Automated Simulation with Parameter Uncertainty from R with NONMEM and NMsim_NWPRI

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Introduction

- Performing simulations with parameter uncertainty is required for several key modeling analyses (such as for covariate evaluation via forest plots and for full clinical trial simulation), however, these simulations are cumbersome to perform as they typically require multiple manual steps and several different software packages to sample model parameters from an estimated covariance matrix and then simulate using the sampled parameters.

- With NMsim [1] and NONMEM[a] it is possible to perform simulations using the parametric parameter uncertainty estimated from a NONMEM covariance step in just a few lines of R code without ever leaving the R console.

- `NMsim_NWPRI` automates the construction and execution of NONMEM simulation control streams using $PRIOR NWPRI for seamless simulation using inverse-Wishart distributed variance parameters.

- The method requires just a few lines of R code, a simulation dataset, and a completed NONMEM model with a successful covariance step (Figure 1).

Objectives

- Demonstrate a simulation with parameter uncertainty using `NMsim_NWPRI`
- Compare the results of `NMsim_NWPRI` with those achieved using `simpar` [4] and `mvrnorm`
- Show how `NMsim_NWPRI` can be combined with NMsim's `modify` argument to modify uncertainty in simulations.
- Show how `NMsim_NWPRI` and `coveffectsplot` [3] can simplify evaluation of covariate effects with forest plots.

Methods and Results

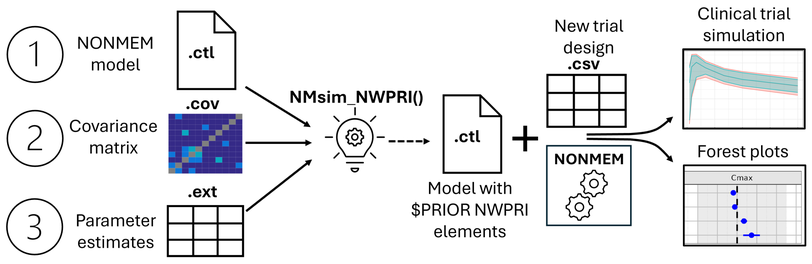

Figure 1: Diagram of NMsim_NWPRI mechanics

Sample parameters and simulate using `NMsim_NWPRI()`

- NMsim_NWPRI() samples parameters from a multivariate-normal and inverse-Wishart uncertainty distribution for fixed and random effects, respectively, using the parameter estimates in the '.ext' file and uncertainty estimates provided in a '.cov' file from a completed NONMEM run .
- Under the hood, NMsim_NWPRI uses the '.ext' and '.cov' files to automatically generate all elements required by the `$PRIOR NWPRI` subroutine in NONMEM (i.e. `$PRIOR`, `$THETAP`, `$THETAPV`, `$OMEGAP`, `$OMEGAPD`, etc.), and then runs the simulation in NONMEM.
- By default, if no simulation dataset is provided, NMsim_NWPRI will simulate the dataset used for estimation, but it is also possible to provide a new simulation design in the `data` argument.

```
library(NMsim)
file.mod = "models/mod_lorlatinib_estimate/mod_lorlatinib_estimate.mod"
simres = NMsim(
  file.mod = file.mod, # Path to NONMEM model
  seed.R = 1019, seed.nm = 1019, # random seeds for reproducibility
  method.sim = NMsim_NWPRI, # Simulation method
  name.sim = "ACOP2025_sim", # output name suffix
  subproblems = 1000, # number of simulations to perform
  path.nonmem = "~/nonmem760/nm760/run/nmfe76", # path to NONMEM
)
```

Figure 2 shows summarised population predictions from a simulation using 1000 parameters sets sampled from a NONMEM model with NMsim_NWPRI.

