SBML Model Report

Model name: "Chickarmane2006 - Stem cell switch irreversible"

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following four authors: Vijayalakshmi Chelliah[1], Carsten Peterson[2], Vijay Chickarmane[3] and Lukas Endler[4] at November 26th 2008 at 1:10 p. m. and last time modified at June fifth 2013 at 4:57 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	12
events	0	constraints	0
reactions	10	function definitions	0
global parameters	32	unit definitions	3
rules	0	initial assignments	0

Model Notes

Chickarmane2006 - Stem cell switch irreversible

[1]EMBL-EBI, viji@ebi.ac.uk
[2]Lund Strategic Research Centre for Stem Cell Biology and Cell Therapy, Lund University, Sweden., carsten@thep.lu.se
[3]Keck Graduate Institute, California, vchickar@caltech.edu
[4]EMBL-EBI, llukas@ebi.ac.uk

Kinetic modeling approach of the transcriptional dynamics of the embryonic stem cell switch.

This model is described in the article:Transcriptional dynamics of the embryonic stem cell switch.Chickarmane V, Troein C, Nuber UA, Sauro HM, Peterson CPLoS Computational Biology. 2006; 2(9):e123

Abstract:

Recent ChIP experiments of human and mouse embryonic stem cells have elucidated the architecture of the transcriptional regulatory circuitry responsible for cell determination, which involves the transcription factors OCT4, SOX2, and NANOG. In addition to regulating each other through feedback loops, these genes also regulate downstream target genes involved in the maintenance and differentiation of embryonic stem cells. A search for the OCT4-SOX2-NANOG network motif in other species reveals that it is unique to mammals. With a kinetic modeling approach, we ascribe function to the observed OCT4-SOX2-NANOG network by making plausible assumptions about the interactions between the transcription factors at the gene promoter binding sites and RNA polymerase (RNAP), at each of the three genes as well as at the target genes. We identify a bistable switch in the network, which arises due to several positive feedback loops, and is switched on/off by input environmental signals. The switch stabilizes the expression levels of the three genes, and through their regulatory roles on the downstream target genes, leads to a binary decision: when OCT4, SOX2, and NANOG are expressed and the switch is on, the self-renewal genes are on and the differentiation genes are off. The opposite holds when the switch is off. The model is extremely robust to parameter changes. In addition to providing a self-consistent picture of the transcriptional circuit, the model generates several predictions. Increasing the binding strength of NANOG to OCT4 and SOX2, or increasing its basal transcriptional rate, leads to an irreversible bistable switch: the switch remains on even when the activating signal is removed. Hence, the stem cell can be manipulated to be self-renewing without the requirement of input signals. We also suggest tests that could discriminate between a variety of feedforward regulation architectures of the target genes by OCT4, SOX2, and NANOG.

This model is hosted on BioModels Database and identified by: MODEL7957942740 .

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 four are predefined by SBML and not mentioned in the model.

2.1 Unit substance

Name arb_substance

Definition dimensionless

2.2 Unit `Volume`

Name arb_volume

Definition dimensionless

2.3 Unit `Time`

Name arb_time

Definition dimensionless

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 2: Properties of all compartments.

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

3.1 Compartment `compartment`

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

4 Species

This model contains twelve species. The boundary condition of seven 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 Condition
OCT4_Gene		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
NANOG_Gene		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
SOX2_Gene		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
targetGene		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
degradation		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
p53		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
A		compartment	dimensionless $\cdot$ l^{-1}	☐	☑
OCT4		compartment	dimensionless $\cdot$ l^{-1}	☐	☐
SOX2		compartment	dimensionless $\cdot$ l^{-1}	☐	☐
NANOG		compartment	dimensionless $\cdot$ l^{-1}	☐	☐
OCT4_SOX2		compartment	dimensionless $\cdot$ l^{-1}	☐	☐
Protein		compartment	dimensionless $\cdot$ l^{-1}	☐	☐

5 Parameters

This model contains 32 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
eta1	eta1		10^{-4}		☑
a1	a1		1.000		☑
a2	a2		0.010		☑
a3	a3		0.500		☑
f	f		1000.000		☑
b1	b1		0.001		☑
b2	b2		0.001		☑
b3	b3		0.001		☑
gamma1	gamma1		1.000		☑
eta5	eta5		10^{-4}		☑
e1	e1		0.010		☑
e2	e2		0.100		☑
f2	f2		0.001		☑
f1	f1		0.001		☑
f3	f3		0.050		☑
gamma2	gamma2		1.000		☑
k1c	k1c		0.050		☑
k2c	k2c		0.001		☑
k3c	k3c		5.000		☑
eta3	eta3		10^{-4}		☑
c1	c1		1.000		☑
c2	c2		0.010		☑
c3	c3		0.500		☑
d1	d1		0.001		☑
d2	d2		0.001		☑
d3	d3		0.001		☑
gamma3	gamma3		1.000		☑
g1	g1		0.100		☑
eta7	eta7		10^{-4}		☑
h1	h1		0.001		☑
h2	h2		1.000		☑
gamma4	gamma4		0.010		☑

