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.

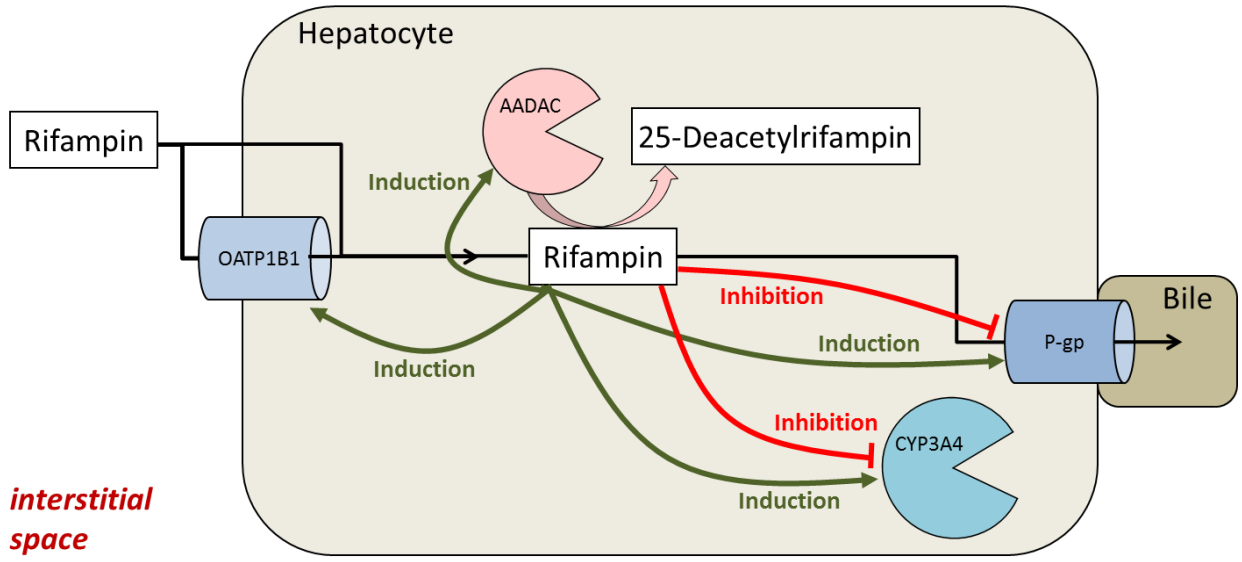
Objectives

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:

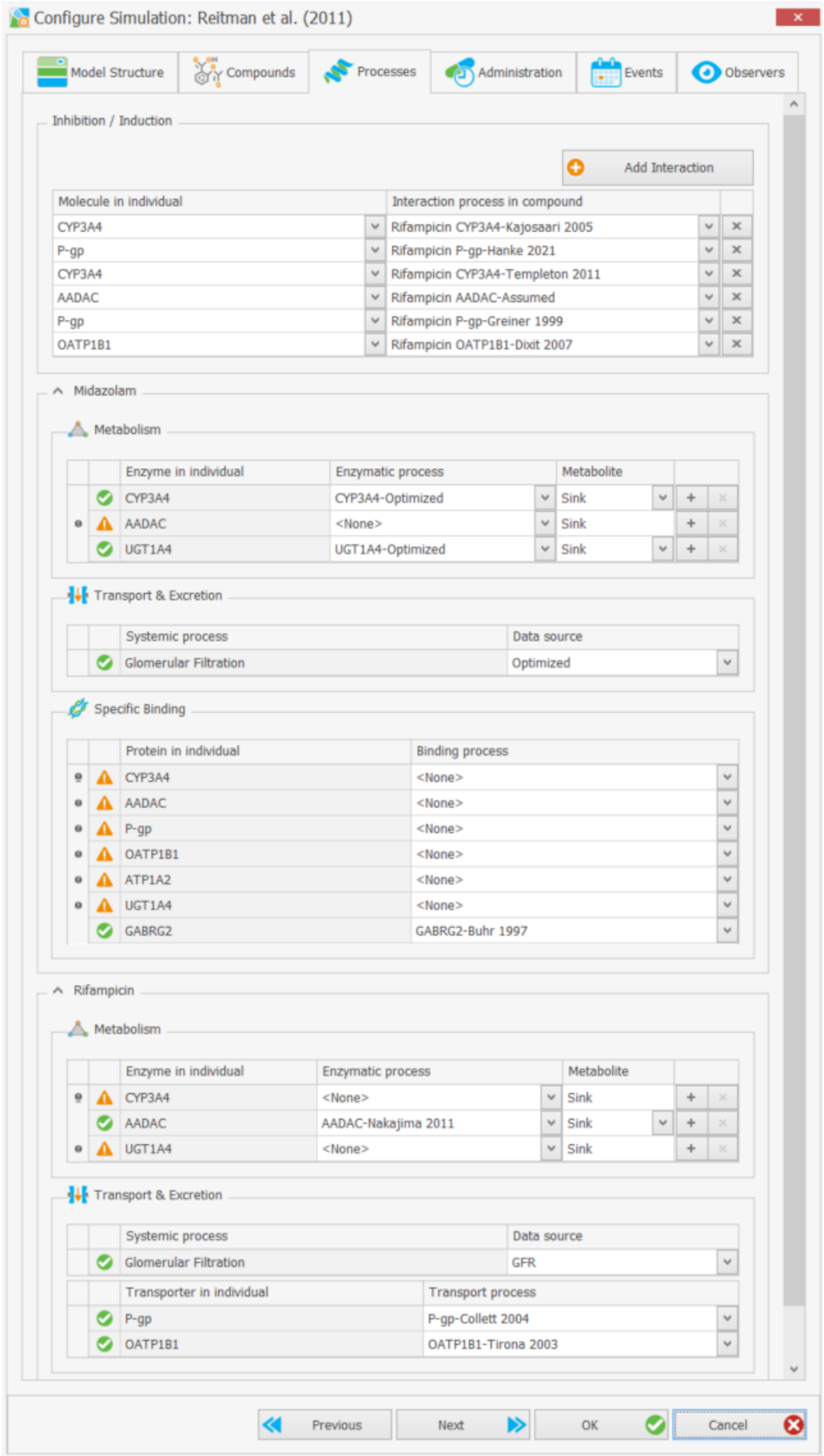
Evaluate the performance of the midazolam model (open Rifampicin-Midazolam-DDI_1.pksim5).

