

Application of a Shiny Workflow in Cardiovascular Effects Evaluations



Leiden Experts on
Advanced
Pharmacokinetics &
Pharmacodynamics

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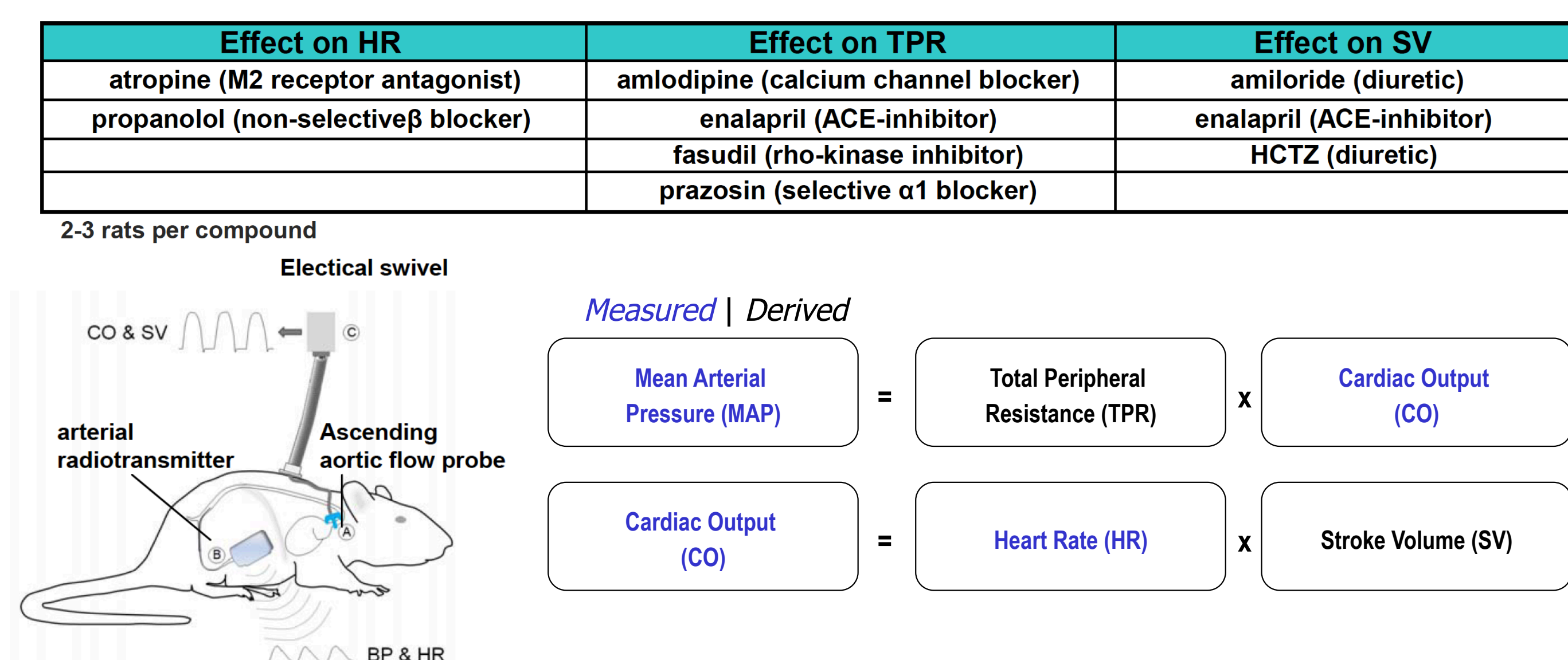
Objective

The objective was to develop a workflow in which established and experimental treatment effects (model structure, data and outcome) can be easily compared, and therefore discussed within a team setting, to support decision-making.

Methods

- A Shiny application [1,2] provides an easy-to-generate and easy-to-use interface to visualize models in R, for instance to present its structure, and to compare model outcomes and observed data.
- A previously reported preclinical Cardiovascular Effects Systems Pharmacology framework [4,5] was transformed from NONMEM to R [3] with an in-house developed R package, and implemented in Shiny.
- The framework contains several library compounds (e.g., propranolol, amlodipine) with their PK and corresponding effects on mean arterial blood pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR), and stroke volume (SV).
- The corresponding observed preclinical data was added to the application. An option was incorporated to interactively visualize the output of new treatments based on its experimental or anticipated PK and PD characteristics, including the possibility to investigate a site of action and a type of exposure-response function. The outcome of the effects could be overlaid and combined, also with available observations.

