Open

Systems Pharmacology

Hands-On Model building exercise

- Stepwise Solution -

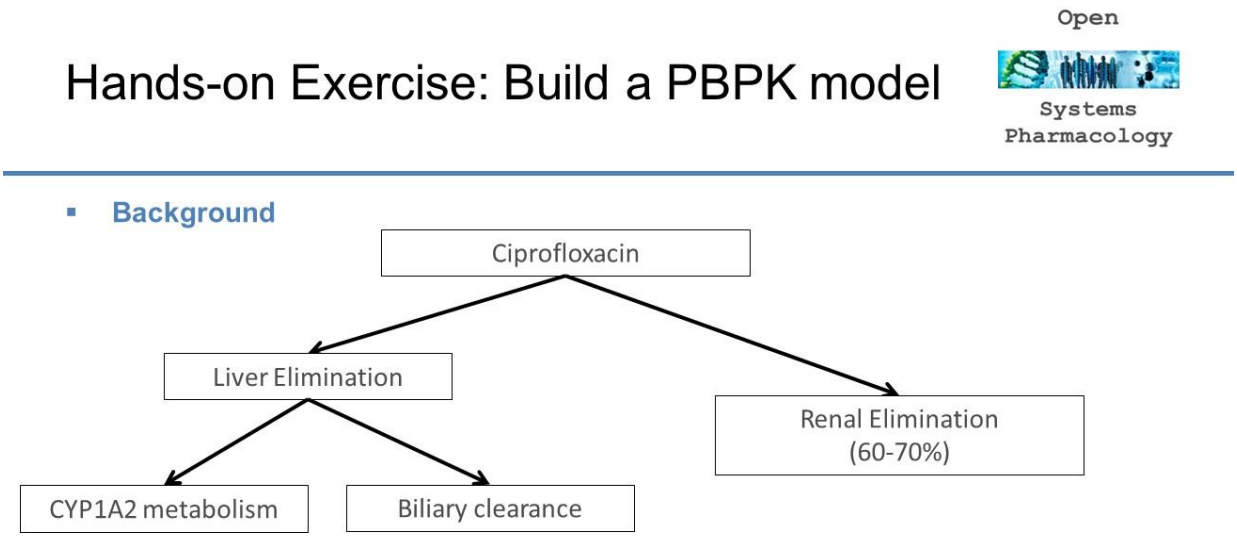
Disclaimer:

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.

Exercise – Setting up a simple PBPK Model

Background

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra-abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others. For some infections it is used in addition to other antibiotics. It can be taken orally or used intravenously.



Objectives

- Learn to set up an (adult model) simulation for Ciprofloxacin and compare simulation to observed data.
- Create building blocks relevant to set up a per os (PO) simulation: administration protocol and formulation
- Parameters predictive for intestinal absorption.
- Learn to compare simulations.

Open **Ex_PBPK_1.pksim5**.

Set up a Simulation

Hands-on Exercise: Build a PBPK model

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Objectives

Use literature values in the model and compare predictions to data.
Start with the file "**PBPK_1.pksim5**"

1. All needed building blocks are already available in the PK-Sim file

2. Create a simulation called "**IV_1**" and select the following options:
    1. Partition coefficient → **PK-Sim standard**
    2. Cellular Permeabilities → **PK-Sim standard**
    3. Lipophilicity → "**Measurement from Drug Bank**"
    4. Specific Intestinal Permeability → **Calculated**
    5. Check that **CYP1A2**, **GFR** and **Biliary secretion** processes are selected
    6. Unselect the renal clearance **TBS** process
    7. Choose the administration **Davis 200 iv**
    8. Run the simulation and drag-and-drop the data on the plot

