A Model-Based Simulation Workflow Enables Automated and Accurate Generation of Clinical Pharmacology Summary Statistics, A Workflow and Case-Study

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Introduction

- Noncompartmental analysis (NCA) is a useful method to calculate pharmacokinetic (PK) parameters, however, limitations due to study design, execution, or nonlinear PK, can lead to inaccurate results.
- A **solution** to this problem is to use a population PK model to simulate the trial designs necessary to calculate PK parameters accurately.
- We demonstrate an **automated** model-based simulation workflow using a collection of functions for calculating PK parameters from simulations performed with `NMsim` [1]. The only requirements for the workflow are a NONMEM installation, a PopPK model written in NONMEM, and the `NMsim` R package.
- The method was demonstrated using a publicly available PopPK model for dacomitib [2].
- With the dacomitinib model we explore how the accumulation ratio and effective half-life can be inaccurately calculated by traditional NCA methods, but accurately calculated via simulation-based methods.

Methods

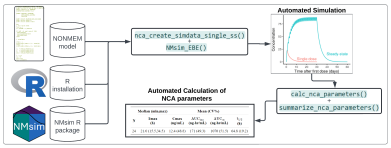

Figure 1: Diagram of methodology

- The workflow for calculating NCA PK parameters is composed of several R functions which work together with `NMsim` to **automatically generate simulation datasets, simulate, and calculate NCA parameters** from the simulations (Figure 1).
- The only requirements for the workflow are (1) a NONMEM model file, (2) an R installation with the `NMsim` package, and (3) basic drug and dosing information (dose compartment, amount, dosing interval, dosing rate, approximate time to reach steady-state, and any covariates).
- The method for calculating NCA statistics is based on two simulations: (1) a single-dose simulation and (2) a multiple dosing simulation to steady state. The single dose simulation allows calculation of all of the standard statistics such as Cmax, Tmax, AUC_{τ}, AUC_{∞}, and $t_{1/2}$. The multiple dose simulation allows calculation of additional parameters like $Cmax_{ss}$, $Tmax_{ss}$, $AUC_{\tau,ss}$, $AUC_{\infty,ss}$, accumulation ratio (AR) and effective half-life (EHL, using Cmax, AUC_{τ}, and AUC_{∞}).

Results

Simulation-based generation of NCA summary statistics with `NMsim`

- To use the workflow the user must supply a model file `file.mod`, a table of subject-level covariates `dt.covs` and dosing information for the drug (`.dose`, `.dose_cmt`, `dose_interval`, etc. See code below).
- A function `nca_create_simdata_single_ss()` is called to build the simulation datasets. A single-dose and multiple dosing dataset with enough doses to reach steady state are generated with the number of subjects based on the subject-level covariate dataset passed in the `.covs` argument. Dense sampling is included for reliable evaluation of NCA calculations on simulation results.

```
set.seed(1234)
# data.frame of covariates and ID's used in `.covs` below.
# `PPI` is a covariate representing proton pump inhibitor use in the dacomitinib
      model
dt.covs = tibble(ID=1:24, PPI = 0)
# create the simulation dataset
simdata = nca_create_simdata_single_ss(
    # Dose of drug to simulate
    .dose = 45*1000,
    # dosing compartment in model
    .dose_cmt = 2,
    # observation compartment in model
    .obs_cmt = 2,
    # dosing interval
    .dose_interval = 24,
    # dose rate (RATE in NONMEM dataset)
    .dose_rate = 0,
    # time to reach steady-state in days for dosed drug
    .days_to_ss = 30,
    # data.frame of subject-level covariates
    .covs = dt.covs
    )
```

```
print(as.data.table(simdata[,-11] %>% group_by(regimen) %>% slice_head(n=2)))
#>       ID  TIME  EVID   CMT   AMT    II  ADDL  RATE   MDV    regimen
#>    <int> <num> <num> <num> <num> <num> <num> <num> <num>     <char>
#> 1:     1     0     1     1 45000     0     0     0     1 singledose
#> 2:     1     0     2     2    NA    NA    NA    NA     1 singledose
#> 3:    25     0     1     1 45000    24    29     0     1         ss
#> 4:    25     0     2     2    NA    NA    NA    NA     1         ss
```

