Simulate modified NONMEM models using NMsim

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Objectives

The new R package NMsim (Delff 2024) provides the capability to perform NONMEM simulations directly from R, without need of model reimplementation. NMsim automates the simulation of NONMEM models and provides a concise interface for modifying the control stream integrated into the simulation command. Thus, efficient automated workflows can be developed to perform simulation based analyses and visualize key results.

Many questions throughout the drug development stages can be addressed by simulating effects of specific changes to model structure or model parameters. We aim to showcase these features through some examples that are highly relevant in pharmacometrics.

Methods

We show examples of the use of the `modify.model` NMsim feature addressing the pharmacometric questions:

- How is the concentration-time profile affected if switching formulation (reducing absorption rate) by a range of fold-values?
- What is the expected conc.-time profile in patients with a certain Drug-Drug Interaction effect on clearance and bioavailability?
- How will a dose delay of different amounts of time affect the predicted exposure?
- How can AUC computation over a coarse time grid be integrated in the simulation via NMsim?

The standard NMsim call requires a NONMEM control stream `file.mod` and a simulation data structure `data` containing dosing events, simulation time steps, and the additional parameters needed in the simulation.

```
library(NMdata) # version 0.1.8
library(NMsim) # version 0.1.4
NMdataConf(path.nonmem = "/opt/NONMEM/nm75/run/nmfe75"
           ,dir.sims="simtmp" #location of sim tmp files
           ,dir.res="simres") #location of sim results
file.mod="examples/nonmem/xgxr021.mod"
simres <- NMsim(file.mod=file.mod
           ,data=dat.sim.varka)
```

Results

Change in formulation

The effect on the concentration-time profile of a change in formulation that reduces absorption rate KA is explored with the use of a scaling factor `KASCALE=c(1,4,10)` included to the NONMEM control stream via the `modify.model` argument. The absorption rate reduction is provided through the NMsim simulation data `dat.sim.varka` containing dosing events, simulation time steps and the value of KASCALE for each simulated patient. The effect of the scaling factor can be either:

(**a**) added at the end of the PK section of the control stream

```
simres.varka <- NMsim(file.mod=file.mod # NONMEM control stream
           ,data=dat.sim.varka # simulation data file
           ,name.sim="varka"
           ,modify.model=list(PK=add("KA=KA/KASCALE")))
```

(**b**) custom subbed-in at the specific line where the typical value for the absorption rate TVKA is defined

```
simres.varka2 <- NMsim(file.mod=file.mod
           ,data=dat.sim.varka
           ,name.sim="varka2"
           ,modify.model=list(PK=function(x) {
           ## identify line number if first definition of TVKA
           idx.line1.TVKA <- min(grep(" *TVKA *=",x))
           ## add /KASCALE after dropping potential comments
           x[idx.line1.TVKA] <-
             paste(sub(";.*","",x[idx.line1.TVKA]),"/KASCALE")
           x}))
```

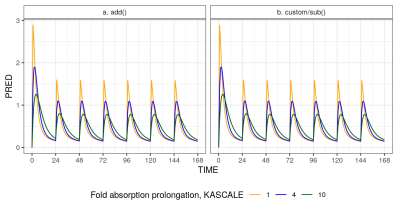

Figure 1: Concentration (PRED) profile as a function of time computed by NMsim modified models **a** (left) and **b** (right). The equivalence and robustness of the two modified models is supported by the matching results, corresponding to reduced PRED values for higher values of KASCALE (lower absorption rate).

Drug-Drug Interaction (DDI)

The effect of DDI on clearance (CL) and bioavailability (F1) is simulated for the following scenarios

scenario	CLSCALE	FSCALE	CLSCALE/FSCALE
noDDI	1	1	1
DDI.1	0.5	1.2	0.42
DDI.2	0.33	1.1	0.3

The DDI driven change in parameters is added at the end of the PK section of the NONMEM control stream via NMsim, and its effect on the concentration-time profile is shown in the figure.

```
simres.DDI <- NMsim(file.mod=file.mod
           ,data=dat.sim.DDI
           ,name.sim="DDI"
           ,modify.model=list(PK=add("CL=CL*CLSCALE"
                                     ,"F1=FSCALE")))
```

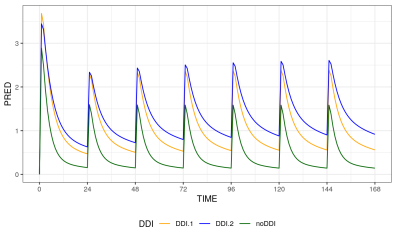

Figure 2: Concentration (PRED) profile as a function of time computed by NMsim modified model for different DDIs. The modified model correctly simulates (i) a higher value of Cmax on day 1 for higher biovalability; (ii) a higher PRED value at steady state for lower apparent clearance effect CLSCALE/FSCALE values.