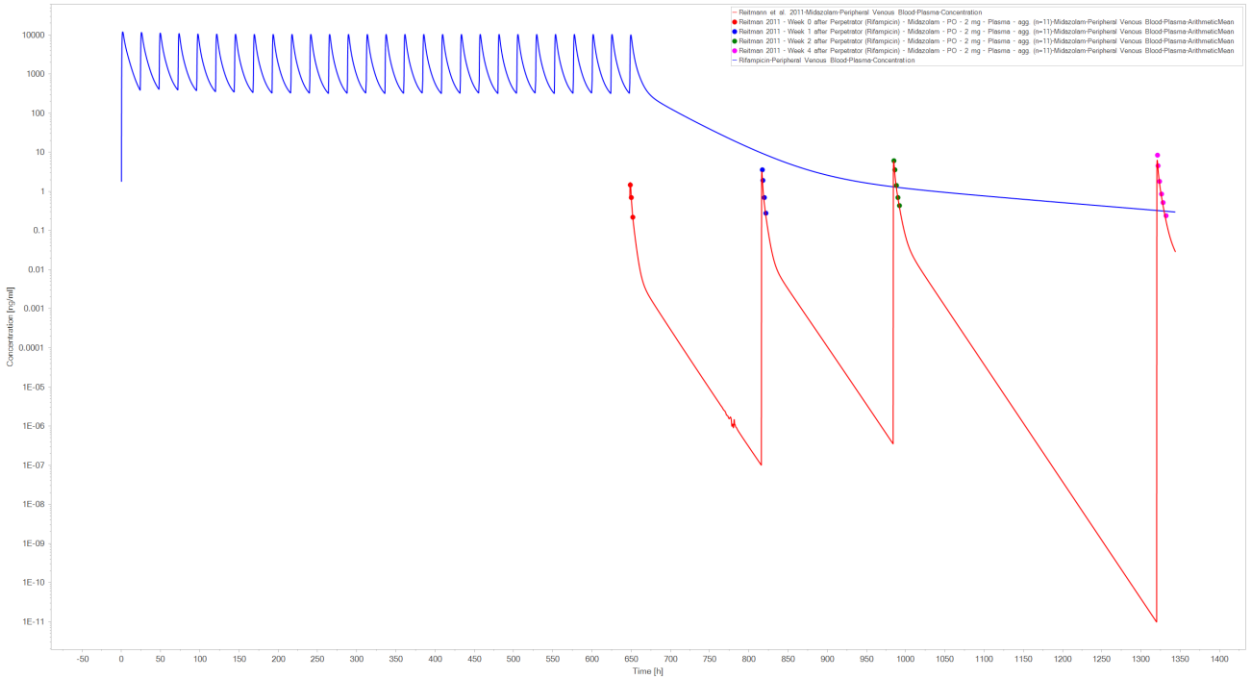
Make yourself familiar with the compound midazolam. In particular, use the configure simulation function to go through the different features and settings of the simulation.