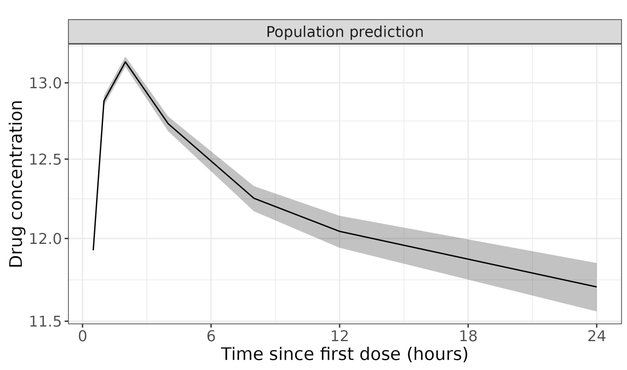

Figure 2: Concentration-time profile of a simulation with uncertainty using NMsim_NWPRI in a single subject. Line = median; ribbon = 95% CI.

Comparing parameters sampled using `mvrnorm`, `simpar`, and `NMsim_NWPRI`

- NMsim has built-in implementations to sample parameters from multivariate normal (`mvrnorm`) and inverse-Wishart (`simpar` [4]) uncertainty distributions.
- NMsim also has functions to simulate from the results of a bootstrap rather than a covariance step (see website).
- `simpar` samples fixed effects from a multivariate normal distribution and random effects from an inverse-Wishart distribution, while `mvrnorm` samples all parameters from a multivariate normal distribution.
- It is possible to use parameters sampled by `simpar` and `mvrnorm` to simulate with NMsim by passing them in the `ext` argument.

```
## sample parameters using simpar
par.simpar =
  NMsim::samplePars(file.mod = file.mod, nsims = 1000,
                    method = "simpar",  seed.R = 1019)
## sample parameters using mvrnorm
par.mvrnorm =
  NMsim::samplePars(file.mod = file.mod, nsims = 1000,
                    method = "mvrnorm", seed.R = 1019)
```

Figure 3 shows a comparison of the distributions of a fixed effect (THETA) and random effect (OMEGA) sampled using NMsim_NWPRI, simpar, and mvrnorm. All three methods give nearly identical results for fixed effects (i.e. THETA1), because they all sample parameters from a multivariate normal distribution. For random effects (i.e. OMEGA11), `simpar` and `NMsim_NWPRI` give nearly identical distributions of parameters with a clearly non-normal distribution, while `mvrnorm` appears gaussian, as expected.

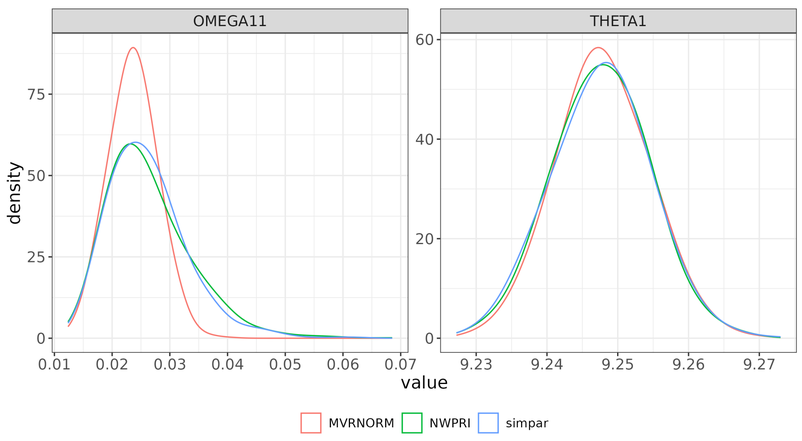

Figure 3: Distributions of 1000 parameters sampled using mvrnorm, simpar, and NMsim_NWPRI.

