Open

Systems Pharmacology

Hands-On Drug-Drug Interaction

- Stepwise Solution -

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.

Drug-Drug Interaction Rifampicin/Midazolam

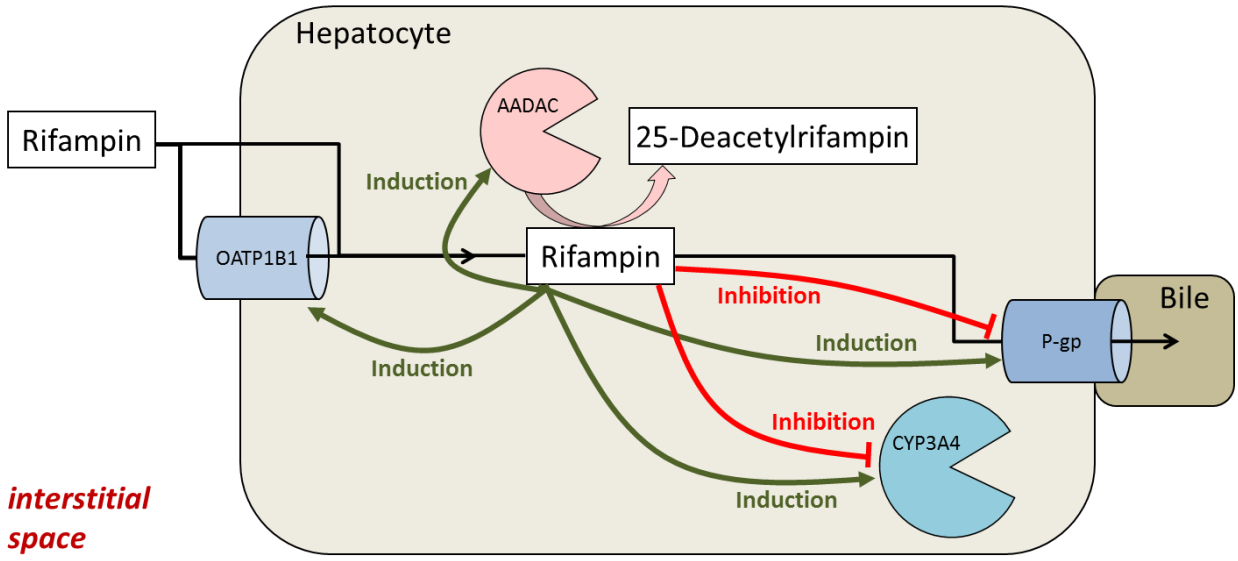
Objectives

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:

Hands-on Exercise
DDI with Rifampicin

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Objective 1:

Evaluate the performance of the rifampicin model (open Ex_DDI_Rif_1.pksim5).

1. Load the compound "Rifampicin" from the compound template database. Make yourself familiar with the compound rifampicin.
2. Load the individual "Standard European Male for DDI" from the individual template database. Make yourself familiar with the individual.
3. Create a simulation according to the study of Baneyx et al. (2013), i.e. use the "Standard European Male for DDI" individual and the compound "Rifampicin". Please check in the "Processes" tab if all processes are mapped appropriately. Furthermore, use the "Baneyx 2013, Rifampin 7 days 600 mg" administration protocol and the "oral solution" formulation.
4. Compare the simulated results to observed data from Baneyx et al. (2013).
   If desired, improve chart layout (e.g. set corresponding simulated and observed data to convenient colors, set min/max for axes, …)

Hands-on Exercise
DDI with Rifampicin

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Objective 2:

Experience the effects of rifampicin pretreatment on midazolam PK using study data from Reitman et al. (2011) If you start new from here use the file EX_DDI_RIF_2.pksim5:

1. Load the compound "Midazolam" from the compound template database. Make yourself familiar with the compound properties of midazolam.
2. Create a simulation according to the study of Reitman et al. (2011). Use the "Standard European Male for DDI" and both compounds "midazolam" and "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. Compare the simulated Midazolam PK to observed data from Reitman et al. (2011). (You can still compare the Rifampicin PK to Baneyx et al. (2013) data.)
   If desired, improve chart layout (e.g. set corresponding simulated and observed data to convenient colors, set min/max for axes, …)
4. 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.

