

SBML Model Report

Model name: “Chickarmane2006 - Stem cell switch reversible”



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: Lukas Endler¹, Vijayalakshmi Chelliah², Carsten Peterson³ and Vijay Chickarmane⁴ at November 25th 2008 at 5:19 p. m. and last time modified at June fifth 2013 at 4:59 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	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 reversible

¹EMBL-EBI, lukas@ebi.ac.uk

²EMBL-EBI, viji@ebi.ac.uk

³Lund Strategic Research Centre for Stem Cell Biology and Cell Therapy, Lund University, Sweden., carsten@thep.lu.se

⁴Keck Graduate Institute, California, vchickar@caltech.edu

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 C. PLoS 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: [MODEL7957907314](#).

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

To the extent possible under law, all copyright and related or neighbouring rights to this encoded model have been dedicated to the public domain worldwide. Please refer to [CC0 Public Domain Dedication](#) for more information.

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 substance

Name arb_substance

Definition dimensionless

2.2 Unit `volume`

Name `arb_volume`

Definition 1

2.3 Unit `time`

Name `arb_time`

Definition dimensionless

2.4 Unit `area`

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

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
compartment			3	1	litre	<input checked="" type="checkbox"/>	

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 Condi- tion
OCT4_Gene		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
NANOG_Gene		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
SOX2_Gene		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
targetGene		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
degradation		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
p53		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
A		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
OCT4		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
SOX2		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
NANOG		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
OCT4_SOX2		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Protein		compartment	$\text{dimensionless} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>

5 Parameters

This model contains 32 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
eta1	eta1		10^{-4}		<input checked="" type="checkbox"/>
a1	a1		1.000		<input checked="" type="checkbox"/>
a2	a2		0.010		<input checked="" type="checkbox"/>
a3	a3		0.200		<input checked="" type="checkbox"/>
f	f		1000.000		<input checked="" type="checkbox"/>
b1	b1		0.001		<input checked="" type="checkbox"/>
b2	b2		0.001		<input checked="" type="checkbox"/>
b3	b3		$7 \cdot 10^{-4}$		<input checked="" type="checkbox"/>
gamma1	gamma1		1.000		<input checked="" type="checkbox"/>
eta5	eta5		10^{-4}		<input checked="" type="checkbox"/>
e1	e1		0.005		<input checked="" type="checkbox"/>
e2	e2		0.100		<input checked="" type="checkbox"/>
f2	f2		$9.95 \cdot 10^{-4}$		<input checked="" type="checkbox"/>
f1	f1		0.001		<input checked="" type="checkbox"/>
f3	f3		0.010		<input checked="" type="checkbox"/>
gamma2	gamma2		1.000		<input checked="" type="checkbox"/>
k1c	k1c		0.050		<input checked="" type="checkbox"/>
k2c	k2c		0.001		<input checked="" type="checkbox"/>
k3c	k3c		5.000		<input checked="" type="checkbox"/>
eta3	eta3		10^{-4}		<input checked="" type="checkbox"/>
c1	c1		1.000		<input checked="" type="checkbox"/>
c2	c2		0.010		<input checked="" type="checkbox"/>
c3	c3		0.200		<input checked="" type="checkbox"/>
d1	d1		0.001		<input checked="" type="checkbox"/>
d2	d2		0.001		<input checked="" type="checkbox"/>
d3	d3		$7 \cdot 10^{-4}$		<input checked="" type="checkbox"/>
gamma3	gamma3		1.000		<input checked="" type="checkbox"/>
g1	g1		0.100		<input checked="" type="checkbox"/>
eta7	eta7		10^{-4}		<input checked="" type="checkbox"/>
h1	h1		0.002		<input checked="" type="checkbox"/>
h2	h2		0.050		<input checked="" type="checkbox"/>
gamma4	gamma4		0.010		<input checked="" type="checkbox"/>

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

Nº	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



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

$$v_1 = \frac{\text{eta1} + a1 \cdot [A] + a2 \cdot [\text{OCT4_SOX2}] + a3 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]}{1 + \frac{\text{eta1}}{f} + b1 \cdot [A] + b2 \cdot [\text{OCT4_SOX2}] + b3 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]} \quad (2)$$

6.2 Reaction J1

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

Reaction equation



Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
OCT4		

Product

Table 10: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

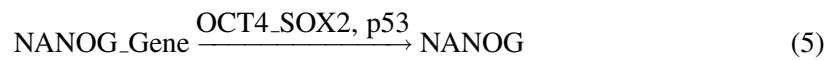
Derived unit contains undeclared units

$$v_2 = \text{gamma1} \cdot [\text{OCT4}] \quad (4)$$

6.3 Reaction J2

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

Reaction equation



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

$$v_3 = \frac{\text{eta5} + e1 \cdot [\text{OCT4_SOX2}] + e2 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]}{1 + \frac{\text{eta5}}{f} + f2 \cdot [\text{OCT4_SOX2}] + f1 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}] + f3 \cdot [\text{p53}]} \quad (6)$$

6.4 Reaction J3

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

Reaction equation



Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
NANOG		

Product

Table 15: Properties of each product.