Use `modify` with `NMsim_NWPRI` to simulate with different parameter uncertainty distributions on the fly

- We can combine `modify` with `NMsim_NWPRI` to change the assumptions of our simulation
- `modify` will run on the NONMEM control stream after being generated by NMsim_NWPRI, so we can use it to increase the uncertainty or change the location of the prior, for any parameter.
- Here we use it to increase the uncertainty of both OMEGA(1,1) (BSV on CL) and THETA(1) (typical CL)
- This approach can be useful when extrapolating into new populations where you don't want to rely too closely on the model estimated uncertainty.

```
simres2 = NMsim(
  file.mod = file.mod, # Path to NONMEM model
  seed.R = 1019, seed.nm = 1019, # random seeds for reproducibility
  method.sim = NMsim_NWPRI, # Simulation method
  name.sim = "ACOP2025_sim_increaseVar", # output name suffix
  subproblems = 1000, # number of simulations to perform
  path.nonmem = "~/nonmem760/nm760/run/nmfe76", # path to NONMEM
  modify = list(
  ## increase uncertainty of THETA(1) (Clearance)
    THETAPV = function(x) {
      str_replace(x, pattern = "THETAPV BLOCK\\(15\\) FIX 4.42842e-05",
                  replacement = "THETAPV BLOCK\\(15\\) FIX 8e-02")},
    ##  decrease  degrees  of  freedom  for  OMEGA(1,1)  which  increases
        uncertainty
    OMEGAPD = function(x) {
      str_replace(x, pattern = "OMEGAPD 33.9933896381028 ",
                  replacement = "OMEGAPD 4.0 ")}
    ),
  table.vars =  "PRED IPRED Y"
)
```

Figure 4 shows a comparison of simulations before and after increasing the assumed uncertainty of the parameters using `NMsim_NWPRI` combined with NMsim's `modify` argument. The top panel shows a comparison of the sampled parameter distributions, while the bottom panel shows summarised population and individual predictions from a simulation of 1000 parameters sets.

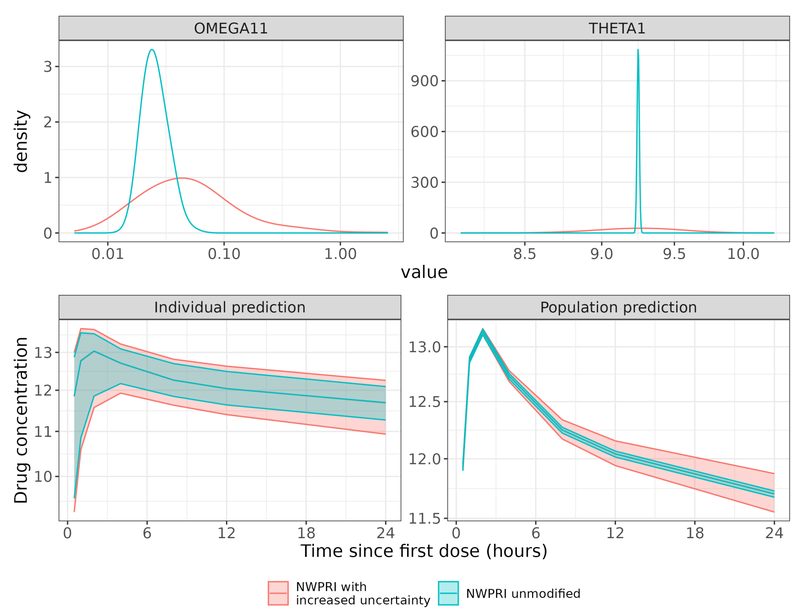

Figure 4: Top panel: Simulated parameter distribution before and after increasing uncertainty. Bottom panel: PK profile of simulation with uncertainty (Line = median; ribbon = 90% CI).