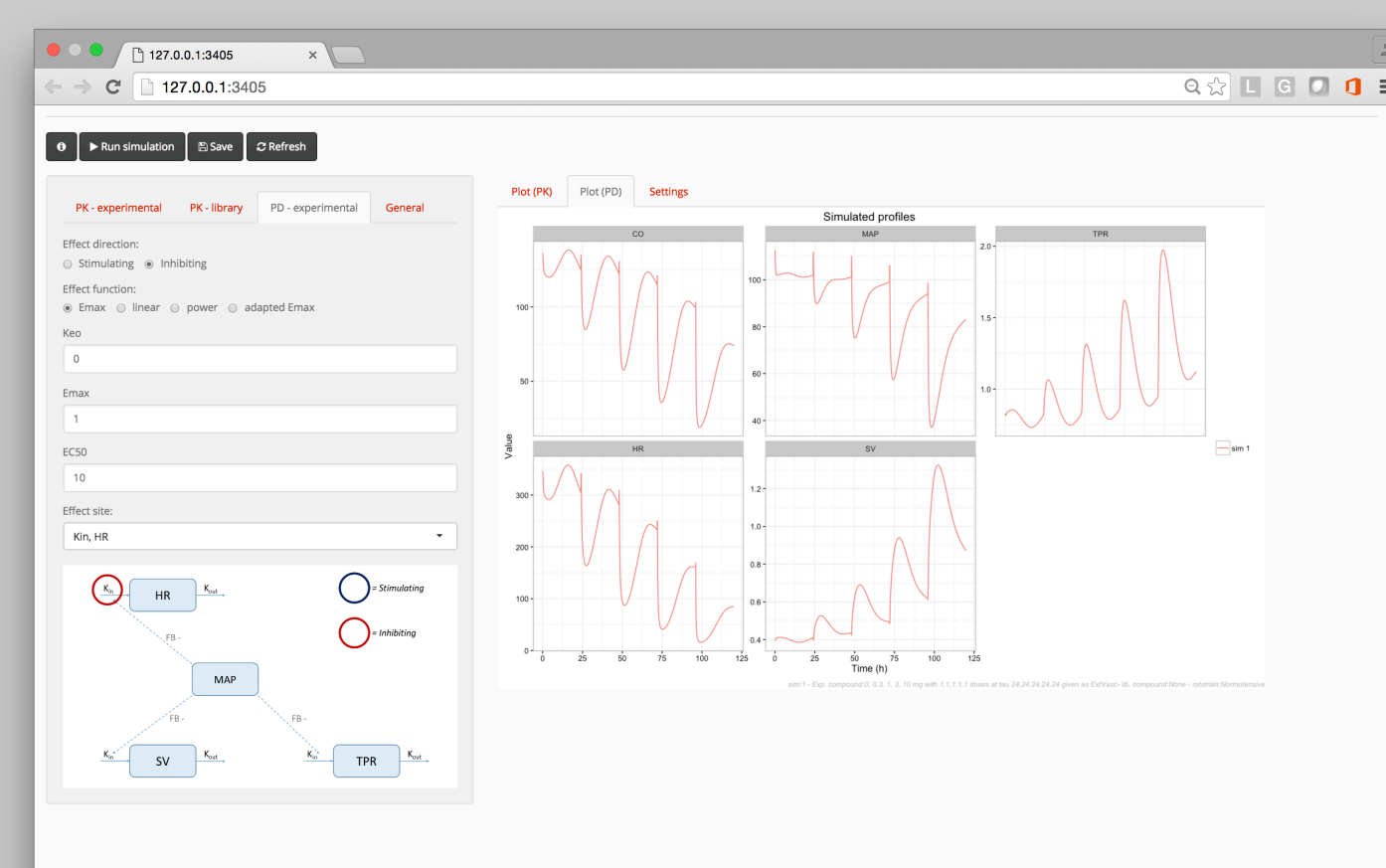
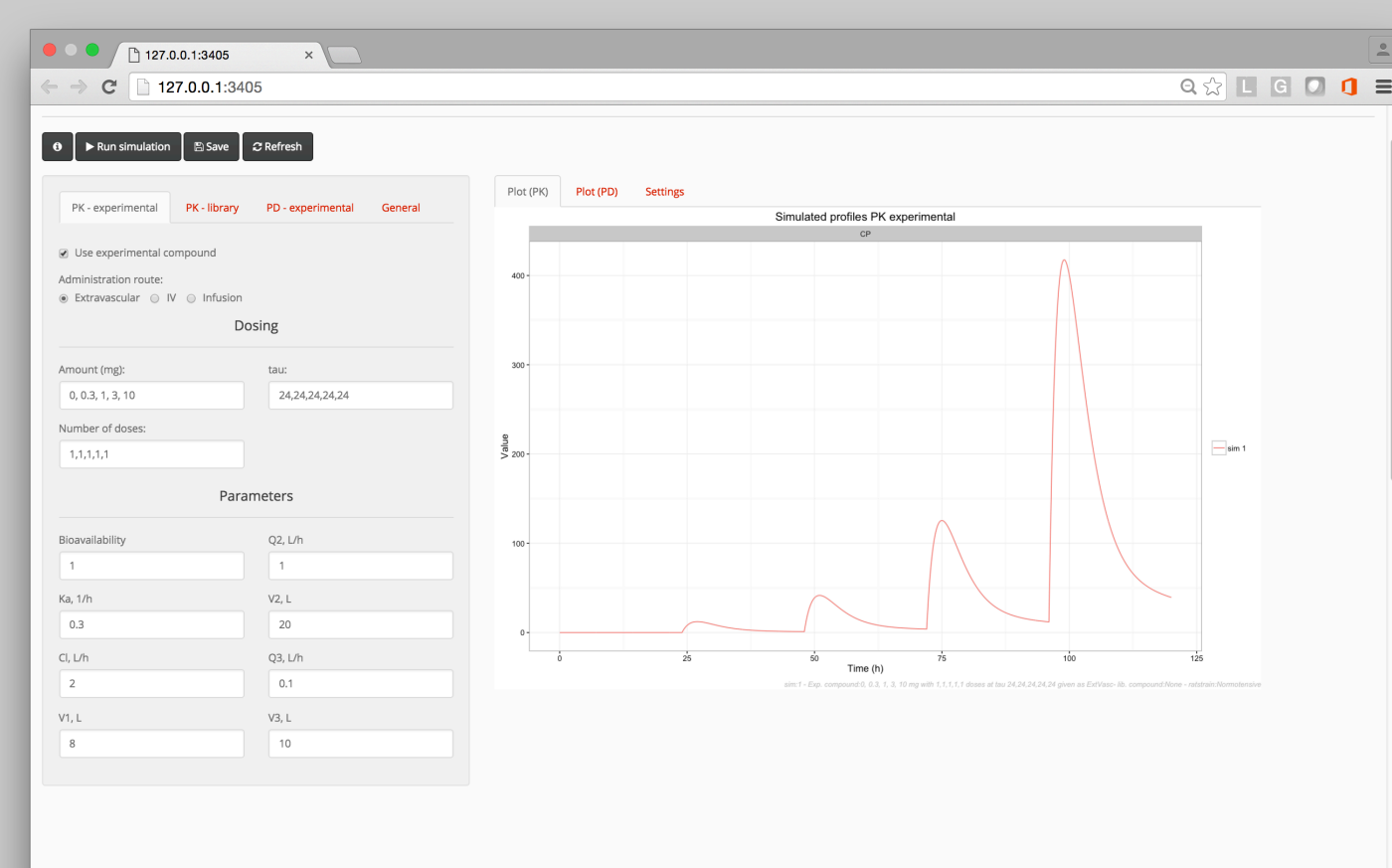
Cardiovascular Effects Systems Pharmacology



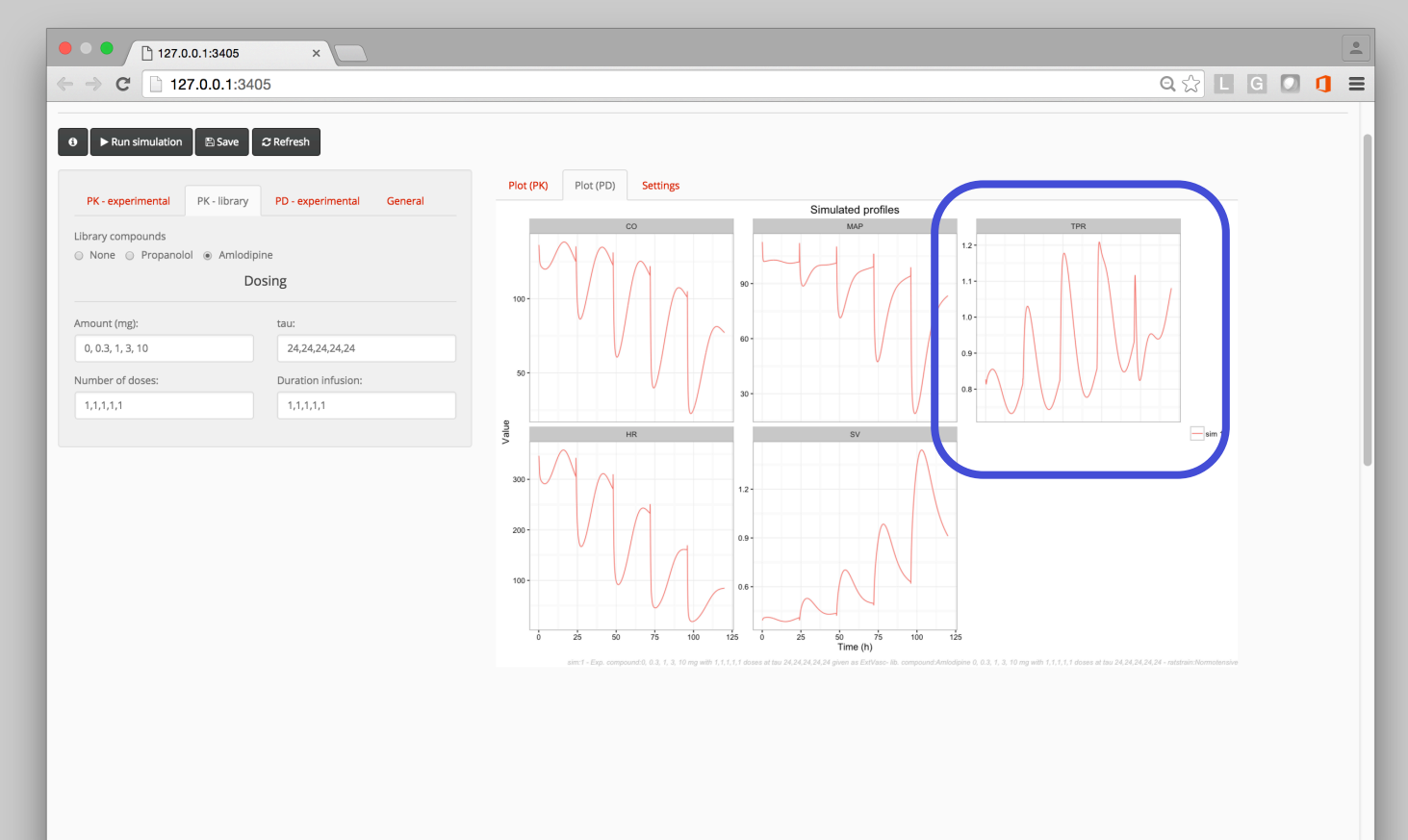
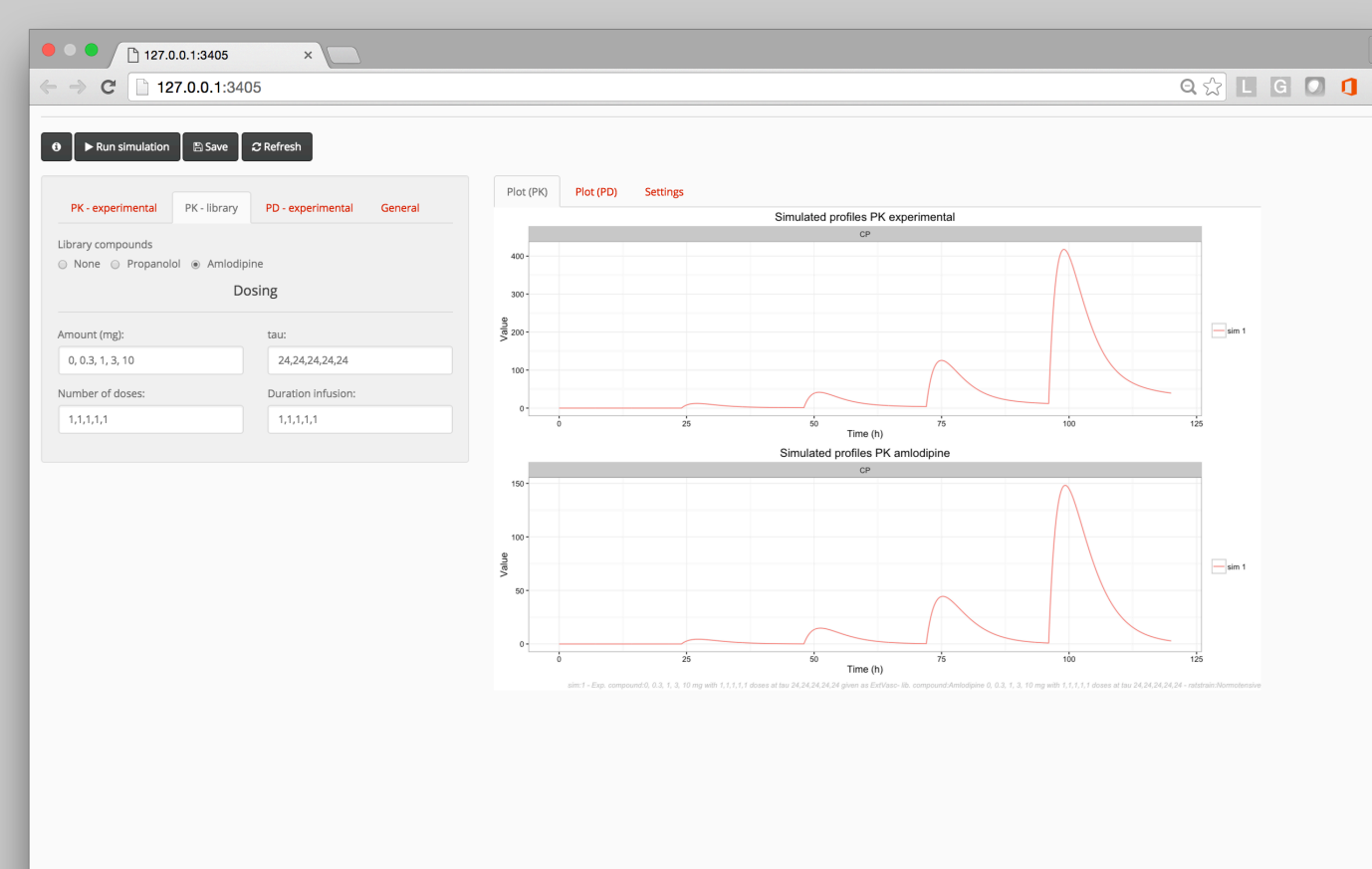
Shiny workflow

