



TOWARD OPEN SCIENCE

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

Cambridge Innovation Center
20 July 2017

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 mrgsolvetc
- 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, η , ε
- 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 its natural habitat

mrgsovle 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 mrgsolute using R bindings to libSBML



NIH Public Access

Author Manuscript

J Clin Pharmacol. Author manuscript; available in PMC 2013 November 01.

Published in final edited form as:

J Clin Pharmacol. 2012 November ; 52(11): 1624–1644. doi:10.1177/0091270011421911.

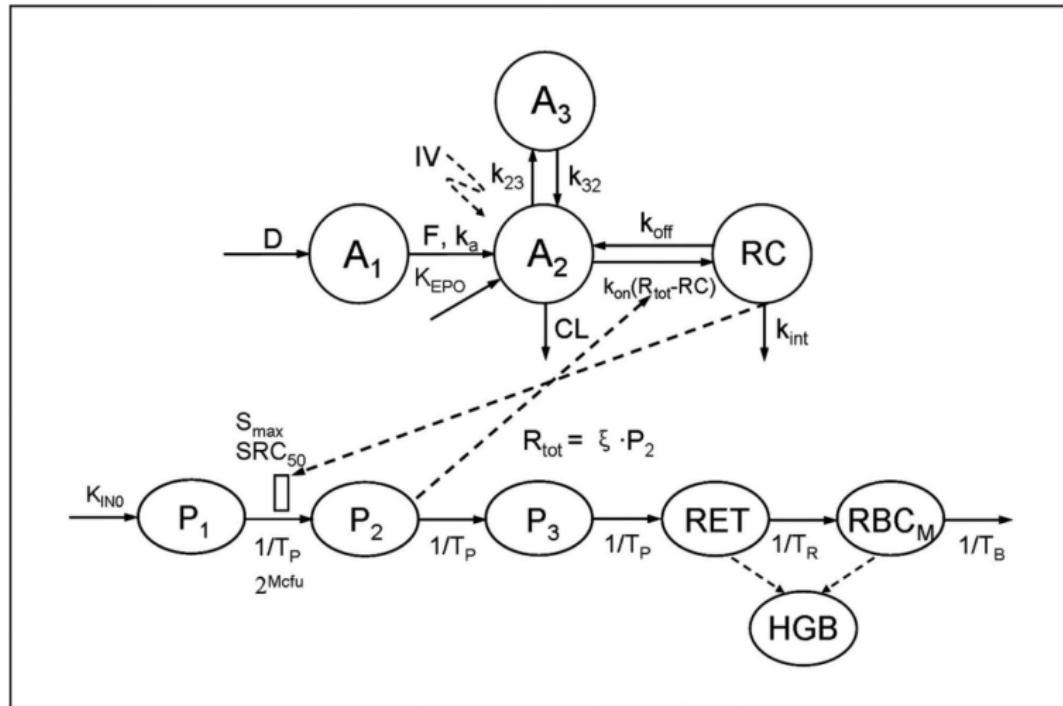
Population Pharmacokinetic and Pharmacodynamic Model-Based Comparability Assessment of a Recombinant Human Epoetin Alfa and the Biosimilar HX575

Xiaoyu Yan, MS, Philip J. Lowe, PhD, Martin Fink, PhD, Alexander Berghout, PhD, Sigrid Balser, PhD, and Wojciech Krzyzanski, PhD

Department of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York (Mr Yan, Dr Krzyzanski); Novartis Pharma AG, Modeling and Simulation, Basel, Switzerland (Dr Lowe, Dr Fink); and Sandoz Biopharmaceuticals, Holzkirchen, Germany (Dr Berghout, Dr Balser).

DDMoRe Repository DDMODEL00000076

EPO Model



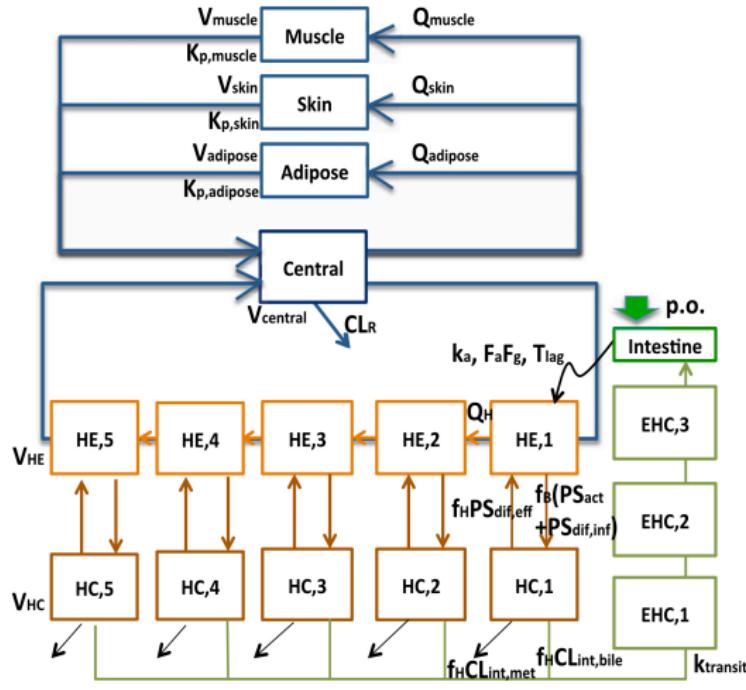
Quantitative Analyses of Hepatic OATP-Mediated Interactions Between Statins and Inhibitors Using PBPK Modeling With a Parameter Optimization Method

T Yoshikado¹, K Yoshida², N Kotani³, T Nakada⁴, R Asaumi⁵, K Toshimoto¹, K Maeda², H Kusuhara² and Y Sugiyama¹

This study aimed to construct a widely applicable method for quantitative analyses of drug–drug interactions (DDIs) caused by the inhibition of hepatic organic anion transporting polypeptides (OATPs) using physiologically based pharmacokinetic (PBPK) modeling. Models were constructed for pitavastatin, fluvastatin, and pravastatin as substrates and cyclosporin A (CsA) and rifampicin (RIF) as inhibitors, where enterohepatic circulations (EHC) of statins were incorporated. By fitting to clinical data, parameters that described absorption, hepatic elimination, and EHC processes were optimized, and the extent of these DDIs was explained satisfactorily. Similar *in vivo* inhibition constant (K_i) values of each inhibitor against OATPs were obtained, regardless of the substrates. Estimated K_i values of CsA were comparable to reported *in vitro* values with the preincubation of CsA, while those of RIF were smaller than reported *in vitro* values (coincubation). In conclusion, this study proposes a method to optimize *in vivo* PBPK parameters in hepatic uptake transporter-mediated DDIs.

CP&T vol. 100 no. 5 pp. 513-23 11/2016

Pitavastatin PBPK model with EHC



CsA PBPK model runs along with statin model (DDI)

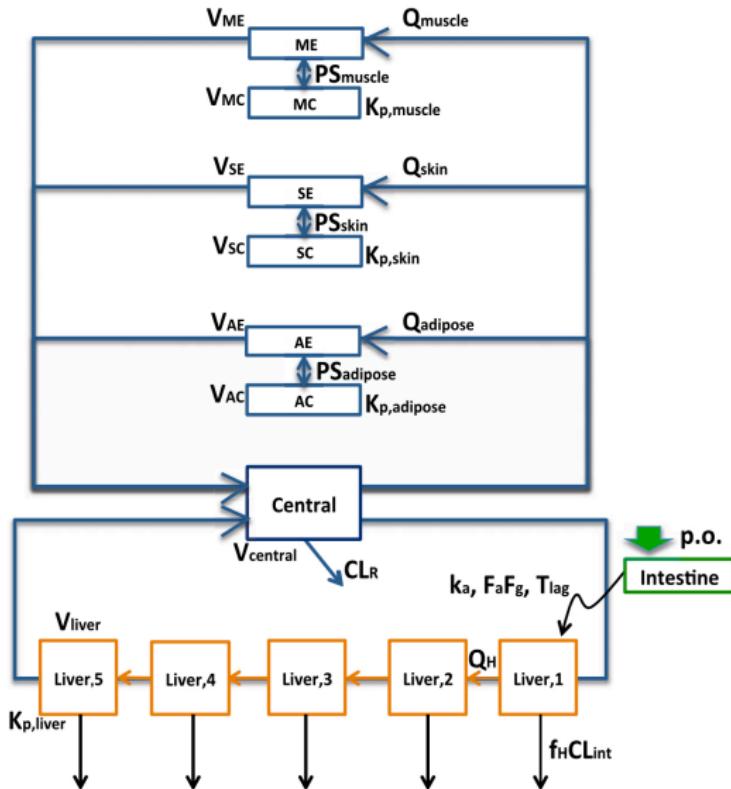
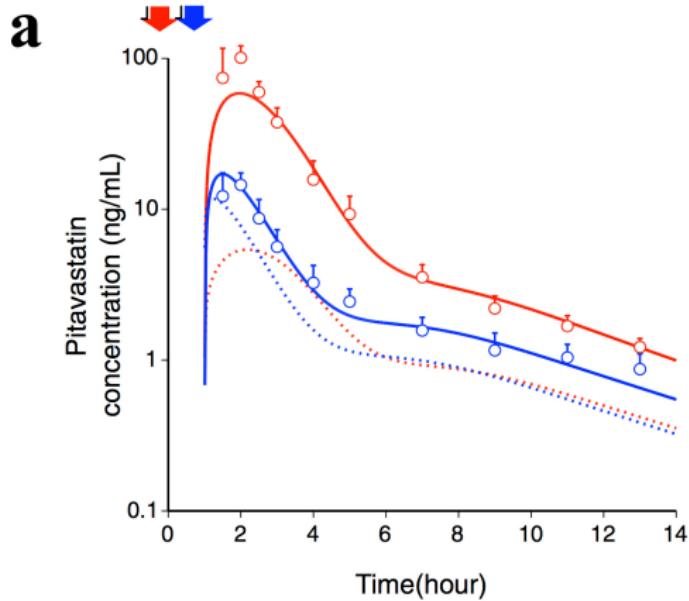


Figure 4a

Pitavastatin (EHC model)



ARTICLE

OPEN

Clinical responses to ERK inhibition in *BRAF^{V600E}*-mutant colorectal cancer predicted using a computational model

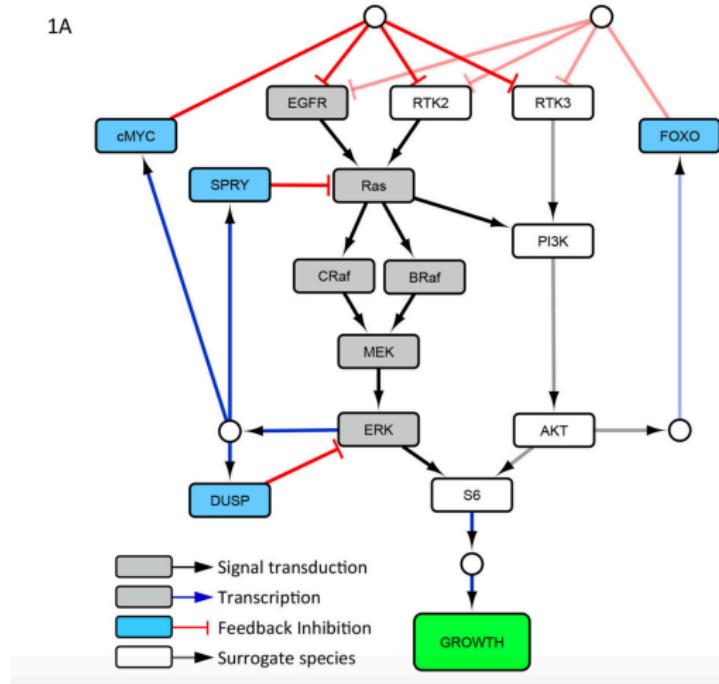
Daniel C. Kirouac¹, Gabriele Schaefer¹, Jocelyn Chan¹, Mark Merchant¹, Christine Orr¹, Shih-Min A. Huang¹, John Moffat¹, Lichuan Liu¹, Kapil Gadkar¹ and Saroja Ramanujan¹

Approximately 10% of colorectal cancers harbor *BRAF^{V600E}* mutations, which constitutively activate the MAPK signaling pathway. We sought to determine whether ERK inhibitor (GDC-0994)-containing regimens may be of clinical benefit to these patients based on data from *in vitro* (cell line) and *in vivo* (cell- and patient-derived xenograft) studies of cetuximab (EGFR), vemurafenib (BRAF), cobimetinib (MEK), and GDC-0994 (ERK) combinations. Preclinical data was used to develop a mechanism-based computational model linking cell surface receptor (EGFR) activation, the MAPK signaling pathway, and tumor growth. Clinical predictions of anti-tumor activity were enabled by the use of tumor response data from three Phase 1 clinical trials testing combinations of EGFR, BRAF, and MEK inhibitors. Simulated responses to GDC-0994 monotherapy (overall response rate = 17%) accurately predicted results from a Phase 1 clinical trial regarding the number of responding patients (2/18) and the distribution of tumor size changes ("waterfall plot"). Prospective simulations were then used to evaluate potential drug combinations and predictive biomarkers for increasing responsiveness to MEK/ERK inhibitors in these patients.

npj Systems Biology and Applications (2017)3:14; doi:10.1038/s41540-017-0016-1

MAPK signaling

Clinical responses to ERK inhibition
DC Kirouac et al.



$$ERK = ERK_b + (ERK_t - ERK_b) \cdot \left(\frac{MEK^{k4}}{\tau_4^{k4} + MEK^{k4}} \right) \cdot \left(1 - \frac{FB_1^{kFB1}}{\tau_{FB1}^{kFB1} + FB_1^{kFB1}} \right) \cdot \left(1 - \frac{ERKi^{ki4}}{\tau_{i4}^{ki4} + ERKi^{ki4}} \right)$$

$$S6 = S6_b + (S6_t - S6_b) \cdot \left(\frac{(w_{OR} \cdot ERK + (1 - w_{OR}) \cdot AKT)^{k6}}{\tau_6^{k6} + (w_{OR} \cdot ERK + (1 - w_{OR}) \cdot AKT)^{k6}} \right)$$

Kirouac et al. Figure 6b