Use NMsim_NWPRI with coveffectsplot to quickly generate forest plots

The example below demonstrates how simple it is to evaluate covariates via forest plots with NMsim_NWPRI, some helper functions included in NMsim (`forestDefineCovs` and `forestSummarize`) and the `coveffectsplot` R package [4].

```
## define covariates (values or quantiles for continuous)
data.ref <- NMdata::NMscanData(file.mod,quiet=TRUE)
covs <- NMsim::forestDefineCovs(
  WNCL=list(ref=100,values=c(15,30,60,120),
            label="Serum Creatinine (mg/dL)"),
  BWT=list(ref=70,values=c(35, 50,90, 120),
               label="Bodyweight (kg)"),
  data=data.ref) ## reference data for covariates
covs[,ID:=.GRP,by=.(type,covvar,covval)] ## add unique IDs
## generate the complete dataset (dosing and sampling at steady state)
doses <- NMcreateDoses(TIME=0,AMT=1e5,ADDL=24,II=24,RATE=-2)
dt.sim <- NMaddSamples(doses, TIME = seq(576, 600, by = 0.25), CMT = 2)
        %>%
  dplyr::select(., -ID) %>%
  cross_join(covs) %>%
  arrange(ID, TIME, EVID)
## run NMsim
simres.forest <- NMsim(
  file.mod, ## path to NONMEM model
  data = dt.sim, # simulation dataset
  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 = 1019
)
## Define exposure metrics
funs.exposure <- list(
  "Cmax" = function(x) max(x$PRED),
  "AUC" = function(x) NMcalc::trapez(x$TIME, x$PRED)
)
## Compute exposure ratios relative to reference
sum.uncertain <-
  NMsim::forestSummarize(simres.forest,  funs.exposure = funs.exposure,
                         by = NULL, cover.ci=.95)
## generate the forest plot
coveffectsplot::forest_plot(data=sum.uncertain, facet_scales="free_y",
                            facet_space="free_y", plot_table_ratio=1.6)
```

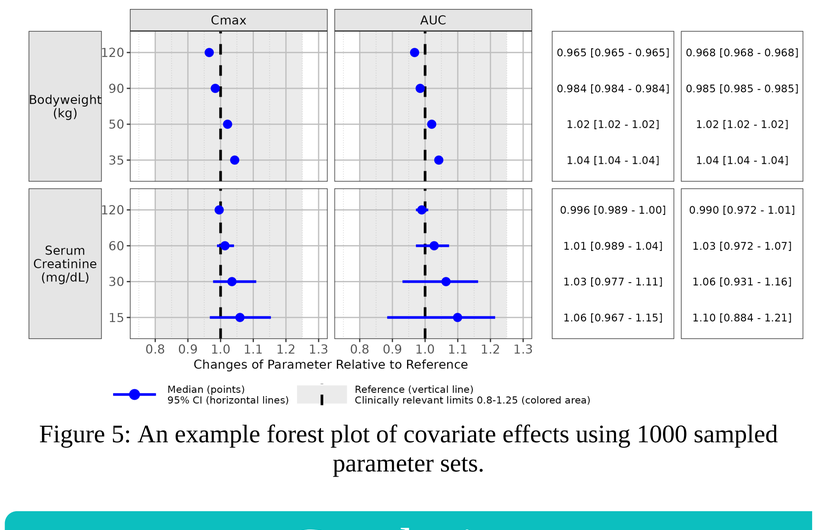

Figure 5: An example forest plot of covariate effects using 1000 sampled parameter sets.

Conclusion

`NMsim_NWPRI` is a powerful tool for simulation with estimated parameter uncertainty using NONMEM's native $PRIOR NWPRI. We showed that the results from `NMsim_NWPRI` are identical to those achieved using `simpar`. We demonstrated using `NMsim_NWPRI` to simulate with user-defined modifications to parameter uncertainty distributions which can be valuable when extrapolating into unknown populations. We demonstrated using NMsim_NWPRI for quick and simple generation of key results including clinical trial simulation and forest plots. 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 ACoP 2025: (M-004) Optimal Sampling Workflows with NMsim and NONMEM!

References:

[1] 2024. NMsim: Seamless Nonmem Simulation Platform. https://cran.r-project.org/web/packages/NMsim
[2] 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.
[3] 2023. simpar. https://mpn.metworx.com/docs/packages/simpar
https://github.com/metrumresearchgroup/simpar

Footnotes:

[a] NMsim_NWPRI works out of the box with NONMEM 7.6.0. Prior NONMEM versions included a bug which would produce incorrect OMEGA distributions when BLOCK OMEGAS were included in the model. NMsim_NWPRI can still reliably sample THETAS with NONMEM 7.5 for simulations without between subject variability using the `typical=TRUE` argument which is quite useful for forest plots.