Dose delay

Deviations in the administration schedule of a drug are simulated including three parameters in the dataset: the dose number DOSCUMN, obtained with `NMdata::addTAPD()`, the specific number of the delayed dose DELAYDOS and the time delay ALAG. The following patient has a 6 hours delay to the administration of dose 2.

TIME	AMT	DOSCUMN	DELAYDOS	ALAG
0	300	1	2	6
24	150	2	2	6
48	150	3	2	6
72	150	4	2	6
96	150	5	2	6
120	150	6	2	6
144	150	7	2	6

The time delay is included in the modified control stream with NMsim adding a single line at the end of the PK section

```
simres.alag <- NMsim(file.mod=file.mod
           ,data=dat.sim.alag.final
           ,name.sim="alag"
           ,modify.model=list(PK=
                 add("IF(DOSCUMN.EQ.DELAYDOS) ALAG1=ALAG")))
```

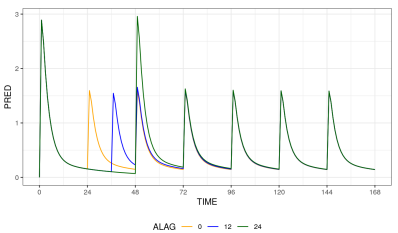

Figure 3: Effect of time delay (0, 12 and 24 hours on dose 2) on concentration (PRED) profile as a function of time computed by NMsim modified model. The implementation of the modified model simply consists of the addition of the vairables DOSCUMN, DELAYDOS, and ALAG to the original data set, and the addition of one line of code to the PK section of the control stream via `modify.model`.

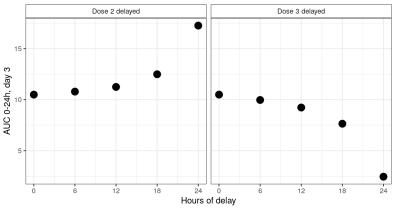

Figure 4: Daily exposure on day 3 as a function of time delay for dose 2 (left) and dose 3 (right). The simulation results predict an increased risk for possible safety concerns (left panel, over-exposure) and loss of efficacy (right panel, under-exposure) as dose time delay gets larger.

AUC

The following example computes daily exposure:

- at post-processing, using trapezoidal method, after the unmodified NONMEM model is simulated on three different fine grids with evenly spaced time steps of 0.25, 1, and 4 hours, respectively, labelled **AUC trapz**

```
sres1 <- NMsim(file.mod=file.mod.auc
           ,data=dat.sim # fine time grid))
stmp=sres1[EVID==2,.(ID,TIME,PRED)]
stmp[,DAY:=(TIME%/%24)+1]
sAUC<-stmp[,.(AUC=pracma::trapz(TIME,PRED)),by=.(ID,DAY)]
```

- at run time, with an NMsim modified script, on a course grid with evenly spaced time steps of 24 hours, labelled **AUC $DES**. Of note, this task requires additions to the control stream in multiple sections.

```
sres2 <- NMsim(file.mod=file.mod.auc
           ,data=dat.sim2
           ,modify.model=list(MODEL=add("COMP=(AUC)")
                 ,DES=add("DADT(3)=A(2)/V2")
                 ,ERROR=add("AUCCUM=A(3)"
                       ,"IF(NEWIND.NE.2) OLDAUCCUM=0"
                       ,"AUCNMSIM = AUCCUM-OLDAUCCUM"
                       ,"OLDAUCCUM = AUCCUM")))
```

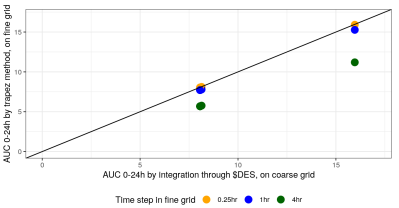

Figure 5: Daily exposures computed at run time ($DES, coarse grid, x-axis) and post-processing time (`trapz`, fine grids, y-axis). AUC (trapz) converges to the value computed with $DES method as the time step is reduced. Includes identity line.

Conclusion

The `modify.model` feature provided by the NMsim R library is a flexible and adaptable tool to explore the implications of various properties of a pharmacometric model. The examples explored show that `modify.model` can effectively be used to

- add or replace lines in the NONMEM control stream in a convenient and intuitive way directly from within the R environment
- change parameter values at simulation-time to efficiently simulate patient/population specific scenarios.

All software, code, and data used are freely available for the audience to modify to their own needs.

See also

See NMsim website for vignettes and news.

Related posters at ACoP 2024

- NMsim - Seamless NONMEM Simulation Platform in R (T32)
- Simulation of clinical trial predictions with model uncertainty using NMsim (T110)
- Building Automated Pharmacometrics Analysis Workflows in R with NMsim (T49)
- A Model-Based Simulation Workflow Enables Automated and Accurate Generation of Clinical Pharmacology Summary Statistics (T103)

References

Delff, Philip. 2024. *NMsim: Seamless Nonmem Simulation Platform*. https://philipdelff.github.io/NMsim/.