nlmixr shinyDashboard Application for Exploration and Visualization of Model Simulations

B Ngara[1,2,3], Z Mulyukov[3], M Fidler[3], K Grosch[3], W Wang[3], M Trame[3]

[1]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe
[2]Letten Foundation Research Center, Harare, Zimbabwe
[3]Pharmacometrics, Novartis Pharma, (Basel) Switzerland, (Fort Worth) USA, (East Hanover) USA, (Cambridge) USA

Introduction

nlmixr is an open source R package for population pharmacokinetic - pharmacodynamic (popPKPD) modelling and simulation. nlmixr has been developed over the last years by a voluntary team spearheaded by Novartis associates.[1-3] A user-friendly shiny simulation tool for nlmixr will allow for interactive communication with clinical teams for quick demonstration of simulation results from popPKPD modeling. The nlmixr shinyDashboard is a graphical user interface tool for the simulation of popPKPD projects with nlmixr as the estimation engine. The application is mainly intended to translate computational outputs into an interdisciplinary language and support discussions on a real-time basis during drug development.

Goal

To develop an nlmixr simulation shinyDashboard application for the exploration and visualization of popPKPD modeling results to illustrate different simulated dosing regimens.

Methods

- The nlmixr simulation shinyDashboard application is a user-friendly interactive interface comprised of a set of different R language codes created using the following R packages: RxODE, nlmixr, ggplot2, dplyr, Shiny and shinyDashboard (Fig.1).[1-7]

- nlmixr simulation shinyDashboard application uses the following key objects to run the simulations:
  - **nlmixr model output** – Contains all model outputs obtained after fitting the model using nlmixr: the ordinary differential equations (ODE) system, population parameter estimates, variance-covariance components and the data input.
  - **Ui.R** – A loop of codes in R language to define the elements and layout of the user interface (UI). The UI for nlmixrSim_shiny contains rows and columns displaying: ODEs, population parameter estimates, dosing strategy and number of subjects or studies used for simulation (here in referred to as events), and the graphical outputs.
  - **Server.R** – A loop of codes in R language with defining instruction to process elements in the model output and to perform model simulations given different scenarios of population parameters and/or events. The server.R also contains functions to produce basic time vs. concentration plots of the simulated data.

- nlmixrSim_shiny application was developed using a one-compartmental model, and was validated using higher order compartmental models.

