e-Campsis™

A Shiny PK/PD model simulator based on Campsis

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INTRODUCTION

e-Campsis (https://calvagone.github.io/ecampsis) is a free Shiny application developed by Calvagone which allows an intuitive and user-friendly set-up of population PK/PD simulations [1]. It is based on the R package Campsis [2], which provides a powerful front end to run model-based simulations with mrgsolve [3] or rxode2 [4].

Objectives

1) Create a user-friendly web application to run interactive PK/PD simulations based on the Campsis language
2) Include a model library containing more than 100 different PK, PD and TMDD models
3) Facilitate modifications of models from the library or writing new models from scratch with a model editor
4) Allow easy yet flexible configuration of dosing, observations and covariates
5) Facilitate side-by-side comparison of different scenarios
6) Ability to download the simulation code to reproduce and/or further adapt offline in R

METHODS

Campsis offers an abstraction layer that delegates the simulation work to rxode2 or mrgsolve. **e-Campsis** is a graphical user interface (GUI) for Campsis and was developed using Shiny [5] and Shiny-dashboard [6]. A free version is currently hosted on shinyapps.io servers and can be accessed without registration at https://ecampsis.shinyapps.io/free/.

The GUI translates user input in text fields, check-boxes and scroll-down boxes to arguments of Campsis functions. Shiny's reactive methods are used for a smooth user experience when interacting with the app.

The key parts that determine a simulation set-up, model, trial design, simulation execution and plotting are accessible via a sidebar menu.
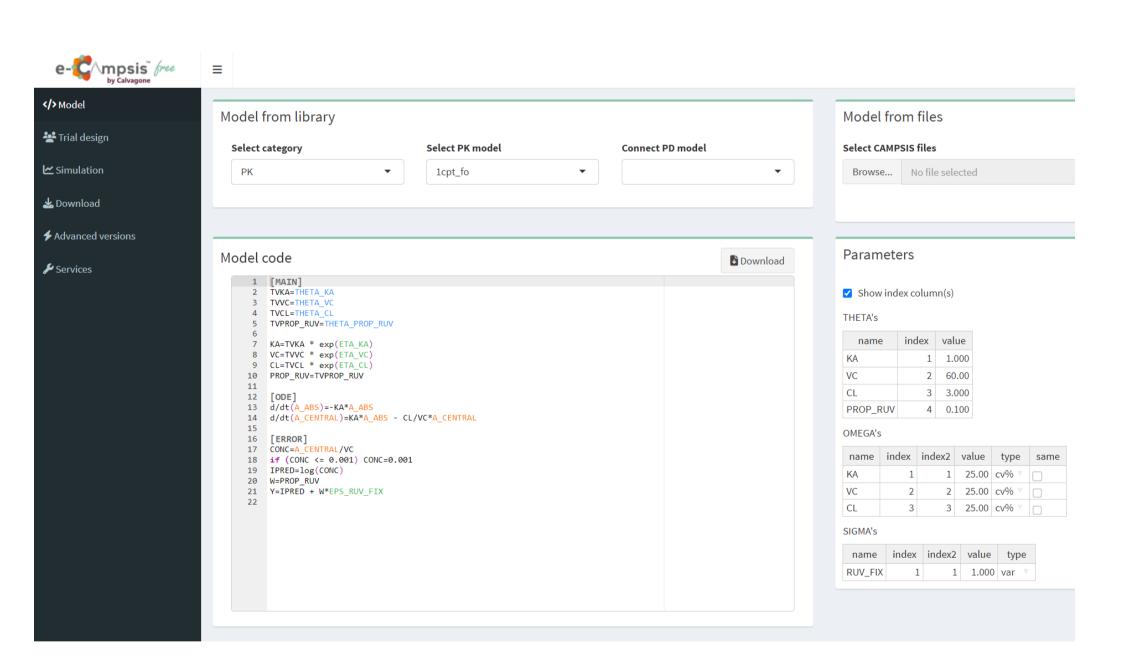
RESULTS

Model section

In the model section the user can select from a wide range of PK models, including:

- 1-3 disposition compartments
- first-, zero-order, transit-, Weibull-absorption
- models with target-mediated drug disposition.

A PD-model can be easily connected to any PK model for full PK/PD simulations.

