An efficient language for model-based trial simulations
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Objectives: Compared to other languages for nonlinear mixed-effect models, Pharsight modeling language (PML) was designed to be good for both model fitting and simulations. The goal is to demonstrate advantages using PML for model-based simulations through an example.

Methods: PML simulation includes two major components. One is for fitted population models and covariate distribution models. The other is for study protocol designs that specify how simulation is conducted and are written in procedures having the capability of “sleep”, branching and looping. This allows users to not only directly simulate fitted models but also do individual-level post-analysis (e.g., calculate AUC and Cmin), which avoids outputting a huge amount of data to do such processing/analysis in third party software and hence saves I/O time. PML codes can also be integrated with R to do statistical analysis and visualization.

Results: The example of demonstrating these is based on the antibiotic study [1], where Monte Carlo simulation was used to find optimal dose. This involves multiple endpoint analysis, non-steady-state and steady-state analysis: calculate probability of target attainment for AUC/MIC and probability of Cmin above some value at day 1 and steady-state. We successfully implemented this example in PML with “steadystate” statement used to automatically detect if steady-state is reached. To have some idea of computational savings for doing individual-level post-analysis in PML, we compared computation times for two methods: one calculates AUC, AUC/MIC and Cmin in PML and does population-level post-analysis in R; and the second method does all the post-analysis in R. We found that the first method integrated PML for post-processing saves over 29% computational time.

Conclusions: We demonstrated how PML can be used to facilitate model-based simulation. This is achieved through seamless integration of fitted population models into simulation and the ability of doing both pre-processing and individual-level post-analysis, and hence avoid manually modifying fitted models for simulation and reduce the need to use different software to do the job.

References: