SBML Model Report

Model name: “Zhu2015 - Combined gemcitabine and birinapant in pancreatic cancer cells - mechanistic PD model”

May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Matthew Grant Roberts[1] at February sixth 2018 at 10:23 a. m. and last time modified at February seventh 2018 at 1:58 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	0	constraints	0
reactions	0	function definitions	0
global parameters	58	unit definitions	2
rules	23	initial assignments	8

Model Notes

Zhu2015 - combined gemcitabine and birinapantin pancreatic cancer cells - mechanistic PD modelMechanistic mathematical model toillustrate the effectiveness of combination chemotherapy involvinggemcitabine and birinapant against pancreatic cancer.

[1]EMBL-EBI, mroberts@ebi.ac.uk

This model is described in the article:Mechanism-based mathematical modeling of combined gemcitabine and birinapant in pancreatic cancer cells.Zhu X, Straubinger RM, Jusko WJ.J Pharmacokinet Pharmacodyn 2015 Oct; 42(5): 477-496

Abstract:

Combination chemotherapy is standard treatment for pancreatic cancer. However, current drugs lack efficacy for most patients, and selection and evaluation of new combination regimens is empirical and time-consuming. The efficacy of gemcitabine, a standard-of-care agent, combined with birinapant, a pro-apoptotic antagonist of Inhibitor of Apoptosis Proteins (IAPs), was investigated in pancreatic cancer cells. PANC-1 cells were treated with vehicle, gemcitabine (6, 10, 20 nM), birinapant (50, 200, 500 nM), and combinations of the two drugs. Temporal changes in cell numbers, cell cycle distribution, and apoptosis were measured. A basic pharmacodynamic (PD) model based on cell numbers, and a mechanism-based PD model integrating all measurements, were developed. The basic PD model indicated that synergistic effects occurred in both cell proliferation and death processes. The mechanism-based model captured key features of drug action: temporary cell cycle arrest in S phase induced by gemcitabine alone, apoptosis induced by birinapant alone, and prolonged cell cycle arrest and enhanced apoptosis induced by the combination. A drug interaction term was employed in the models to signify interactions of the combination when data were limited. When more experimental information was utilized, values approaching 1 indicated that specific mechanisms of interactions were captured better. PD modeling identified the potential benefit of combining gemcitabine and birinapant, and characterized the key interaction pathways. An optimal treatment schedule of pretreatment with gemcitabine for 24-48 h was suggested based on model predictions and was verified experimentally. This approach provides a generalizable modeling platform for exploring combinations of cytostatic and cytotoxic agents in cancer cell culture studies.

This model is hosted on BioModels Database and identified by: BIOMD0000000669.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

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 `volume`

Name volume

Definition ml

2.2 Unit `substance`

Name substance

Definition mmol

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
`Pancreas`	Pancreas		3	1	litre	☑	

3.1 Compartment `Pancreas`

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

Name Pancreas

4 Species

This model contains seven species. The boundary condition of seven of these species is set to `true` so that these species' amount cannot be changed by any reaction. 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
`G1`	G1	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`S`	S	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`G2`	G2	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`R_apo`	R_apo	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`R_other`	R_other	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`R_total`	R_total	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑
`R_live`	R_live	`Pancreas`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☐	☑

5 Parameters

This model contains 58 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Inh_1	Inh_1		0.642		☐
IR50	IR50		123000.000		☑
Inh_3	Inh_3		0.483		☐
Imax_3	Imax_3		0.753		☑
k3	k3		0.222		☑
k1	k1		0.357		☑
k_apo	k_apo		0.004		☑
k2	k2		0.114		☑
Imax_g	Imax_g		0.878		☑
C_g	C_g		20.000		☑
C_b	C_b		500.000		☑
Hi_g	Hi_g		4.340		☑
Hs_b	Hs_b		1.240		☑
Hi_b	Hi_b		1.000		☑
Hs_g	Hs_g		3.000		☑
Tlag_re	Tlag_re		81.324		☐
Tlag_sg	Tlag_sg		38.700		☑
k_other	k_other		$2.97 \cdot 10^{-4}$		☐
Hother_g	Hother_g		0.100		☑
Smax_b	Smax_b		3.720		☑
Psi_i	Psi_i		0.949		☑
Psi_s	Psi_s		1.260		☑
Smax_g	Smax_g		2.740		☑
SC50_g	SC50_g		23.600		☑
SC50_b	SC50_b		50.100		☑
k_comb2	k_comb2		$7.75 \cdot 10^{-4}$		☑
k_comb1	k_comb1		$9.19 \cdot 10^{-4}$		☑
k_repair	k_repair		0.050		☑
Tlag_r	Tlag_r		55.721		☐
k_delay	k_delay		18.600		☑
R_0	R_0		236000.000		☑
f_G1__0	f(G1)_0		48.100		☑
f_S__0	f(S)_0		10.800		☑
f_apo__0	f(apo)_0		5.000		☑
f_other__0	f(other)_0		1.500		☑
f1	f1		0.467		☑