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! You can add interaction processes by clicking on “Add Interaction”, select the “Molecules in the individual” and “Interaction process in compound” for matching. There should be CYP3A4-Templeton 2011, AADAC-assumed, OATP1B1-Dixit 2007 and P-gp-Greiner 1999 induction processes as well as CYP3A4 Kajosaari 2005 and P-gp-Hanke-2021 inhibition 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, …)


Configure Simulation: Reitman et al. (2011)
Model Structure
Compounds
Processes
Administration
Events
Observers
Inhibition / Induction
Add Interaction
Molecule in individual
Interaction process in compound
CYP3A4
Rifampicin CYP3A4-Kajosaari 2005
P-gp
Rifampicin P-gp-Hanke 2021
CYP3A4
Rifampicin CYP3A4-Templeton 2011
AADAC
Rifampicin AADAC-Assumed
P-gp
Rifampicin P-gp-Greiner 1999
OATP1B1
Rifampicin OATP1B1-Dixit 2007
Midazolam
Metabolism
Enzyme in individual
Enzymatic process
Metabolite
CYP3A4
CYP3A4-Optimized
Sink
AADAC
<None>
Sink
UGT1A4
UGT1A4-Optimized
Sink
Transport & Excretion
Systemic process
Data source
Glomerular Filtration
Optimized
Specific Binding
Protein in individual
Binding process
CYP3A4
<None>
AADAC
<None>
P-gp
<None>
OATP1B1
<None>
ATP1A2
<None>
UGT1A4
<None>
GABRG2
GABRG2-Buhr 1997
Rifampicin
Metabolism
Enzyme in individual
Enzymatic process
Metabolite
CYP3A4
<None>
Sink
AADAC
AADAC-Nakajima 2011
Sink
UGT1A4
<None>
Sink
Transport & Excretion
Systemic process
Data source
Glomerular Filtration
GFR
Transporter in individual
Transport process
P-gp
P-gp-Collett 2004
OATP1B1
OATP1B1-Tirona 2003
Previous
Next
OK
Cancel

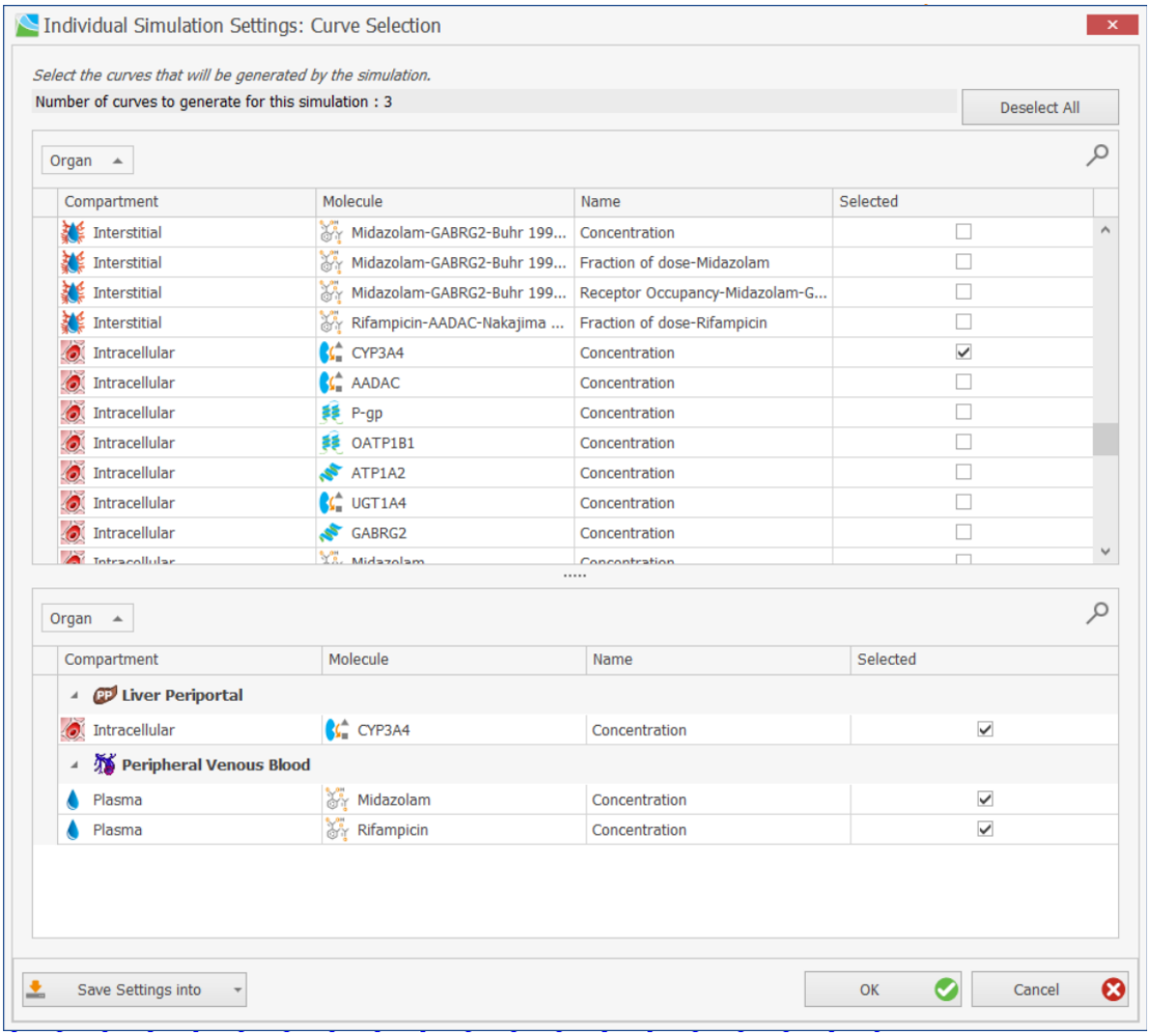

Reitmann et al. 2011-Midazolam-Peripheral Venous Blood Plasma-Concentration
Reitman 2011 - Week 0 after Perpetrator (Rifampicin) - Midazolam - PO - 2 mg - Plasma - agg. (n=11)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
Reitman 2011 - Week 1 after Perpetrator (Rifampicin) - Midazolam - PO - 2 mg - Plasma - agg. (n=11)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
Reitman 2011 - Week 2 after Perpetrator (Rifampicin) - Midazolam - PO - 2 mg - Plasma - agg. (n=11)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
Reitman 2011 - Week 4 after Perpetrator (Rifampicin) - Midazolam - PO - 2 mg - Plasma - agg. (n=11)-Midazolam-Peripheral Venous Blood-Plasma-ArithmeticMean
Rifampicin-Peripheral Venous Blood-Plasma-Concentration
Concentration [ng/ml]
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
1E-05
1E-06
1E-07
1E-08
1E-09
1E-10
1E-11
-50
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
1050
1100
1150
1200
1250
1300
1350
1400
Time [h]

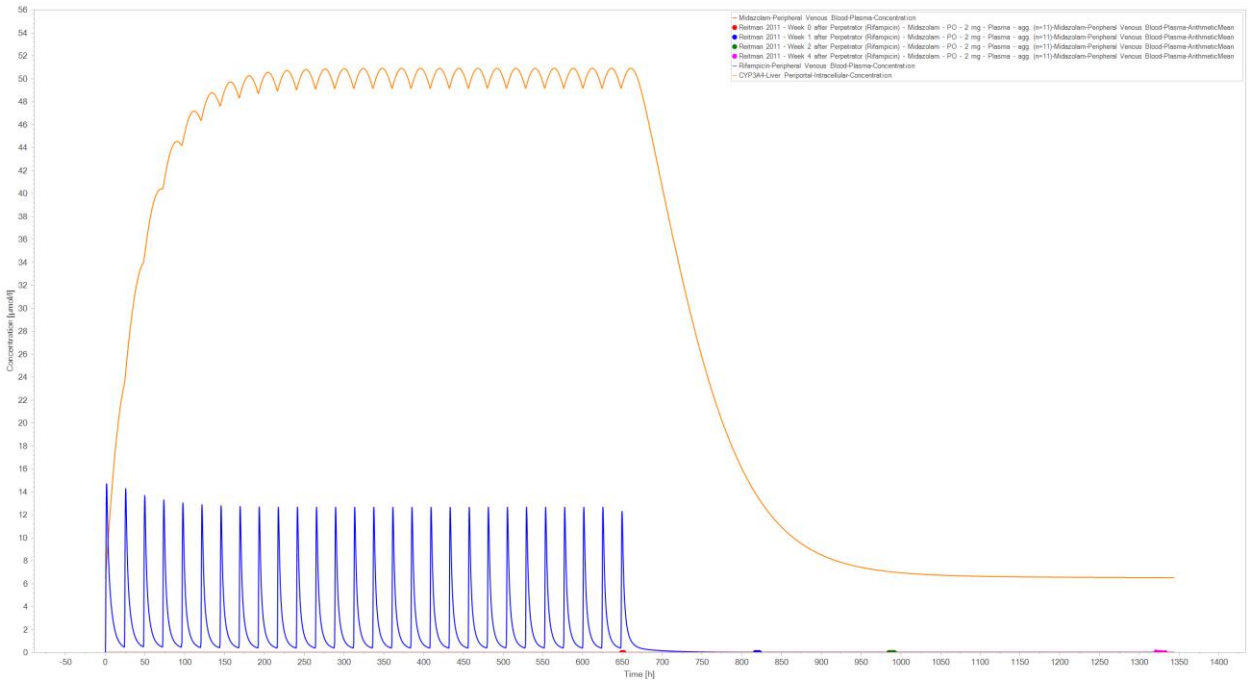
Objective 3:

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**.