SBML Model Report

Model name: "Nyman2012_InsulinSignalling"

May 6, 2016

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 Elin Nyman[2] at July 27th 2012 at 12:02 a. m. and last time modified at August nineth 2012 at 3:53 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	9
events	0	constraints	0
reactions	11	function definitions	0
global parameters	19	unit definitions	0
rules	3	initial assignments	0

Model Notes

This model is from the article:
Mechanistic explanations for counter-intuitive phosphorylation dynamics of the insulin receptor and insulin receptor substrate-1 in response to insulin in murine adipocytes.
Nyman E, Fagerholm S, Jullesson D, Strlfors P, Cedersund G. FEBS J. 2012 Jan 16. 22248283 ,

[1]EMBL-EBI, viji@ebi.ac.uk
[2]Linkoping University, elin.nyman@gmail.com

Abstract:
Insulin signaling through insulin receptor (IR) and insulin receptor substrate-1 (IRS1) is important for insulin control of target cells. We have previously demonstrated a rapid and simultaneous overshoot behavior in the phosphorylation dynamics of IR and IRS1 in human adipocytes. Herein, we demonstrate that in murine adipocytes a similar overshoot behavior is not simultaneous for IR and IRS1. The peak of IRS1 phosphorylation, which is a direct consequence of the phosphorylation and the activation of IR, occurs earlier than the peak of IR phosphorylation. We used a conclusive modeling framework to unravel the mechanisms behind this counter-intuitive order of phosphorylation. Through a number of rejections, we demonstrate that two fundamentally different mechanisms may create the reversed order of peaks: (i) two pools of phosphorylated IR, where a large pool of internalized IR peaks late, but phosphorylation of IRS1 is governed by a small plasma membrane-localized pool of IR with an early peak, or (ii) inhibition of the IR-catalyzed phosphorylation of IRS1 by negative feedback. Although (i) may explain the reversed order, this two-pool hypothesis alone requires extensive internalization of IR, which is not supported by experimental data. However, with the additional assumption of limiting concentrations of IRS1, (i) can explain all data. Also, (ii) can explain all available data. Our findings illustrate how modeling can potentiate reasoning, to help draw nontrivial conclusions regarding competing mechanisms in signaling networks. Our work also reveals new differences between human and murine insulin signaling. Database The mathematical model described here has been submitted to the Online Cellular Systems Modelling Database and can be accessed at http://jjj.biochem.sun.ac.za/database/nyman/index.html free of charge.

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 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

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

3.1 Compartment `default`

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

Name default

4 Species

This model contains nine species. Section 8 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
IR	IR	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRins	IRins	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRp	IRp	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRiP	IRiP	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRi	IRi	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRS	IRS	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IRSiP	IRSiP	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
X	X	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Xp	Xp	default	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains 19 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1a	k1a		0.153		☑
k1aBasic	k1aBasic		0.038		☑
k1b	k1b		$3.4699 \cdot 10^{-6}$		☑
k1c	k1c		0.574		☑
k1d	k1d		4.788		☑
k1e	k1e		$5.25027 \cdot 10^{-5}$		☑
k1f	k1f		119.353		☑
k1g	k1g		4.149		☑
k1r	k1r		37954.700		☑
k21	k21		538004.000		☑
k22	k22		$1.7252 \cdot 10^{-6}$		☑
km2	km2		262759.000		☑
km23	km23		88.910		☑
k3	k3		$8.62917 \cdot 10^{-5}$		☑
km3	km3		0.133		☑
ins	ins		100.000		☑
measIRS1	measIRS1		0.000		⊟
measIRp	measIRp		0.000		⊟
IRmem	IRmem		0.000		⊟

6 Rules

This is an overview of three rules.

