Simple, Automatic Noncompartmental Analysis: The PKNCA R Package

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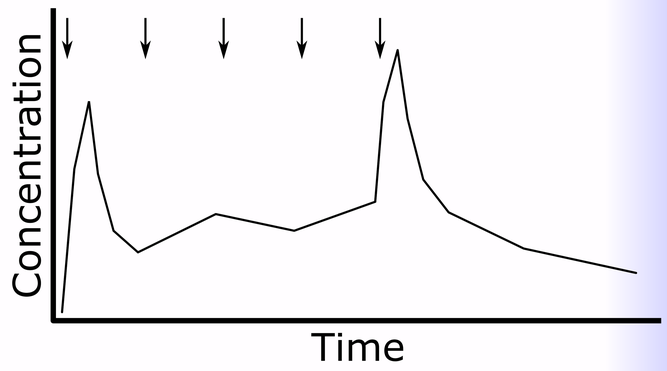
Objective: Noncompartmental analysis (NCA) of pharmacokinetic (PK) data has typically been the realm of specialized software that does not integrate easily with data workflows. The goal of this project was to build an NCA analysis engine in R that can perform all required analyses, plotting, and summarization.

Methods: Standard methods for noncompartmental analysis were implemented with the algorithms in Gabrielsson and Weiner [1]. For each subject in each period, the tool automatically determines the NCA parameters appropriate for calculation based on concentration-time and dosing data. The information used for automatic determination of the correct parameters include selections based on route of administration, single or multiple dosing, the dosing interval (if multiple dosing), and if steady-state has been achieved. The NCA calculated during any given interval including C_{max}, T_{max}, AUC and AUMC with linear or linear-up/log-down integration, $t_{1/2}$, T_{ss} (time to steady-state) with either a monoexponential rise or the stepwise linear method [2], CL or CL/F, V_{ss}, T_{last}, C_{last}, and interpolated or extrapolated concentrations. All settings, data cleaning, and summarization functions can be customized by the NCA analyst. Also, a NONMEM-ready dataset can be easily created after loading the data.

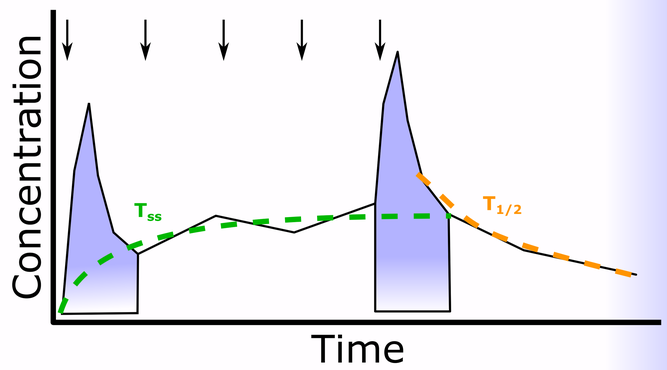
Results: The PKNCA R package has been integrated into an internal tool used for rapid, automated data analysis of Phase 1 studies, AMP (Automated Monitoring of Phase 1). Calculation results are identical when compared with validated internal and external software. The integration of NCA calculations into the dose-escalation study monitoring workflow has improved speed and reproducibility of the data for review.

Conclusions: The PKNCA R package was developed and will be made available to the public on CRAN. The package targets 100% test coverage of the code, and as open source in R is easily integrated in almost any workflow.

```
# Setup business rules
PKNCA.options(...)
# Load concentration data
myconc <- PKNCAconc(conc~time|subject, data=concdf)
# Load dosing data
mydose <- PKNCAdose(~time|subject, data=dosedf)
# Combine them to prepare for analysis
alldata <-
 PKNCAdata(data.conc=myconc, data.dose=mydose)
# Analyze the data
nca.results <- pk.nca(alldata)
# Summarize the results
plot(alldata)
plot(nca.results)
summary(nca.results)
summary(nca.results, type="listing")
```



Simple interface:
Four commands convert PK data into NCA results. There are two ways to plot the results, and either a tabular summary or listing of the calculated parameters. The tool can handle multiple subjects, studies, analytes, and matrices (e.g. plasma vs blood).



Reproducible Results
Calculation options and business rules are stored along with the session information so that results are fully tracable and reproducible. Options can't be changed within calculation results (you must repeat the calculation from the data).

Automatic Selections, Customize Anything
pk.nca will automatically:
Find the dosing interval,
Find the times when dense PK are taken,
Determine if the data are single- or multiple-dose,
Determine if multiple-dose data reach steady-state,
Not report parameters that are scientifically invalid (e.g. CL_{ss} when not at steady-state),
Choose the most likely parameters to calculate,
Calculate intermediate parameters,
Generate summary tables for requested parameters,
Generate summary plots for requested parameters.

Your Rules Rule
The PKNCA.options function allows you to customize the calculations and reporting to fit your business rules:
Missing and BLQ sample handling (with options for before, between, or after above LOQ measurements),
AUC calculation method,
T_{max} selection,
Minimum points for half-life,
Minimum span ratio for half-life,
Minimum r-squared for half-life,
Maximum AUC_{inf} % extrapolation,
Defaults for single-dose AUCs,
Maximum fraction missing for summary statistics.

Availability
The package is currently available on github:
https://github.com/billdenney/pknca
It will soon be submitted to CRAN

References
[1] Gabrielsson J, Weiner D (2006). Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications, Fourth Edition. Stockholm, Sweden: Swedish Pharmaceutical Press.
[2] Panebianco DL, Maes A. Estimating time to steady state using the effective rate of drug accumulation. Pharm Stat. (2011) 10 (1):27-33.