Compare the **Observed Data** with your **Simulation Results!**

- Make yourself familiar with the given **Expression profiles, Individual**, **Compound** and **Administration Protocol**.
- Click "**Simulation**" in the "**Create**" **Group** of the "**Modeling**" ribbon tab.
- Create the **Simulation** "**IV_1**" using the predefined building blocks
    - **Individual**: "Healthy Individual Cipro" → next
    - **Compound**: "Ciprofloxacin", leave **Partition coefficients** and **Cellular permeabilities** on "**PKSim Standard**", Choose "**Measurement from Drug Bank**" for **Lipophilicity** and select "**Calculated**" for **Specific intestinal permeability**. → next
    - Select **processes**: **CYP1A2** → "**CYP1A2-DB**", **Renal Clearances** → "**NONE**", **Glomerular Filtration** → **"GFR"**, **Biliary Clearance** → **"BC"**
    - **Administration Protocol**: "Davis 200iv"
    - **Events** → nothing to do → click **OK**
- Have a look at the "**Settings"** in the appearing simulation (output intervals and time-point resolution).
- Click "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" ribbon tab.
- Select the predefined "**Peripheral Venous Blood Plasma Ciprofloxacin Concentration**" and click "**OK**".
- The simulation is processed.
- Drag & Drop the Data "**Davis et al 200mg iv**" into the **Results Window**.

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_2.pksim5**")*

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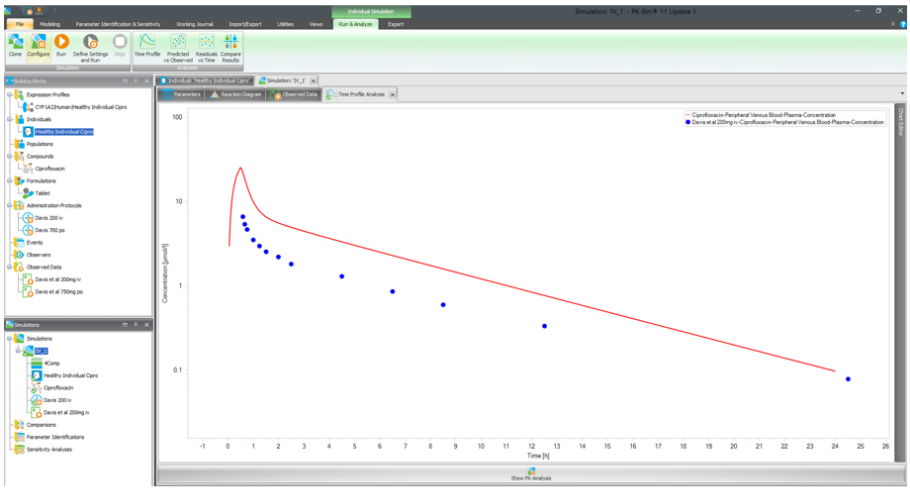

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **PBPK_2.pksim5**.

Hands-on Exercise: Build a PBPK model

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Objectives

Optimize the Lipophilicity value. Start with the file "**PBPK_2.pksim5**"

1. Optional: Add lipophilicity to your **Favorites** parameters
2. Clone the simulation IV_1 and rename it **IV_2.** Select lipophilicity parameter named **"Optimized lipo"**
3. Right click on the simulation IV_2 and select "**Start parameter identification**"
4. Verify that the data and the parameter section are correctly configured.
5. Run the parameter identification
6. Select the tab "Results" and import the new parameter in the simulation and run it again.

Compare the **Observed Data** with your **Simulation Results!**

Parameter Identification

- (You can find "**Lipophilicity**" in the "**Parameters**" Tab of the simulation. Go to **Compounds → Ciprofloxacin** and select the check-box in the **Favorites** column)
- **Clone Simulation** "**IV_1**" for the pharmacokinetics of Ciprofloxacin and re-name the simulation from "**IV_1**" to "**IV_2**". Click "**next**" or directly select the **Compound** tab within the "**Cloning Simulation**" window and change the **Lipophilicity** to **"Optimized lipo".** Click **"OK".**
- Right-click the simulation "**IV_2**" in the simulation window and select "**Start parameter identification**"
- Check outputs and the selected data in the "**Data**" tab.
- In the "**Parameters**" tab check, that the right parameter is already selected (has been automatically taken from the selected list of **favorites**). Alternatively, the parameter can be found in the parameter list to the left under "**Molecule**" → "**Lipophilicity**" (and can be added to the "**Identification Parameters**" Box/List via the "**Add**" button.
- Check the **Configuration** tab and then click "**Run**" (top left of screen). Be sure to quickly also click on "**Show Visual Feedback**" to see the progress of the optimization.
- (Close Progress Window) Go to the tab "**Results**" and click "**Transfer to Simulation**" to import the identified value for "**Lipophilicity**" into the simulation "**IV_2**".

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_3.pksim5**")*

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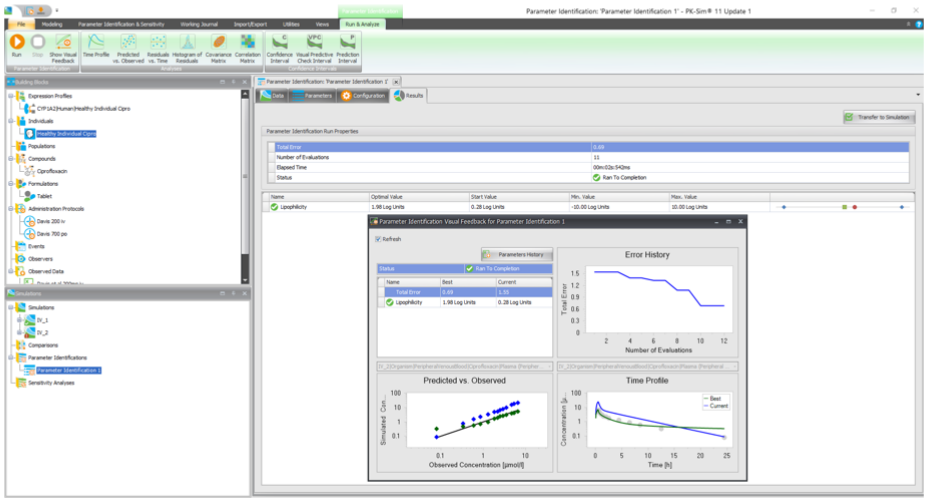

- Select simulation "**IV_2**" and click "**Run**"
- Select the **Results** tab and again compare **Observed Data** and **Simulation**!

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_3.pksim5**")*

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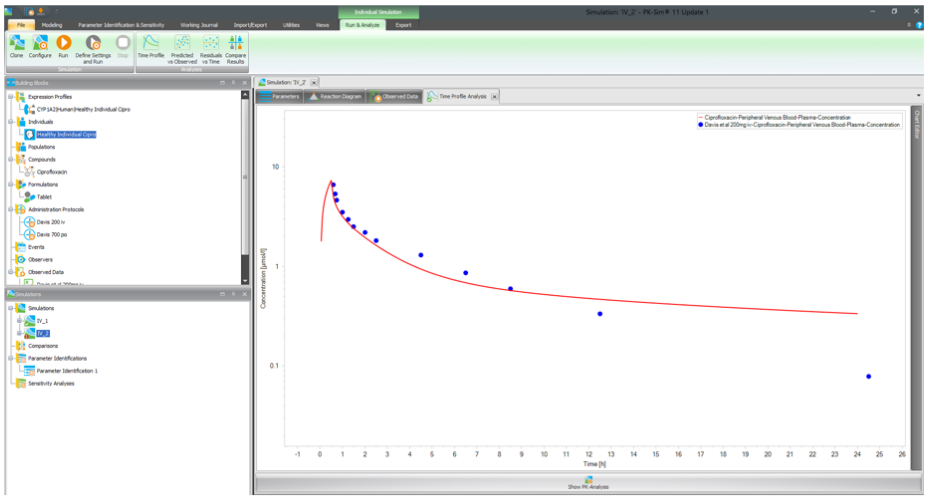

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **PBPK_3.pksim5**.

Hands-on Exercise: Build a PBPK model

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Objectives

Compare renal excretion to data and estimate tubular secretion and lipophilicity.
Start with the file "**PBPK_3.pksim5**"