6.1 Rule measIRS1

Rule measIRS1 is an assignment rule for parameter measIRS1:

$$\text{measIRS1} = [\text{IRSiP}] \tag{1}$$

Derived unit $\text{mol} \cdot \text{l}^{-1}$

6.2 Rule measIRp

Rule measIRp is an assignment rule for parameter measIRp:

$$\text{measIRp} = [\text{IRp}] + [\text{IRiP}] \tag{2}$$

Derived unit $\text{mol} \cdot \text{l}^{-1}$

6.3 Rule IRmem

Rule IRmem is an assignment rule for parameter IRmem:

$$\text{IRmem} = [\text{IRp}] + [\text{IRins}] + [\text{IR}] \tag{3}$$

Derived unit $\text{mol} \cdot 1^{-1}$

7 Reactions

This model contains eleven 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	v1a	v1a	$\mathrm{IR} \longrightarrow \mathrm{IRins}$	
2	v1b	v1b	$\mathrm{IRins} \longrightarrow \mathrm{IR}$	
3	v1c	v1c	$\mathrm{IRins} \longrightarrow \mathrm{IRp}$	
4	v1d	v1d	$\mathrm{IRp} \longrightarrow \mathrm{IRiP}$	
5	v1e	v1e	$\mathrm{IRiP} \xrightarrow{\mathrm{Xp}} \mathrm{IRi}$	
6	v1g	v1g	$\mathrm{IRp} \longrightarrow \mathrm{IR}$	
7	v1r	v1r	$\mathrm{IRi} \longrightarrow \mathrm{IR}$	
8	v2	v2	$\mathrm{IRS} \xrightarrow{\mathrm{IRiP,\ IRp,\ Xp}} \mathrm{IRSiP}$	
9	vm2	vm2	$\mathrm{IRSiP} \longrightarrow \mathrm{IRS}$	
10	v3	v3	$\mathrm{X} \xrightarrow{\mathrm{IRSiP}} \mathrm{Xp}$	
11	vm3	vm3	$\mathrm{Xp} \longrightarrow \mathrm{X}$	

7.1 Reaction v1a

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

Name v1a

Reaction equation

$$\mathrm{IR} \longrightarrow \mathrm{IRins} \tag{4}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
IR	IR	

Product

Table 7: Properties of each product.

Id	Name	SBO
IRins	IRins	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{k1a} \cdot \mathrm{ins} \cdot [\mathrm{IR}] + \mathrm{k1aBasic} \cdot [\mathrm{IR}] \tag{5}$$

7.2 Reaction v1b

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

Name v1b

Reaction equation

$$\mathrm{IRins} \longrightarrow \mathrm{IR} \tag{6}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
IRins	IRins	

Product

Table 9: Properties of each product.

Id	Name	SBO
IR	IR	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{k1b} \cdot [\mathrm{IRins}] \tag{7}$$

7.3 Reaction v1c

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

Name v1c

Reaction equation

$$\mathrm{IRins} \longrightarrow \mathrm{IRp} \tag{8}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
IRins	IRins	

Product

Table 11: Properties of each product.

Id	Name	SBO
IRp	IRp	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{k1c} \cdot [\mathrm{IRins}] \tag{9}$$

7.4 Reaction `v1d`

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

Name v1d

Reaction equation

$$\mathrm{IRp} \longrightarrow \mathrm{IRiP} \tag{10}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
`IRp`	IRp	

Product

Table 13: Properties of each product.

Id	Name	SBO
`IRiP`	IRiP	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{k1d} \cdot [\mathrm{IRp}] \tag{11}$$

7.5 Reaction `v1e`

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

Name v1e

Reaction equation

$$\mathrm{IRiP} \xrightarrow{\mathrm{Xp}} \mathrm{IRi} \tag{12}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
IRiP	IRiP	

Modifier

Table 15: Properties of each modifier.

Id	Name	SBO
Xp	Xp	

Product

Table 16: Properties of each product.

Id	Name	SBO
IRi	IRi	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = [\mathrm{IRiP}] \cdot \left(\mathrm{k1e} + \frac{\mathrm{k1f} \cdot [\mathrm{Xp}]}{1 + [\mathrm{Xp}]} \right) \tag{13}$$

7.6 Reaction v1g

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

Name v1g

Reaction equation

$$\mathrm{IRp} \longrightarrow \mathrm{IR} \tag{14}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
IRp	IRp	

Product

Table 18: Properties of each product.

Id	Name	SBO
IR	IR	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{k1g} \cdot [\mathrm{IRp}] \tag{15}$$

7.7 Reaction v1r

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

Name v1r

Reaction equation

$$\mathrm{IRi} \longrightarrow \mathrm{IR} \tag{16}$$

Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
IRi	IRi	

Product

Table 20: Properties of each product.

