1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by Mike Cooling\(^1\) at April 28\(^{th}\) 2009 at 11:55 a.m. and last time modified at April eighth 2016 at 5:21 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.

<table>
<thead>
<tr>
<th>Element</th>
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<th>Element</th>
<th>Quantity</th>
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Model Notes

This a model from the article:

**Modeling hypertrophic IP3 transients in the cardiac myocyte.**


**Abstract:**

Cardiac hypertrophy is a known risk factor for heart disease, and at the cellular level is caused

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by a complex interaction of signal transduction pathways. The IP3-calcineurin pathway plays an important role in stimulating the transcription factor NFAT which binds to DNA cooperatively with other hypertrophic transcription factors. Using available kinetic data, we construct a mathematical model of the IP3 signal production system after stimulation by a hypertrophic alpha-adrenergic agonist (endothelin-1) in the mouse atrial cardiac myocyte. We use a global sensitivity analysis to identify key controlling parameters with respect to the resultant IP3 transient, including the phosphorylation of cell-membrane receptors, the ligand strength and binding kinetics to precoupled (with G(\alpha)GDP) receptor, and the kinetics associated with precoupling the receptors. We show that the kinetics associated with the receptor system contribute to the behavior of the system to a great extent, with precoupled receptors driving the response to extracellular ligand. Finally, by reparameterizing for a second hypertrophic alpha-adrenergic agonist, angiotensin-II, we show that differences in key receptor kinetic and membrane density parameters are sufficient to explain different observed IP3 transients in essentially the same pathway.

This model was taken from the CellML repository and automatically converted to SBML. The original model was: Cooling M, Hunter P, Crampin EJ. (2007) - version02

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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

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 Compartment

This model contains one compartment.

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3.1 Compartment Compartment

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

SBO:0000290 physical compartment
## 4 Species

This model contains 13 species. Section 7 provides further details and the derived rates of change of each species.

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</table>
### 6 Rules

This is an overview of 37 rules.

#### 6.1 Rule P

Rule P is a rate rule for species P:

\[
\frac{d}{dt}P = J13 - (J9 + J8) \tag{1}
\]

#### 6.2 Rule Pg

Rule Pg is a rate rule for species Pg:

\[
\frac{d}{dt}Pg = J9 - (J11 + J13) \tag{2}
\]

#### 6.3 Rule Pc

Rule Pc is a rate rule for species Pc:

\[
\frac{d}{dt}Pc = J8 + J12 - J10 \tag{3}
\]
6.4 Rule Pcg
Rule Pcg is a rate rule for species Pcg:
\[
\frac{d}{dt}Pcg = J10 + J11 - J12
\]  

6.5 Rule IP3
Rule IP3 is a rate rule for species IP3:
\[
\frac{d}{dt}IP3 = Cpc \cdot (J14 + J15) - J16
\]  

6.6 Rule Gd
Rule Gd is a rate rule for species Gd:
\[
\frac{d}{dt}Gd = J7 + J13 + J12 - (J2 + J3)
\]  

6.7 Rule Gt
Rule Gt is a rate rule for species Gt:
\[
\frac{d}{dt}Gt = J6 - (J7 + J9 + J10)
\]  

6.8 Rule Ca
Rule Ca is a rate rule for species Ca:
\[
\frac{d}{dt}Ca = Cpc \cdot (1) \cdot (J8 + J11)
\]  

6.9 Rule R
Rule R is a rate rule for species R:
\[
\frac{d}{dt}R = 1 \cdot (J1 + J2)
\]  

6.10 Rule R1
Rule R1 is a rate rule for species R1:
\[
\frac{d}{dt}R1 = J1 + J6 - J3
\]
6.11 Rule Rg

Rule Rg is a rate rule for species Rg:

\[ \frac{d}{dt} Rg = J2 - J4 \] (11)

6.12 Rule Rlgp

Rule Rlgp is a rate rule for species Rlgp:

\[ \frac{d}{dt} Rlgp = J5 \] (12)

6.13 Rule Rlg

Rule Rlg is a rate rule for species Rlg:

\[ \frac{d}{dt} Rlg = J3 - J5 + J4 - J6 \] (13)

6.14 Rule Cc

Rule Cc is an assignment rule for parameter Cc:

\[ Cc = \frac{1}{Vc \cdot 602.2} \] (14)

6.15 Rule Cp

Rule Cp is an assignment rule for parameter Cp:

\[ Cp = \frac{1}{Vc \cdot Rpc} \] (15)

6.16 Rule Cpc

Rule Cpc is an assignment rule for parameter Cpc:

\[ Cpc = \frac{Cc}{Cp} \] (16)

6.17 Rule J13

Rule J13 is an assignment rule for parameter J13:

\[ J13 = kf13 \cdot [Pg] \] (17)
6.18 Rule J12
Rule J12 is an assignment rule for parameter J12:
\[ J12 = kf12 \cdot [Pcg] \] (18)

6.19 Rule kr11
Rule kr11 is an assignment rule for parameter kr11:
\[ kr11 = kf11 \cdot Kd11 \] (19)

6.20 Rule J11
Rule J11 is an assignment rule for parameter J11:
\[ J11 = kf11 \cdot [Pg] \cdot [Ca] - kr11 \cdot [Pcg] \] (20)

6.21 Rule J10
Rule J10 is an assignment rule for parameter J10:
\[ J10 = kf10 \cdot [Pc] \cdot [Gt] - kr10 \cdot [Pcg] \] (21)

6.22 Rule J8
Rule J8 is an assignment rule for parameter J8:
\[ J8 = kf8 \cdot [P] \cdot [Ca] - kr8 \cdot [Pc] \] (22)

6.23 Rule J9
Rule J9 is an assignment rule for parameter J9:
\[ J9 = kf9 \cdot [P] \cdot [Gt] - kr9 \cdot [Pg] \] (23)

6.24 Rule J16
Rule J16 is an assignment rule for parameter J16:
\[ J16 = kf16 \cdot [IP3] \] (24)

6.25 Rule J14
Rule J14 is an assignment rule for parameter J14:
\[ J14 = \frac{kf14 \cdot [Pc] \cdot PIP2}{\frac{Km14}{c_{pc}} + PIP2} \] (25)
6.26 Rule J15

Rule J15 is an assignment rule for parameter J15:

\[ J15 = \frac{kf15 \cdot [Pcg] \cdot PIP2}{Km15_{cpc} + PIP2} \]  \hspace{1cm} (26)

6.27 Rule J7

Rule J7 is an assignment rule for parameter J7:

\[ J7 = kf7 \cdot [Gt] \]  \hspace{1cm} (27)

6.28 Rule L

Rule L is an assignment rule for parameter L:

\[
L = \begin{cases} 
Ls & \text{if } (\text{time} < \text{ts} + 0.15) \land (\text{time} \geq \text{ts}) \\
\frac{\text{Ls}}{1 + \exp(80 \cdot (\text{time} - \text{ts} - 0.05))} & \text{if } \text{time} \geq \text{ts} + 0.15 \\
0 & \text{otherwise}
\end{cases}
\]  \hspace{1cm} (28)

6.29 Rule kr1

Rule kr1 is an assignment rule for parameter kr1:

\[ kr1 = kf1 \cdot Kd1 \]  \hspace{1cm} (29)

6.30 Rule J1

Rule J1 is an assignment rule for parameter J1:

\[ J1 = kf1 \cdot [R] \cdot L - kr1 \cdot [Rl] \]  \hspace{1cm} (30)

6.31 Rule kr2

Rule kr2 is an assignment rule for parameter kr2:

\[ kr2 = kf2 \cdot Kd2 \]  \hspace{1cm} (31)

6.32 Rule J2

Rule J2 is an assignment rule for parameter J2:

\[ J2 = kf2 \cdot [R] \cdot [Gd] - kr2 \cdot [Rg] \]  \hspace{1cm} (32)
6.33 Rule J3

Rule J3 is an assignment rule for parameter J3:

\[ J3 = kf3 \cdot [Rl] \cdot [Gd] - kr3 \cdot [Rlg] \quad (33) \]

6.34 Rule kr4

Rule kr4 is an assignment rule for parameter kr4:

\[ kr4 = kf4 \cdot Kd4 \quad (34) \]

6.35 Rule J4

Rule J4 is an assignment rule for parameter J4:

\[ J4 = kf4 \cdot L \cdot [Rg] - kr4 \cdot [Rlg] \quad (35) \]

6.36 Rule J5

Rule J5 is an assignment rule for parameter J5:

\[ J5 = kf5 \cdot [Rlg] \quad (36) \]

6.37 Rule J6

Rule J6 is an assignment rule for parameter J6:

\[ J6 = kf6 \cdot [Rlg] \quad (37) \]

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 Gd

Name Gd

SBO:0000296 macromolecular complex

Initial concentration 10000 mol·l\(^{-1}\)

Involved in rule Gd

One rule which determines this species’ quantity.
7.2 Species Gt

Name Gt

SBO:0000296 macromolecular complex

Initial concentration 0 mol·l⁻¹

Involved in rule Gt

One rule which determines this species’ quantity.

7.3 Species R

Name R

SBO:0000244 receptor

Initial concentration 13.9 mol·l⁻¹

Involved in rule R

One rule which determines this species’ quantity.

7.4 Species Rl

Name Rl

SBO:0000297 protein complex

Initial concentration 0 mol·l⁻¹

Involved in rule Rl

One rule which determines this species’ quantity.

7.5 Species Rg

Name Rg

SBO:0000296 macromolecular complex

Initial concentration 5.06 mol·l⁻¹

Involved in rule Rg

One rule which determines this species’ quantity.
7.6 **Species** Rlg

Name Rlg

*SBO:0000296* macromolecular complex

Initial concentration 0 mol·l⁻¹

Involved in rule Rlg

One rule which determines this species’ quantity.

7.7 **Species** Rlgp

Name Rlgp

*SBO:0000296* macromolecular complex

Initial concentration 0 mol·l⁻¹

Involved in rule Rlgp

One rule which determines this species’ quantity.

7.8 **Species** IP3

Name IP3

*SBO:0000252* polypeptide chain

Initial concentration 0.015 mol·l⁻¹

Involved in rule IP3

One rule which determines this species’ quantity.

7.9 **Species** Pc

Name Pc

*SBO:0000296* macromolecular complex

Initial concentration 9.09 mol·l⁻¹

Involved in rule Pc

One rule which determines this species’ quantity.
7.10 **Species** Pcg

**Name** Pcg

**SBO:0000296** macromolecular complex

**Initial concentration** 0 mol·l\(^{-1}\)

**Involved in rule** Pcg

One rule which determines this species’ quantity.

7.11 **Species** P

**Name** P

**SBO:0000252** polypeptide chain

**Initial concentration** 90.9 mol·l\(^{-1}\)

**Involved in rule** P

One rule which determines this species’ quantity.

7.12 **Species** Pg

**Name** Pg

**SBO:0000296** macromolecular complex

**Initial concentration** 0 mol·l\(^{-1}\)

**Involved in rule** Pg

One rule which determines this species’ quantity.

7.13 **Species** Ca

**Name** Ca

**SBO:0000247** simple chemical

**Initial concentration** 0.1 mol·l\(^{-1}\)

**Involved in rule** Ca

One rule which determines this species’ quantity.
A Glossary of Systems Biology Ontology Terms

**SBO:0000009 kinetic constant**: Numerical parameter that quantifies the velocity of a chemical reaction

**SBO:0000027 Michaelis constant**: Substrate concentration at which the velocity of reaction is half its maximum. Michaelis constant is an experimental parameter. According to the underlying molecular mechanism it can be interpreted differently in terms of microscopic constants

**SBO:0000153 forward rate constant**: Numerical parameter that quantifies the forward velocity of a chemical reaction. This parameter encompasses all the contributions to the velocity except the quantity of the reactants

**SBO:0000156 reverse rate constant**: Numerical parameter that quantifies the forward velocity of a chemical reaction. This parameter encompasses all the contributions to the velocity except the quantity of the reactants.

**SBO:0000196 concentration of an entity pool**: The amount of an entity per unit of volume.

**SBO:0000244 receptor**: Participating entity that binds to a specific physical entity and initiates the response to that physical entity. The original concept of the receptor was introduced independently at the end of the 19th century by John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915). Langley JN. On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J Physiol. 1905 Dec 30;33(4-5):374-413

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

**SBO:0000252 polypeptide chain**: Naturally occurring macromolecule formed by the repetition of amino-acid residues linked by peptidic bonds. A polypeptide chain is synthesized by the ribosome. CHEBI:1654

**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:0000296 macromolecular complex**: Non-covalent complex of one or more macromolecules and zero or more simple chemicals

**SBO:0000297 protein complex**: Macromolecular complex containing one or more polypeptide chains possibly associated with simple chemicals. CHEBI:3608

**SBO:0000356 decay constant**: Kinetic constant characterising a mono-exponential decay. It is the inverse of the mean lifetime of the continuant being decayed. Its unit is “per tim”.

**SBO:0000468 volume**: A quantity representing the three-dimensional space occupied by all or part of an object
**SBO:0000515 concentration of substrate:** The amount of a specific entity pool substrate present per unit of volume. The participant role 'substrate' is defined in SBO:0000015