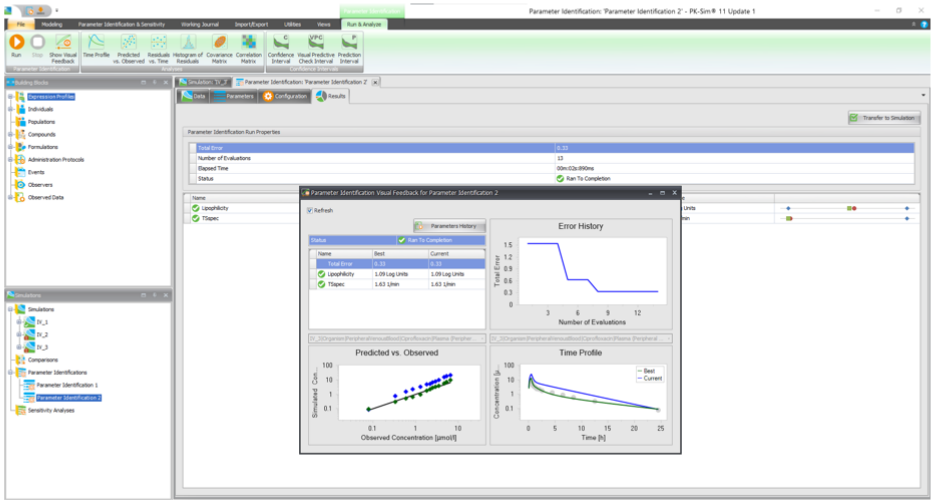
1. Select "**Define settings and run**" and add the output "**Kidney | Urine | Fraction excreted**" and run the simulation. **Select the output from the chart editor**.
2. Renal excretion is **approx. 15%,** while we know from literature it should be **60-70%** for IV administration.
3. Clone the simulation "IV_1" and name the clones simulation "**IV_3**", select lipophilicity parameter named **"Optimized lipo"** and select the **renal clearance** in the **Processes** tab. Then click **OK**.
4. Select the new added parameter as **Favorites**
5. Start a **new parameter identification** by right-click on the simulation
6. Set the **boundaries of the renal clearance** parameter between 0 and 100 and run the optimization.
7. **Import the parameters** in the simulation and **compare the simulation with the data**, including fraction excreted in the urine.

Clone and configure a second Simulation and redo Parameter Identification

- Select simulation "**IV_2**" and click "**Define Settings and Run**" in the "**Simulation**" group of the "**Run & Analyze**" tab.
- Additional to the predefined "**Peripheral Venous Blood Plasma Ciprofloxacin Concentration**" select "**Kidney → Urine → Fraction Excreted**" and click "**OK**".
- Check the simulation results ("**Time Profile Analysis**" tab) and select the "**Fraction excreted**" for display in the chart editor. The fraction is only approx. **15 %** but we know it should be around **60-70%** after IV administration.
- **Clone** Simulation "**IV_1**" (right-click on simulation → clone) for the pharmacokinetics of Cipro and re-name the simulation from "**IV_1**" to "**IV_3**". Again click "**next**" (or directly select the **Compound** tab within the current "**Cloning Simulation**" window) and change the **Lipophilicity** to **"Optimized lipo".** In the **Process** tab activate additional renal clearance by selecting **Renal Clearances → "TBS".** Click **"OK".**
- (Add the (specific) rate parameter for "**Tubular Secretion**" as favorite. Try to find it yourself in the "**Parameters**" tab of the Simulation "**IV_3**")
- Right-click the simulation "**IV_3**" in the simulation window and select "**Start parameter identification**"
- Again check outputs and the selected data in the "**Data**" tab.
- In the "**Parameters**" tab check, that the right parameters are already selected (have again been automatically taken from the list of **favorites**). Alternatively, the parameter can be found in the parameter list to the left under "**Kidney**" → "**Tubular Secretion**" (and can be added to the "**Identification Parameters**" Box/List via the "**Add**" button). Set the boundaries of the renal clearance parameter between 0 and 100.
- Check the **Configuration** tab and then click "**Run**" (top left of screen). Be sure to quickly also click on "**Show Visual Feedback**" to see the progress of the optimization.

