

Open



Systems Pharmacology

Hands-On exercise -
Rifampicin-Midazolam
DDI

Disclaimer:

Examples described herein have been designed to teach physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) modeling with PK-Sim® and MoBi®. Cases may have been simplified to focus on relevant didactic aspects and may not necessarily describe the best model variant.

Exercise – Setting up a drug-drug interaction simulation with Rifampicin as a perpetrator and Midazolam as a victim drug.

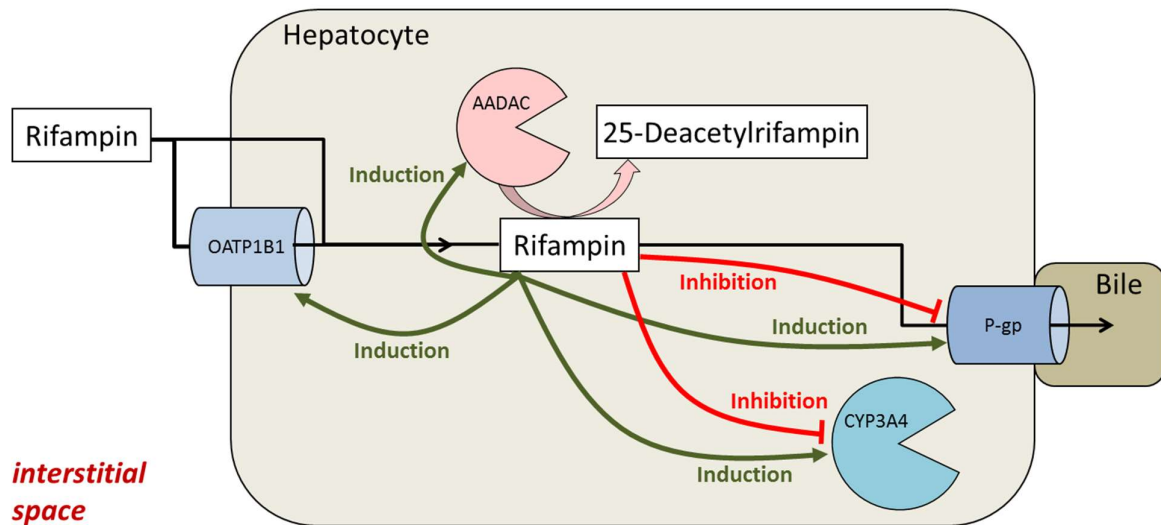
Objectives

Learn to create a simulation with multiple compounds and compare simulation to observed data

Learn to model complex drug-drug interactions with concurrent inhibition and induction of one enzyme and concurrent interactions with transporters by a perpetrator drug

Learn to output additional curves, such as time-varying enzyme concentrations in specific organs.

Features of the Rifampicin PBPK model:



Instructions:

Objective 1:

Evaluate the performance of the midazolam model (open Rifampicin-Midazolam-DDI_1.pksim5).

Make yourself familiar with the compound midazolam. In particular, use the configure simulation function to go through the different features and settings of the simulation.

Objective 2:

Experience the effects of rifampicin pretreatment on midazolam PK using study data from Reitman et al. (2011):

1. Load the compound "Rifampicin" from the compound template database. Make yourself familiar with the compound properties of rifampicin.
2. Create a simulation according to the study of Reitman et al. (2011). To do so, clone the simulation "Midazolam 3 mg PO (solution)" and additionally select the compound "Rifampicin". Make sure that all processes are incorporated into the simulation appropriately; in particular there should be CYP3A4, AADAC, OATP1B1 and P-gp induction and CYP3A4 inhibition (Kajosaari 2005) by rifampicin. Please use the respective administration protocols for both compounds and the "oral solution" as formulation in both cases.
3. Set the simulation end time to 1344h (under Parameters→Settings)
4. Run the simulation, remove the old observed midazolam data (by right clicking on the data in the simulations window), and drag and drop the midazolam data with rifampicin into the chart. If desired, improve chart layout (e.g. set corresponding simulated and observed data to convenient colors, set min/max for axes, ...)