Id	Name	SBO
degradation		

Kinetic Law

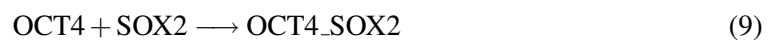
Derived unit contains undeclared units

$$v_4 = \text{gamma2} \cdot [\text{NANOG}] \quad (8)$$

6.5 Reaction J4

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

Reaction equation



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

$$v_5 = k1c \cdot [\text{OCT4}] \cdot [\text{SOX2}] - k2c \cdot [\text{OCT4_SOX2}] \quad (10)$$

6.6 Reaction J5

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

Reaction equation



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

$$v_6 = k3c \cdot [\text{OCT4_SOX2}] \quad (12)$$

6.7 Reaction J6

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

Reaction equation



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

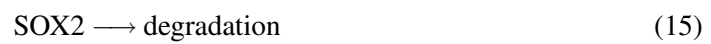
Derived unit contains undeclared units

$$v_7 = \frac{\text{eta3} + c1 \cdot [A] + c2 \cdot [\text{OCT4_SOX2}] + c3 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]}{1 + \frac{\text{eta3}}{f} + d1 \cdot [A] + d2 \cdot [\text{OCT4_SOX2}] + d3 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]} \quad (14)$$

6.8 Reaction J7

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

Reaction equation



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

$$v_8 = \text{gamma3} \cdot [\text{SOX2}] \quad (16)$$

6.9 Reaction J8

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

Reaction equation



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

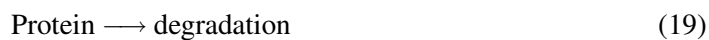
Derived unit contains undeclared units

$$v_9 = \frac{g1 \cdot [\text{OCT4_SOX2}] + \text{eta7}}{1 + \frac{\text{eta7}}{f} + h1 \cdot [\text{OCT4_SOX2}] + h2 \cdot [\text{OCT4_SOX2}] \cdot [\text{NANOG}]} \quad (18)$$

6.10 Reaction J9

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

Reaction equation



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

$$v_{10} = \text{gamma4} \cdot [\text{Protein}] \quad (20)$$

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 amount 0 dimensionless

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:

$$\frac{d}{dt}\text{OCT4_Gene} = 0 \quad (21)$$

7.2 Species NANOG_Gene

Initial amount 0 dimensionless

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:

$$\frac{d}{dt}\text{NANOG_Gene} = 0 \quad (22)$$

7.3 Species SOX2_Gene

Initial amount 0 dimensionless

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:

$$\frac{d}{dt}\text{SOX2_Gene} = 0 \quad (23)$$

7.4 Species targetGene

Initial amount 0.01 dimensionless

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:

$$\frac{d}{dt}\text{targetGene} = 0 \quad (24)$$

7.5 Species degradation

Initial amount 0 dimensionless

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:

$$\frac{d}{dt}\text{degradation} = 0 \quad (25)$$

7.6 Species p53

Initial amount 0 dimensionless

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:

$$\frac{d}{dt}p53 = 0 \quad (26)$$

7.7 Species A

Initial amount 10 dimensionless

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:

$$\frac{d}{dt}A = 0 \quad (27)$$

7.8 Species OCT4

Initial amount 0.01 dimensionless

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

$$\frac{d}{dt}OCT4 = v_1 - v_2 - v_5 \quad (28)$$

7.9 Species SOX2

Initial amount 0.01 dimensionless

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

$$\frac{d}{dt}SOX2 = v_7 - v_5 - v_8 \quad (29)$$

7.10 Species NANOG

Initial amount 0.01 dimensionless

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).

$$\frac{d}{dt}NANOG = v_3 - v_4 \quad (30)$$

7.11 Species OCT4_SOX2

Initial amount 0.1 dimensionless

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).

$$\frac{d}{dt}\text{OCT4_SOX2} = v_5 - v_6 \quad (31)$$

7.12 Species Protein

Initial amount 0 dimensionless

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

$$\frac{d}{dt}\text{Protein} = v_9 - v_{10} \quad (32)$$

SBML2^{AT}EX 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.

^aCenter for Bioinformatics Tübingen (ZBIT), Germany

^bCalifornia Institute of Technology, Beckman Institute BNMC, Pasadena, United States

^cEuropean Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom

^dEML Research gGmbH, Heidelberg, Germany