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_4.pksim5**")*

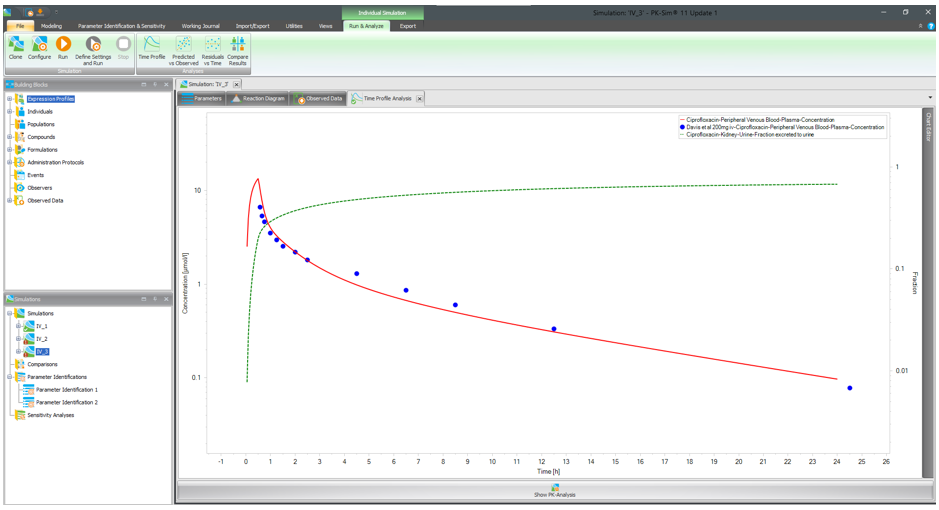


- (Close Progress Window) Go to the tab "**Results**" and click "**Transfer to Simulation**" to import the identified value for the 2 parameters into the simulation "**IV_3**".
- Select simulation "**IV_3**" and click "**Run**"
- Select the **Results** tab and again compare **Observed Data** and **Simulation**!

Select the "**Fraction excreted**" again for IV_3 and compare with IV_2 values

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_4.pksim5**")*



In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **PBPK_4.pksim5**.

Hands-on Exercise: Build a PBPK model

Objectives

Build an oral model from the IV model just built.
Start with the file "**PBPK_4.pksim5**"

1. **Commit** the new estimated parameter in the **Compound building block** by right click on the compound in the simulation IV_3
2. **Create** an oral **administration protocol** named "Davis 700 po" of **700 mg** and a **formulation** using a **Weibull** function with a **Dissolution Time (50%)** of **4 min** and a **Dissolution Shape** of **"0.8".**
3. Clone simulation IV_3, rename it **Oral_1** and select the newly created administration protocol as well as the formulation.
4. **Delete the IV data in the cloned simulation** by right click on the data in the simulation and run the simulation
5. Drug and drop the oral data and compare the predictions to the data

Oral Absorption - Create A Formulation

- First we transfer the identified parameters in simulation "IV_3" to our base building blocks by right-click in on the "Ciprofloxacin" building block in the simulation and selecting "Commit to Building Block…".
- Click "**Formulation**" in the "**Create**" group of the "**Modeling**" ribbon tab or right click on "**Formulations**" in the "**Building Blocks**" **Explorer** and select "**Add Formulation**".
- Oral administration of a Ciprofloxacin tablet will be simulated. The tablet will start to disintegrate already during the residence time in the stomach. Initialize the **Formulation** by defining a name ("**Tablet**"). To reflect the dissolution properties of the tablet choose e.g. "**Weibull**" **with a** "**Dissolution Time (50%)**" of "**4 min**" and a "**Dissolution Shape**" of "**0.8**". Click "**OK**".
- Create a corresponding oral administration protocol by clicking "**Modeling**" → "**Administration Protocol**" (or via context menu of the "**Administration Protocols**" Building Block). Name it "**Davis 700 po**", select "**Administration Type**" → **Oral**, set **Dose** to **700 mg** (NOT mg/kg) and click "**OK**".

Oral Absorption - Create A Simulation

- **Clone** Simulation "**IV_3**" (right-click on simulation → **clone**) and re-name the simulation from "**IV_3**" to "**Oral_1**". Go to the "**Administration**" Tab and select "**Davis 700 po**". Select the corresponding **Formulation** "**Tablet**" and click **"OK".**

Load and Compare to Observed Data

- Right-click on the observed data "**Davis 200 iv**" of the new simulation "**Oral_1**" and select "**Remove…**".
- Run the simulation. Drag & Drop the "Davis et al. 700mg po" data into the **Results** (**Time Profile Analysis**) window.
- To further optimize the data fit, you may start parameter identification on oral absorption properties. These include parameters of the formulation ("**Tablet**" →

"**Dissolution Shape**" & "**Dissolution time (50% dissolved)**") or solubility ("**Molecule**" → "**Solubility at reference pH**") and intestinal permeability ("**Molecule**" → "**Specific intestinal permeability (transcellular)**"). Use **Monte Carlo** as algorithm in the **Configuration** tab and restrict **number of iterations** to 200 for a slow computer and 1000 for a multi core computer.

