO
Ime2	Ime2	

Kinetic Law

Derived unit contains undeclared units

 $v_6 = \text{vol}(V) \cdot \text{ODE_Ime2_1_1_1_1}([\text{Ime2}], \text{c_2}, \text{c_3}, \text{dime_2}, [\text{pIme1}], [\text{pUme6}], \text{sime_2}, \text{sprim} \text{£28}\text{£2})$

$$\begin{aligned} & \text{ODE_Ime2_1_1_1_1} \left([\text{Ime2}], \text{c_2}, \text{c_3}, \text{dime_2}, [\text{pIme1}], [\text{pUme6}], \text{sime_2}, \text{sprimeime_2} \right) \\ &= \text{sime_2} \cdot [\text{pUme6}] \cdot [\text{pIme1}] + \frac{\text{sprimeime_2} \cdot [\text{Ime2}]^5}{\text{c_2}^5 + [\text{Ime2}]^5} - \frac{\text{dime_2} \cdot [\text{Ime2}]}{\text{c_3} + [\text{Ime2}]} \end{aligned} \tag{29}$$

ODE_Ime2_1_1_1_1 ([Ime2], c_2, c_3, dime_2, [pIme1], [pUme6], sime_2, sprimeime_2)

$$= sime_2 \cdot [pUme6] \cdot [pIme1] + \frac{sprimeime_2 \cdot [Ime2]^5}{c_2^5 + [Ime2]^5} - \frac{dime_2 \cdot [Ime2]}{c_3 + [Ime2]}$$
(30)

Id **SBO** Name Value Unit Constant c_2 c_2 1.4 c_3 c_3 2.0 8.0 $dime_2$ dime_2 $sime_2$ 10.0 $sime_2$ sprimeime_2 3.0 sprimeime_2

Table 22: Properties of each parameter.

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 Rim11

Name Rim11

Notes Serine/threonine-protein kinase RIM11

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

This species takes part in five reactions (as a product in rim11_1 and as a modifier in rim11_1, pume6_1, ime1_1, pime1_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Rim}11 = v_1 \tag{31}$$

7.2 Species pUme6

Name pUme6

Notes Phosphorylated Transcriptional regulatory protein UME6

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

This species takes part in two reactions (as a product in pume6_1 and as a modifier in ime2_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pUme6} = v_2 \tag{32}$$

7.3 Species pSok2

Name pSok2

Notes phosphorylated Protein SOK2

Initial concentration $0.99999999999971 \text{ mol} \cdot l^{-1}$

This species takes part in three reactions (as a product in sok2_1 and as a modifier in sok2_1, ime1_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pSok2} = v_3 \tag{33}$$

7.4 Species Ime1

Name Ime1

Notes Meiosis-inducing protein 1

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

This species takes part in three reactions (as a product in ime1_1 and as a modifier in sok2_1, pime1_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ime1} = v_4 \tag{34}$$

7.5 Species pIme1

Name pIme1

Notes phosphorylated Meiosis-inducing protein 1

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

This species takes part in three reactions (as a product in pime1_1 and as a modifier in pime1_1, ime2_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pIme1} = v_5 \tag{35}$$

7.6 Species Ime2

Name Ime2

Notes Meiosis induction protein kinase IME2/SME1

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

This species takes part in two reactions (as a product in ime2_1 and as a modifier in ime1_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ime2} = v_6 \tag{36}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000216 phosphorylation: Addition of a phosphate group (-H2PO4) to a chemical entity

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

SBO:0000330 dephosphorylation: Removal of a phosphate group (-H2PO4) from a chemical entity.

SBO:0000393 production: Generation of a material or conceptual entity.

 $\mathfrak{BML2}^{d}$ 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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