Simcyp Simulator within the DDMoRe Interoperability Framework – Proof of Concept Cases

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Objectives

A corner stone of model-informed drug development is interoperability among various models, tools and platforms. The Innovative Medicines Initiative's Drug Disease Model Resources (DDMoRe) consortium aims at establishing such a framework (http://www.ddmore.eu/). As part of this initiative the Simcyp population based physiologically-based pharmacokinetic and pharmacodynamics (PBPK/PD) platform has been further developed to operate within the DDMoRe framework. In this study two proof of concept case studies using the Simcyp Simulator in a workflow are presented.

Methods

Case 1: Using the Model Description Language Integrated Development Environment (MDL-IDE) and leveraging Simcyp-specific functions within the DDMoRe R package, data were generated for adult individuals (of healthy, renal impairment, and cirrhotic populations) as well as PK profiles for Metoprolol using Simcyp Simulator Version 15. These data were generated in the Standard Output (SO) format and several Comma Separated Values (CSV) files which were parsed by an R script within the MDL-IDE in order to visualise the simulated individuals' parameters and concentration time profiles. The data were then used to construct a table containing dosing and concentration profiles and covariates and passed within the mdl file to NONMEM for compartmental estimation task to check that the interoperability is seamless.

Case 2 : The MDL-IDE was used to create and execute an R script which utilised functions within a freely available Simcyp R package to run a simulation using version 15 of the Simcyp Simulator. This made use of a pre-saved Simcyp workspace to simulate a full PBPK model of Midazolam after intravenous administration to paediatric and adult populations. The predicted concentration profiles and the relevant PK parameters were retrieved (again using the Simcyp R package) for general comparison.

Results

While the DDMoRe interoperability framework support is still a 'work in progress', capabilities of the Simcyp Simulator (i.e. running simulations and generating populations) were successfully used from within the MDL-IDE on a local Windows machine to produce population, compound, and trial design dependent data in the form of a SO file. This was achieved through the use of new Simcyp features, including; the Simcyp functions within the DDMoRe R package, and the Simcyp Console application. The simulated metoprolol profiles for virtual healthy adult individuals with different CYP2D6 phenotypes and trial database was submitted for additional tasks within the DDMoRe interoperability framework (Figure 1) including visualization of the data, estimation task (NONMEM) and goodness of fit checks (Xpose).

The Simcyp R Package, which was developed independent of the DDMoRe project, was successfully used from DDMoRe R Package within MDL-IDE to run Simcyp workspaces and access the simulated data for midazolam in paediatric and adult populations. The data were visualize using other R packages within the MDL-IDE (figure 2).

