



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



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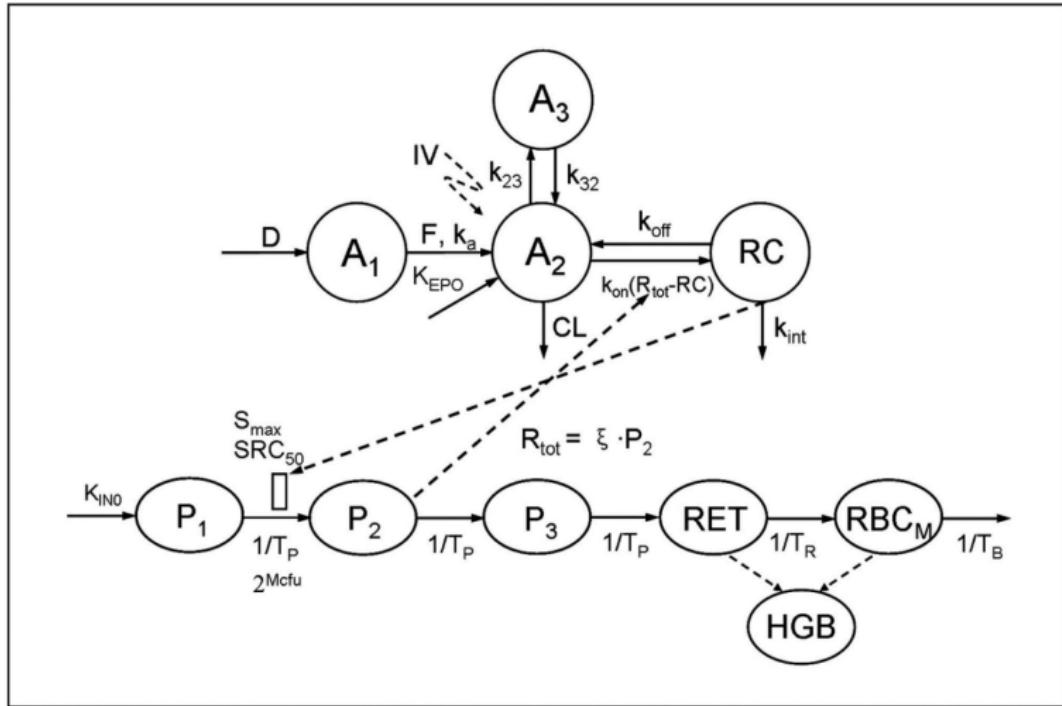
Population Pharmacokinetic and Pharmacodynamic Model-Based Comparability Assessment of a Recombinant Human Epoetin Alfa and the Biosimilar HX575

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).

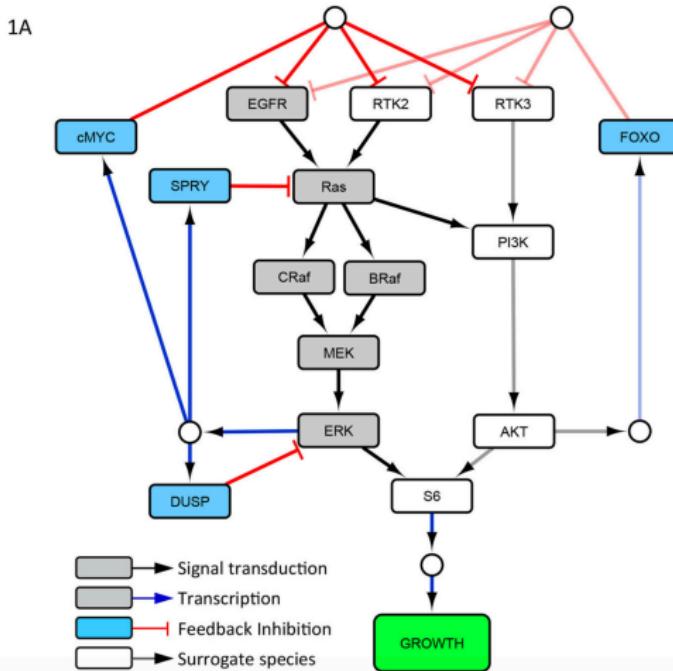
DDMoRe Repository DDMODEL00000076

EPO Model



MAPK signalling

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

