**SBML Model Report**

# Model name: “Shrestha2010-_HyperCalcemia_PTHresponse”

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## 1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Vijayalakshmi Chelliah[1] and Rajiv P Shrestha[2] at November 15th 2010 at 2:42 p. m. and last time modified at October nineth 2014 at 4:16 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 | 2 |
| species types | 0 | species | 3 |
| events | 0 | constraints | 0 |
| reactions | 0 | function definitions | 0 |
| global parameters | 21 | unit definitions | 0 |
| rules | 9 | initial assignments | 0 |

### Model Notes

This a model from the article:
**A mathematical model of parathyroid hormone response to acute changes in plasma ionized calcium concentration in humans.**

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Shrestha RP, Hollot CV, Chipkin SR, Schmitt CP, Chait Y. Math Biosci.2010 Jul;226(1):46-57.
20406649,

**Abstract:**

A complex bio-mechanism, commonly referred to as calcium homeostasis, regulates plasma ionized calcium (Ca(2+)) concentration in the human body within a narrow range which is crucial for maintaining normal physiology and metabolism. Taking a step towards creating a complete mathematical model of calcium homeostasis, we focus on the short-term dynamics of calcium homeostasis and consider the response of the parathyroid glands to acute changes in plasma Ca(2+) concentration. We review available models, discuss their limitations, then present a two-pool, linear, time-varying model to describe the dynamics of this calcium homeostasis subsystem, the Ca-PTH axis. We propose that plasma PTH concentration and plasma Ca(2+) concentration bear an asymmetric reverse sigmoid relation. The parameters of our model are successfully estimated based on clinical data corresponding to three healthy subjects that have undergone induced hypocalcemic clamp tests. In the first validation of this kind, with parameters estimated separately for each subject we test the model's ability to predict the same subject's induced hypercalcemic clamp test responses. Our results demonstrate that a two-pool, linear, time-varying model with an asymmetric reverse sigmoid relation characterizes the short-term dynamics of the Ca-PTH axis.

The model corresponds to hypercalcemic clamp test explained in the paper and parameter values used in the model are that of „subject 1„. In order to obtain the plots corresponding to „subject 2„ and „subject 3„ the following parameters to be changed: lambda_1, lambda_2, m1, m2, R, beta, x1_n, x2_n, x2_min, x2_max, t0, Ca0, Ca1 and alpha.

| parameter | Subject 1 | Subject 2 | Subject 3 |
|---|---|---|---|
| lambda_1 | 0.0125 | 0.0122 | 0.0269 |
| lambda_2 | 0.5595 | 0.4642 | 0.4935 |
| m1 | 112.5200 | 150.0000 | 90.8570 |
| m2 | 15.0000 | 15.0000 | 15.0000 |
| R | 1.2162 | 1.1627 | 1.1889 |
| beta | 10e+06 | 10e+06 | 10e+06 |
| x1_n | 490.7800 | 452.8200 | 298.8200 |
| x2_n | 6.6290 | 9.5894 | 5.4600 |
| x2_min | 0.6697 | 1.4813 | 0.8287 |
| x2_max | 14.0430 | 17.8710 | 15.1990 |
| Ca0 | 1.2200 | 1.2513 | 1.2480 |
| Ca1 | 0.2624 | 0.2267 | 0.2132 |
| t0 | 575 | 575 | 575 |
| alpha | 0.0569 | 0.0563 | 0.0421 |

Chelliah V, Li L, He E, Henry A, Stefan MI, Snoep JL, Hucka M, Le Novre N, Laibe C (2010) BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models. BMC Syst Biol., 4:92.

# 2 Unit Definitions

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

## 2.1 Unit `substance`

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

**Definition** mol

## 2.2 Unit `volume`

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

**Definition** l

## 2.3 Unit `area`

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

**Definition** $m^2$

## 2.4 Unit `length`

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

**Definition** m

## 2.5 Unit `time`

**Notes** Second is the predefined SBML unit for `time`.

**Definition** s

# 3 Compartments

This model contains two compartments.

Table 3: Properties of all compartments.

| Id | Name | SBO | Spatial Dimensions | Size | Unit | Constant | Outside |
|---|---|---|---|---|---|---|---|
| PTG_pool | PTG_pool | 0000290 | 3 | 1 | litre | ☑ | |
| Plasma_pool | Plasma_pool | 0000290 | 3 | 1 | litre | ☑ | |

## 3.1 Compartment `PTG_pool`

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

**Name** PTG_pool

**SBO:0000290** physical compartment

## 3.2 Compartment `Plasma_pool`

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

**Name** Plasma_pool

**SBO:0000290** physical compartment

# 4 Species

This model contains three species. Section 7 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 |
|---|---|---|---|---|---|
| `x1` | PTH_in_PTG | `PTG_pool` | $\mathrm{mol} \cdot \mathrm{l}^{-1}$ | $\boxminus$ | $\boxminus$ |
| `x2` | PTH_in_Plasma | `Plasma_pool` | $\mathrm{mol} \cdot \mathrm{l}^{-1}$ | $\boxminus$ | $\boxminus$ |
| `Ca` | Ca_in_Plasma | `Plasma_pool` | $\mathrm{mol} \cdot \mathrm{l}^{-1}$ | $\boxminus$ | $\boxminus$ |

# 5 Parameters

This model contains 21 global parameters.

Table 5: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k | k | 0000002 | 9.844 | | ☐ |
| lambda_Ca | lambda_Ca | | 170.000 | | ☐ |
| m_Ca | m_Ca | | 170.000 | | ☐ |
| m1 | m1 | 0000002 | 112.520 | | ☑ |
| m2 | m2 | 0000002 | 15.000 | | ☑ |
| beta | beta | 0000002 | 1000000.000 | | ☑ |
| R | R | 0000002 | 1.216 | | ☑ |
| lambda_1 | lambda_1 | 0000002 | 0.013 | | ☑ |
| lambda_2 | lambda_2 | 0000002 | 0.560 | | ☑ |
| A | A | | 0.049 | | ☐ |
| B | B | | $4.9 \cdot 10^{-4}$ | | ☐ |
| S | S | | 1.216 | | ☐ |
| Ca0 | Ca0 | | 1.220 | | ☑ |
| Ca1 | Ca1 | | 0.262 | | ☑ |
| t0 | t0 | | 575.000 | | ☑ |
| alpha | alpha | | 0.057 | | ☑ |
| x1_n | x1_n | | 490.780 | | ☑ |
| x2_n | x2_n | | 6.629 | | ☑ |
| x2_min | x2_min | | 0.670 | | ☑ |
| x2_max | x2_max | | 14.043 | | ☑ |
| Ca0_baseline | Ca0_baseline | | 1.255 | | ☑ |

# 6 Rules

This is an overview of nine rules.

## 6.1 Rule lambda_Ca

Rule lambda_Ca is an assignment rule for parameter lambda_Ca:

$$\text{lambda\_Ca} = \frac{\text{A} - \text{B}}{1 + \left(\frac{[\text{Ca}]}{\text{S}}\right)^{\text{m\_Ca}}} + \text{B} \tag{1}$$

### 6.2 Rule `m_Ca`

Rule `m_Ca` is an assignment rule for parameter `m_Ca`:

$$\mathrm{m\_Ca} = \frac{\mathrm{m1}}{1 + \exp\left(\mathrm{beta} \cdot \left(\mathrm{R} - [\mathrm{Ca}]\right)\right)} + \mathrm{m2} \tag{2}$$

### 6.3 Rule `Ca`

Rule `Ca` is an assignment rule for species `Ca`:

$$\mathrm{Ca} = \begin{cases} \mathrm{Ca0} & \text{if time} < \mathrm{t0} \\ \mathrm{Ca0} + \mathrm{Ca1} \cdot \left(1 - \exp\left(\mathrm{alpha} \cdot \left(\mathrm{time} - \mathrm{t0}\right)\right)\right) & \text{otherwise} \end{cases} \tag{3}$$

### 6.4 Rule `x1`

Rule `x1` is a rate rule for species `x1`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x1} = \mathrm{k} - \mathrm{lambda\_Ca} \cdot [\mathrm{x1}] - \mathrm{lambda\_1} \cdot [\mathrm{x1}] \tag{4}$$

### 6.5 Rule `x2`

Rule `x2` is a rate rule for species `x2`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x2} = \mathrm{lambda\_Ca} \cdot [\mathrm{x1}] - \mathrm{lambda\_2} \cdot [\mathrm{x2}] \tag{5}$$

### 6.6 Rule `S`

Rule `S` is an assignment rule for parameter `S`:

$$\mathrm{S} = \mathrm{Ca0\_baseline} \cdot \left(\frac{\left(\mathrm{x1\_n} \cdot \mathrm{B} - \mathrm{lambda\_2} \cdot \mathrm{x2\_n}\right)}{\mathrm{x1\_n} \cdot \mathrm{A} - \mathrm{lambda\_2} \cdot \mathrm{x2\_n}}\right)^{\frac{1}{\mathrm{m\_Ca}}} \tag{6}$$

### 6.7 Rule `k`

Rule `k` is an assignment rule for parameter `k`:

$$\mathrm{k} = \mathrm{lambda\_2} \cdot \mathrm{x2\_n} + \mathrm{lambda\_1} \cdot \mathrm{x1\_n} \tag{7}$$

### 6.8 Rule `A`

Rule `A` is an assignment rule for parameter `A`:

$$\mathrm{A} = \frac{\mathrm{lambda\_1} \cdot \mathrm{lambda\_2} \cdot \mathrm{x2\_max}}{\mathrm{k} - \mathrm{lambda\_2} \cdot \mathrm{x2\_max}} \tag{8}$$

### 6.9 Rule B

Rule B is an assignment rule for parameter B:

$$B = \frac{\text{lambda\_1} \cdot \text{lambda\_2} \cdot \text{x2\_min}}{\text{k} - \text{lambda\_2} \cdot \text{x2\_min}} \tag{9}$$

## 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.

### 7.1 Species x1

**Name** PTH_in_PTG

**SBO:0000245** macromolecule

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

**Involved in rule** x1

One rule which determines this species' quantity.

### 7.2 Species x2

**Name** PTH_in_Plasma

**SBO:0000245** macromolecule

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

**Involved in rule** x2

One rule which determines this species' quantity.

### 7.3 Species Ca

**Name** Ca_in_Plasma

**SBO:0000247** simple chemical

**Initial concentration** $1.22\ \text{mol} \cdot \text{l}^{-1}$

**Involved in rule** Ca

One rule which determines this species' quantity.

## A Glossary of Systems Biology Ontology Terms

**SBO:0000002 quantitative systems description parameter:** A numerical value that defines certain characteristics of systems or system functions. It may be part of a calculation, but its value is not determined by the form of the equation itself, and may be arbitrarily assigned

**SBO:0000245 macromolecule:** Molecular entity mainly built-up by the repetition of pseudo-identical units. CHEBI:3383

**SBO:0000247 simple chemical:** Simple, non-repetitive 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

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