Hands-on Exercise: Build a PBPK model

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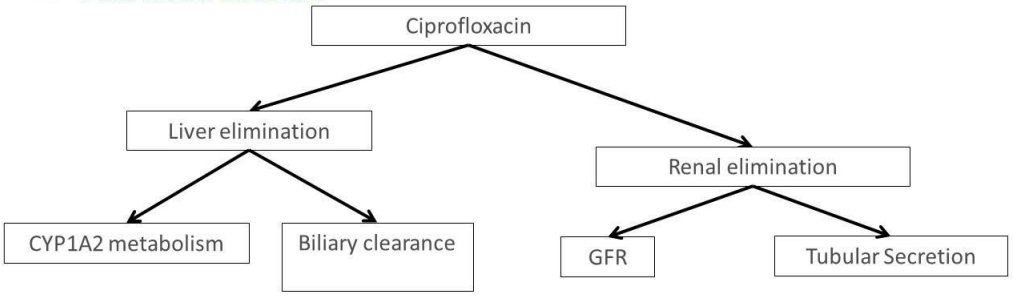
- **Final model structure**



Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_5.pksim5**")*

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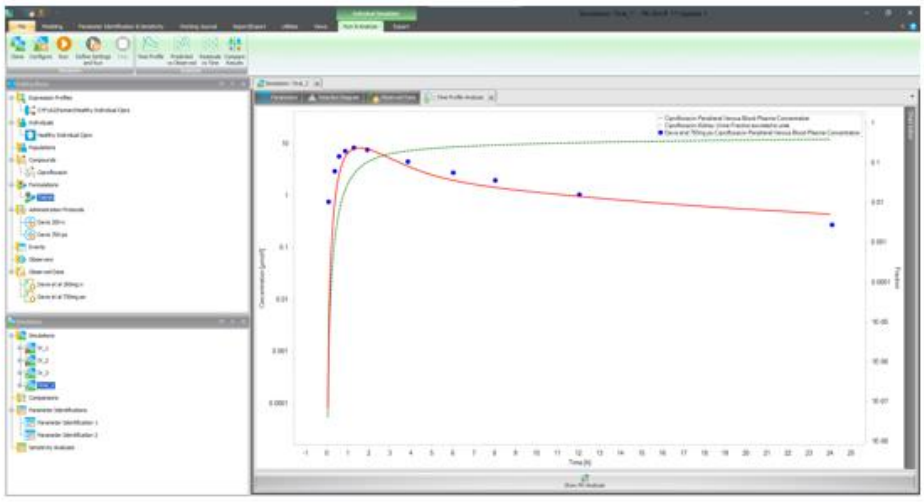

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **PBPK_5.pksim5**.

Hands-on Exercise: Build a PBPK model

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Objectives

Simulate the PK of a healthy population after oral administration of ciprofloxacin.
Start with the file "**PBPK_5.pksim5**"

1. **Create** a **European population ("Healthy European Pop 18-80 yrs")** based on the ciprofloxacin individual with the following demographics: Age: 18-80 years, 100 individuals with 50% females. Make yourself familiar with the population distribution, particularly, the distribution of enzymes (see Enzymes, Transporters and Binding partners → Ontogeny factor
2. **Clone** simulation Oral_1 , **exchange the individual** by the newly created population, and name it to **"Oral_pop".**
3. **Run** the population simulation
4. **Select Plasma** to be displayed, set scaling to Log and select Median and 5th to 95th percentiles to be displayed
5. **Add** a second time profile tab and **select Urine** to be displayed, set scaling to Linear, choose a different color and select Median as well as 5th to 95th percentiles to be displayed

Oral Absorption Pop - Create A Population

- Create a European population by clicking on "**Population**" in the "**Create**" group of the "**Modeling**" ribbon tab or right click on "**Populations**" in the "**Building Blocks**" **Explorer** and select "**Add Population**".
- Initialize the **Population** by defining a name ("**Healthy European Pop 18-80 yrs**") and properties **"Number of individuals"**: of **100**, **"Proportion of females %**" of **50**. Define your "**Population parameters Ranges**" by the "**Age**" of **18-80 years** and click "**Next**" till **"OK"**.
- Make yourself familiar with the distribution of parameters in the generated virtual population by having a look in the distribution tab of the population.

Oral Absorption Pop – Simulate A Population

- Clone the simulation **"Oral_1"** (right-click on simulation → **clone**) and re-name the simulation from "**Oral_1**" to "**Oral_pop**". Under the "**Model Structure**" Tab and select "**Healthy European Pop 18-80 yrs**" to make a simulation for the newly created population. Click "**Next**" and click **"OK".**
- Click "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" ribbon tab.
- Select Plasma concentration by selecting **"Plasma"** and click **"Add".**
- Select **"Log"** as the scaling output under **"Scaling".**
- Select the output the median and the 90% confidence interval by ticking the box of "**Median"** and **"Range 5% to 95%".**

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_6.pksim5**")*

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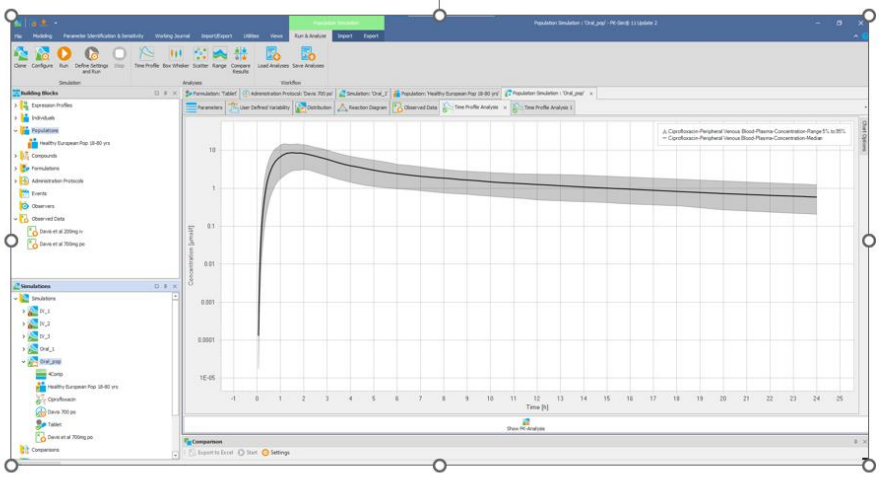

- Add another simulation to see the fraction excreted in urine by clicking on **"Time Profile"** in the "**Analyses**" group of the "**Run & Analyze**" ribbon tab. Select fraction urine by selecting **"Urine"** and click **"Add".**
- And select again the "**Median"** and **"Range 5% to 95%"** by ticking the boxes.

Hands-on Exercise: Build a PBPK model

*(you can start from this point with file "**PBPK_6.pksim5**")*

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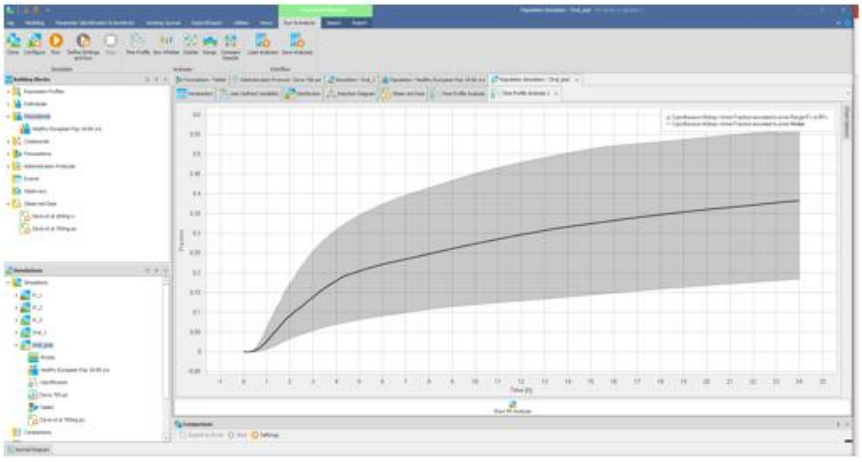

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Hands-on Exercise: Build a PBPK model

Open Systems Pharmacology

Objectives

Simulate the PK of a healthy population after oral administration of ciprofloxacin.
Start with the file "**PBPK_6.pksim5**"

1. **Edit** the **Plasma PK** plot to stratify the population by age: **select age** in the Population parameters and **create** an **age grouping:** young (18-40 years), middle-aged (40-65 years) and elderly (≥ 65 years).
2. **Save** Grouping
3. **Select** the age grouping by colors
4. **Edit** the **Urinary excretion** plot in the same way as the Plasma PK plot by **loading** the previously created age grouping