Moreover, the user can:

- upload a previously saved Campsis model
- edit model code in the editor window, including syntax highlighting
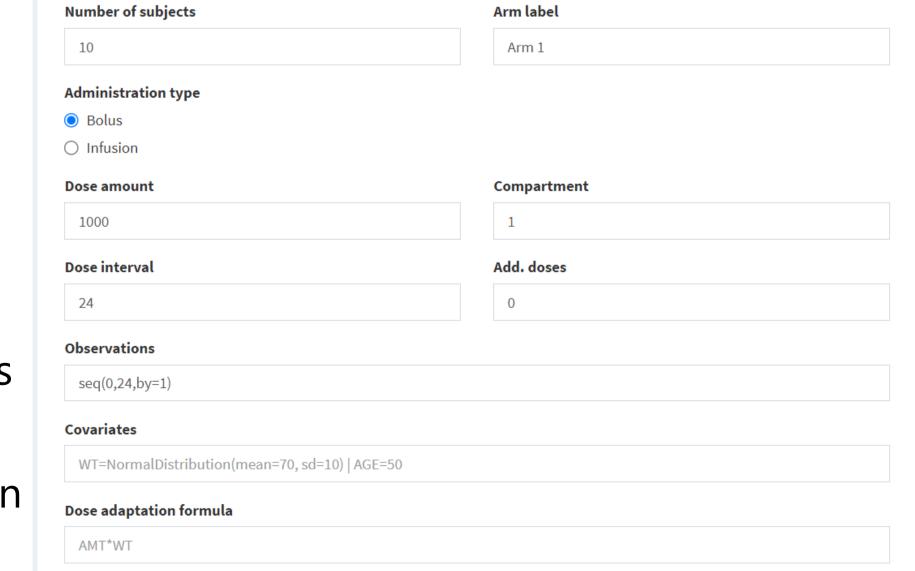- enter parameter values in tables

Trial design section

Here the user can configure the following, separately for each study arm:

- number of subjects
- route of administration
- dosing schedule
- observation time points
- covariates
- formula for covariate-based dosing

Since the covariate field accepts R-code as input, any type of distribution can be entered, using a Campsis wrapper-function like:

`WT=NormalDistribution(mean=70,sd=10)`

In fact, any R-code that evaluates to a vector of length *Nsubjects* is possible, e.g.:

`WT=rep(c(60,70,80,90,100),2)` would produce a vector of length 10 with 5 distinct values.

Further customization of the simulation dataset is possible by directly entering the relevant Campsis code in an editor window.

Simulation section

The following simulation settings are configured here:

- seed number,
- simulation engine (rxode2 or mrgsolve)
- use of variability components (IIV and/or RUV)
- set-up of scenarios with Campsis code

Model parameters are listed in a separate box and will trigger an immediate re-execution of the simulation when changed.
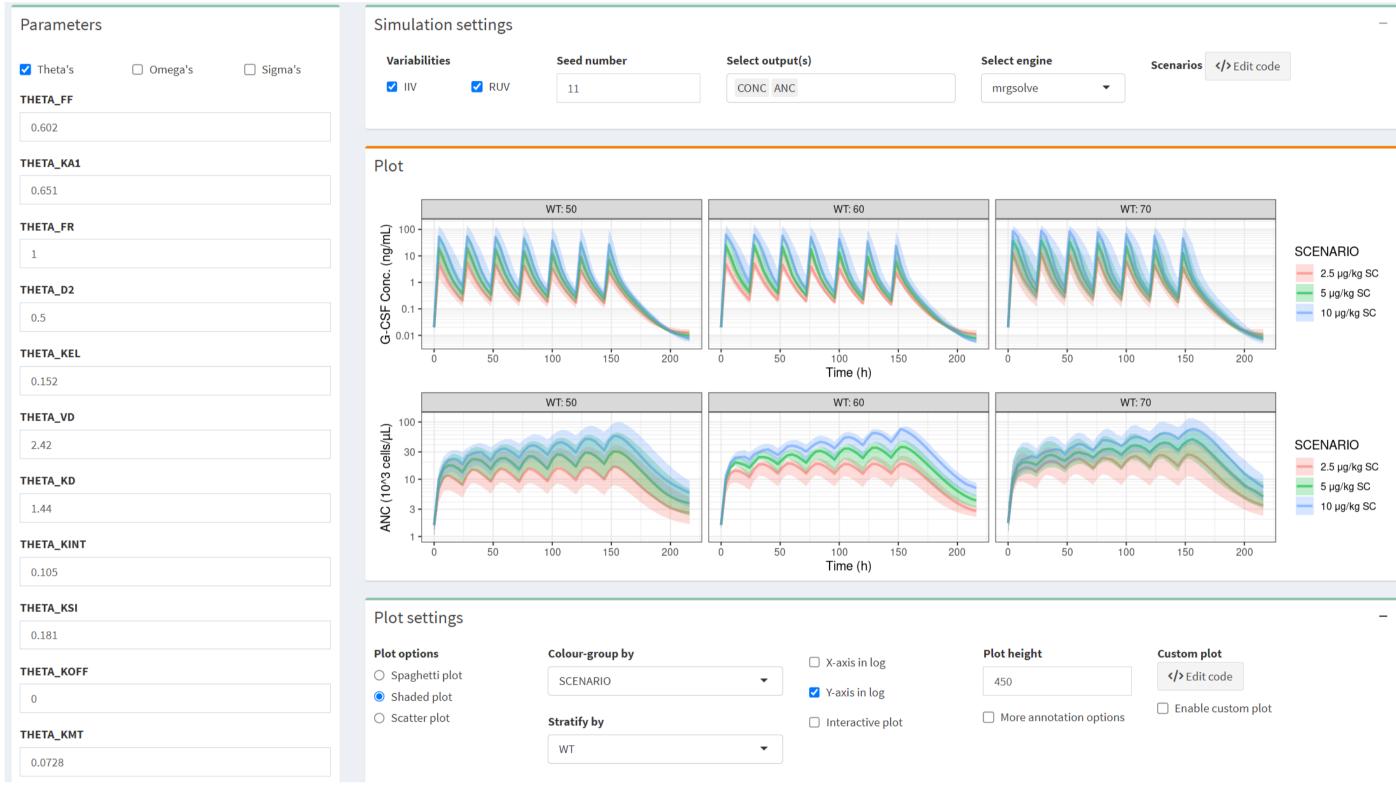
The results are visualized in the plotting window and can be customized by:

- color-grouping or stratification by e.g., study arm, scenario, a covariate etc.
- show individual profiles ('Spaghetti plot') or a shaded ribbon (median and 90% prediction interval)
- adding reference lines

If multiple output variables are selected (e.g., concentration and response) the plot will be facetted accordingly, showing both variables in separate panels.

Further customization is possible by adding R-code for plotting in a separate code editor.

Download section

Once the simulation is fully configured, the complete R code can be downloaded to reproduce or further refine the simulation offline.
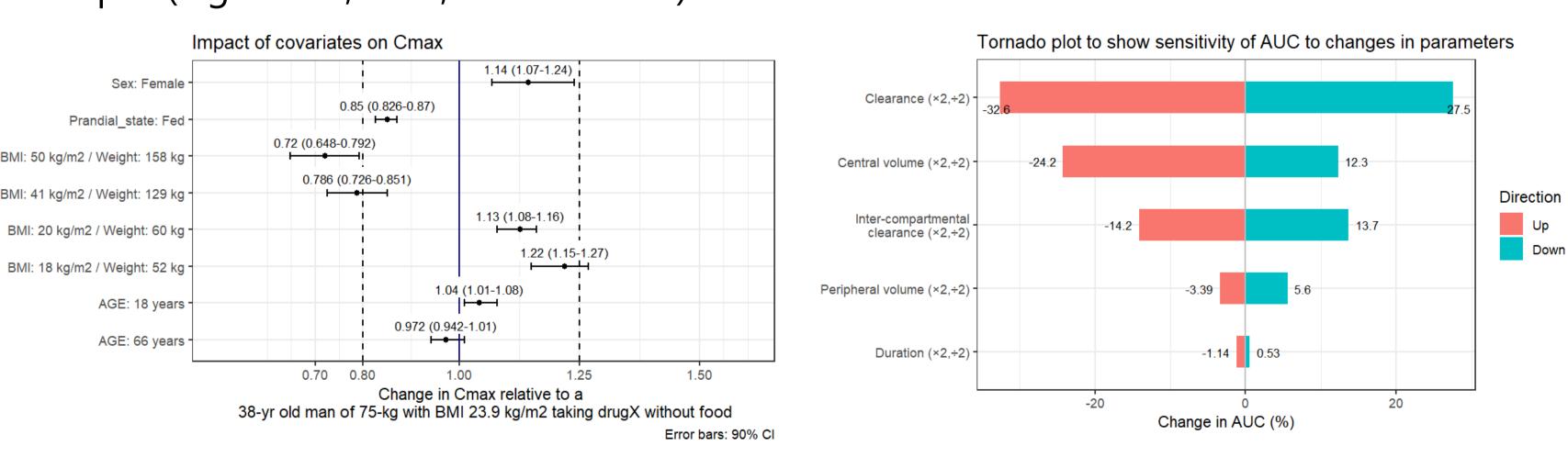

CONCLUSION AND OUTLOOK

- **e-Campsis** has a clearly structured and lean user interface that facilitates the configuration of PK/PD simulations in an intuitive way.
- Custom R-code allows for flexibility in the simulations.
- It helps users to quickly set up simulation projects that can be expanded and edited offline using the Campsis package in R.
- Fast execution and customizable output plots facilitate interactive simulations in team meetings.

We are currently working on an advanced version, with additional functionality such as:

- saving all settings of your simulation project within the Shiny environment
- importing external data into plots for visual comparison to simulations
- sampling of covariates from external databases like e.g. NHANES
- running trial replicates, taking into account parameter uncertainty
- post-processing of simulation results, applying for example NCA or statistical tests for efficient generation of forest plots and tornado plots on derived simulation output (e.g. Cmax, AUC, effect at 24h)

REFERENCES

[1] https://www.Calvagone.com
[2] https://calvagone.github.io/ or www.campsis.org
[3] https://github.com/metrumresearchgroup/mrgsolve
[4] https://github.com/nlmixr2/rxode2
[5] https://shiny.posit.co/
[6] https://rstudio.github.io/shinydashboard/