- A single set of ETAs are generated using `simPopEtas_asis()` (similar to the NMsim function `simPopEtas()`) so that identical subjects (with the same ETAS) are compared across the single- and multiple-dose simulations.

```
file.mod = here("models/mod_dacomitinib_transit_iiv.mod")
Nsub = nrow(distinct(dt.covs, ID))
sim.file.phi = here("simres/simulated_etas_mod_dacomitinib_transit.phi")
dt.etas = simPopEtas_asis(
  file.mod = file.mod,
  N = Nsub,
  seed = 1234
)
# re-use the generated ETAS across both simulations
dt.etas = bind_rows(dt.etas, mutate(dt.etas, ID = ID+Nsub))
NMsim::genPhiFile(data = dt.etas, file = sim.file.phi )
```

- The dataset is simulated with NONMEM using `NMsim` with the `NMsim_EBE()` method which allows us to pass in a `.phi` file containing ETA values for each ID in the dataset. Figure 2 shows the concentration-time profiles of the single- and multiple-dose simulations for a single subject (panels A and B), and for the full population (panels C and D).

```
sim.result =
  NMsim(
    # path to NONMEM model
    file.mod = file.mod,
    # Simulation method that uses provided ETAs (in .phi file)
    method.sim = NMsim_EBE,
    # PHI file generated above by NMsim::genPhiFile()
    file.phi = sim.file.phi,
    method.update.inits = "none",
    data = simdata,
    name.sim = "single_ss"
  )
```

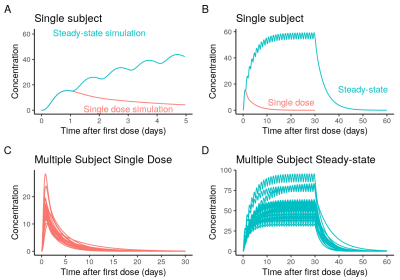

Figure 2: Simulated concentration time profiles produced by the automated workflow.

- NCA PK parameters are calculated for each individual in the simulation via `calc_nca_parameters()` and these PK parameters are summarized by `summarize_nca_parameters()` which produces the output shown in Table 1.

```
subject_pars =
  calc_nca_parameters(
    .simdata = sim.result,
    .conc_col = "IPRED",
    .dosing_interval = 24
  )
subject_pars = left_join(subject_pars, dt.covs) # add back covariates
par_summary =
  summarise_nca_parameters(.nca_pars = subject_pars, .by = "PPI")
```

Table 1: PK parameters from single- and multiple-dose simulations.

		Median (min,max)	Mean (CV%)				
Regimen	**N**	**Tmax (h)**	**Cmax (ng/mL)**	**AUC_{tau} (ng·hr/mL)**	**AUC_{∞} (ng·hr/mL)**	**$t_{1/2}$ (h)**	**$EHL_{AUC_{tau}}$**
Single dose	24	21.0 (15.5,34.5)	15.7 (27.1)	222 (32.4)	1310 (24.9)	64.8 (19.2)	–
Multiple dose	24	15.0 (13.0,18.0)	56.8 (24.9)	1200 (24.9)	5810 (36.2)	–	87.0 (34.8)

Accumulation Ratio can be more accurately calculated via simulation for drugs with long absorption half-life

- Accumulation ratio (AR) and effective half-life (EHL) are commonly reported parameters for multiple-dose PK studies, and are particularly important for determining dosing in drugs with nonlinear PK. The AR is commonly calculated by dividing an exposure metric (usually $AUC_{0-\tau}$ or Cmax) at steady state by the same metric after a single dose.
- $AUC_{\infty,single-dose}$ and $AUC_{\infty,steady-state}$ are not obtained from the same subjects in most drug development programs and therefore cannot be used to calculate the AR, however, it is possible to obtain these values for the same individual using simulation.
- Table 2 shows the AR and EHL for dacomitinib, demonstrating that AR and EHL are highly dependent on the PK parameter used to calculate them.

Table 2: Dacomitinib accumulation ratio (AR) and effective half-life (EHL) calculated with different exposure metrics.

	Mean (CV%)					
N	**$AR_{AUC_{tau}}$**	**$AR_{AUC_{\infty}}$**	**AR_{Cmax}**	**$EHL_{AUC_{tau}}$**	**$EHL_{AUC_{\infty}}$**	**EHL_{Cmax}**
24	5.74 (31.6)	4.37 (18.0)	3.67 (15.5)	87.0 (34.8)	64.1 (20.5)	52.3 (18.3)

- Dacomitinib has linear PK, and the $t_{1/2}$ calculated from a single-dose population simulation was 64.8 hours (Table 1). The EHL calculated using $AR_{AUC_{\infty}}$ was closest to the true $t_{1/2}$ when compared to $AR_{AUC_{\tau}}$ and AR_{Cmax} (Table 2).
- The proportion of AUC captured by $AUC_{0-\tau}$ versus AUC_{∞} for dacomitinib is relatively small (Figure 3 A), which helps explain why the EHL based on $AUC_{0-\tau}$ is less accurate for dacomitinib.

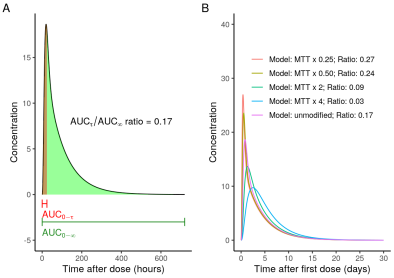

Figure 3: AUC tau versus AUC infinity for dacominitib

- Figure 3 (B) shows that faster or slower absorption (controlled by mean transit time (MTT)) can change the $AUC_{0-\tau}$ to AUC_{∞} ratio. Table 3 shows that in general $EHL_{AUC_{\infty}}$ is more accurate than $EHL_{AUC_{\tau}}$ or EHL_{Cmax} across a range of $AUC_{0-\tau}$ to AUC_{∞} ratios.

Table 3: Dacomitinib effective half-life (EHL) across models with different MTT and AUC tau to AUC infinity ratios.

			Mean (CV%)		
model	**N**	**AUC_{tau}/AUC_{∞}**	**$EHL_{AUC_{tau}}$**	**$EHL_{AUC_{\infty}}$**	**EHL_{Cmax}**
MTT x 0.25	24	0.27	48.8 (24.1)	58.0 (22.4)	39.3 (24.0)
MTT x 0.50	24	0.24	57.6 (27.9)	59.9 (21.8)	43.1 (21.3)
unmodified	24	0.17	87.0 (34.8)	64.1 (20.5)	52.3 (18.3)
MTT x 2	24	0.087	183 (42.0)	72.5 (18.5)	70.5 (16.4)
MTT x 4	24	0.033	510 (47.3)	89.5 (15.8)	100 (15.7)

Conclusions

- PopPK model simulations can be an essential tool to calculate accurate PK parameters.
- The publicly available simulation-based workflow presented can serve as a resource for researchers in need of a method to calculate PK parameters via simulation due to data limitations in PK studies.
- Accumulation ratio and effective half-life can be more accurately calculated using AUC_{∞} compared with AUC_{τ} or Cmax for drugs with a long absorption half-life, as was shown for dacominitib, and this method is usually only possible with a simulation-based approach.

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

[1] Delff P, 2024. *NMsim: Seamless 'Nonmem' Simulation Platform.* https://philipdelff.github.io/NMsim/

[2] Ruiz-Garcia A, Weiwei T, Li J, Haughey M, Masters J, Hibma J, and Lin S. 2020. "Pharmacokinetic Models to Characterize the Absorption Phase and the Influence of a Proton Pump Inhibitor on the Overall Exposure of Dacomitinib." Pharmaceutics 4 (April): 330. https://doi.org/10.3390/pharmaceutics12040330.