Combination Treatment

Experimental Compound – Pharmacokinetics and Pharmacodynamics

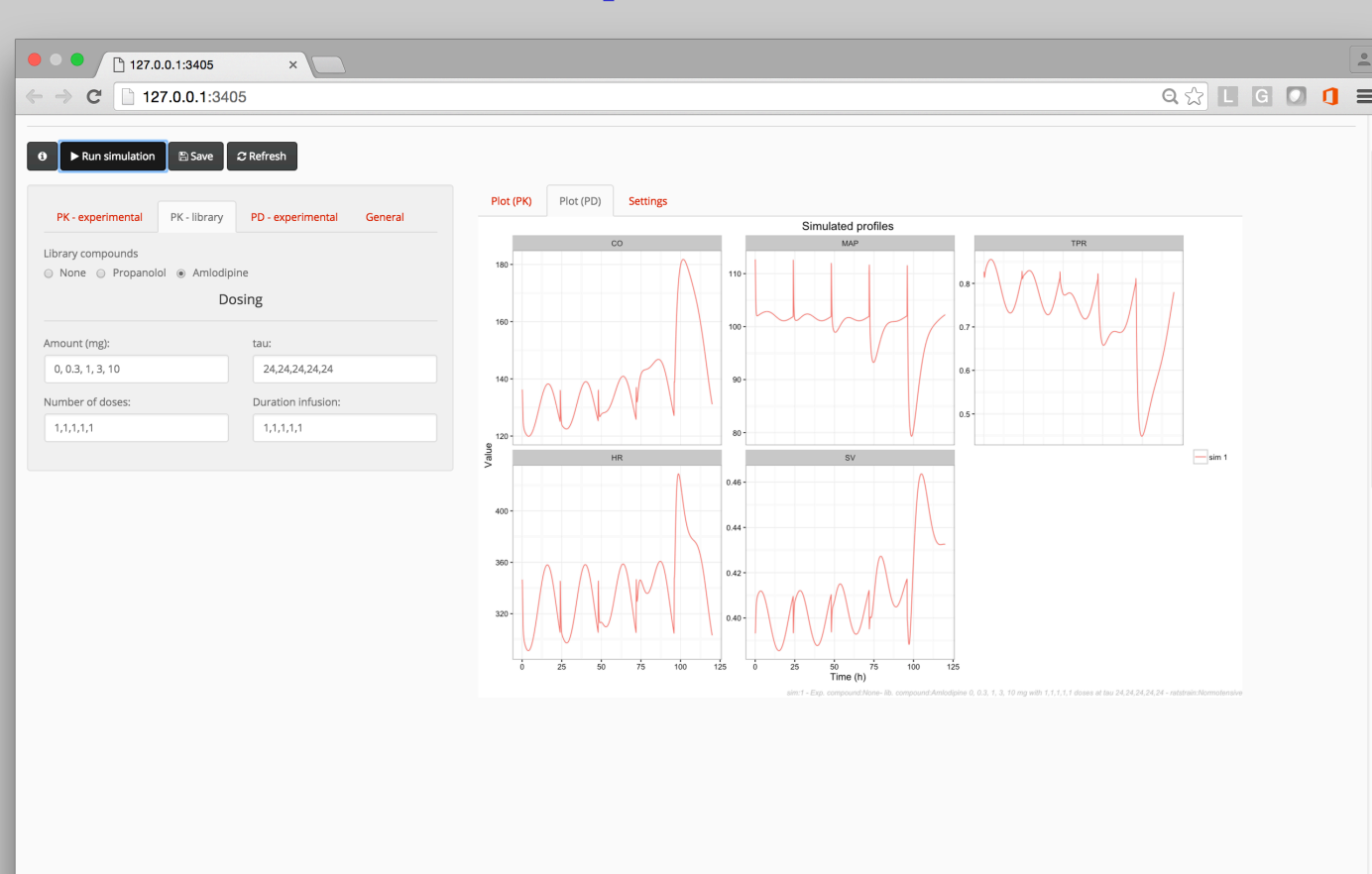