Model Structure
 Compounds
 Processes
 Administration
 Events
 Observers

Configure Simulation: Reitmann et al. 2011

Inhibition / Induction

+

 Add Interaction

Molecule in individual	Interaction process in compound		
CYP3A4	Rifampicin CYP3A4-Kajosaari 2005		x
P-gp	Rifampicin P-gp-Reitman 2011		x
CYP3A4	Rifampicin CYP3A4-Templeton 2011		x
AADAC	Rifampicin AADAC-Assumed		x
P-gp	Rifampicin P-gp-Greiner 1999		x
OATP1B1	Rifampicin OATP1B1-Dixit 2007		x

Midazolam

Metabolism

	Enzyme in individual	Enzymatic process	Metabolite			
<input checked="" type="checkbox"/>	CYP3A4	CYP3A4-Optimized	Sink		+	x
<input checked="" type="checkbox"/>	AADAC	<None>	Sink		+	x
<input checked="" type="checkbox"/>	UGT1A4	UGT1A4-Optimized	Sink		+	x

Transport & Excretion

	Systemic process	Data source
<input checked="" type="checkbox"/>	Glomerular Filtration	Optimized

Specific Binding

	Protein in individual	Binding process	
<input checked="" type="checkbox"/>	CYP3A4	<None>	
<input checked="" type="checkbox"/>	AADAC	<None>	
<input checked="" type="checkbox"/>	P-gp	<None>	
<input checked="" type="checkbox"/>	OATP1B1	<None>	
<input checked="" type="checkbox"/>	ATP1A2	<None>	
<input checked="" type="checkbox"/>	UGT1A4	<None>	
<input checked="" type="checkbox"/>	GABRG2	GABRG2-Buhr 1997	

Rifampicin

Metabolism

	Enzyme in individual	Enzymatic process	Metabolite			
<input checked="" type="checkbox"/>	CYP3A4	<None>	Sink		+	x
<input checked="" type="checkbox"/>	AADAC	AADAC-Nakajima 2011	Sink		+	x
<input checked="" type="checkbox"/>	UGT1A4	<None>	Sink		+	x

Transport & Excretion

	Systemic process	Data source
<input checked="" type="checkbox"/>	Glomerular Filtration	GFR

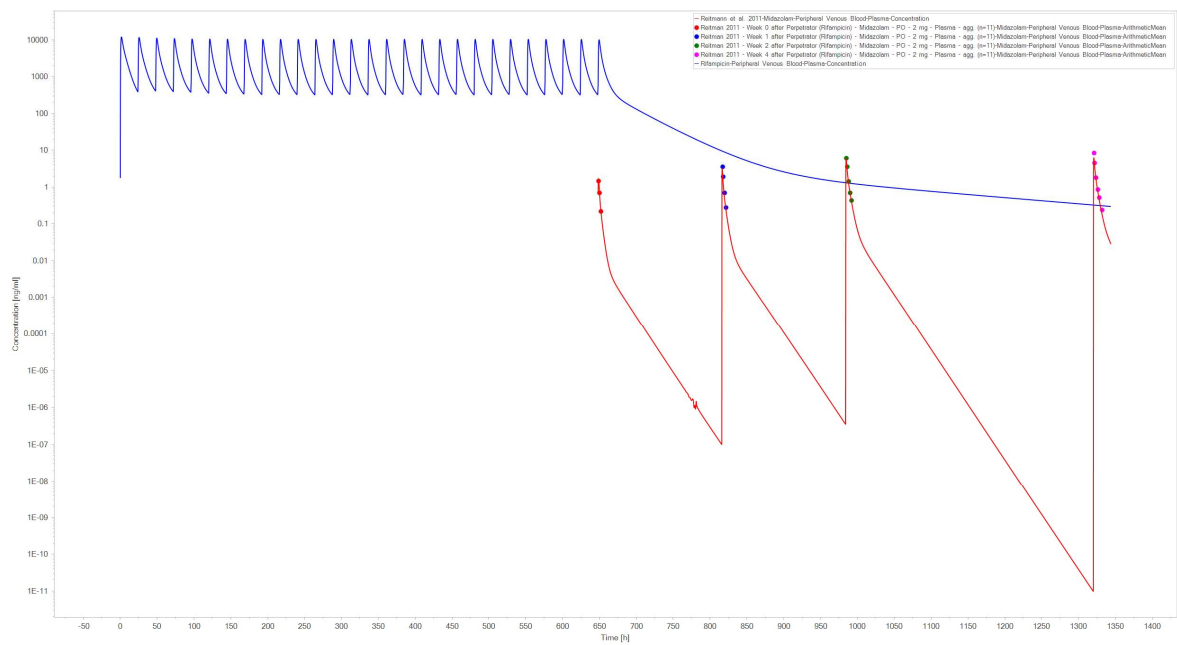
	Transporter in individual	Transport process	
<input checked="" type="checkbox"/>	P-gp	P-gp-Collett 2004	
<input checked="" type="checkbox"/>	OATP1B1	OATP1B1-Tirona 2003	

