A diagnostic tool for population models using non-compartmental analysis: *nca_ppc* functionality for R

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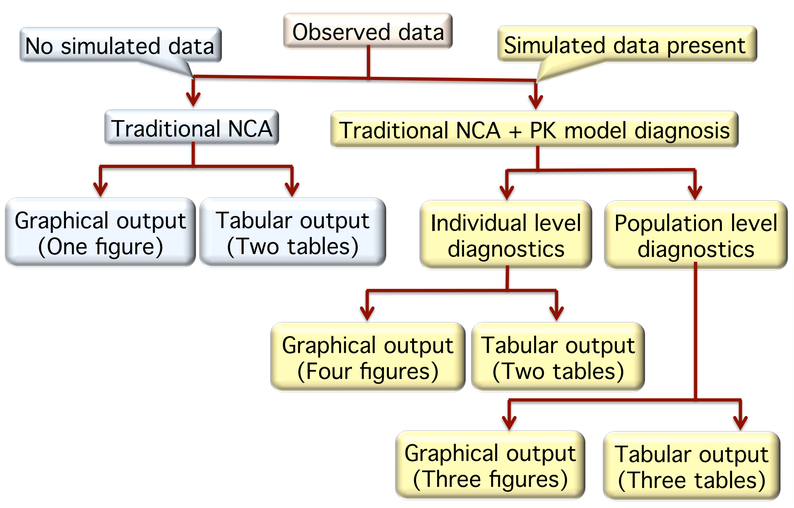
Introduction

Non-compartmental analysis (NCA) calculates pharmacokinetic (PK) metrics related to the systemic exposure to a drug following administration, e.g. AUC, Cmax. A number of software tools (such as Kinetica[1], WinNonlin[2], PK module[3] in R, Scientist[4], PKSolver[5]) are available that can perform the traditional NCA. In this work we extended the use of NCA as a pharmacometric model diagnostic employing the principles of a posterior predictive check[6]. We developed a new functionality in R[7], ***nca_ppc,*** that (i) provides a simple and flexible method to estimate the NCA metrics from the observed data and (ii) compares them with the same estimated from multiple data sets simulated from the PK model to be diagnosed, thus helping to bridge the gap between NCA and population model analyses. In addition, the normalized prediction distribution error (NPDE) of the simulated PK metrics are calculated for each individual[8].

Workflow of *nca_ppc* functionality



Usage: *nca_ppc (origFile, simFile, ...)*

nca_ppc function accepts 42 different arguments related to observed and simulated data, filtering and grouping variables, estimation method etc.

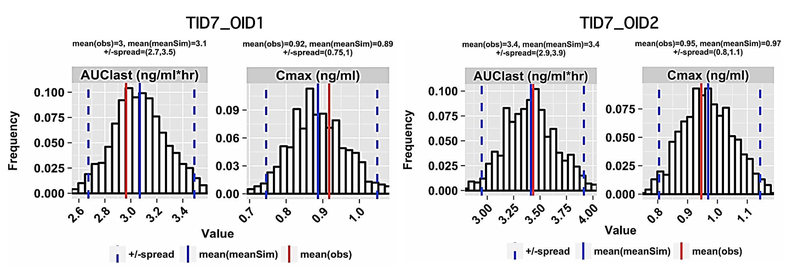
Case study of *nca_ppc*

The *nca_ppc* functionality is illustrated using data from a study of the central imidazoline antagonist moxonidine in 74 congestive heart failure patients for which a population model was developed[9].

- Dose type: extravascular non-steady-state dose
- Total number of subjects in the input file: 74
- Number of treatment arms: 3 (TID 7, 8, 9)
- Number of occasions: 2 (OID 1, 2)
- Number of simulations: 1000

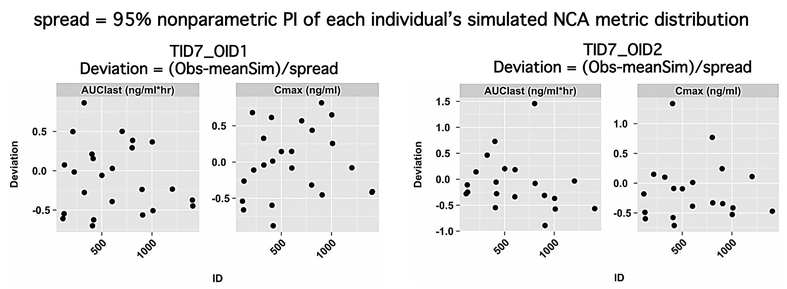
Treatment ID	Occasion ID	Daily dose (ng)	No. of individuals	No. of outliers
7	1	200	24	0
7	2	200	21	2
8	1	200	26	1
8	2	400	25	1
9	1	200	24	1
9	2	600	24	0