Experimental Compound + Amlodipine – Pharmacokinetics and Pharmacodynamics

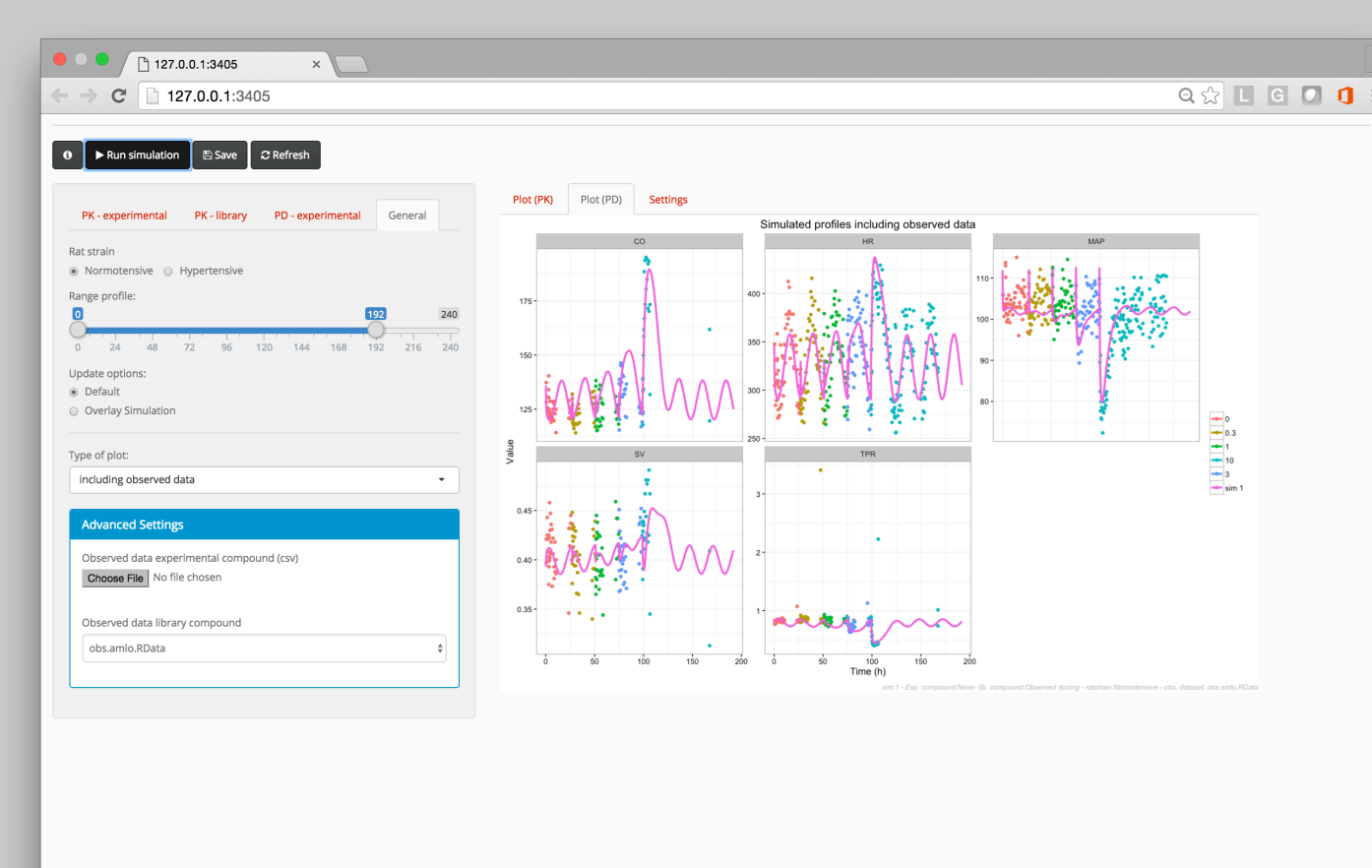


Population Characteristics

