SBML Model Report

Model name: “Komarova2003_BoneRemodeling”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by Harish Dharuri[1] at July 30th 2007 at 8:56 p. m. and last time modified at October nineth 2014 at 4:24 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	7
events	4	constraints	0
reactions	6	function definitions	0
global parameters	13	unit definitions	2
rules	3	initial assignments	0

Model Notes

This a model from the article:
Mathematical model predicts a critical role for osteoclast autocrine regulation in the control of bone remodeling.
Komarova SV, Smith RJ, Dixon SJ, Sims SM, Wahl LM Bone2003 Aug;33(2):206-15 14499354,
Abstract:

[1]California Institute of Technology, hdharuri@cds.caltech.edu

Bone remodeling occurs asynchronously at multiple sites in the adult skeleton and involves resorption by osteoclasts, followed by formation of new bone by osteoblasts. Disruptions in bone remodeling contribute to the pathogenesis of disorderssuch as osteoporosis, osteoarthritis, and Paget's disease. Interactions among cells of osteoblast and osteoclast lineages are critical in the regulation of bone remodeling. We constructed a mathematical model of autocrine and paracrine interactions among osteoblasts and osteoclasts that allowed us to calculate cell population dynamics and changes in bone mass at a discrete site of bone remodeling. Themodel predicted different modes of dynamic behavior: a single remodeling cycle in response to an external stimulus, a series of internally regulated cycles of bone remodeling, or unstable behavior similar to pathological bone remodeling in Paget's disease. Parametric analysis demonstrated that the mode of dynamic behaviorin the system depends strongly on the regulation of osteoclasts by autocrine factors, such as transforming growth factor beta. Moreover, simulations demonstratedthat nonlinear dynamics of the system may explain the differing effects of immunosuppressants on bone remodeling in vitro and in vivo. In conclusion, the mathematical model revealed that interactions among osteoblasts and osteoclasts result in complex, nonlinear system behavior, which cannot be deduced from studies of each cell type alone. The model will be useful in future studies assessing the impact of cytokines, growth factors, and potential therapies on the overall process ofremodeling in normal bone and in pathological conditions such as osteoporosis and Paget's disease.

The model reproduces Fig 2A and Fig 2B of the paper. Note that the Y-axis scale is not right, the osteoblast steadystate is approximatley 212 and not 0 as depicted in the figure. Also, there is atypo in the equation for x2_bar which has been corrected here. Model successfully tested on MathSBML.

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 `substance`

Name number

Definition item

2.2 Unit `time`

Name day

Definition 86400 s

2.3 Unit `volume`

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

Definition l

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	☑	

3.1 Compartment `compartment`

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

4 Species

This model contains seven species. Section 9 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
`x1`	Osteoclast	`compartment`	item	$\boxminus$	$\boxminus$
`x2`	Osteoblast	`compartment`	item	$\boxminus$	$\boxminus$
`x1_bar`	Steady state osteoclast	`compartment`	item	$\boxminus$	$\boxminus$
`x2_bar`	Steady state osteoblast	`compartment`	item	$\boxminus$	$\boxminus$
`z`	Bone mass	`compartment`	item	$\boxminus$	$\boxminus$
`y1`	Cells actively resorbing bone	`compartment`	item	$\boxminus$	$\boxminus$
`y2`	Cells actively forming bone	`compartment`	item	$\boxminus$	$\boxminus$

5 Parameters

This model contains 13 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
alpha1			3.000		☑
alpha2			4.000		☑
beta1			0.200		☑
beta2			0.020		☑
g11			0.500		☑
g21			−0.500		☑
g12			1.000		☑
g22			0.000		☑
k1			0.240		☑
k2			0.002		☑
gamma			0.000		☐
flag-_resorption			0.000		☐
flag-_formation			0.000		☐

6 Rules

This is an overview of three rules.

6.1 Rule gamma

Rule gamma is an assignment rule for parameter gamma:

$$\text{gamma} = \text{g12} \cdot \text{g21} - (1 - \text{g11}) \cdot (1 - \text{g22}) \tag{1}$$

6.2 Rule x1_bar

Rule x1_bar is an assignment rule for species x1_bar:

$$[\text{x1\_bar}] = \left(\frac{\text{beta1}}{\text{alpha1}}\right)^{\frac{1-\text{g22}}{\text{gamma}}} \cdot \left(\frac{\text{beta2}}{\text{alpha2}}\right)^{\frac{\text{g21}}{\text{gamma}}} \tag{2}$$

6.3 Rule x2_bar

Rule x2_bar is an assignment rule for species x2_bar:

$$[\mathrm{x2\_bar}] = \left(\frac{\mathrm{beta1}}{\mathrm{alpha1}}\right)^{\frac{\mathrm{g12}}{\mathrm{gamma}}} \cdot \left(\frac{\mathrm{beta2}}{\mathrm{alpha2}}\right)^{\frac{1-\mathrm{g11}}{\mathrm{gamma}}} \tag{3}$$

7 Events

This is an overview of four events. 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.

7.1 Event event_0000001

Notes When the osteoclast number is greater than the steady state osteoclast number the flag is set to 1, this insures that in reaction R5, y1 is equal to the difference of x1 and x1_bar. When x1 is greater than x1_bar the difference is set to zero by setting the flag to zero. The same procedure is used for bone formation.

Trigger condition

$$\mathrm{x1} > \mathrm{x1\_bar} \tag{4}$$

Assignment

$$\mathrm{flag\_resorption} = 1 \tag{5}$$

7.2 Event event_0000003

Trigger condition

$$\mathrm{x1} \leq \mathrm{x1\_bar} \tag{6}$$

Assignment

$$\mathrm{flag\_resorption} = 0 \tag{7}$$

7.3 Event event_0000002

Trigger condition

$$\mathrm{x2} > \mathrm{x2\_bar} \tag{8}$$

Assignment

$$\mathrm{flag\_formation} = 1 \tag{9}$$

7.4 Event event_0000004

Trigger condition

$$\mathrm{x2} \leq \mathrm{x2\_bar} \tag{10}$$

Assignment

$$\mathrm{flag\_formation} = 0 \tag{11}$$

8 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 5: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	R1	Osteoclast production	$\emptyset \xrightleftharpoons{\text{x2}} \text{x1}$	
2	R2	Osteoclast removal	$\text{x1} \xrightleftharpoons{} \emptyset$	
3	R3	Osteoblast production	$\emptyset \xrightleftharpoons{\text{x1}} \text{x2}$	
4	R4	Osteoblast removal	$\text{x2} \xrightleftharpoons{} \emptyset$	
5	R5	Bone resorption	$\text{z} \xrightleftharpoons{\text{x1, x1\_bar}} \emptyset$	
6	R6	Bone formation	$\emptyset \xrightleftharpoons{\text{x2, x2\_bar}} \text{z}$	

8.1 Reaction R1

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

Name Osteoclast production

Reaction equation

$$\emptyset \xrightleftharpoons{\text{x2}} \text{x1} \tag{12}$$

Modifier

Table 6: Properties of each modifier.

Id	Name	SBO
x2	Osteoblast	

Product

Table 7: Properties of each product.

Id	Name	SBO
x1	Osteoclast	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{alpha1} \cdot \text{x1}^{\text{g11}} \cdot \text{x2}^{\text{g21}} \tag{13}$$

8.2 Reaction R2

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

Name Osteoclast removal

Reaction equation

$$\text{x1} \rightleftharpoons \emptyset \tag{14}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
x1	Osteoclast	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{beta1} \cdot \text{x1} \tag{15}$$

8.3 Reaction R3

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

Name Osteoblast production

Reaction equation

$$\emptyset \xrightleftharpoons{\text{x1}} \text{x2} \tag{16}$$

Modifier

Table 9: Properties of each modifier.

Id	Name	SBO
x1	Osteoclast	

Product

Table 10: Properties of each product.

Id	Name	SBO
x2	Osteoblast	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{alpha2} \cdot \text{x1}^{\text{g12}} \cdot \text{x2}^{\text{g22}} \tag{17}$$

8.4 Reaction R4

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

Name Osteoblast removal

Reaction equation

$$\mathrm{x2} \rightleftharpoons \emptyset \tag{18}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
x2	Osteoblast	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{beta2} \cdot \mathrm{x2} \tag{19}$$

8.5 Reaction R5

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

Name Bone resorption

Reaction equation

$$\mathrm{z} \xrightleftharpoons{\mathrm{x1},\ \mathrm{x1\_bar}} \emptyset \tag{20}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
z	Bone mass	

Modifiers

Table 13: Properties of each modifier.

Id	Name	SBO
x1	Osteoclast	
x1_bar	Steady state osteoclast	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{flag\_resorption} \cdot \text{k1} \cdot (\text{x1} - \text{x1\_bar}) \tag{21}$$

8.6 Reaction R6

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

Name Bone formation

Reaction equation

$$\emptyset \xrightleftharpoons{\text{x2, x2\_bar}} \text{z} \tag{22}$$

Modifiers

Table 14: Properties of each modifier.

Id	Name	SBO
x2	Osteoblast	
x2_bar	Steady state osteoblast	

Product

Table 15: Properties of each product.

Id	Name	SBO
z	Bone mass	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \text{flag\_formation} \cdot \text{k2} \cdot (\text{x2} - \text{x2\_bar}) \tag{23}$$

9 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.

9.1 Species x1

Name Osteoclast

Initial amount 11 item

This species takes part in four reactions (as a reactant in R2 and as a product in R1 and as a modifier in R3, R5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x1} = v_1 - v_2 \tag{24}$$

9.2 Species x2

Name Osteoblast

Initial amount 212 item

This species takes part in four reactions (as a reactant in R4 and as a product in R3 and as a modifier in R1, R6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x2} = v_3 - v_4 \tag{25}$$

9.3 Species x1_bar

Name Steady state osteoclast

Initial amount 0 item

Involved in rule x1_bar

This species takes part in one reaction (as a modifier in R5) and is also involved in one rule which determines this species' quantity.

9.4 Species x2_bar

Name Steady state osteoblast

Initial amount 0 item

Involved in rule x2_bar

This species takes part in one reaction (as a modifier in R6) and is also involved in one rule which determines this species' quantity.

9.5 Species z

Name Bone mass

Initial amount 100 item

This species takes part in two reactions (as a reactant in R5 and as a product in R6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{z} = v_6 - v_5 \tag{26}$$

9.6 Species y1

Name Cells actively resorbing bone

Initial amount 0 item

This species does not take part in any reactions. Its quantity does hence not change over time:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{y1} = 0 \tag{27}$$

9.7 Species y2

Name Cells actively forming bone

Initial amount 0 item

This species does not take part in any reactions. Its quantity does hence not change over time:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{y2} = 0 \tag{28}$$

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