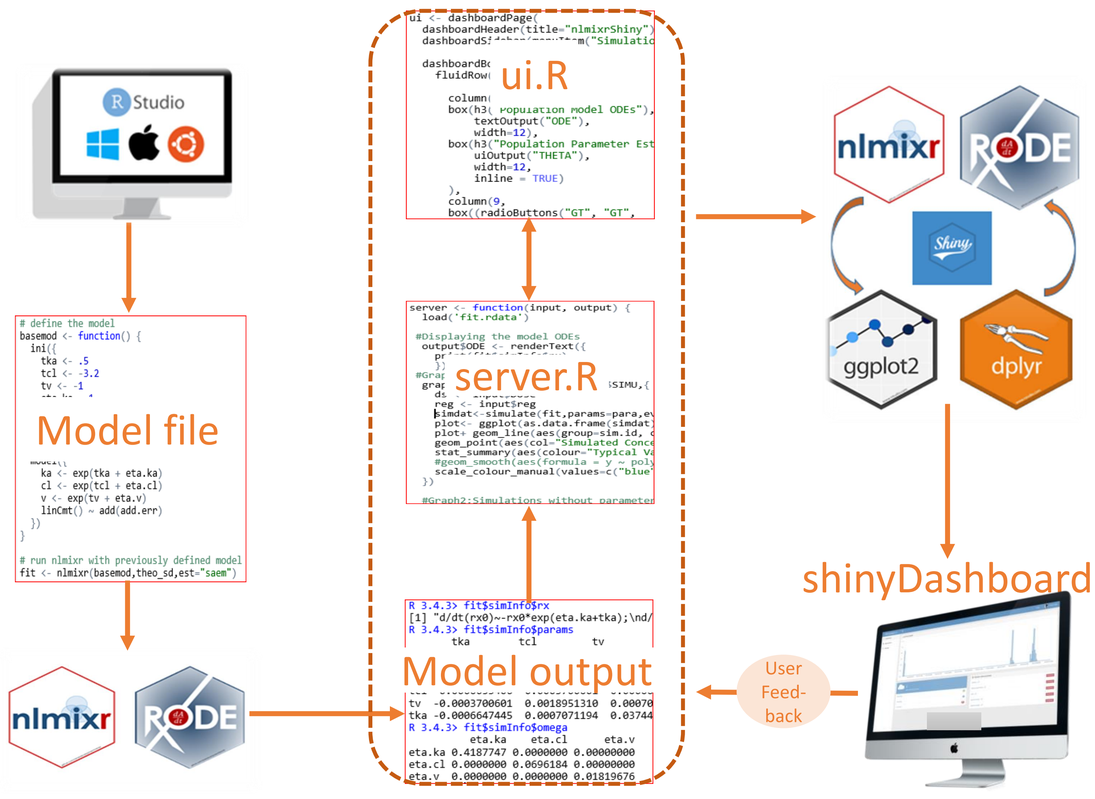

Figure 1: Schematic flow in creating nlmixrSim_Shiny application

Results

Interactive input-output dashboard display

- The current version of the nlmixr simulation shinyDashboard application can display i) final population parameter estimates from the nlmixr model output, and ii) various simulation plots showing individual and median simulation profiles with and without parameter uncertainty as well as Visual Predictive Checks (Fig.2 – Fig.4).

- Plots are reactive to changes in model parameter estimates, dosing amount, dosing schedules, number of subjects and number of simulated studies.

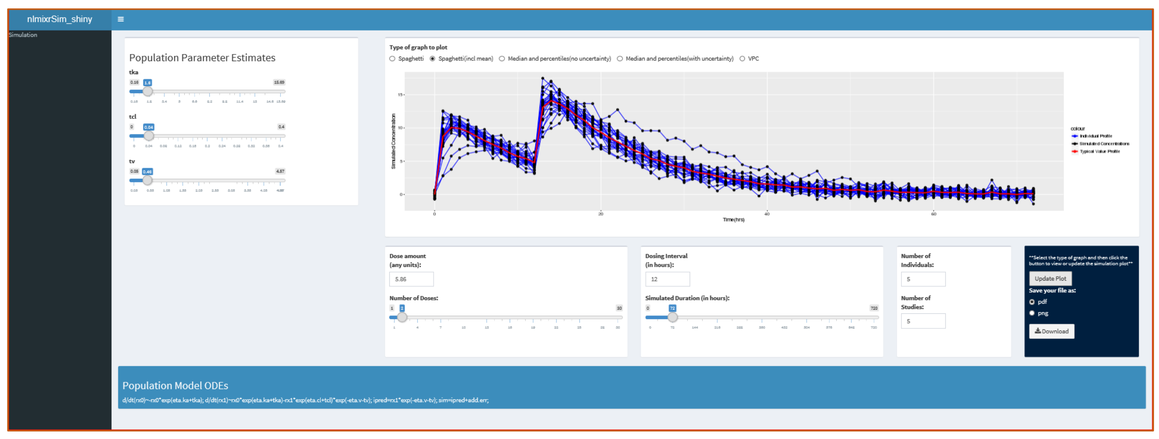

Figure 2: Spaghetti plots. The spaghetti plots have the option to show the mean line.

