



RESEARCH GROUP | SYSTEMS PHARMACOLOGY

## TOWARD OPEN SCIENCE

Translating literature-reported quantitative pharmacology models for simulation and interactive visual exploration

Cambridge Innovation Center  
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# Implementaton of Lit-Reported QSP Models in mrgsolve

- About mrgsolve / background
- mrgsolve workflow in R
  - ▶ Yan et al. Pop PK and PD of Recombinant EPO and biosimilar. J Clin Pharmacol. 2012 November ; 52(11): 1624–1644
  - ▶ Introduce mrgsolvetk
- Parameter estimation in statin PBPK model
  - ▶ Yoshikado et al. Hepatic OATP-mediated DDI between pitavastatin and cyclosporin. CP&T volume 100 number 5 2016
  - ▶ `minqa::newuoa`, `RcppDE::DEoptim`, `MCMCpack::bayes`
- Sensitivity analyses and Dose-Response
  - ▶ Kirouac et al. Clinical responses to ERK inhibition with GDC-0994 as mono- and combination therapy in colorectal cancer. npj Systems Biology and Applications (2017) 14
  - ▶ Translate from SBML to mrgsolve
- Work with the Kirouac model in a Rshiny app

# About mrgsolve

- R package for simulation from ODE-based models
  - ▶ Free, OpenSource, GitHub, CRAN
- Language
  - ▶ Models written in C++ inside model specification format
  - ▶ General purpose solver: ODEPACK / DLSODA (FORTRAN)
  - ▶ Simulation workflow in R
- Hierarchical (population) simulation
  - ▶ ID,  $\eta$ ,  $\varepsilon$
- Integrated PK functionality
  - ▶ Bolus, infusion, F, ALAG, SS etc, handled under the hood
  - ▶ 1- and 2-cmt PK models in closed-form
- Extensible using R, C++, Rcpp, boost, RcppArmadillo
- R is it's natural habitat

# mrgsolve started as QSP modeling tool

- Motivation: large bone/mineral homeostasis model (CaBone)
- History using
  - ▶ Berkeley Madonna
  - ▶ WinBUGS
  - ▶ NONMEM (attempted)
- 2010: write R front end to deSolve
- 2012: write C++ interface to DLSODA
- Develop dosing / event capability
- More recently, expose functionality provided by
  - ▶ Rcpp - vectors, matrices, functions, environments, random numbers
  - ▶ boost - numerical tools in C++
  - ▶ users' own C++ code (functions, data structures, classes)
- Translator from SBML to mrgsolve using R bindings to libSBML