Id	Name	SBO
IR	IR	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{k1r} \cdot [\mathrm{IRi}] \tag{17}$$

7.8 Reaction v2

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

Name v2

Reaction equation

$$\mathrm{IRS} \xrightarrow{\mathrm{IRiP,\ IRp,\ Xp}} \mathrm{IRSiP} \tag{18}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
IRS	IRS	

Modifiers

Table 22: Properties of each modifier.

Id	Name	SBO
IRiP	IRiP	
IRp	IRp	
Xp	Xp	

Product

Table 23: Properties of each product.

Id	Name	SBO
IRSiP	IRSiP	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \frac{\text{k21} \cdot [\text{IRS}] \cdot ([\text{IRp}] + \text{k22} \cdot [\text{IRiP}])}{1 + \text{km23} \cdot [\text{Xp}]} \tag{19}$$

7.9 Reaction vm2

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

Name vm2

Reaction equation

$$\text{IRSiP} \longrightarrow \text{IRS} \tag{20}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
IRSiP	IRSiP	

Product

Table 25: Properties of each product.

Id	Name	SBO
IRS	IRS	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \text{km2} \cdot [\text{IRSiP}] \tag{21}$$

7.10 Reaction v3

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

Name v3

Reaction equation

$$\text{X} \xrightarrow{\text{IRSiP}} \text{Xp} \tag{22}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
X	X	

Modifier

Table 27: Properties of each modifier.

Id	Name	SBO
IRSiP	IRSiP	

Product

Table 28: Properties of each product.

Id	Name	SBO
Xp	Xp	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \mathrm{k3} \cdot [\mathrm{X}] \cdot [\mathrm{IRSiP}] \tag{23}$$

7.11 Reaction vm3

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

Name vm3

Reaction equation

$$\mathrm{Xp} \longrightarrow \mathrm{X} \tag{24}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
Xp	Xp	

Product

Table 30: Properties of each product.

Id	Name	SBO
X	X	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \text{km3} \cdot [\text{Xp}] \tag{25}$$

8 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.

8.1 Species `IR`

Name IR

Initial concentration $8.94067597532632\ \text{mol} \cdot \text{l}^{-1}$

This species takes part in four reactions (as a reactant in `v1a` and as a product in `v1b`, `v1g`, `v1r`).

$$\frac{\text{d}}{\text{d}t}\text{IR} = v_2 + v_6 + v_7 - v_1 \tag{26}$$

8.2 Species `IRins`

Name IRins

Initial concentration $0.59688996214639\ \text{mol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in `v1b`, `v1c` and as a product in `v1a`).

$$\frac{\text{d}}{\text{d}t}\text{IRins} = v_1 - v_2 - v_3 \tag{27}$$

8.3 Species IRp

Name IRp

Initial concentration $0.0383525925240207\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in v1d, v1g and as a product in v1c and as a modifier in v2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRp} = v_3 - v_4 - v_6 \tag{28}$$

8.4 Species IRiP

Name IRiP

Initial concentration $0.424076631823384\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in v1e and as a product in v1d and as a modifier in v2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRiP} = v_4 - v_5 \tag{29}$$

8.5 Species IRi

Name IRi

Initial concentration $4.83863890758515\cdot 10^{-6}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in v1r and as a product in v1e).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRi} = v_5 - v_7 \tag{30}$$

8.6 Species IRS

Name IRS

Initial concentration $9.43998194225544\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in v2 and as a product in vm2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRS} = v_9 - v_8 \tag{31}$$

8.7 Species IRSiP

Name IRSiP

Initial concentration $0.560018057744573\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in vm2 and as a product in v2 and as a modifier in v3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRSiP} = v_8 - v_9 \tag{32}$$

8.8 Species X

Name X

Initial concentration $9.99635886407151\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in v3 and as a product in vm3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{X} = v_{11} - v_{10} \tag{33}$$

8.9 Species Xp

Name Xp

Initial concentration $0.00364113592848386\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in vm3 and as a product in v3 and as a modifier in v1e, v2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Xp} = v_{10} - v_{11} \tag{34}$$

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