

SBML Model Report

Model name: “Zhu2015 - Combined gemcitabine and birinapant in pancreatic cancer cells - basic 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 Roberts¹ at February fifth 2018 at 12:05 a. m. and last time modified at February seventh 2018 at 1:04 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	14
events	0	constraints	0
reactions	10	function definitions	0
global parameters	26	unit definitions	2
rules	6	initial assignments	7

Model Notes

Zhu2015 - Combined gemcitabine and birinapant in pancreatic cancer cells - basic PD model-
Mathematical model to illustrate the effectiveness of combination chemotherapy involving gem-
citabine and birinapant against pancreatic cancer.

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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: [BIOMD0000000668](#).

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

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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 m²

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	<input checked="" type="checkbox"/>	

3.1 Compartment Pancreas

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

Name Pancreas

4 Species

This model contains 14 species. The boundary condition of six of these species is set to `true` so that these species' amount cannot be changed by any reaction. Section 9 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
Ra	Ra	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Rd	Rd	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Inh_g	Inh_g	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Inh_b	Inh_b	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Sti_g	Sti_g	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Sti_b	Sti_b	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Sti_g1	Sti_g1	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_g2	Sti_g2	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_g3	Sti_g3	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_g4	Sti_g4	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_b1	Sti_b1	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_b2	Sti_b2	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_b3	Sti_b3	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Sti_b4	Sti_b4	Pancreas	$\text{mmol} \cdot \text{ml}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>

5 Parameters

This model contains 26 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Ra_0	Ra_0		307000.000		✓
Rd_0	Rd_0		1940.000		✓
Rss	Rss		5490000.000		✓
kg	kg		0.021		✓
kd	kd		$3.85 \cdot 10^{-4}$		✓
Imax_g	Imax_g		0.991		✓
Imax_b	Imax_b		0.375		✓
IC50_g	IC50_g		20.800		✓
IC50_b	IC50_b		145.000		✓
Hi_g	Hi_g		3.570		✓
Hi_b	Hi_b		1.060		✓
Smax_g	Smax_g		4.090		✓
Smax_b	Smax_b		17.500		✓
SC50_g	SC50_g		14.000		✓
SC50_b	SC50_b		168.000		✓
Hs_g	Hs_g		5.000		✓
Hs_b	Hs_b		0.984		✓
ktau_g	ktau_g		0.086		✓
ktau_b	ktau_b		0.611		✓
Psi_i	Psi_i		1.000		✓
Psi_s	Psi_s		1.000		✓
C_g	C_g		0.000		✓
C_b	C_b		0.000		✓
ModelValue_2	Initial for Rss		5490000.000		✓
ModelValue_4	Initial for kd		$3.85 \cdot 10^{-4}$		✓
ModelValue_3	Initial for kg		0.021		✓

6 Initialassignments

This is an overview of seven initialassignments.

6.1 Initialassignment Ra

Derived unit contains undeclared units

Math Ra_0

6.2 Initialassignment Rd

Derived unit contains undeclared units

Math Rd_0

6.3 Initialassignment Psi_i

Derived unit contains undeclared units

$$\mathbf{Math} \begin{cases} 0.583 & \text{if } (C_b \neq 0) \wedge (C_g \neq 0) \\ 1 & \text{otherwise} \end{cases}$$

6.4 Initialassignment Psi_s

Derived unit contains undeclared units

$$\mathbf{Math} \begin{cases} 0.582 & \text{if } (C_b \neq 0) \wedge (C_g \neq 0) \\ 1 & \text{otherwise} \end{cases}$$

6.5 Initialassignment $ModelValue_2$

Derived unit contains undeclared units

Math Rss

6.6 Initialassignment $ModelValue_4$

Derived unit contains undeclared units

Math kd

6.7 Initialassignment $ModelValue_3$

Derived unit contains undeclared units

Math kg

7 Rules

This is an overview of six rules.

7.1 Rule `Inh_g`

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

$$\text{Inh_g} = \frac{\text{Imax_g} \cdot \text{C_g}^{\text{Hi_g}}}{(\text{Psi_i} \cdot \text{IC50_g})^{\text{Hi_g}} + \text{C_g}^{\text{Hi_g}}} \quad (1)$$

7.2 Rule `Inh_b`

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

$$\text{Inh_b} = \frac{\text{Imax_b} \cdot \text{C_b}^{\text{Hi_b}}}{(\text{Psi_i} \cdot \text{IC50_b})^{\text{Hi_b}} + \text{C_b}^{\text{Hi_b}}} \quad (2)$$

7.3 Rule `Sti_g`

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

$$\text{Sti_g} = \frac{\text{Smax_g} \cdot \text{C_g}^{\text{Hs_g}}}{(\text{Psi_s} \cdot \text{SC50_g})^{\text{Hs_g}} + \text{C_g}^{\text{Hs_g}}} \quad (3)$$

7.4 Rule `Sti_b`

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

$$\text{Sti_b} = \frac{\text{Smax_b} \cdot \text{C_b}^{\text{Hs_b}}}{(\text{Psi_s} \cdot \text{SC50_b})^{\text{Hs_b}} + \text{C_b}^{\text{Hs_b}}} \quad (4)$$

7.5 Rule `Ra`

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

$$\begin{aligned} \frac{d}{dt}\text{Ra} = & (1 - [\text{Inh_g}]) \cdot (1 - [\text{Inh_b}]) \cdot \text{ModelValue_3} \cdot [\text{Ra}] \cdot \left(1 - \frac{[\text{Ra}]}{\text{ModelValue_2}}\right) \\ & - (1 + [\text{Sti_g4}]) \cdot (1 + [\text{Sti_b4}]) \cdot \text{ModelValue_4} \cdot [\text{Ra}] \end{aligned} \quad (5)$$

7.6 Rule `Rd`

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

$$\frac{d}{dt}\text{Rd} = (1 + [\text{Sti_g4}]) \cdot (1 + [\text{Sti_b4}]) \cdot \text{ModelValue_4} \cdot [\text{Ra}] - \text{ModelValue_4} \cdot [\text{Rd}] \quad (6)$$

8 Reactions

This model contains ten 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

Nº	Id	Name	Reaction Equation	SBO
1	g_death- _stimulus- _delay_1	g_death_stimulus delay 1	Sti_g \longrightarrow Sti_g1	
2	g_death- _stimulus- _delay_2	g_death_stimulus delay 2	Sti_g1 \longrightarrow Sti_g2	
3	g_death- _stimulus- _delay_3	g_death_stimulus delay 3	Sti_g2 \longrightarrow Sti_g3	
4	g_death- _stimulus- _delay_4	g_death_stimulus delay 4	Sti_g3 \longrightarrow Sti_g4	
5	g_death- _stimulus- _delay_4- _degradation	g_death_stimulus delay 4 degradation	Sti_g4 $\longrightarrow \emptyset$	
6	b_death- _stimulus- _delay_1	b_death_stimulus delay 1	Sti_b \longrightarrow Sti_b1	
7	b_death- _stimulus- _delay_2	b_death_stimulus delay 2	Sti_b1 \longrightarrow Sti_b2	

Nº	Id	Name	Reaction Equation	SBO
8	b_death- _stimulus- _delay_3	b_death_stimulus delay 3	Sti_b2 \longrightarrow Sti_b3	
9	b_death- _stimulus- _delay_4	b_death_stimulus delay 4	Sti_b3 \longrightarrow Sti_b4	
10	b_death- _stimulus- _delay_4- _degradation	b_death_stimulus delay 4 degradation	Sti_b4 $\longrightarrow \emptyset$	

8.1 Reaction `g_death_stimulus_delay_1`

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

Name `g_death_stimulus_delay_1`

Reaction equation



Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
<code>Sti_g</code>	<code>Sti_g</code>	

Product

Table 7: Properties of each product.

Id	Name	SBO
<code>Sti_g1</code>	<code>Sti_g1</code>	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}(\text{Pancreas}) \cdot \text{ktau_g} \cdot [\text{Sti_g}] \quad (8)$$

8.2 Reaction `g_death_stimulus_delay_2`

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

Name `g_death_stimulus_delay_2`

Reaction equation



Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
Sti_g1	Sti_g1	

Product

Table 9: Properties of each product.

Id	Name	SBO
Sti_g2	Sti_g2	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_g}} \cdot [\text{Sti_g1}] \quad (10)$$

8.3 Reaction g_death_stimulus_delay_3

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

Name g_death_stimulus delay 3

Reaction equation



Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
Sti_g2	Sti_g2	

Product

Table 11: Properties of each product.

Id	Name	SBO
Sti_g3	Sti_g3	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{vol}(\text{Pancreas}) \cdot \text{ktau_g} \cdot [\text{Sti_g2}] \quad (12)$$

8.4 Reaction g_death_stimulus_delay_4

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

Name g_death_stimulus delay 4

Reaction equation



Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Sti_g3	Sti_g3	

Product

Table 13: Properties of each product.

Id	Name	SBO
Sti_g4	Sti_g4	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{vol}(\text{Pancreas}) \cdot \text{ktau_g} \cdot [\text{Sti_g3}] \quad (14)$$

8.5 Reaction `g_death_stimulus_delay_4_degradation`

This is an irreversible reaction of one reactant forming no product.

Name `g_death_stimulus_delay_4_degradation`

Reaction equation



Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
<code>Sti_g4</code>	<code>Sti_g4</code>	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{vol}(\text{Pancreas}) \cdot \text{ktau_g} \cdot [\text{Sti_g4}] \quad (16)$$

8.6 Reaction `b_death_stimulus_delay_1`

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

Name `b_death_stimulus_delay_1`

Reaction equation



Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
<code>Sti_b</code>	<code>Sti_b</code>	

Product

Table 16: Properties of each product.

Id	Name	SBO
<code>Sti_b1</code>	Sti_b1	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_b}} \cdot [\text{Sti_b}] \quad (18)$$

8.7 Reaction `b_death_stimulus_delay_2`

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

Name `b_death_stimulus delay 2`

Reaction equation



Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
<code>Sti_b1</code>	Sti_b1	

Product

Table 18: Properties of each product.

Id	Name	SBO
<code>Sti_b2</code>	Sti_b2	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_b}} \cdot [\text{Sti_b1}] \quad (20)$$

8.8 Reaction `b_death_stimulus_delay_3`

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

Name `b_death_stimulus_delay_3`

Reaction equation



Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
<code>Sti_b2</code>	<code>Sti_b2</code>	

Product

Table 20: Properties of each product.

Id	Name	SBO
<code>Sti_b3</code>	<code>Sti_b3</code>	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_b}} \cdot [\text{Sti_b2}] \quad (22)$$

8.9 Reaction `b_death_stimulus_delay_4`

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

Name `b_death_stimulus_delay_4`

Reaction equation



Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
Sti_b3	Sti_b3	

Product

Table 22: Properties of each product.

Id	Name	SBO
Sti_b4	Sti_b4	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_b}} \cdot [\text{Sti_b3}] \quad (24)$$

8.10 Reaction b_death_stimulus_delay_4_degradation

This is an irreversible reaction of one reactant forming no product.

Name b_death_stimulus delay 4 degradation

Reaction equation



Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
Sti_b4	Sti_b4	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{vol}(\text{Pancreas}) \cdot k_{\text{tau_b}} \cdot [\text{Sti_b4}] \quad (26)$$

9 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.

9.1 Species [Ra](#)

Name Ra

Initial concentration 307000 mmol · ml⁻¹

Initial assignment Ra

Involved in rule [Ra](#)

One rule determines the species' quantity.

9.2 Species [Rd](#)

Name Rd

Initial concentration 1940 mmol · ml⁻¹

Initial assignment Rd

Involved in rule [Rd](#)

One rule determines the species' quantity.

9.3 Species [Inh_g](#)

Name Inh_g

Initial concentration 0 mmol · ml⁻¹

Involved in rule [Inh_g](#)

One rule determines the species' quantity.

9.4 Species `Inh_b`

Name `Inh_b`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule `Inh_b`

One rule determines the species' quantity.

9.5 Species `Sti_g`

Name `Sti_g`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule `Sti_g`

This species takes part in one reaction (as a reactant in `g_death_stimulus_delay_1`). Not this but one rule determines the species' quantity because this species is on the boundary of the reaction system.

9.6 Species `Sti_b`

Name `Sti_b`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

Involved in rule `Sti_b`

This species takes part in one reaction (as a reactant in `b_death_stimulus_delay_1`). Not this but one rule determines the species' quantity because this species is on the boundary of the reaction system.

9.7 Species `Sti_g1`

Name `Sti_g1`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `g_death_stimulus_delay_2` and as a product in `g_death_stimulus_delay_1`).

$$\frac{d}{dt} \text{Sti_g1} = v_1 - v_2 \quad (27)$$

9.8 Species `Sti_g2`

Name `Sti_g2`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `g_death_stimulus_delay_3` and as a product in `g_death_stimulus_delay_2`).

$$\frac{d}{dt} \text{Sti_g2} = v_2 - v_3 \quad (28)$$

9.9 Species `Sti_g3`

Name `Sti_g3`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `g_death_stimulus_delay_4` and as a product in `g_death_stimulus_delay_3`).

$$\frac{d}{dt} \text{Sti_g3} = v_3 - v_4 \quad (29)$$

9.10 Species `Sti_g4`

Name `Sti_g4`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `g_death_stimulus_delay_4_degradation` and as a product in `g_death_stimulus_delay_4`).

$$\frac{d}{dt} \text{Sti_g4} = v_4 - v_5 \quad (30)$$

9.11 Species `Sti_b1`

Name `Sti_b1`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `b_death_stimulus_delay_2` and as a product in `b_death_stimulus_delay_1`).

$$\frac{d}{dt} \text{Sti_b1} = v_6 - v_7 \quad (31)$$

9.12 Species `Sti_b2`

Name `Sti_b2`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `b_death_stimulus_delay_3` and as a product in `b_death_stimulus_delay_2`).

$$\frac{d}{dt}\text{Sti_b2} = v_7 - v_8 \quad (32)$$

9.13 Species `Sti_b3`

Name `Sti_b3`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `b_death_stimulus_delay_4` and as a product in `b_death_stimulus_delay_3`).

$$\frac{d}{dt}\text{Sti_b3} = v_8 - v_9 \quad (33)$$

9.14 Species `Sti_b4`

Name `Sti_b4`

Initial concentration $0 \text{ mmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in `b_death_stimulus_delay_4_degradation` and as a product in `b_death_stimulus_delay_4`).

$$\frac{d}{dt}\text{Sti_b4} = v_9 - v_{10} \quad (34)$$

SBML²TeX 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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