Objective: To develop computer software facilitating large-scale simulation from hierarchical, ordinary differential equation (ODE) based models typically employed in drug development.

Methods: Specific software requirements were specified to enable a modern and efficient simulation platform. A C++ interface between R and the ODEPACK solver DLSODA was developed using Rcpp. C++ classes were developed to abstract solver setup, data sets and records, and PK dosing events. S4 classes and methods were created to represent the model in R as an updatable object. The modeler creates a model specification file consisting of R and C++ code that is parsed, compiled, and dynamically loaded into the R session. Input data are passed in and simulated data are returned as R objects, so disk access is never required during the simulation cycle after compiling.

Results: The following software requirements were met:

- NMTRAN-like input data sets
- Bolus, infusion, compartment on/off and reset functionality
- Bioavailability, ALAG, SS, II, ADDL, MTIME
- Multivariate normal random effects simulated using RcppArmadillo
- Compatible with parameter estimation and design packages in R (nlme, saemix, PopED, PFIM)
- Integration with data summary (dplyr) and plotting (ggplot, lattice) packages
- Parallelization with existing R infrastructure (mclapply) or Sun Grid Engine (qapply)
- Compatible with output from many different model estimation platforms
- Easily integrated with Shiny to create model-visualization applications

Benchmark:

- Simulation of 4- and 26-week trials of 1000 patients with daily oral dosing as an indirect response model with 1-compartment PK took 1.35 and 9.01 seconds (average, 10 replicates), respectively, on MacBookPro 2.4GHz

Conclusions: mrgsolve is a powerful and efficient tool for simulation from ODE-based PK/PD and systems pharmacology models. The resulting computational efficiency facilitates model exploration and application, both during model development and decision-making phases of a drug development program.

References: