SBML Model Report

Model name: “Haffez2017 - RAR interaction with synthetic analogues”

March 17, 2017

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following seven authors: Varun Kothamachu[1], Hesham Haffez[2], Chris Redfern[3], Andy Whiting[4], Ehmke Pohl[5], Roy Valentine[6] and David Chisholm[7] at January 31st 2013 at 10:18 a. m. and last time modified at March 17th 2017 at 5:01 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	5
events	0	constraints	0
reactions	2	function definitions	0
global parameters	0	unit definitions	2
rules	0	initial assignments	0

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Model Notes

This model is described in the article:The molecular basis of the interactions between synthetic retinoic acid analogues and the retinoic acid receptorsHesham Haffez, David R. Chisholm, Roy Valentine, Ehmke Pohl, Christopher Redfern and Andrew WhitingMedChemComm

Abstract:

All-trans-retinoic acid (ATRA) and its synthetic analogues EC23 and EC19 direct cellular differentiation by interacting as ligands for the retinoic acid receptor (RAR, and) family of nuclear receptor proteins. To date, a number of crystal structures of natural and synthetic ligands complexed to their target proteins have been solved, providing molecular level snap-shots of ligand binding. However, a deeper understanding of receptor and ligand flexibility and conformational freedom is required to develop stable and effective ATRA analogues for clinical use. Therefore, we have used molecular modelling techniques to define RAR interactions with ATRA and two synthetic analogues, EC19 and EC23, and compared their predicted biochemical activities to experimental measurements of relative ligand affinity and recruitment of coactivator proteins. A comprehensive molecular docking approach that explored the conformational space of the ligands indicated that ATRA is able to bind the three RAR proteins in a number of conformations with one extended structure being favoured. In contrast the biologically-distinct isomer, 9-cis-retinoic acid (9CRA), showed significantly less conformational flexibility in the RAR binding pockets. These findings were used to inform docking studies of the synthetic retinoids EC23 and EC19, and their respective methyl esters. EC23 was found to be an excellent mimic for ATRA, and occupied similar binding modes to ATRA in all three target RAR proteins. In comparison, EC19 exhibited an alternative binding mode which reduces the strength of key polar interactions in RAR/ but is well-suited to the larger RAR binding pocket. In contrast, docking of the corresponding esters revealed the loss of key polar interactions which may explain the much reduced biological activity. Our computational results were complemented using an in vitro binding assay based on FRET measurements, which showed that EC23 was a strongly binding, pan-agonist of the RARs, while EC19 exhibited specificity for RAR, as predicted by the docking studies. These findings can account for the distinct behaviour of EC23 and EC19 in cellular differentiation assays, and additionally, the methods described herein can be further applied to the understanding of the molecular basis for the selectivity of different retinoids to RAR, and .

This model is hosted on BioModels Database and identified by: BIOMD0000000629.

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

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 time

Name time

Definition 60 s

2.2 Unit substance

Name substance

Definition µmol

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
RAR_retinoids	Cytoplasm	0000290	3	1	litre	☑	

3.1 Compartment RAR_retinoids

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

Name Cytoplasm

SBO:0000290 physical compartment

4 Species

This model contains five species. Section 6 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
L	Ligand	RAR_retinoids	$\mu mol \cdot l^{-1}$	⊟	⊟
LR	Ligand-Receptor	RAR_retinoids	$\mu mol \cdot l^{-1}$	⊟	⊟
R	Receptor	RAR_retinoids	$\mu mol \cdot l^{-1}$	⊟	⊟
CA	CoActivator	RAR_retinoids	$\mu mol \cdot l^{-1}$	⊟	⊟
LRCA	Ligand-Receptor-CoActivator	RAR_retinoids	$\mu mol \cdot l^{-1}$	⊟	⊟

5 Reactions

This model contains two 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 4: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	LR_complx	Ligand-Receptor complex formation	$L + R \rightleftharpoons LR$	0000297
2	LRCA_complx	Ligand-Receptor-CoActivator complex formation	$LR + CA \rightleftharpoons LRCA$	0000297

5.1 Reaction LR_complx

This is a reversible reaction of two reactants forming one product.

Name Ligand-Receptor complex formation

SBO:0000297 protein complex

Reaction equation

$$\mathrm{L} + \mathrm{R} \rightleftharpoons \mathrm{LR} \tag{1}$$

Reactants

Table 5: Properties of each reactant.

Id	Name	SBO
L	Ligand	
R	Receptor	

Product

Table 6: Properties of each product.

Id	Name	SBO
LR	Ligand-Receptor	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{RAR\_retinoids}) \cdot (\mathrm{k1} \cdot [\mathrm{L}] \cdot [\mathrm{R}] - \mathrm{k2} \cdot [\mathrm{LR}]) \tag{2}$$

Table 7: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		0.6		☑
k2	k2		0.1		☑

5.2 Reaction LRCA_complx

This is a reversible reaction of two reactants forming one product.

Name Ligand-Receptor-CoActivator complex formation

SBO:0000297 protein complex

Reaction equation

$$\mathrm{LR} + \mathrm{CA} \rightleftharpoons \mathrm{LRCA} \tag{3}$$

Reactants

Table 8: Properties of each reactant.

Id	Name	SBO
LR	Ligand-Receptor	
CA	CoActivator	

Product

Table 9: Properties of each product.

Id	Name	SBO
LRCA	Ligand-Receptor-CoActivator	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{RAR\_retinoids}) \cdot (\mathrm{k1} \cdot [\mathrm{LR}] \cdot [\mathrm{CA}] - \mathrm{k2} \cdot [\mathrm{LRCA}]) \tag{4}$$

Table 10: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		0.014		☑
k2	k2		0.200		☑

6 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.

6.1 Species L

Name Ligand

SBO:0000280 ligand

Notes `Ligand is either natural retinoid (ATRA), or synthetic retinoid as EC19, EC23,...`

Initial concentration $5 \cdot 10^{-4}$ µmol$\cdot$l^{-1}

This species takes part in one reaction (as a reactant in LR_complx).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{L} = -v_1 \tag{5}$$

6.2 Species LR

Name Ligand-Receptor

SBO:0000296 macromolecular complex

Notes `Ligand-Receptor represents the intermediate complex formation between ligand and re`
`The formation of this complex is controlled by k1/k2 ratio which represents the liga`
`The higher k1/k2 ratio, the better binding interaction of ligand to its cognate rece`

Initial concentration 0 µmol$\cdot$l^{-1}

This species takes part in two reactions (as a reactant in LRCA_complx and as a product in LR-_complx).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{LR} = v_1 - v_2 \tag{6}$$

6.3 Species R

Name Receptor

SBO:0000244 receptor

Notes `Examples of receptors; Retinoic acid receptor (RAR)-alpha,-beta and -gamma.`
`The principle is the same and the concentrations used here are for RAR-alpha`

Initial concentration $0.0035\ \mu\text{mol} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a reactant in LR_complx).

$$\frac{\text{d}}{\text{d}t}\text{R} = -v_1 \tag{7}$$

6.4 Species CA

Name CoActivator

SBO:0000459 stimulator

Notes Examples for co-activators:
steroid receptor co-activator-1 (SRC-1), co-activator-X (COACT-X) and CREB binding p

Initial concentration $30\ \mu\text{mol} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a reactant in LRCA_complx).

$$\frac{\text{d}}{\text{d}t}\text{CA} = -v_2 \tag{8}$$

6.5 Species LRCA

Name Ligand-Receptor-CoActivator

SBO:0000296 macromolecular complex

Notes Ligand-Receptor-CoActivator represents the final complex formation between ligand,
The formation of this complex is controlled by k3/k4 ratio which represents the liga
The higher k3/k4 ratio, the better binding interaction of the intermediate complex t

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

This species takes part in one reaction (as a product in LRCA_complx).

$$\frac{\text{d}}{\text{d}t}\text{LRCA} = v_2 \tag{9}$$

A Glossary of Systems Biology Ontology Terms

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:0000280 ligand: In biochemistry, a ligand is an effector, a physical entity that binds to a site on a receptor's surface by intermolecular forces

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:0000459 stimulator: Substance that accelerates the velocity of a chemical reaction without itself being consumed or transformed.

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.

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