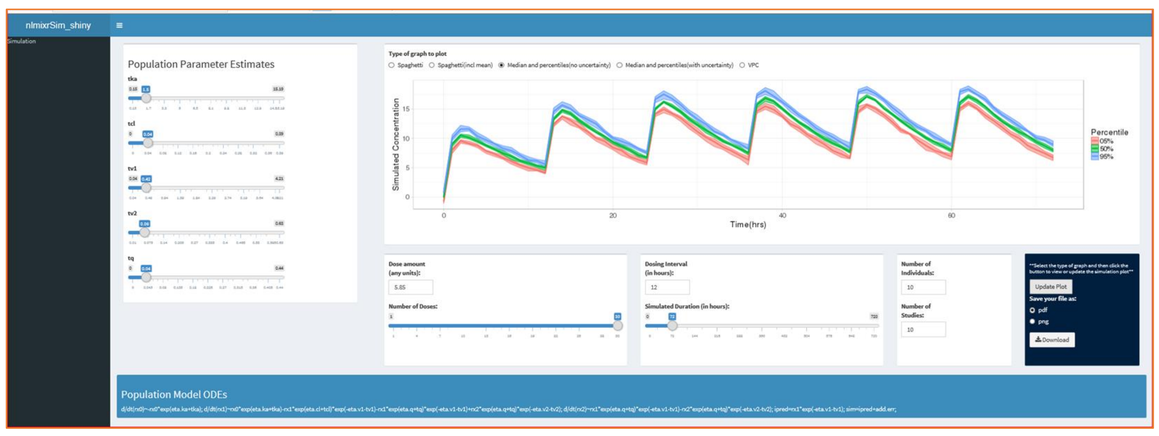

Figure 3: Simulation plots show the median, 5h and 95th percentiles of the simulated data with and without parameter uncertainty.

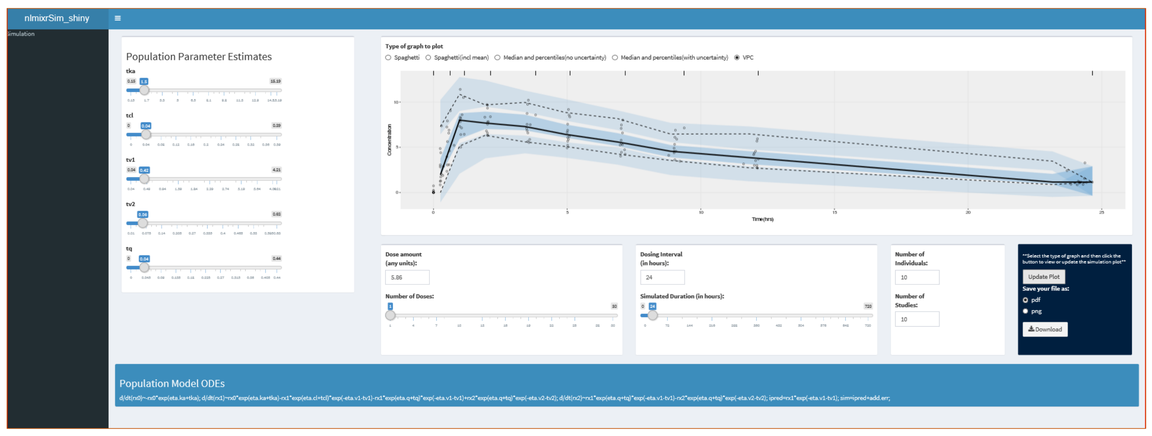

Figure 4: Visual Predictive Check for model evaluation

Conclusions

- A user-friendly nlmixr simulation shinyDashboard application was developed to perform interactive model simulations using nlmixr and RxODE.
- The developed application can be used for interactive visualizations of simulated time-concentration profiles for different dosing regimens.
- The current shinyDashboard application will be further developed to include additional features and functionalities not included yet.

Impact

- nlmixr project presents an opportunity to use an open-source R based software for popPKPD modeling and simulation free of license fees
- nlmixr can be used for training the next generation of Pharmacometricians in popPKPD modeling and simulation.
- nlmixr simulation shinyDashboard will improve flexibility in communicating and discussing popPKPD modeling and simulation results.
- Experience learned in developing nlmixr simulation shinyDashboard can also be applied to other areas of modeling and simulation when using R language code.

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