Previous

Next

OK

Cancel

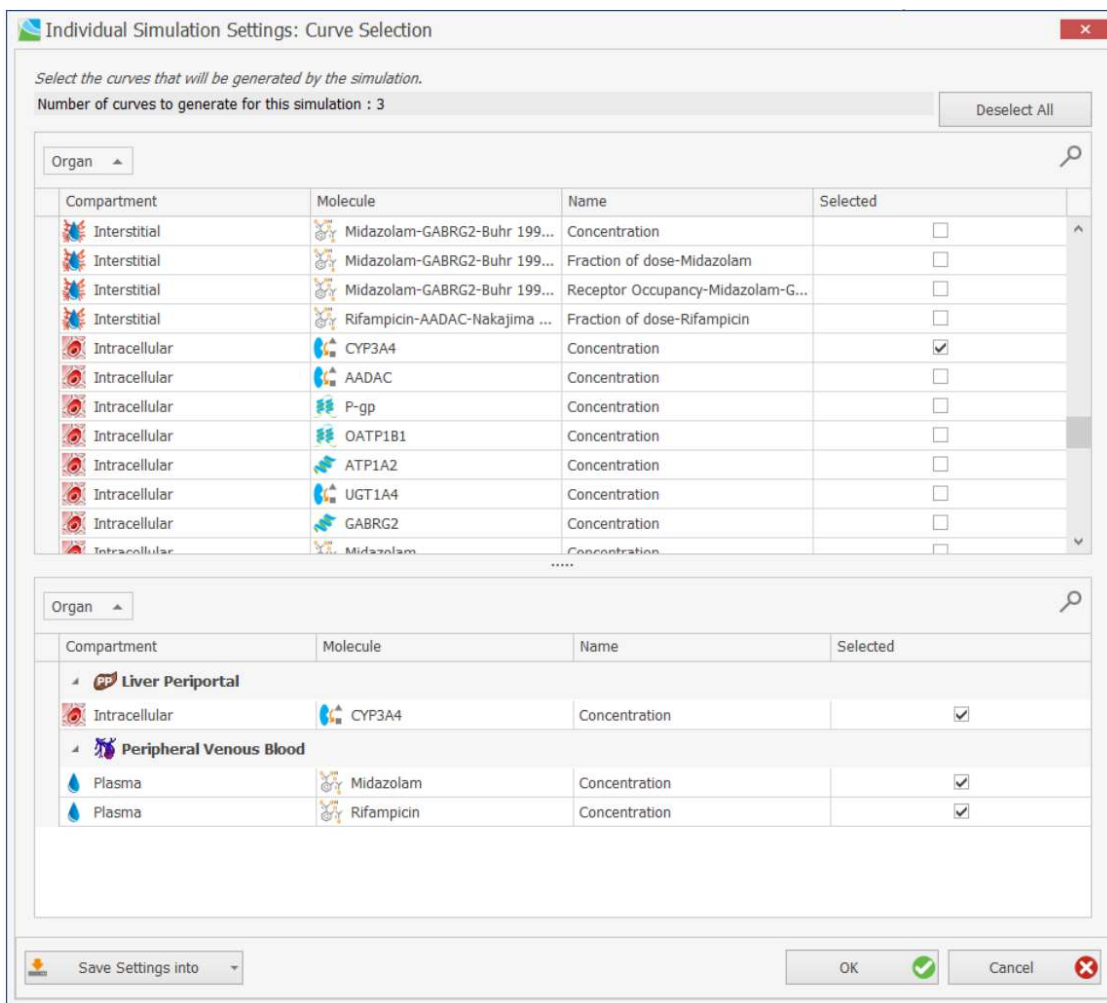


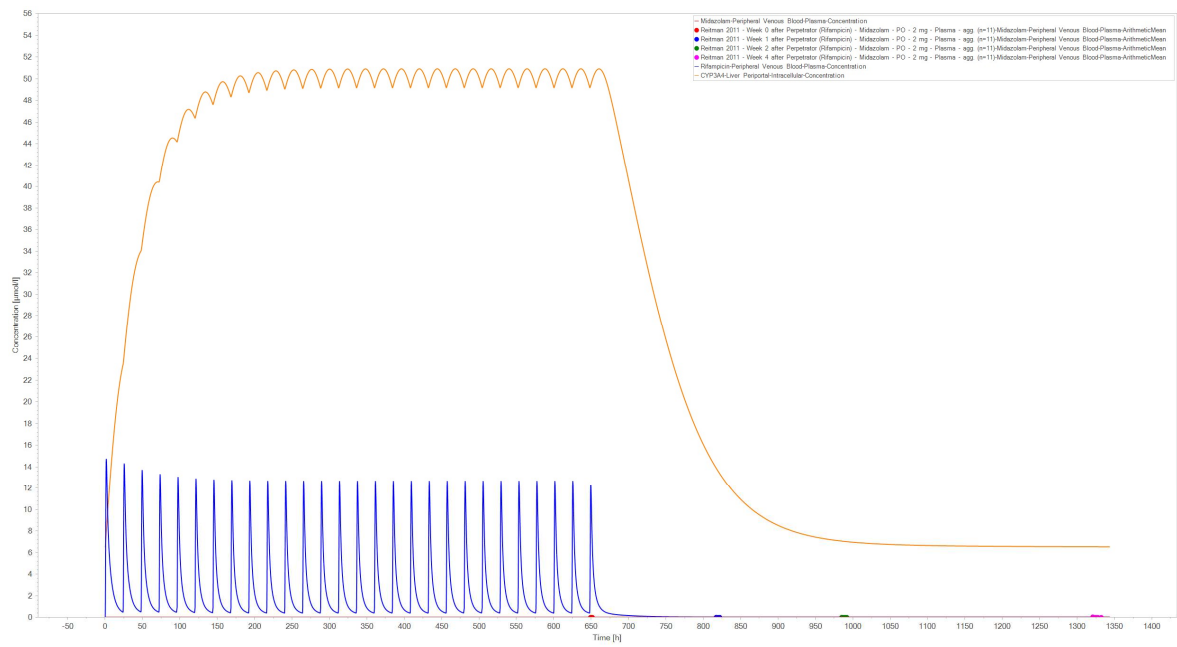
Objective 3:

Experience the effects of rifampicin treatment on the time-course of CYP3A4 abundance in the liver (if you start from here, open the file “Rifampicin-Midazolam-DDI_2.pksim5”:

Assess time-course of CYP3A4 abundance in hepatocytes to visualize the effect of induction: Create new “Time Profile Analyses” tab. Click “Define Settings and run simulation” and include “Liver periportal|intracellular|CYP3A4”. Check “Liver periportal|intracellular|CYP3A4” concentrations in the “Chart Editor” to be displayed.

If desired, open the chart editor and improve chart layout e.g., by selecting only rifampicin and CYP3A4 concentrations in the repository of available outputs, setting the scale of the Y-axis to linear etc.





*In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Rifampicin-Midazolam-DDI End.pksim5**.*