e-Campsis documentation

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Chapter 1

About

e-Campsis is a free web application developed by Calvagone that provides an intuitive and user-friendly interface for setting up population PK/PD simulations. The app is built on the R-package campsis, which serves as a powerful frontend for running model-based simulations using *mrgsolve* or *rxode2*.

1.1 e-Campsis versions

1.1.1 e-Campsis free

e-Campsis free is, as the name suggests, freely accessible to everyone without registration at https://ecampsis.shinyapps.io/free/.

It comes with certain limitations regarding the size of the simulation and misses some functionality of the pro-version.

1.1.2 e-Campsis free+

If you want to simulate up to 16 arms or scenarios, 100 subjects/arm and 250 observations/arm we invite you to become an authorized user of *e-Campsis free+*.

Please send us the pre-filled email below and you will get an invitation to register as soon as possible:

1.1.3 e-Campsis pro

The professional version of e-Campsis is available as a yearly subscription and includes the following additional functionality:

- Save/load e-campsis projects
- NONMEM code import
- Number of arms, scenarios, subjects, observations only limited by memory
- Advanced customization of plots
- NCA & summary statistics
- Sensitivity analysis*
- Forest plots
- Upload of external data for plotting*
- Bootstrap covariates from external file or NHANES*
- Replicate simulation with parameter uncertainty
- Import rxode2 and mrgsolve simulation code*
- Personalized support via email

* *Under development.*

For further information, contact us at the following e-mail address: campsis@calvagone.com

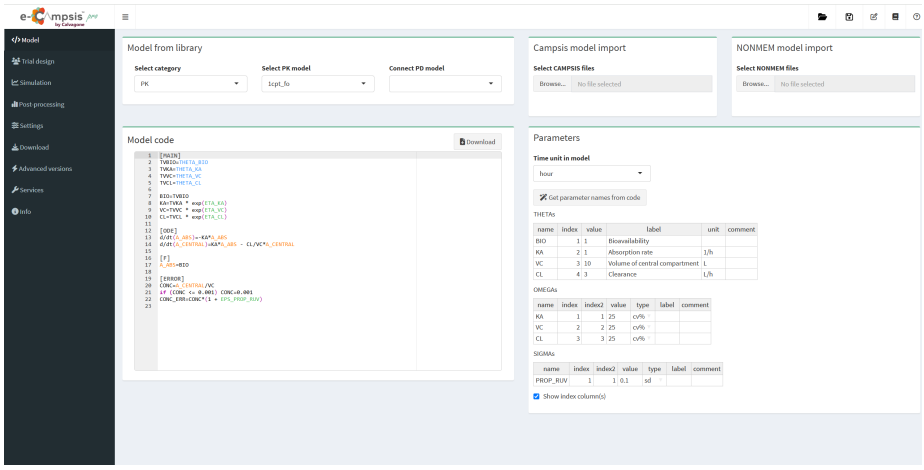
1.2 Application interface

The app consists of 5 main sections:

- **Model**: a powerful model editor to edit your Campsis model online. Try out one of the numerous models available from the library and adapt it to your needs.
- **Trial design**: an easy-to-use interface to quickly set-up the dosing regimen, observation times and covariates.
- **Simulation**: a single screen dedicated to the simulation configuration and visualization of the results. Explore different scenarios of parameter settings quickly and interactively.
- **Post-processing**: here you can define summary variables such as non-compartmental PK parameters that you want to derive from your simulation results and show them in a table.
- **Forest plots**: Easily define and generate nice-looking forest plots and explore the impact of covariates on any outcome parameter.
- **Download**: last but not least, download the model, parameters and the whole code of the simulation to reproduce what you see in the app on your computer using the open-source package campsis.

Chapter 2

Model tab



2.1 Model from library

When entering the app, a simple PK model is already loaded by default.

A different PK model can be selected from a large library (“Select PK model”).

In “Select category”, NONMEM models or models for target-mediated drug disposition (TMDD) can be also loaded.

A PD model can be connected (“Connect PD model”) to the PK model. This is done internally via campsismod (see here). If you do this you may have to check that the right PK output goes into the PD part of the model.

2.2 Campsis model import

An existing Campsis model can be uploaded from this box (including files *model.campsis*, *omega.csv*, *theta.csv* and *sigma.csv*).

2.3 NONMEM model import (pro-version)

In the pro version, an existing NONMEM control file (extension *.mod* and *.ctl*) can be uploaded from this box. The parameter estimates will be extracted from the NONMEM control file unless you also select the corresponding *.ext* file. In this case the final parameter estimates will be used.

When you start the import for the first time it may take a short while (2-3 minutes) for the functionality to be available. A notification will popup when done and you may need to select the NONMEM files you want to import again.

We have tested the translation of NONMEM models to Campsis for a number of models, but it is possible that some models are not correctly translated or fail. If you encounter such a model, please let us know and we will try to fix it.

In many cases you model will not run immediately after import. This is because you likely have variables (e.g. covariates or flagging variables) in your model that are not defined. You can either edit the model code directly in the editor window (e.g. TRT = 1) or you can define the variables in the "Trial design" as a covariate.

2.4 Model code

The model code is shown in the editor window where it can be easily modified. Please note that the code is case sensitive (e.g. *log*, *exp*, *sqrt* should be used). The power function is *pow(x,d)*, x to the power of d. You can add comments using the # symbol.

Clicking on the "Download" button, Campsis model code will be downloaded as a ZIP folder, including *model.campsis*, *omega.csv*, *theta.csv* and *sigma.csv*.

2.5 Parameters

The list of parameters for THETA, OMEGA and SIGMA is given in this box. Their values and labels can be changed. Comments can be added.

The type for OMEGA and SIGMA can be changed: sd, var, covar, cv, cv%, cor, for standard deviation, variance, covariance, coefficient of variation, coefficient of variation (as %) or correlation, respectively.

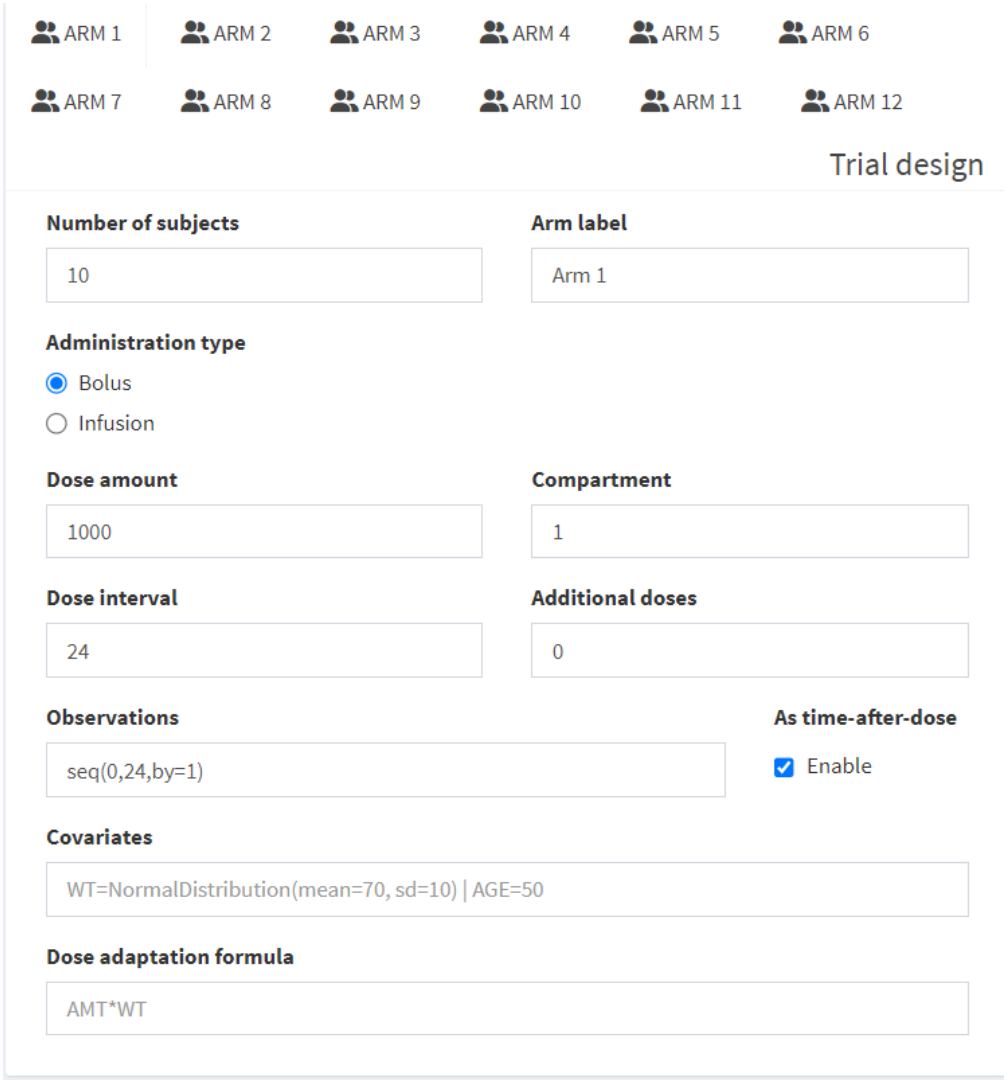
Correlations between omegas can be added by right-clicking on a cell in the OMEGA table. For example, enter “KA, VC” as name, 1 and 2 in index and index2, and add the correlation value.

Clicking on “Get parameter names from code”, the code will be scanned for the strings *THETA_name*, *ETA_name* and *EPS_name* and the names will be extracted and added to the table.

Chapter 3

Trial design

3.1 Trial design



The study arms can be configured here.

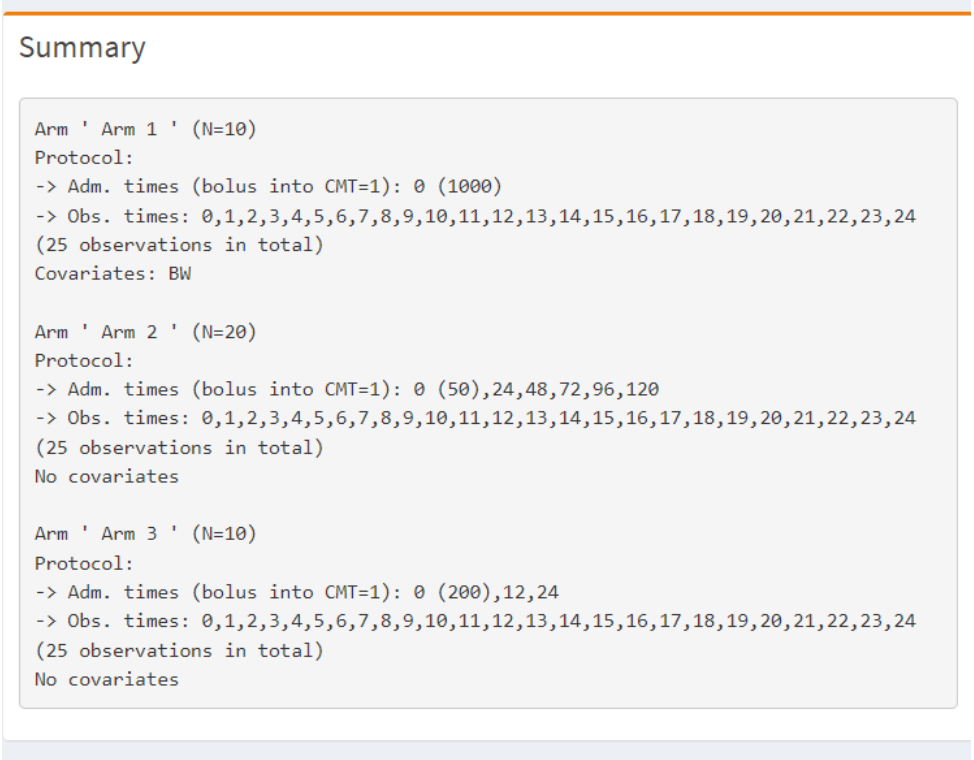
For each arm tab, the following information can be entered:

- Number of subjects
  - When set to 0 this arm is switched off.
- Arm label
  - Enter here the text that should appear on plots and tables identifying the study arm
- Administration type (bolus or infusion)
  - If infusion is selected, you can choose whether the infusion is in the Model or in the Dataset; if the latter, the infusion duration can be entered
  - Infusion into the Model means that the infusion duration is controlled by a parameter in the model. This is useful in cases where the infusion is actually not a real infusion but rather a 0-order input and you may have variability or covariates associate with it (e.g. a slow release formulation). See here for more information:
- Dose amount and compartment
  - The amount given into the specified compartment.
- Dosing interval and additional doses
  - The amount is repeatedly administered at a given interval for N additional doses (i.e. number of dosing events in addition to the first one)
- Observations (observation time)
  - to be written in R vector notation, e.g. *`seq(0,24,by=1)`*`or c(seq(0, 5), seq(0, 5)+168, seq(0,5)+336, seq(0,504,6))`
  - Enable the "as-time-after-dose" box, if you want to replicate the observation schedule after each dose
  - Be mindful with the number of observations that you choose as they contribute significantly to the size of the simulation and may cause memory issues.
- Covariates
  - Covariates or indicator variables that are used in the model code
  - You can enter a single values: e.g. `BW=70|FLAG=1|SEX=1|BW=70`
  - Or use the Campsis distribution functions, e.g:
    - `BW=NormalDistribution(mean=70, sd=10)`
    - `BW=LogNormalDistribution(meanlog=log(70), sdlog=0.2)`
    - `HT=UniformDistribution(min=150, max=190)`