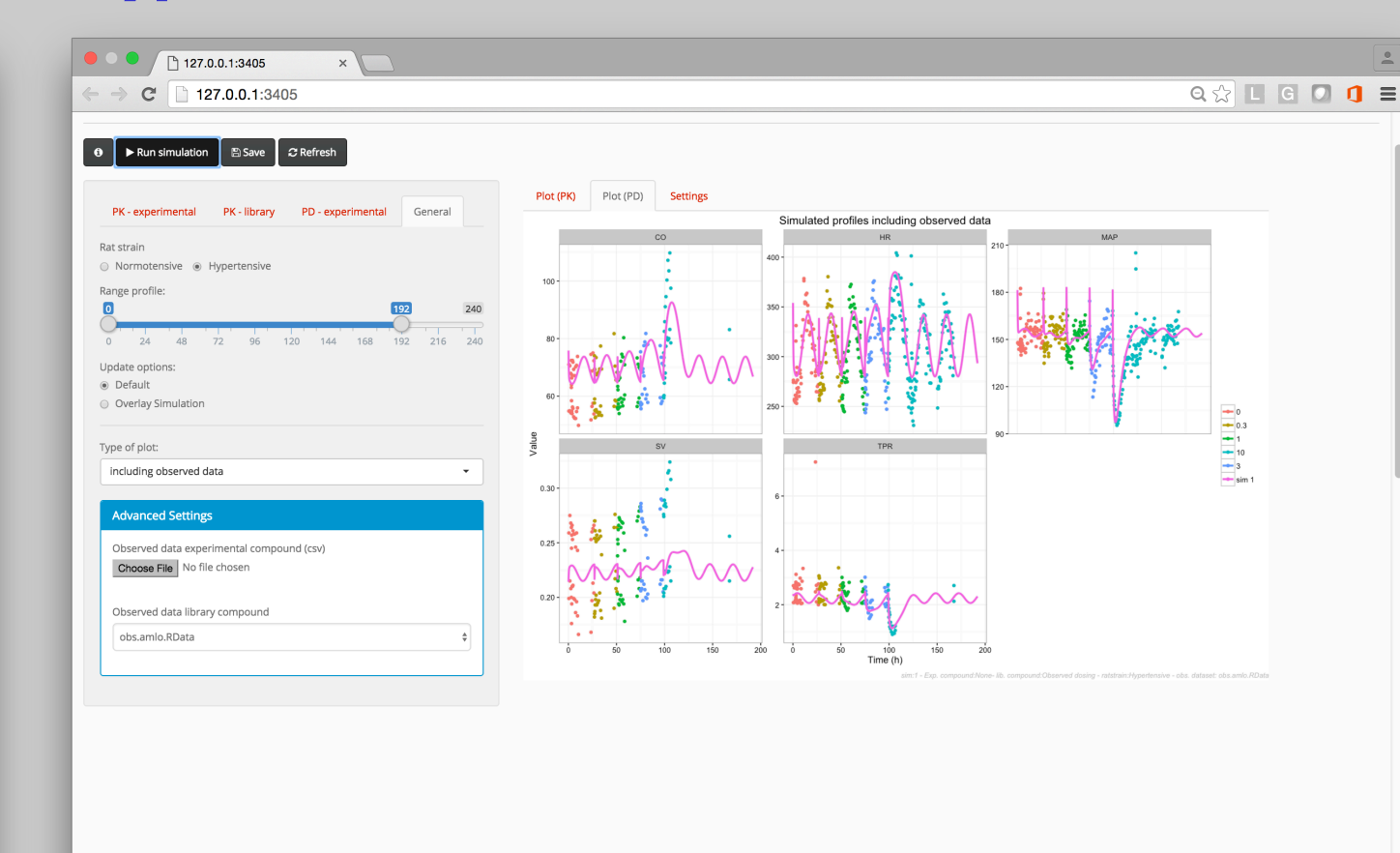
Amlodipine – Prediction



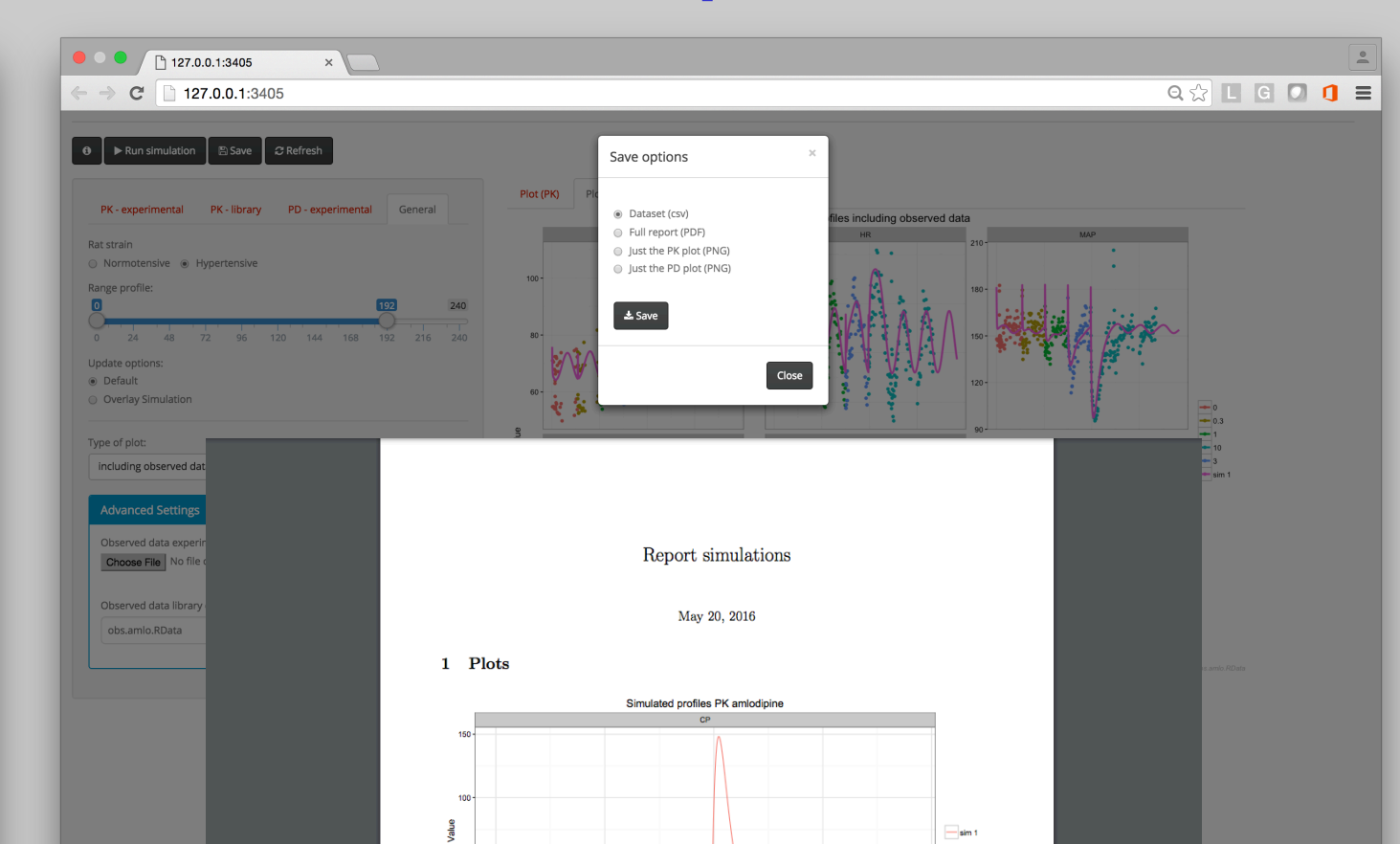
Normotensive – Prediction and observation