Id	Name	SBO	Value	Unit	Constant
Imax_b	Imax_b		0.177		☑
IC50_g	IC50_g		6.000		☑
IC50_b	IC50_b		154.000		☑
k_tau	k_tau		0.376		☑
Kother_g	Kother_g		10^{-5}		☑
Kother_b	Kother_b		0.006		☑
Hother_b	Hother_b		1.000		☑
Inh_g	Inh_g		0.874		☐
Inh_b	Inh_b		0.135		☐
Sti_g	Sti_g		0.000		☐
Sti_other_g	Sti_other_g		$1.34928284767356 \cdot 10^{-5}$		☐
Sti_other_b	Sti_other_b		2.750		☐
Sti_b	Sti_b		3.455		☐
Sti_apo_g	Sti_apo_g		0.000		☑
Sti_apo_b	Sti_apo_b		0.000		☑
f_G2__0	f(G2)_0		34.600		☑
CURVE_G1	CURVE_G1		0.481		☐
CURVE_S	CURVE_S		0.108		☐
CURVE_G2	CURVE_G2		0.346		☐
CURVE-_FIGURE-_7a_d_g	CURVE_FIGURE-_7a/d/g		0.935		☐
CURVE-_FIGURE-_7b_r_h	CURVE_FIGURE-_7b/r/h		0.050		☐
CURVE-_FIGURE-_7c_f_i	CURVE_FIGURE-_7c/f/i		0.000		☑

6 Initialassignments

This is an overview of eight initialassignments.

6.1 Initialassignment G1

Derived unit contains undeclared units

Math $\frac{\mathrm{f\_G1\_\_0} \cdot \mathrm{R\_0}}{100}$

6.2 Initialassignment S

Derived unit contains undeclared units

Math $\frac{\mathrm{f\_S\_\_0} \cdot \mathrm{R\_0}}{100}$

6.3 Initialassignment G2

Derived unit contains undeclared units

Math $\frac{\mathrm{f\_G2\_\_0} \cdot \mathrm{R\_0}}{100}$

6.4 Initialassignment R_apo

Derived unit contains undeclared units

Math $\frac{\mathrm{f\_apo\_\_0} \cdot \mathrm{R\_0}}{100}$

6.5 Initialassignment R_other

Derived unit contains undeclared units

Math $\frac{\mathrm{f\_other\_\_0} \cdot \mathrm{R\_0}}{100}$

6.6 Initialassignment Psi_i

Derived unit contains undeclared units

Math $\begin{cases} 0.949 & \text{if } (\mathrm{C\_b} \neq 0) \wedge (\mathrm{C\_g} \neq 0) \\ 1 & \text{otherwise} \end{cases}$

6.7 Initialassignment Psi_s

Derived unit contains undeclared units

Math $\begin{cases} 1.26 & \text{if } (\mathrm{C\_b} \neq 0) \wedge (\mathrm{C\_g} \neq 0) \\ 1 & \text{otherwise} \end{cases}$

6.8 Initialassignment f_G2__0

Derived unit contains undeclared units

Math $100 - \mathrm{f\_apo\_\_0} - \mathrm{f\_G1\_\_0} - \mathrm{f\_S\_\_0} - \mathrm{f\_other\_\_0}$

7 Rules

This is an overview of 23 rules.

7.1 Rule R_total

Rule R_total is an assignment rule for species R_total:

$$\mathrm{R\_total} = [\mathrm{G1}] + [\mathrm{S}] + [\mathrm{G2}] + [\mathrm{R\_apo}] + [\mathrm{R\_other}] \tag{1}$$

Derived unit $\mathrm{mmol} \cdot \mathrm{ml}^{-1}$

7.2 Rule R_live

Rule R_live is an assignment rule for species R_live:

$$\mathrm{R\_live} = [\mathrm{G1}] + [\mathrm{S}] + [\mathrm{G2}] \tag{2}$$

Derived unit $\mathrm{mmol} \cdot \mathrm{ml}^{-1}$

7.3 Rule Inh_1

Rule Inh_1 is an assignment rule for parameter Inh_1:

$$\mathrm{Inh\_1} = \frac{[\mathrm{R\_live}]}{\mathrm{IR50} + [\mathrm{R\_live}]} \tag{3}$$

7.4 Rule Inh_3

Rule Inh_3 is an assignment rule for parameter Inh_3:

$$\mathrm{Inh\_3} = \frac{\mathrm{Imax\_3} \cdot [\mathrm{R\_live}]}{\mathrm{IR50} + [\mathrm{R\_live}]} \tag{4}$$

7.5 Rule k_other

Rule k_other is an assignment rule for parameter k_other:

$$\mathrm{k\_other} = \begin{cases} 2.97 \cdot 10^{-4} & \text{if } (\mathrm{C\_b} \neq 0) \wedge (\mathrm{C\_g} \neq 0) \\ 0 & \text{otherwise} \end{cases} \tag{5}$$

7.6 Rule Tlag_r

Rule Tlag_r is an assignment rule for parameter Tlag_r:

$$\mathrm{Tlag\_r} = \begin{cases} 0 & \text{if } \mathrm{C\_g} = 0 \\ \mathrm{k\_delay} \cdot \ln \mathrm{C\_g} & \text{otherwise} \end{cases} \tag{6}$$

7.7 Rule Tlag_re

Rule Tlag_re is an assignment rule for parameter Tlag_re:

$$\mathrm{Tlag\_re} = (1 + \mathrm{k\_comb1} \cdot \mathrm{C\_b}) \cdot \mathrm{Tlag\_r} \tag{7}$$

7.8 Rule Inh_g

Rule Inh_g is an assignment rule for parameter Inh_g:

$$\mathrm{Inh\_g} = \begin{cases} \frac{\mathrm{Imax\_g} \cdot \mathrm{C\_g}^{\mathrm{Hi\_g}}}{\mathrm{IC50\_g}^{\mathrm{Hi\_g}} + \mathrm{C\_g}^{\mathrm{Hi\_g}}} \\ \begin{cases} \frac{\mathrm{Imax\_g} \cdot \mathrm{C\_g}^{\mathrm{Hi\_g}}}{\mathrm{IC50\_g}^{\mathrm{Hi\_g}} + \mathrm{C\_g}^{\mathrm{Hi\_g}}} \cdot \exp\left(1 \cdot \mathrm{k\_repair} \cdot (\mathrm{time} - \mathrm{Tlag\_r})\right) \\ \begin{cases} \frac{\mathrm{Imax\_g} \cdot \mathrm{C\_g}^{\mathrm{Hi\_g}}}{(\mathrm{Psi\_i} \cdot \mathrm{IC50\_g})^{\mathrm{Hi\_g}} + \mathrm{C\_g}^{\mathrm{Hi\_g}}} \\ \begin{cases} \frac{\mathrm{Imax\_g} \cdot \mathrm{C\_g}^{\mathrm{Hi\_g}}}{(\mathrm{Psi\_i} \cdot \mathrm{IC50\_g})^{\mathrm{Hi\_g}} + \mathrm{C\_g}^{\mathrm{Hi\_g}}} \cdot \exp\left(1 \cdot (1 - \mathrm{k\_comb2} \cdot \mathrm{C\_b}) \cdot \mathrm{k\_repair} \cdot (\mathrm{time} - \mathrm{Tlag\_re})\right) & \text{if } (\mathrm{C\_b} \neq 0 \\ 0 & \text{otherwise} \end{cases} \end{cases} \end{cases} \end{cases} \tag{8}$$

7.9 Rule Inh_b

Rule Inh_b is an assignment rule for parameter Inh_b:

$$\mathrm{Inh\_b} = \frac{\mathrm{Imax\_b} \cdot \mathrm{C\_b}^{\mathrm{Hi\_b}}}{\mathrm{IC50\_b}^{\mathrm{Hi\_b}} + \mathrm{C\_b}^{\mathrm{Hi\_b}}} \tag{9}$$

7.10 Rule Sti_g

Rule Sti_g is an assignment rule for parameter Sti_g:

$$\mathrm{Sti\_g} = \begin{cases} 0 & \text{if time} \leq \mathrm{Tlag\_sg} \\ \frac{\mathrm{Smax\_g} \cdot \mathrm{C\_g}^{\mathrm{Hs\_g}}}{\mathrm{SC50\_g}^{\mathrm{Hs\_g}} + \mathrm{C\_g}^{\mathrm{Hs\_g}}} & \text{otherwise} \end{cases} \tag{10}$$

7.11 Rule Sti_other_g

Rule Sti_other_g is an assignment rule for parameter Sti_other_g:

$$\mathrm{Sti\_other\_g} = \mathrm{Kother\_g} \cdot \mathrm{C\_g}^{\mathrm{Hother\_g}} \tag{11}$$

7.12 Rule Sti_other_b

Rule Sti_other_b is an assignment rule for parameter Sti_other_b:

$$\mathrm{Sti\_other\_b} = \mathrm{Kother\_b} \cdot \mathrm{C\_b}^{\mathrm{Hother\_b}} \tag{12}$$

7.13 Rule Sti_b

Rule Sti_b is an assignment rule for parameter Sti_b:

$$\mathrm{Sti\_b} = \frac{\mathrm{Smax\_b} \cdot \mathrm{C\_b}^{\mathrm{Hs\_b}}}{\left(\mathrm{Psi\_s} \cdot \mathrm{SC50\_b}\right)^{\mathrm{Hs\_b}} + \mathrm{C\_b}^{\mathrm{Hs\_b}}} \tag{13}$$

7.14 Rule CURVE_G1

Rule CURVE_G1 is an assignment rule for parameter CURVE_G1:

$$\mathrm{CURVE\_G1} = \frac{[\mathrm{G1}]}{[\mathrm{R\_total}]} \tag{14}$$

Derived unit dimensionless

7.15 Rule CURVE_S

Rule CURVE_S is an assignment rule for parameter CURVE_S:

$$\mathrm{CURVE\_S} = \frac{[\mathrm{S}]}{[\mathrm{R\_total}]} \tag{15}$$

Derived unit dimensionless

7.16 Rule CURVE_G2

Rule CURVE_G2 is an assignment rule for parameter CURVE_G2:

$$\mathrm{CURVE\_G2} = \frac{[\mathrm{G2}]}{[\mathrm{R\_total}]} \tag{16}$$

Derived unit dimensionless

7.17 Rule CURVE_FIGURE_7a_d_g

Rule CURVE_FIGURE_7a_d_g is an assignment rule for parameter CURVE_FIGURE_7a_d_g:

$$\mathrm{CURVE\_FIGURE\_7a\_d\_g} = \frac{[\mathrm{R\_live}]}{[\mathrm{R\_total}]} \tag{17}$$

Derived unit dimensionless

7.18 Rule CURVE_FIGURE_7b_r_h

Rule CURVE_FIGURE_7b_r_h is an assignment rule for parameter CURVE_FIGURE_7b_r_h:

$$\mathrm{CURVE\_FIGURE\_7b\_r\_h} = \frac{[\mathrm{R\_apo}]}{[\mathrm{R\_total}]} \tag{18}$$

Derived unit dimensionless

7.19 Rule G1

Rule G1 is a rate rule for species G1:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{G1} = 2 \cdot (1 - \mathrm{Inh\_3}) \cdot (1 - \mathrm{Inh\_b}) \cdot \mathrm{k3} \cdot [\mathrm{G2}] - (1 - \mathrm{Inh\_1}) \cdot (1 - \mathrm{Inh\_b}) \cdot \mathrm{k1} \cdot [\mathrm{G1}] - (1 + \mathrm{Sti\_apo\_g}) \cdot (1 + \mathrm{Sti\_apo\_b}) \cdot \mathrm{k\_apo} \cdot [\mathrm{G1}] - (1 + \mathrm{Sti\_other\_g}) \cdot (1 + \mathrm{Sti\_other\_b}) \cdot \mathrm{k\_other} \cdot [\mathrm{G1}] \tag{19}$$

7.20 Rule S

Rule S is a rate rule for species S:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{S} = (1 - \mathrm{Inh\_1}) \cdot (1 - \mathrm{Inh\_b}) \cdot \mathrm{k1} \cdot [\mathrm{G1}] - (1 - \mathrm{Inh\_g}) \cdot \mathrm{k2} \cdot [\mathrm{S}] - (1 + \mathrm{Sti\_apo\_g}) \cdot (1 + \mathrm{Sti\_apo\_b}) \cdot \mathrm{k\_apo} \cdot [\mathrm{S}] - (1 + \mathrm{Sti\_other\_g}) \cdot (1 + \mathrm{Sti\_other\_b}) \cdot \mathrm{k\_other} \cdot [\mathrm{S}] \tag{20}$$

7.21 Rule G2

Rule G2 is a rate rule for species G2:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{G2} = (1 - \mathrm{Inh\_g}) \cdot \mathrm{k2} \cdot [\mathrm{S}] - (1 - \mathrm{Inh\_3}) \cdot (1 - \mathrm{Inh\_b}) \cdot \mathrm{k3} \cdot [\mathrm{G2}] - (1 + \mathrm{Sti\_apo\_g}) \cdot (1 + \mathrm{Sti\_apo\_b}) \cdot \mathrm{k\_apo} \cdot [\mathrm{G2}] - (1 + \mathrm{Sti\_other\_g}) \cdot (1 + \mathrm{Sti\_other\_b}) \cdot \mathrm{k\_other} \cdot [\mathrm{G2}] \tag{21}$$

7.22 Rule R_apo

Rule R_apo is a rate rule for species R_apo:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{R\_apo} = (1 + \mathrm{Sti\_apo\_g}) \cdot (1 + \mathrm{Sti\_apo\_b}) \cdot \mathrm{k\_apo} \cdot ([\mathrm{G1}] + [\mathrm{S}] + [\mathrm{G2}]) - (1 + \mathrm{Sti\_apo\_g}) \cdot (1 + \mathrm{Sti\_apo\_b}) \cdot \mathrm{f1} \cdot \mathrm{k\_apo} \cdot [\mathrm{R\_apo}] \tag{22}$$

7.23 Rule R_other

Rule R_other is a rate rule for species R_other:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{R\_other} = (1 + \mathrm{Sti\_other\_g}) \cdot (1 + \mathrm{Sti\_other\_b}) \cdot \mathrm{k\_other} \cdot ([\mathrm{G1}] + [\mathrm{S}] + [\mathrm{G2}]) - \mathrm{k\_other} \cdot [\mathrm{R\_other}] \tag{23}$$

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.

8.1 Species G1

Name G1

Initial concentration $113516\ \mathrm{mmol\cdot ml^{-1}}$

Initial assignment G1

Involved in rule G1

One rule determines the species' quantity.

8.2 Species S

Name S

Initial concentration $25488\ \mathrm{mmol\cdot ml^{-1}}$

Initial assignment S

Involved in rule S

One rule determines the species' quantity.

8.3 Species G2

Name G2

Initial concentration $81656\ \mathrm{mmol\cdot ml^{-1}}$

Initial assignment G2

Involved in rule G2

One rule determines the species' quantity.

8.4 Species R_apo

Name R_apo

Initial concentration $11800\ \mathrm{mmol\cdot ml^{-1}}$

Initial assignment R_apo

Involved in rule R_apo

One rule determines the species' quantity.

8.5 Species R_other

Name R_other

Initial concentration $3540 \text{ mmol} \cdot \text{ml}^{-1}$

Initial assignment R_other

Involved in rule R_other

One rule determines the species' quantity.

8.6 Species R_total

Name R_total

Initial concentration $236000 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule R_total

One rule determines the species' quantity.

8.7 Species R_live

Name R_live

Initial concentration $220660 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule R_live

One rule determines the species' quantity.

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