  - It is also possible to enter a vector of values like so: `BW=c(50,60,70,80,90)` This is useful if you want to explore only certain specific covariate values. However, in this case you need to make sure that the length of the vector equals the number of subjects in the arm.r
  - See here for more information about covariates:

- Dose adaptation formula
  - Useful if the dose has to be adapted to the body weight; e.g. `AMT*BW`

3.2 Summary



Here you will see a summary of your trial design. Especially when you have multiple arms with different schedules it is useful to have a look here and check if the design was correctly specified.

3.3 Custom dataset

When you click on “Edit dataset” a window will pop-up that allows you to specify complex dosing schedules using the Campsis functions.

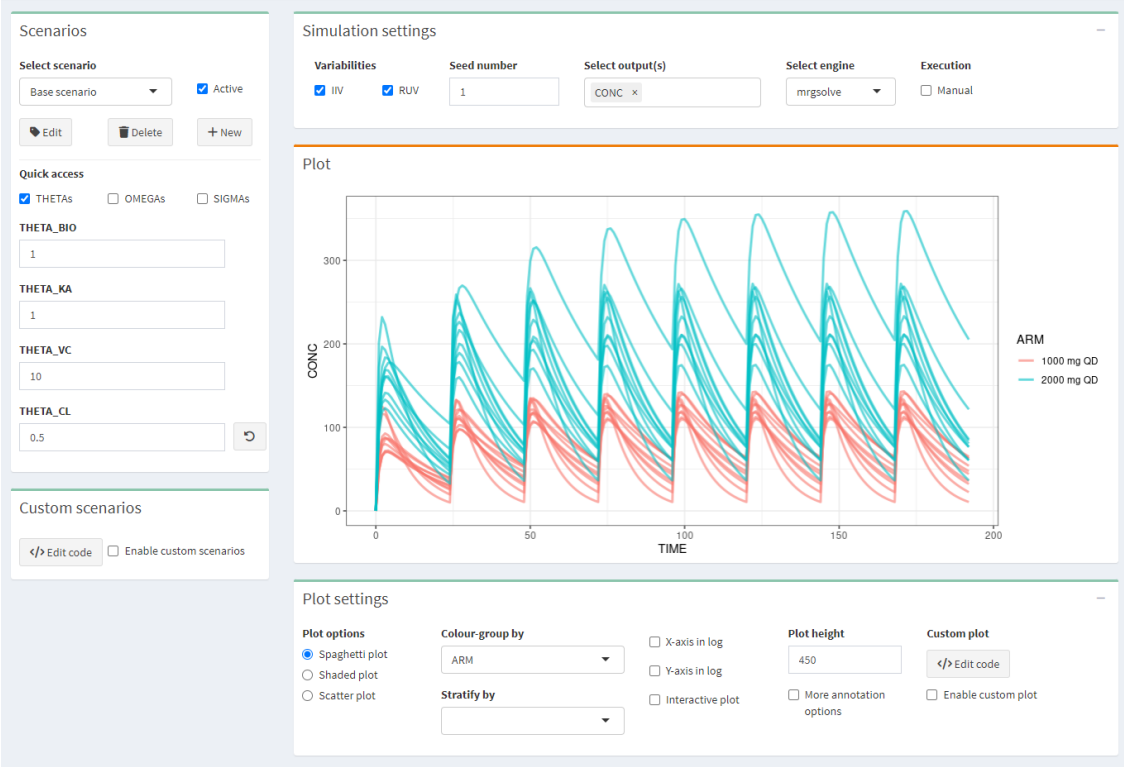
```
# Trial design
arm1 <- Arm(subjects=10, label="Arm 1") %>%
    add(Bolus(time=0, amount=1000, compartment=1, ii=24, addl=0)) %>%
    add(Covariate("BW", c(50,60,70,80,90))) %>%
    add(Observations(0 %>% purrr::map(~.x + (seq(0,24,by=1))) %>% purrr::list_

arm2 <- Arm(subjects=20, label="Arm 2") %>%
    add(Bolus(time=0, amount=50, compartment=1, ii=24, addl=5)) %>%
    add(Observations(seq(0,24,by=1)))

arm3 <- Arm(subjects=10, label="Arm 3") %>%
    add(Bolus(time=0, amount=200, compartment=1, ii=12, addl=2)) %>%
    add(Observations(seq(0,24,by=1)))

dataset <- Dataset() %>%
    add(c(arm1, arm2, arm3)) %>%
    add(DatasetConfig(exportTSLD=TRUE, exportTDOS=TRUE))
```


Here you can enter for example loading doses or specific titration schemes etc.

See the Campsis help for details on how to enter complex trial designs.

Chapter 4

Simulation



4.1 Scenarios

Make several scenarios that you want to compare. For each scenario, parameter values can be changed. If you use scenarios, make sure to apply the appropriate stratification or color-grouping in the Plot settings.

4.2 Simulation settings

- IIV/RUV: Should the inter-individual and residual variability be taken into account in the simulations? Check IIV or RUV boxes accordingly. **IMPORTANT:** If you simulate only 1 subject with the intention of simulating a typical profile, make sure that IIV is switch off!
- Seed: a seed number can be used.
- Select output(s): select one or several outputs you would like to look at.
- Select engine: choose one of the two simulation packages rxode2 or mrgsolve.
- Execution/Manual: check the box to make any changes without updating the plot and, when all is configured, click the "play" button ▷

4.3 Plot settings

Click "+" to pull the tab down.

- Three plot options can be chosen:
  - spaghetti plot: overlay of the individual profiles of the selected output(s) versus time
  - shaded plot: median of the simulated output(s) versus time with 5th and 95th percentiles of the simulations
  - scatter plot: relationship between two selected outputs
- Colour-group by: profiles will have different colors by ARM or SCENARIO
- Stratify-group by: split the plots by ARM or SCENARIO
- X-axis or Y-axis in log: select to show the X- or Y-axis on log scale
- Interactive plot: when checked, more options on plots are available (from Plotly)
- Plot height: adjust the height of the figure
- More annotation options: allows to customize the plot
  - Plot title

  - X-axis label, limits, breaks
  - Y-axis label, limits, breaks
  - Footnote
  - Horizontal/Vertical line(s): add one or several horizontal or vertical line(s) to the plot, and select colours and type
  - Facet scales: scales for facet can be fixed, free, or free in one dimension
  - Facet nrow: number of facets per row
  - Facet scaled: include or not the facet variable name

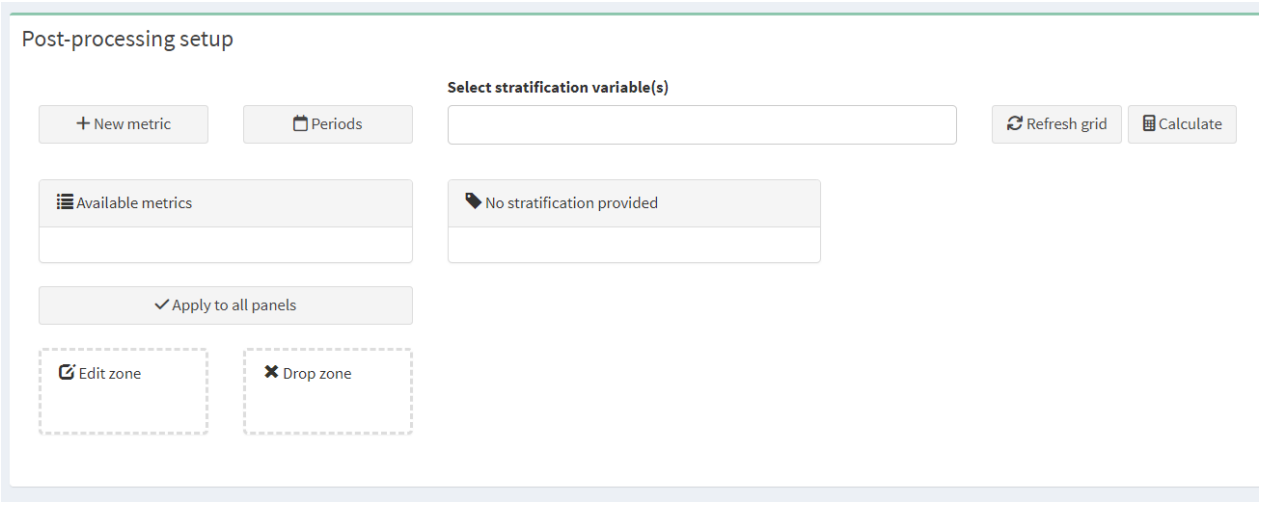
- Custom plot (pro version): R-code can be edited to directly customize the plot, then check "enable custom plot" to update the plot after editing the code. Click "Generate code from GUI" to update the code from the plot.

Chapter 5

Post-processing (pro version only)

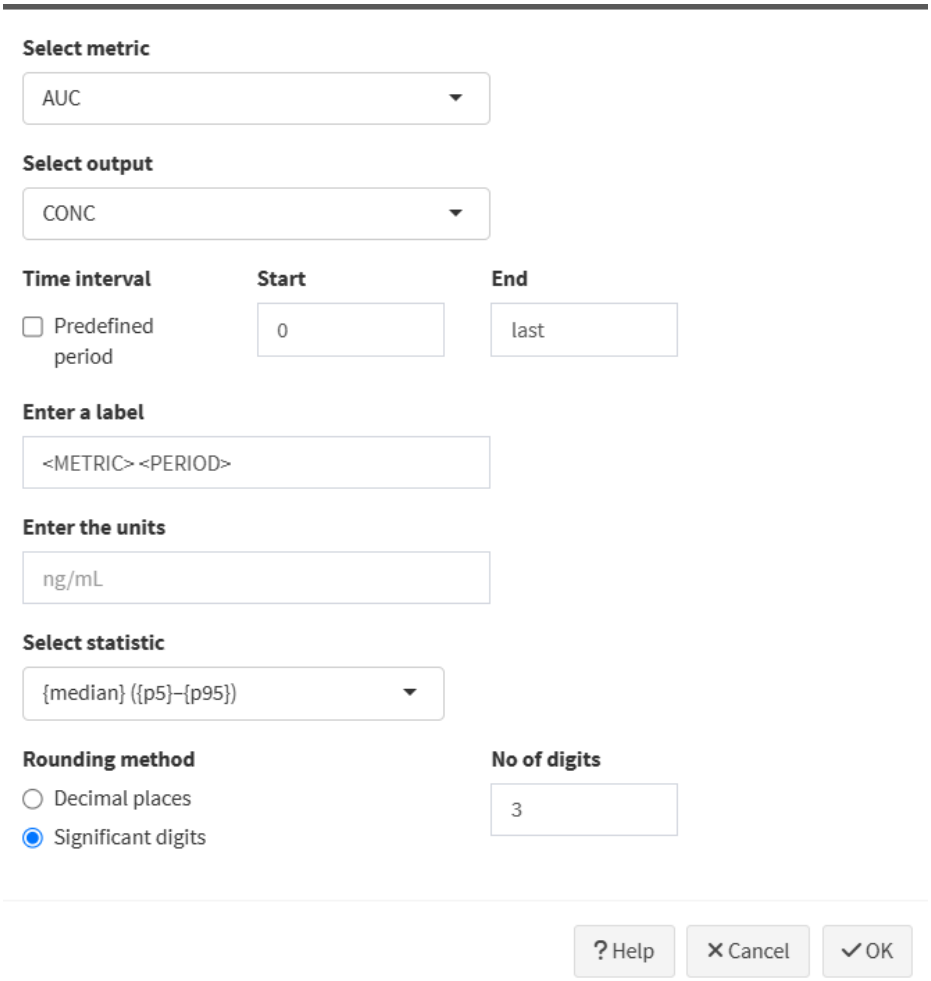
5.1 Step-by-step guide

After a simulation has completed, you can apply post-processing calculations to the simulation results. This way you can for example calculate non-compartmental PK parameters. The post-processing calculation will be performed for each individual separately, but the results can easily be summarized in a table.



The steps are:

1. Add the metrics you are interested in



- Select the output variable that a metric should be derived from (e.g. concentration; must be defined in the [ERROR] section of the model code)
- All metrics are computed within a specified time interval
- Currently the following NCA metrics are available:
  - AUC: area under the curve, calculated with the trapezoidal method
  - Cmax: the maximum value of the selected output variable
  - Tmax: the time at which the maximum value occurred
  - Cmin: the lowest value in the interval
  - Ctrough: the last value in the interval
  - Cavg: the average concentration derived as: AUC/length_time_interval