Simulation With Parameter Uncertainty Using NMsim

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Introduction

The new R package, `NMsim` [1,2], provides the capability to perform simulations of NONMEM models directly from R without the need for model reimplementation. Using only paths to control stream(s) and a simulation data set provided by the user, `NMsim` can incorporate model parameter uncertainty through several different methods, from running a covariance step to evaluating bootstrap results, allowing calculations of confidence intervals and summarization of covariate effects, e.g. forest plots. `NMsim` can also be used for clinical trial simulations via a multi-model simulation in NONMEM, implemented entirely in R. We aim to show these features through examples that are highly relevant in pharmacometrics.

Objectives

Using simple adjustments to `NMsim` function calls we will demonstrate how to:

- Incorporate model parameter uncertainty from bootstrap results for an example typical subject
- Incorporate model parameter uncertainty from a covariance step for an example typical subject
- Perform a clinical trial simulation on a virtual population
- Use simulation with parameter uncertainty to evaluate covariate effects and generate a forest plot using `coveffectsplot` [3]

These applications of `NMsim` are performed entirely in R, automatically interpreting existing NONMEM control streams and outputs to quickly and easily generate the appropriate NONMEM simulation framework. There is no need to reimplement the model or manually modify existing files.

Detailed vignettes and prior poster presentations are available at: https://NMautoverse.github.io/NMsim/

Table 1: Comparison of simulation methods using NMsim

METHOD	PROS	CONS
bootstrap	- no covariance step - captures all parameter correlations - non-parametric	- requires bootstrap prior to NMsim - user must choose which bootstrap runs to accept - slow: NONMEM run per bootstrap run
mvrnorm	- parameter sampling is performed directly in R - captures all parameter correlations	- requires covariance step - normally-distributed OMEGA/SIGMA - slow: NONMEM run per sample run
NWPRI	- samples from correct parameter distributions† - fast: only one NONMEM run (SUBPROBLEMS)	- requires covariance step - requires NONMEM 7.6 for sampling of OMEGA/SIGMA params - OMEGA/SIGMA correlations within modeled block structure only‡
simpar	- parameter sampling is performed directly in R - samples from correct parameter distributions†	- requires simpar installation - requires covariance step - OMEGA/SIGMA correlations within modeled block structure only‡ - slow: NONMEM run per sample run

† Uses normal distributions for THETAs and inverse-Wishart distributions for OMEGA/SIGMAs.

‡ simulations reproduce parameter correlations for given blocked OMEGA/SIGMA structures, rather than all parameter correlations

Methods

Sample from a bootstrap

1000 bootstrapped models were previously estimated with `psn` and read in using NMdata.

```
#read in bootstrapped models
library(NMdata) ## version 0.2.0
dir.bs <- "NMsim-forest-models/xgxr134_bs_N1000/m1"
exts.bs <- list.files(dir.bs,pattern=".+\\.ext$",
                      recursive=T,full.names = TRUE)
ext <- NMreadExt(exts.bs,as.fun="data.table")
```

Sample from `mvrnorm`

Model parameters are sampled 1000 times with parameter uncertainty from the variance-covariance matrix. THETAs, OMEGA, and SIGMA are normally-distributed.

```
library(NMsim) ## version 0.2.3
ext <- samplePars(file.mod=file.mod,nsims=1000,
                  method="mvrnorm",seed.R=6789)
```

Sample from `simpar`

- Model parameters are sampled 1000 times with parameter uncertainty from the variance-covariance matrix. THETAs are normally-distributed, OMEGA and SIGMA are sampled from the Inverse-Wishart distribution.
- Requires simpar package installation
- `simpar` is preferred prior to NONMEM 7.6.0, due to NONMEM's NWPRI incorrectly sampling OMEGA and SIGMA

```
ext <- samplePars(file.mod=file.mod,nsims=1000,
                  method="simpar",seed.R=6789)
```

Run simulation with parameter uncertainty

- Bootstrap, mvrnorm, and simpar methods can all be run with the same command, changing only the input to `ext` (Figure 1).
- For a clinical trial simulation (Figure 2), the default value of `typical` (FALSE) should be used to include between-subject variability

```
simres <- NMsim(file.mod ## path to NONMEM model
                ,data=data.sim, ## simulation dataset
                ,name.sim="PAGE2025_sim" ## output name suffix
                ,method.sim=NMsim_VarCov ## sampling with mvrnorm
                ,ext=ext ## input parameters
                ,typical=TRUE ## FALSE to include BSV
                ,table.vars=cc(PRED,IPRED) ## output table variables
                ,sge=TRUE ## TRUE if submitting to a cluster
                ,nc=1) ## number of cores
```

Sample using NONMEM's NWPRI

- This method uses NONMEM's built in `$PRIOR` NWPRI statement
- Model parameters are sampled 1000 times with parameter uncertainty from the variance-covariance matrix.
- THETAs are normally-distributed, OMEGA and SIGMA are sampled from the Inverse-Wishart disitribution
- Use `typical=TRUE` for a typical subject (no BSV; Figure 1)
- From NONMEM 7.6.0 on, NWPRI is preferred due to its significantly faster run time

```
nwpri.sim <-
  NMsim(file.mod=file.mod,
        data=dt.sim,
        name.sim="PAGE2025_nwpri",
        method.sim=NMsim_NWPRI,
        table.vars="PRED IPRED Y",
        subproblems=1000) ## subproblems for $SIMULATION
```

Covariate effects using `NMsim` then `coveffectsplot`

The example below shows how NMsim can perform 1000 model runs to evaluate the impact of covariate effects relative to a reference subject.

```
## define covariates (values or quantiles for continuous)
covs <- forestDefineCovs(
  AGE=list(ref=55,values=c(35,45,65,75),label="Age (years)"),
  WEIGHTB=list(ref=median,quantiles=c(10,25,75,90)/100,
               label="Bodyweight (kg)"),
  MALEN=list(ref=c(Female=0), values=c(Male=1), label="Sex"),
  data=data.ref) ## reference data for covariates
covs[,ID:=.GRP,by=.(type,covvar,covval)] ## add unique IDs

doses <- NMcreateDoses(TIME=0,AMT=30,ADDL=29,II=24)
## generate the complete dataset (sampling at steady state)
dt.sim <- NMaddSamples(doses,TIME=seq(720,744,by=0.25),CMT=2)

#run NMsim
simres <- NMsim(file.mod ## path to NONMEM model
                ,data=dt.sim, # simulation dataset
                ,name.sim="nwpri_forest"
                ,method.sim=NMsim_NWPRI ## sampling with NWPRI
                ,subproblems=1000 ## nmb parameter sets sampled
                ,typical=TRUE ## no BSV included
                ,table.vars=cc(PRED,IPRED)
                ,seed.R=342)

## Define exposure metrics
funs.exposure <- list(
    "Cmax"=function(x) max(x$IPRED)
   ,"AUC"=function(x) NMcalc::trapez(x$TIME,x$IPRED))
## Compute exposure ratios relative to reference
sum.uncertain <- forestSummarize(simres,
                                 funs.exposure = funs.exposure,
                                 by=cc(period),
                                 cover.ci=.95)
```

Results

Figure 1 describes the median and 95% confidence interval of simulated concentration-time profiles (n = 1000) for a typical subject at each dose level using the four methods (bootstrap, mvrnorm, NWPRI, simpar), which all produce comparable results.

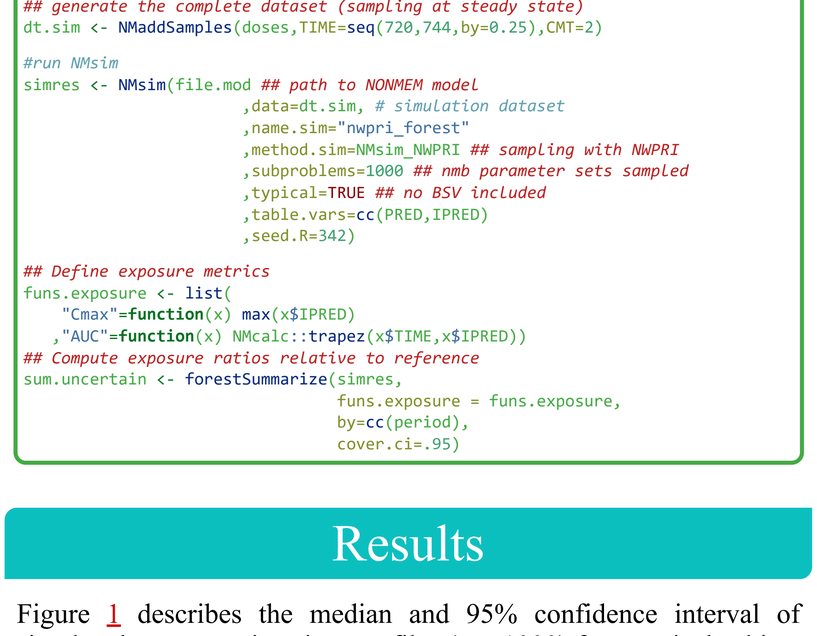

Figure 1: Typical subject simulated by different NMsim methods

Figure 2 describes the median and 95% confidence interval from two different clinical trial simulations containing 20 or 200 new subjects per dose level, respectively. Across all simulated trials and individuals, the median simulated profiles without individual or residual variability (PRED) demonstrate the effect of parameter uncertainty only, while profiles including individual variability (IPRED), and or both individual and residual variability (Y) illustrate the combinatorial effect of multiple sources of variability.

When the number of subjects is large (N=200), individual and residual variability have little effect on simulated outcomes, and only the effect of parameter uncertainty is reflected in confidence intervals seen (Figure 2, purple). In contrast, with only 20 subjects per trial arm (green), both individual and residual variability are evident, with individual variability dominating the variability in exposure.

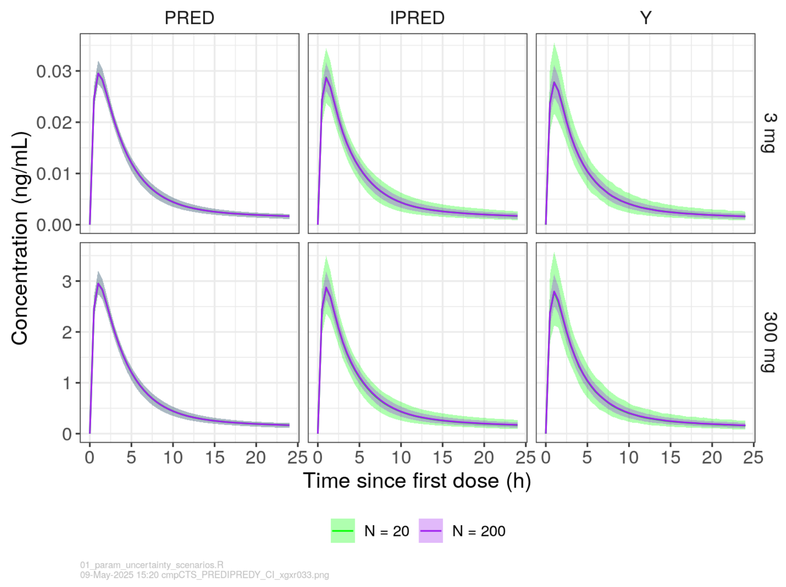

Figure 2: Clinical trial simulations using simpar and NMsim

Figure 3 shows an example forest plot produced by simulating 1000 subjects with parameter uncertainty. A more detailed overview of how `coveffectsplot` is used can be found in the vignettes section [See *Supplementary Information*] and documentation for the `coveffectsplot` package [3].

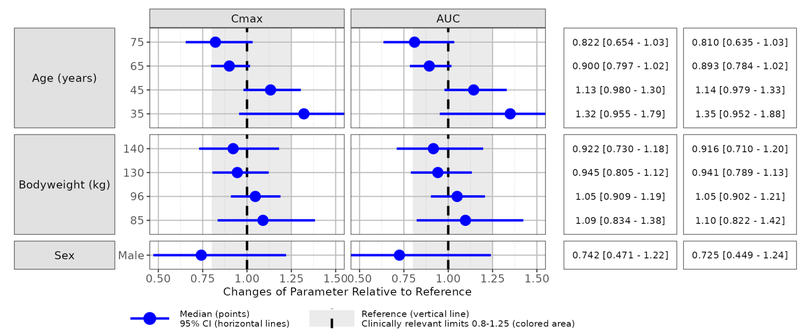

Figure 3: Example forest plot using NMsim and coveffectsplot

Figure 4 compares the results of all four sampling methods (bootstrap, mvrnorm, simpar, NWPRI) .

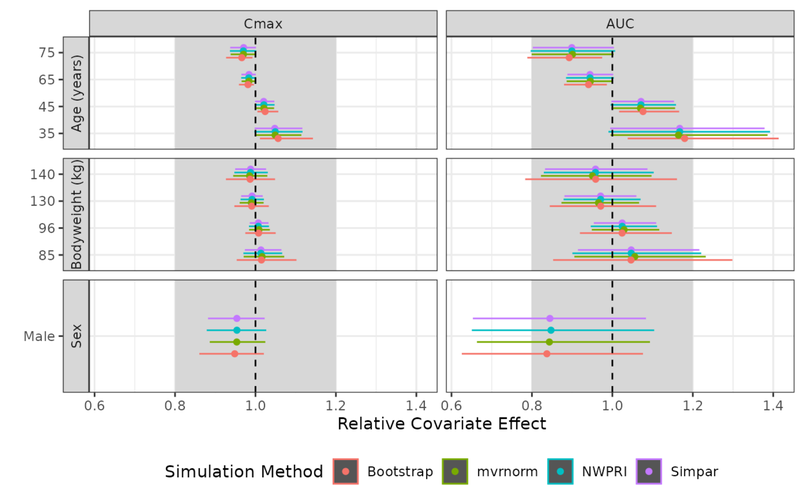

Figure 4: Forest plot by different NMsim methods

Conclusion

`NMsim` is a powerful tool for simulation, capable of generating parameters with uncertainty based on a non-parametric bootstrap, as well as parametric methods such as NONMEM's native NWPRI. `NMsim` accepts externally sampled parameters, and is compatible with parameter sampling using `simpar`.

This flexibility of `NMsim` allows for quick and simple generation of key results including clinical trial simulation and forest plots for exploring covariate effects. We hope these examples will aid pharmacometricians in making simulation with uncertainty easily accessible and facilitate the automation of essential drug development tasks.

Supplementary Information

Learn about how NMsim can help with:

- Visual Predictive Checks
- Modifying NONMEM models on the fly
- Simulation of known subjects using EBEs and more…

See the NMsim website for code, more publications, vignettes, and news, and check out our other poster at PAGE 2025: NMsim - Seamless NONMEM simulation platform in R!

References:

[1] 2024. NMsim: An R package that can simulate Nonmem models. https://philipdelff.github.io/NMsim
[2] 2024. NMsim: Seamless Nonmem Simulation Platform. https://cran.r-project.org/web/packages/NMsim
[3] Marier J-F, Teuscher N, Mouksassi M-S. Evaluation of covariate effects using forest plots and introduction to the coveffectsplot R package. CPT Pharmacometrics Syst Pharmacol. 2022; 11:1283-1293.
[4] 2023. simpar. https://mpn.metworx.com/docs/packages/simpar
https://github.com/metrumresearchgroup/simpar