6 Reactions

This model contains ten 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

№	Id	Name	Reaction Equation	SBO
1	J0		$\text{OCT4\_Gene} \xrightarrow{\text{A, OCT4\_SOX2, NANOG}} \text{OCT4}$	
2	J1		$\text{OCT4} \longrightarrow \text{degradation}$	
3	J2		$\text{NANOG\_Gene} \xrightarrow{\text{OCT4\_SOX2, p53}} \text{NANOG}$	
4	J3		$\text{NANOG} \longrightarrow \text{degradation}$	
5	J4		$\text{OCT4} + \text{SOX2} \longrightarrow \text{OCT4\_SOX2}$	
6	J5		$\text{OCT4\_SOX2} \longrightarrow \text{degradation}$	
7	J6		$\text{SOX2\_Gene} \xrightarrow{\text{A, OCT4\_SOX2, NANOG}} \text{SOX2}$	
8	J7		$\text{SOX2} \longrightarrow \text{degradation}$	
9	J8		$\text{targetGene} \xrightarrow{\text{OCT4\_SOX2, NANOG}} \text{Protein}$	
10	J9		$\text{Protein} \longrightarrow \text{degradation}$	

6.1 Reaction J0

This is an irreversible reaction of one reactant forming one product influenced by three modifiers.

Reaction equation

$$\text{OCT4\_Gene} \xrightarrow{\text{A, OCT4\_SOX2, NANOG}} \text{OCT4} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
OCT4_Gene		

Modifiers

Table 7: Properties of each modifier.

Id	Name	SBO
A		
OCT4_SOX2		
NANOG		

Product

Table 8: Properties of each product.

Id	Name	SBO
OCT4		

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \frac{\text{eta1} + \text{a1} \cdot [\text{A}] + \text{a2} \cdot [\text{OCT4\_SOX2}] + \text{a3} \cdot [\text{OCT4\_SOX2}] \cdot [\text{NANOG}]}{1 + \frac{\text{eta1}}{\text{f}} + \text{b1} \cdot [\text{A}] + \text{b2} \cdot [\text{OCT4\_SOX2}] + \text{b3} \cdot [\text{OCT4\_SOX2}] \cdot [\text{NANOG}]} \tag{2}$$

6.2 Reaction J1

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

Reaction equation

$$\text{OCT4} \longrightarrow \text{degradation} \tag{3}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
OCT4		

Product

Table 10: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{gamma1} \cdot [\text{OCT4}] \tag{4}$$

6.3 Reaction J2

This is an irreversible reaction of one reactant forming one product influenced by two modifiers.

Reaction equation

$$\text{NANOG\_Gene} \xrightarrow{\text{OCT4\_SOX2, p53}} \text{NANOG} \tag{5}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
NANOG_Gene		

Modifiers

Table 12: Properties of each modifier.

Id	Name	SBO
OCT4_SOX2		
p53		

Product

Table 13: Properties of each product.

Id	Name	SBO
NANOG		

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \frac{\mathrm{eta5} + \mathrm{e1} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{e2} \cdot [\mathrm{OCT4\_SOX2}] \cdot [\mathrm{NANOG}]}{1 + \frac{\mathrm{eta5}}{\mathrm{f}} + \mathrm{f2} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{f1} \cdot [\mathrm{OCT4\_SOX2}] \cdot [\mathrm{NANOG}] + \mathrm{f3} \cdot [\mathrm{p53}]} \tag{6}$$

6.4 Reaction J3

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

Reaction equation

$$\mathrm{NANOG} \longrightarrow \mathrm{degradation} \tag{7}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
NANOG		

Product

Table 15: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{gamma2} \cdot [\text{NANOG}] \tag{8}$$

6.5 Reaction J4

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

Reaction equation

$$\text{OCT4} + \text{SOX2} \longrightarrow \text{OCT4\_SOX2} \tag{9}$$

Reactants

Table 16: Properties of each reactant.

Id	Name	SBO
OCT4		
SOX2		

Product

Table 17: Properties of each product.

Id	Name	SBO
OCT4_SOX2		

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{k1c} \cdot [\text{OCT4}] \cdot [\text{SOX2}] - \text{k2c} \cdot [\text{OCT4\_SOX2}] \tag{10}$$

6.6 Reaction J5

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

Reaction equation

$$\text{OCT4\_SOX2} \longrightarrow \text{degradation} \tag{11}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
OCT4_SOX2		

Product

Table 19: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{k3c} \cdot [\mathrm{OCT4\_SOX2}] \tag{12}$$

6.7 Reaction J6

This is an irreversible reaction of one reactant forming one product influenced by three modifiers.