Oral Absorption Pop – Analyze the different age-bins

- **Edit** the **Plasma PK** plot to stratify the population by age. Right-click on the graph in the **"Time Profile Analysis"** plot of **Plasma** and click on **"Edit".**
- Select **"Age"** under the **"Characteristics of individual"** in the **"Population parameters**" and click on **"Add"**.
- **Create** an age grouping by clicking on **"Create Grouping"**. **Name** your grouping: **"Age Grouping"**. Double click on the + to add an entry. Fill in the minimums and maximums **18-40, 40-65** and **65-80** and label them **"Young"**, **"Middle-aged"** and **"Elderly"**, respectively.
- **Save** the created grouping
- Click twice on **"Next"**. Under the tab **"Time Profile Analysis"** drag the **"Age Grouping"** under the **"Available Parameters"** to **"Colors"** to simulate the different age-bins and analyze them by color. Click on **"OK"**.

Hands-on Exercise: Build a PBPK model

*(you can see the end of this exercise in file "**PBPK_7.pksim5**")*

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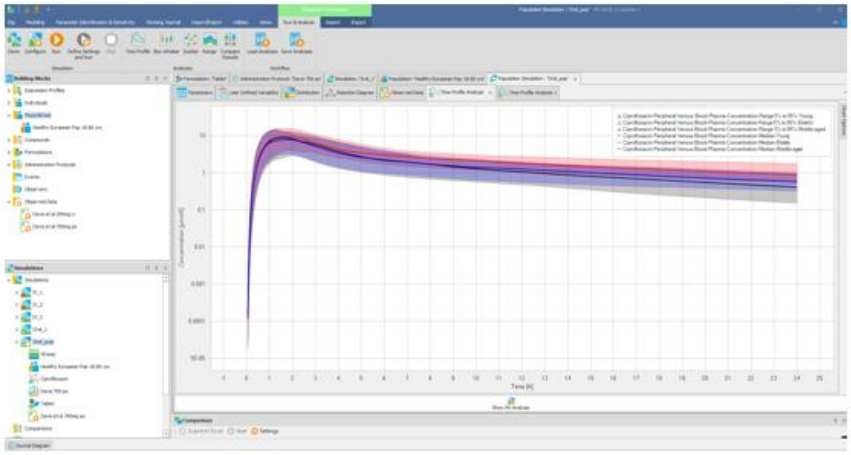

- Repeat the age grouping in the fraction excreted to urine plot by clicking on the **"Time Profile Analysis 1"** tab in your simulation.
- Repeat the previous steps when right-clicking on the graph and click on **"Edit"**. Load the previously saved grouping and apply it to the fraction excreted to urine plot in the same way.

Hands-on Exercise: Build a PBPK model

*(you can see the end of this exercise in file "**PBPK_7.pksim5**")*

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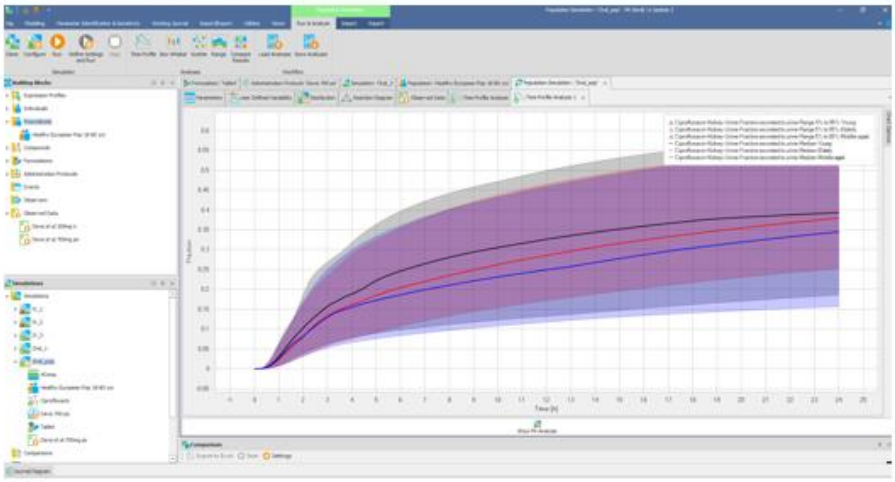

In case you wish see the end of this exercise and you did not perform the exercise described above, please open file **PBPK_7.pksim5**.