Comparison of the population mean



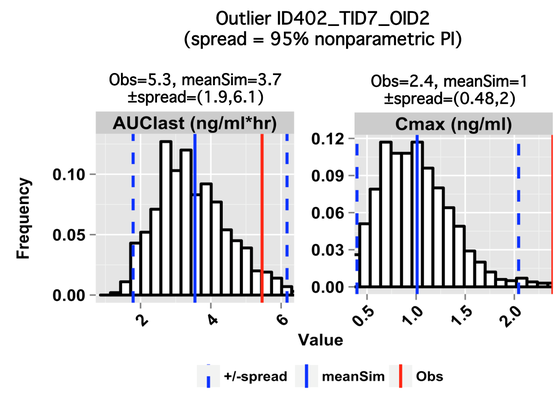
- Histogram of the population mean of the PK metrics obtained from the simulated data set
- Model misspecification is indicated if the observed value lies outside the 95% nonparametric PI

Deviation of the individual's NCA metrics from the observed values



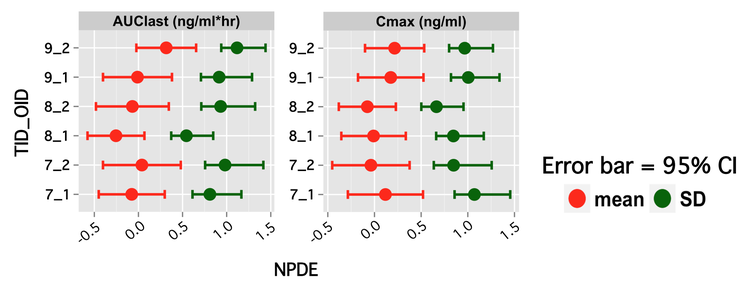
- Negative value of the deviation implies over-prediction of the PK metric, and vice versa.
- An individual with *abs(deviation)* > 1 is identified as an outlier for the specific population group under the given PK model.

Distribution of the NCA metrics of the model specific individual outliers



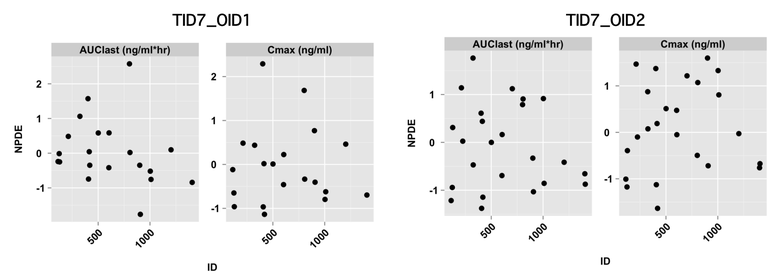
- ID 4012 is an outlier for TID 7 and OID 2
- Observed value for Cmax is outside the 95% nonparametric PI obtained form the simulated data

Forest plot for NPDE analysis for the various treatment arms and occasions



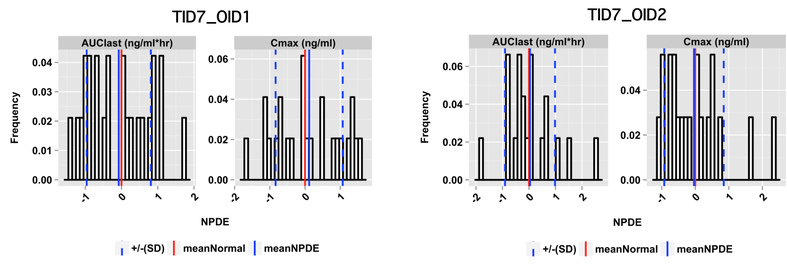
- Population mean (•) and SD (•) of the NPDE values of the PK metrics used for model diagnosis
- For an acceptable PK model, the population mean and SD along with their confidence interval should encompass 0 and 1, respectively

Individual NPDE analysis



- NPDE values of all individuals within a given treatment arm and occasion
- Negative value of the NPDE implies over-prediction of the PK metric, while a positive value of the NPDE implies under-prediction.

Distribution of the population NPDE



- Mean and standard deviation of the NPDE distribution is compared with that of a normal distribution to assess the PK model performance

Tabular outputs

- **ncaOutput.tsv:** Observed and mean simulated values of PK statistics for each individual along with their deviation and NPDE values
- **Obs_Stat.tsv:** A set of statistical parameters calculated for the observed PK statistics
- **Sim_Stat.tsv:** A set of statistical parameters calculated for the simulated PK statistics
- **ncaSimData.tsv:** Simulated concentration-time profile of all individuals
- **ncaSimEst.tsv:** Estimated PK statistics for each individual obtained from each simulation

Conclusion

- The *nca_ppc* is a versatile and flexible functionality that can perform traditional NCA as well as simulation-based diagnostic tests for a given population-PK model. It produces a comprehensive set of graphical and tabular output to summarize the results. The output is easy to interpret and to use in evaluation of a population model.
- *nca_ppc* results for moxonidine indicated that the PK model is adequate regarding the NCA metrics
- However, *nca_ppc* was also able to quantitatively identify the model-specific outliers
- This program also produces a complete report in HTML format.

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