Conclusions

The Simcyp Simulator is the unique PBPK platform that now comes bundled with a command line console which works within the DDMoRe Interoperability Framework. This new functionality allows DDMoRe partners with a Simcyp Simulator licence to run simulations and generate populations in scripted workflows with other software such as NONMEM and PSN, Monolix, PFIM, and PopED. The Simcyp Console may be used independently of DDMoRe framework and users can benefit from the Simulator's vast databases of populations, compounds and PBPK/PD models through other platforms such as Matlab and R.
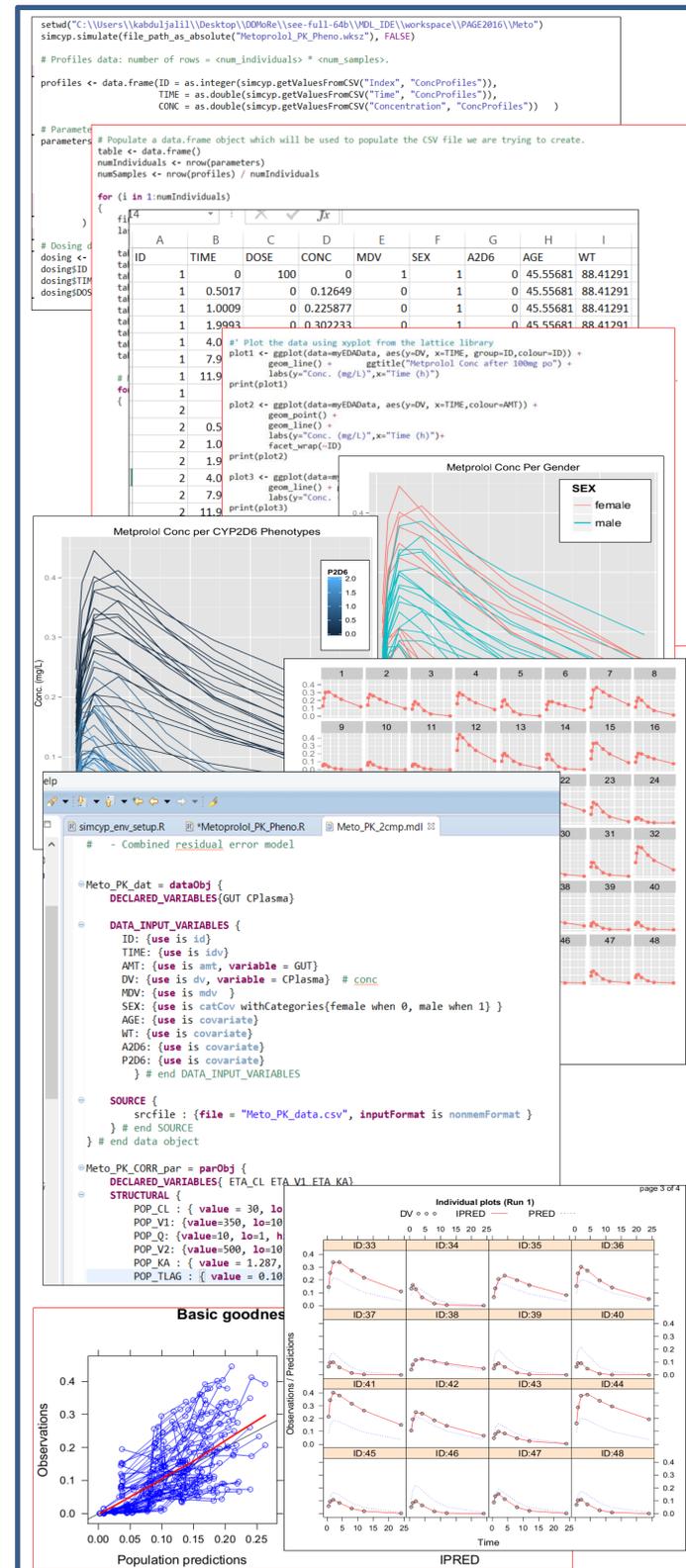

Figure 1. Interoperability of Simcyp Simulator with DDMoRe framework
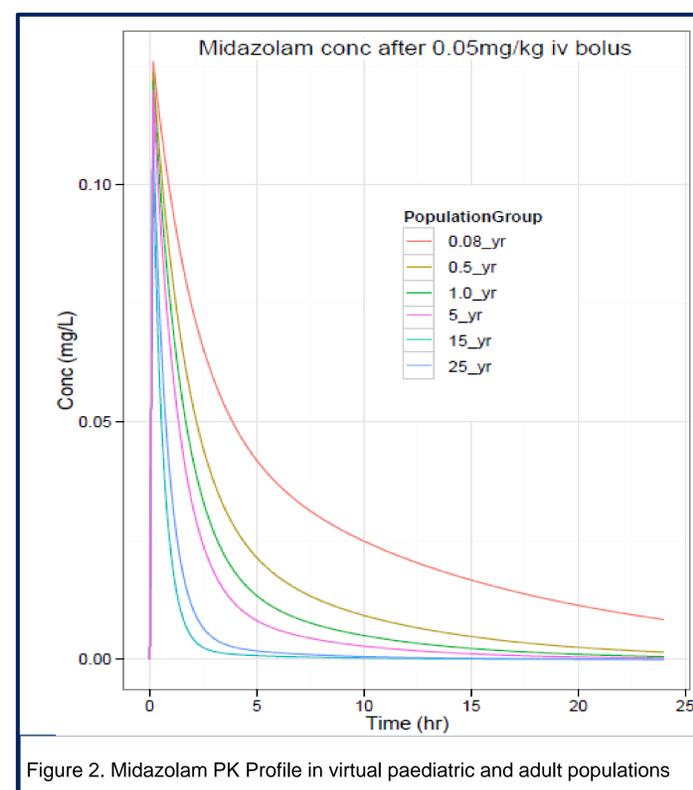
Figure 2. Midazolam PK Profile in virtual paediatric and adult populations