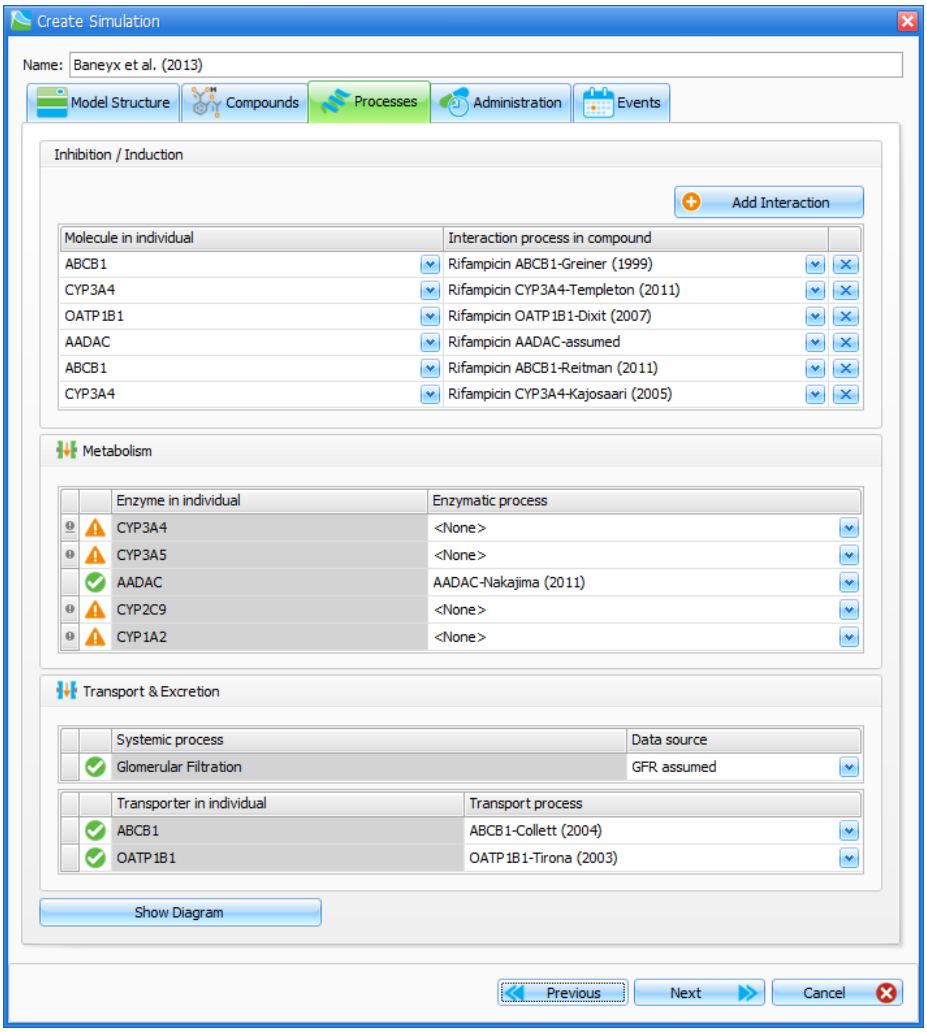
Solution:

Open **Ex_DDI_RIF_1.pksim5**.

Objective 1: Evaluate the performance of the rifampicin model

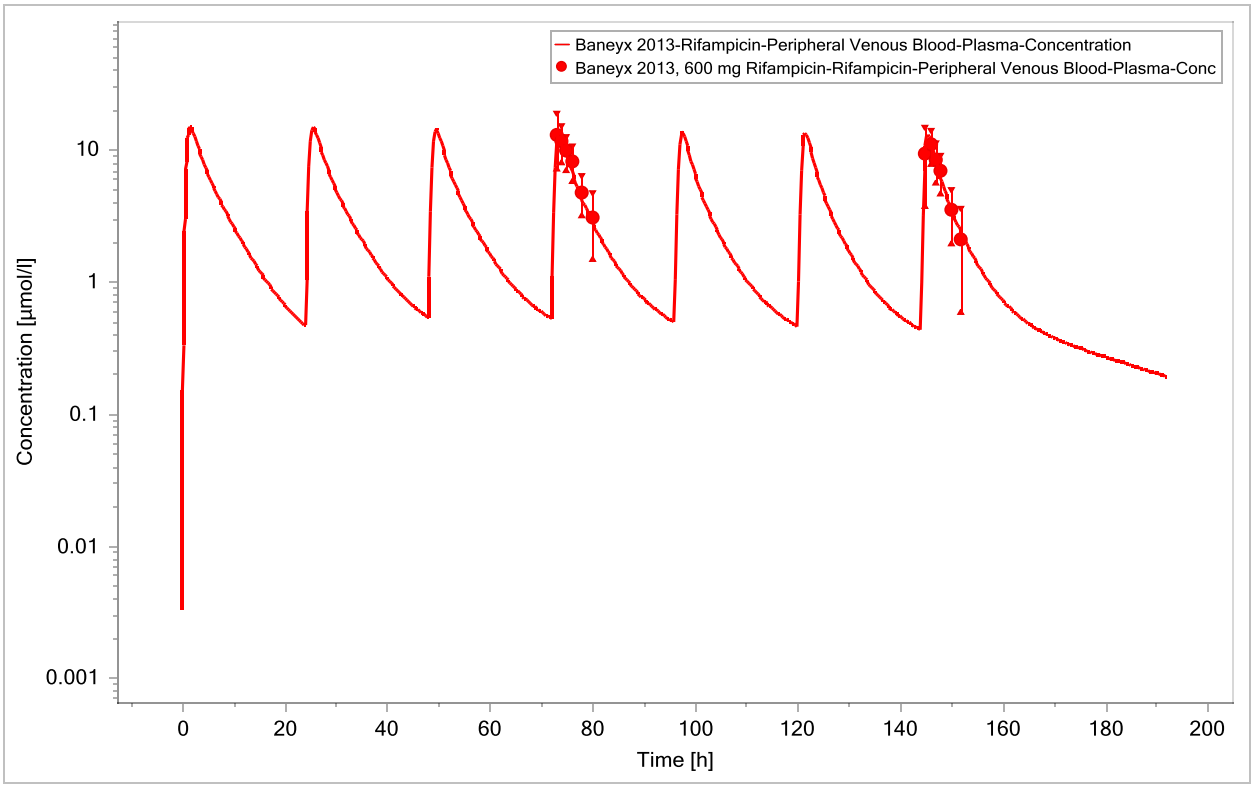
Set up a Simulation

- Load the compound "Rifampicin" from the compound template database.
  Make yourself familiar with the compounds rifampicin. In particular, go to the "ADME" properties tab in the compound "Rifampicin", select Inhibition and Induction. Please note that the rifampicin is an inducer of CYP3A4 and ABCB1 (gene name of the P-gp transporter) but also a competitive inhibitor of CYP3A4.
  If you explore "Metabolism" and "Transport & Excretion", you can see that rifampicin is transported by OATP1B1 (active uptake) and P-gp (active efflux), that it is metabolized via AADAC (a liver esterase) and that there is glomerular filtration in the kidney. Hence, rifampicin induces its own transport via P-gp.
- Load the individual "Standard European Male for DDI" from the individual template database.
  Make yourself familiar with the indvidual, in particular check that CYP3A4, OATP1B1, P-gp (ABCB1) and AADAC are expressed. Here, you also have access to the enzyme/transporter turnover (half-lifes).
- Make yourself familiar with the Administration Protocol "Baneyx 2013, Rifampin 7 days 600 mg".
- Click in the "**Create**" group of the "**Modeling**" tab on "**Simulation**". Create a simulation according to the study of "Baneyx 2013" (use this as name), i.e. use the provided "Standard European Male for DDI" individual and the compound rifampicin. Please check in the "Processes" tab if all processes are mapped appropriately (in this study, we include the CYP3A4 and P-gp induction and inhibition by rifampicin as well as AADAC and OATP1B1 induction. Furthermore, use the "Baneyx 2013, Rifampin 7 days 600 mg" administration protocol, "oral solution" formulation.



Run Simulation and Compare to Observed Data

- Run the simulation
- Compare the simulated results to observed data from Baneyx et al. (2013). To do so, drag and drop the observed data “Baneyx 2013, 600 mg Rifampicin” from the observed data building block onto the chart.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to convenient colors, set min/max for Y-axis, try different legend positions
- Note the effect of the P-gp auto-induction on rifampicin plasma concentrations (look at the trough levels!)



In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_DDI_RIF_2.pksim5**.

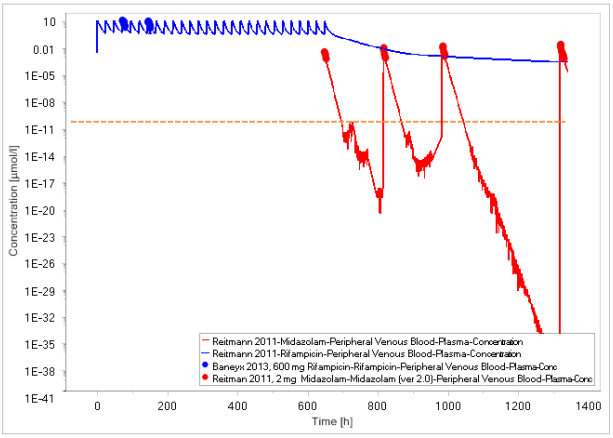
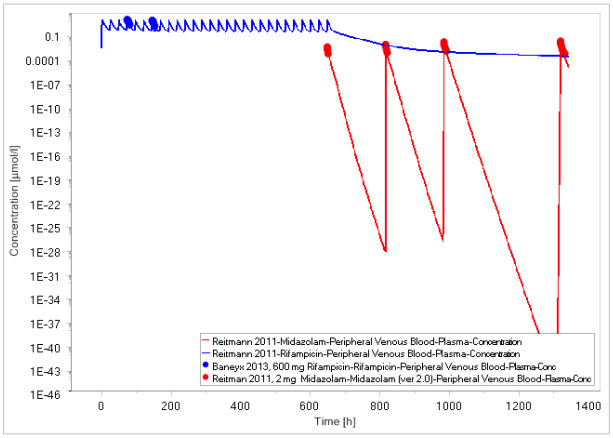
Objective 2: Experience the effects of rifampicin pretreatment on midazolam PK using study data from Reitman et al. (2011):

Set up a Simulation

- Load the compound "Midazolam" from the compound template database.
  Make yourself familiar with the compound properties of midazolam
- Make yourself familiar with the Administration Protocols "Reitman 2011, **Midazolam** 2 mg po" and "Reitman 2011, **Rifampin** 600 mg po".
- Click in the "**Create**" group of the "**Modeling**" tab on "**Simulation**". Name the new simulation "Reitman et al. (2011)". Use the provided "Healthy human" and both compounds "midazolam" and "rifampicin". Make sure that all processes are incorporated into the simulation appropriately; in particular there should be CYP3A4 and P-gp induction and inhibition by rifampicin as well as AADAC and OATP1B1 induction. Please use the respective administration protocols for both compounds and the "oral solution" as formulation in both cases.

Run Simulation and Compare to Observed Data

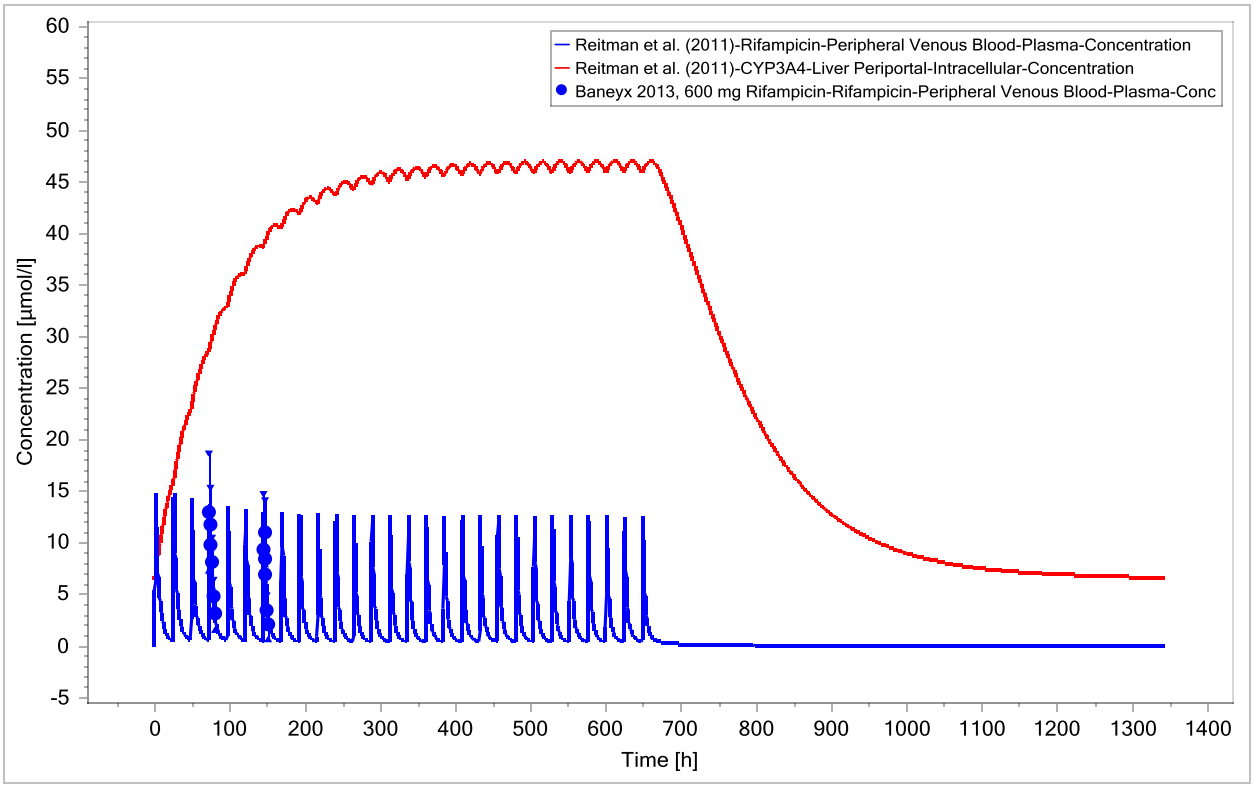
- Run the simulation
- Compare the simulated results to observed data from Reitman et al. (2011). To do so, drag and drop the observed data "Reitman 2011, 2 mg Midazolam" from the observed data building block onto the chart.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to convenient colors, set min/max for Y-axis, change unit of X-axis to "day(s)", try different legend positions and zooms.

absTol = 1E-10, relTol = 1E-5 Computing time: 1 min 28 sec	absTol = 1E-20, relTol = 1E-15 Computing time: 38 min 51 sec
	

- **PK-Sim default absolute and relative tolerance represent a useful trade-off between speed and noise**
- **If desired, tolerances can be adjusted**

Experience the effect of rifampicin treatment on the time-course of CYP3A4 abundance in the liver

- Open a second analysis window by clicking on "**Time Profile**" in the "**Analyses**" group in the "**Run & Analyze**" tab.
- Click on "**Define Settings and Run**" in the "**Simulation**" group of the "**Run & Analyze**" tab. Select as additional output "Liver Periportal" – "Intracellular" – "CYP3A4" – "Concentration" and click on "OK".
- Open the chart editor and improve chart layout, e.g. 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 **Ex_DDI_RIF_3.pksim5**.