Hypertensive – Prediction and observation

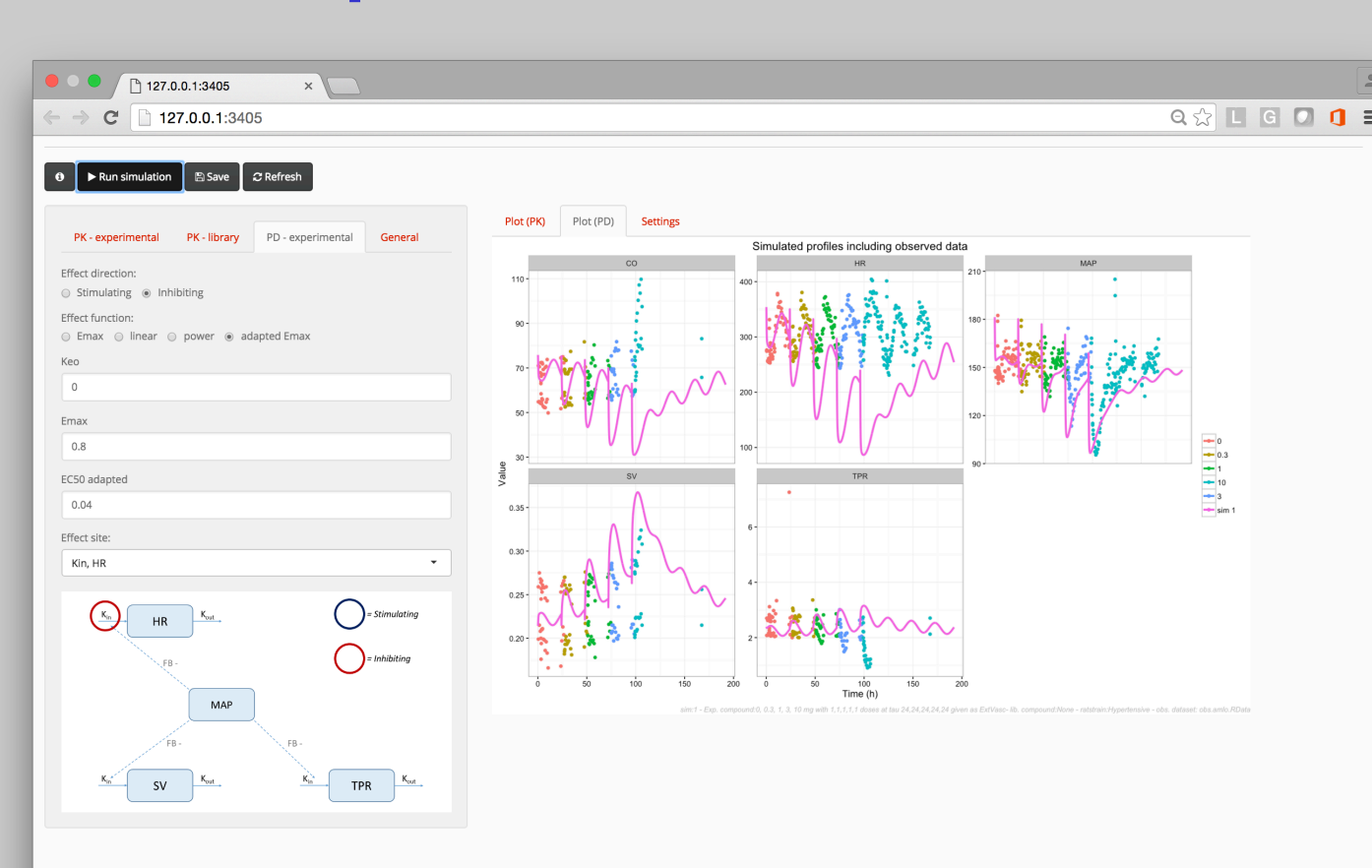


Save and Export Results

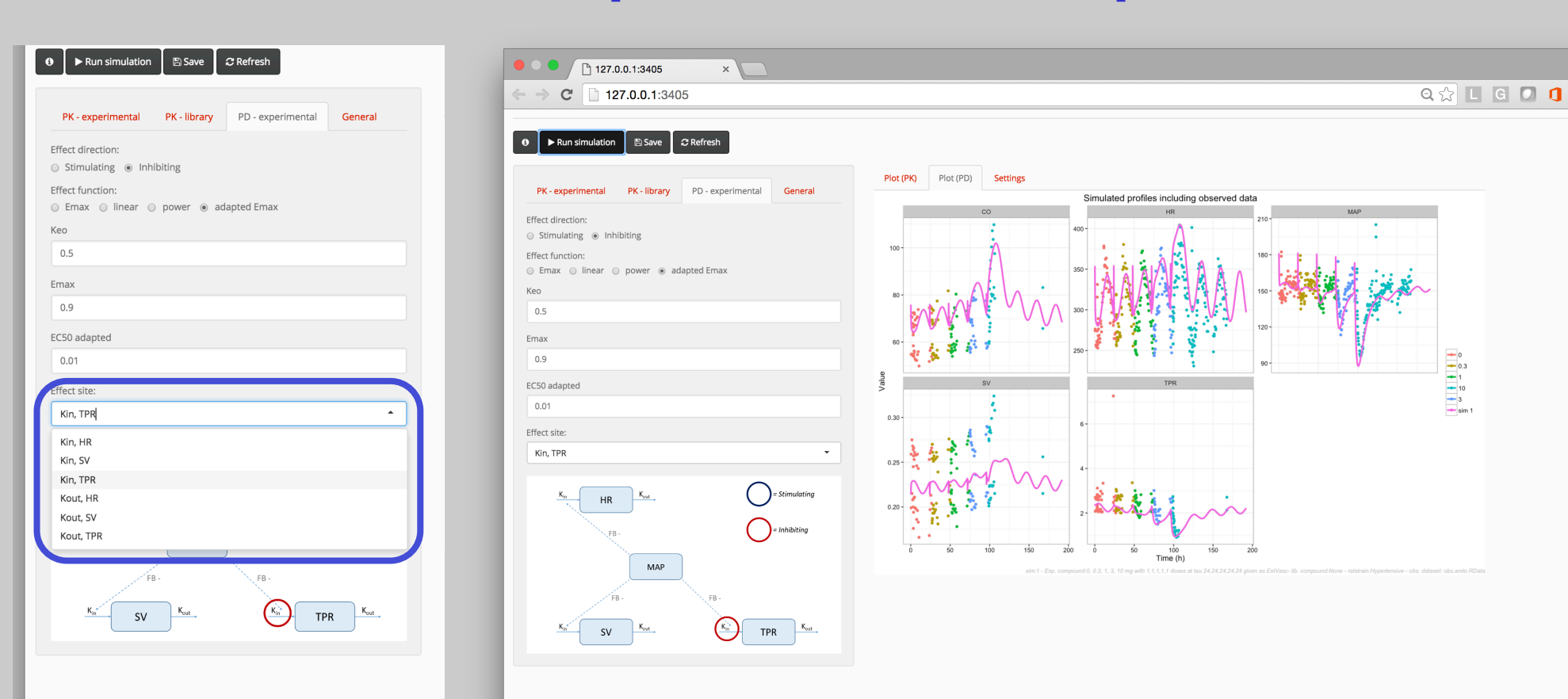


Explore Pharmacological Mechanism

Experimental data – Prediction



Experimental data – Updated Prediction



The Shiny workflow provides a means to

- visualize the behavior and structure of complex systems pharmacology models,
- compare treatment effects and observations,
- enable team discussions (address "what-if" questions), and
- support decision-making within a broader team.

Future application

Due to the modular setup of the application, it can be extended to include items like additional treatment effects, data, and analysis workflows (e.g. optimize selected model structures in NONMEM), and it can easily be converted to be used within different projects.

[1] RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL <http://www.rstudio.com/>

[2] <http://shiny.rstudio.com/>

[3] R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>

[4] Snelder N, et al., Mechanism-based PKPD modeling of cardiovascular effects in conscious rats – an application to fingolimod, PAGE 22 (2013) Abstr 2686 [www.page-meeting.org/?abstract=2686]

[5] Snelder N, et al., Drug effects on the CVS in conscious rats: separating cardiac output into heart rate and stroke volume using PKPD modelling. Br J Pharmacol. 2014 Nov;171(22):5076-92