Reaction equation

$$\mathrm{SOX2\_Gene} \xrightarrow{\mathrm{A,\ OCT4\_SOX2,\ NANOG}} \mathrm{SOX2} \tag{13}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
SOX2_Gene		

Modifiers

Table 21: Properties of each modifier.

Id	Name	SBO
A		

Id	Name	SBO
OCT4_SOX2		
NANOG		

Product

Table 22: Properties of each product.

Id	Name	SBO
SOX2		

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \frac{\mathrm{eta3} + \mathrm{c1} \cdot [\mathrm{A}] + \mathrm{c2} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{c3} \cdot [\mathrm{OCT4\_SOX2}] \cdot [\mathrm{NANOG}]}{1 + \frac{\mathrm{eta3}}{\mathrm{f}} + \mathrm{d1} \cdot [\mathrm{A}] + \mathrm{d2} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{d3} \cdot [\mathrm{OCT4\_SOX2}] \cdot [\mathrm{NANOG}]} \tag{14}$$

6.8 Reaction J7

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

Reaction equation

$$\mathrm{SOX2} \longrightarrow \mathrm{degradation} \tag{15}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
SOX2		

Product

Table 24: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{gamma3} \cdot [\mathrm{SOX2}] \tag{16}$$

6.9 Reaction J8

This is an irreversible reaction of one reactant forming one product influenced by two modifiers.

Reaction equation

$$\mathrm{targetGene} \xrightarrow{\mathrm{OCT4\_SOX2},\ \mathrm{NANOG}} \mathrm{Protein} \tag{17}$$

Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
targetGene		

Modifiers

Table 26: Properties of each modifier.

Id	Name	SBO
OCT4_SOX2		
NANOG		

Product

Table 27: Properties of each product.

Id	Name	SBO
Protein		

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \frac{\mathrm{g1} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{eta7}}{1 + \frac{\mathrm{eta7}}{\mathrm{f2}} + \mathrm{h1} \cdot [\mathrm{OCT4\_SOX2}] + \mathrm{h2} \cdot [\mathrm{OCT4\_SOX2}] \cdot [\mathrm{NANOG}]} \tag{18}$$

6.10 Reaction J9

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

Reaction equation

$$\text{Protein} \longrightarrow \text{degradation} \tag{19}$$

Reactant

Table 28: Properties of each reactant.

Id	Name	SBO
`Protein`		

Product

Table 29: Properties of each product.

Id	Name	SBO
`degradation`		

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{gamma4} \cdot [\text{Protein}] \tag{20}$$

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 OCT4_Gene

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

This species takes part in one reaction (as a reactant in J0), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{OCT4\_Gene} = 0 \tag{21}$$

7.2 Species NANOG_Gene

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

This species takes part in one reaction (as a reactant in J2), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{NANOG\_Gene} = 0 \tag{22}$$

7.3 Species SOX2_Gene

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

This species takes part in one reaction (as a reactant in J6), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{SOX2\_Gene} = 0 \tag{23}$$

7.4 Species targetGene

Initial concentration $0.01 \text{ dimensionless} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a reactant in J8), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{targetGene} = 0 \tag{24}$$

7.5 Species degradation

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

This species takes part in five reactions (as a product in J1, J3, J5, J7, J9), which do not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{degradation} = 0 \tag{25}$$

7.6 Species p53

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

This species takes part in one reaction (as a modifier in J2), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p53} = 0 \tag{26}$$

7.7 Species A

Initial concentration $10 \text{ dimensionless} \cdot \mathrm{l}^{-1}$

This species takes part in two reactions (as a modifier in J0, J6), which do not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{A} = 0 \tag{27}$$

7.8 Species OCT4

Initial concentration $0.01 \text{ dimensionless} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in J1, J4 and as a product in J0).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{OCT4} = v_1 - v_2 - v_5 \tag{28}$$

7.9 Species SOX2

Initial concentration $0.01 \text{ dimensionless} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in J4, J7 and as a product in J6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{SOX2} = v_7 - v_5 - v_8 \tag{29}$$

7.10 Species NANOG

Initial concentration $0.01 \text{ dimensionless} \cdot \mathrm{l}^{-1}$

This species takes part in five reactions (as a reactant in J3 and as a product in J2 and as a modifier in J0, J6, J8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NANOG} = v_3 - v_4 \tag{30}$$

7.11 Species OCT4_SOX2

Initial concentration $0.1 \text{ dimensionless} \cdot \text{l}^{-1}$

This species takes part in six reactions (as a reactant in J5 and as a product in J4 and as a modifier in J0, J2, J6, J8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{OCT4\_SOX2} = v_5 - v_6 \tag{31}$$

7.12 Species Protein

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

This species takes part in two reactions (as a reactant in J9 and as a product in J8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{Protein} = v_9 - v_{10} \tag{32}$$

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.

[a]Center for Bioinformatics Tübingen (ZBIT), Germany
[b]California Institute of Technology, Beckman Institute BNMC, Pasadena, United States
[c]European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom
[d]EML Research gGmbH, Heidelberg, Germany