Power calculation methods to detect covariates effect when combining observed and simulated data.

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Introduction

Monte Carlo Mapped Power (MCMP) has been developed as an alternative and rapid method [1], relative to the stochastic simulation and re-estimation (SSE) method, for power calculations using non-linear mixed effect models based on the likelihood ratio test. The aim of this work is to compare the MCMP and SSE methods when calculating the power to identify covariate effect in a combined healthy volunteer / patient population. A specific example based on a population PK model for a monoclonal antibody is presented.

Methods

Routine implementation of MCMP [1] and SSE methods are available in PsN [2] for power calculations to aid the design of a planned study. We borrowed the same principles to calculate the power to detect a patient specific bioavailability (F) in a dataset which combines existing rich PK data from healthy volunteers and simulated sparse PK data representative of a patient population.

Study setup and PK model

- A 2-compartment PK model for a monoclonal antibody with first-order absorption and elimination, previously developed using a rich dataset in healthy volunteers (n=62), was used.
- Patient population PK data were simulated based on the design of an ongoing study with sparse sampling (4 samples from each of the 100 simulated subjects).
- Bioavailability estimate in healthy volunteer was 38%.
- Patient simulated data assumed a lower bioavailability of 27%. All other PK parameters were the same as for healthy volunteers, with between–subject variability (BSV) of 27% on clearance (CL)
- Higher BSV on CL (50%) was also considered for the patient population.

Extended MCMP method implementation

- The observed healthy volunteer data were combined with 100 simulated patient data
- The combined dataset was re-estimated in NONMEM® 7.3 using the reduced PK model (single bioavailability for both healthy volunteers and patients), and full PK model (separate patient bioavailability).
- To avoid differences in the individual objective function values for the observed subjects (iOFV), all parameters, other than the patient specific bioavailability and the residual error, were fixed to the values estimated from the observed data.
- The power to identify the patient specific bioavailability for a given sample size N, was calculated from the change in iOFV between the full and reduced models [1] using a bootstrap approach in R.

SSE Method Implementation

- The observed healthy volunteer data (n = 62) were combined with N = 5, 8 and 12 subjects, randomly sampled from a simulated patient master database. For each N, 100 datasets were created.
- The reduced model (single bioavailability) and the full model (separate patient bioavailability) were fitted to each of the 100 datasets in turn.
- The likelihood ratio test was used to judge whether the bioavailability estimate of the patient population was significant, requiring a drop of 3.84 units (at the 5% level of significance).
- The power to detect a separate patient specific bioavailability was calculated as the number of estimates considered to be significant, relative to the total number of estimates obtained (=100).
- A similar procedure was repeated for the high CL BSV scenario (50%) in the patient population. In this case both the reduced and full models had a different CL BSV parameter for the patient population, and still only differed by a single parameter: the patient specific bioavailability.

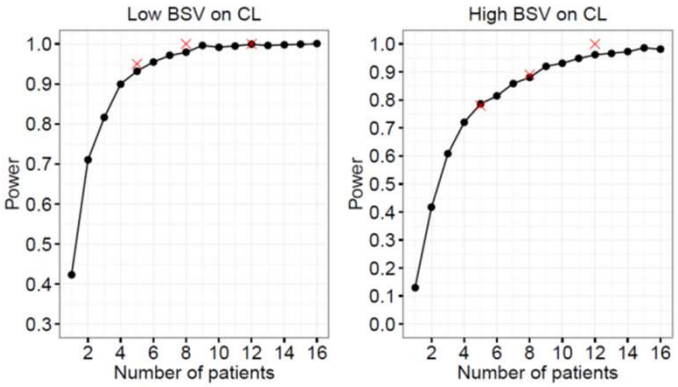
R-script to calculate power (extended MCMP method)

```
# Set the seed
set.seed(123456)

# Set number of patients in each study and number of resampling
n <- 15 # Sample size (Number of patient in each study)
N <- 1000 #numbers of bootstrap (studies)

#Delta is difference in individual objective function value estimated with full and reduced PK model
#ID<1000 are healthy volunteer observed data, for these subjects sum of delta should be zero
#ID≥1000 are simulated patient population
resamples <- lapply(1:N, function(i)
  sum(sample(obj$Delta[obj$ID>=1000],n)) + sum(obj$Delta[obj$ID<1000]))

# Power calculation: Number of time when Delta > 3.84 at p value 0.05
power <- sum(ifelse(unlist(resamples) <= -3.84,1,0))/N
```

Results

- The results from the extended MCMP method are consistent with the power calculations derived using the SSE method.
- Assuming low clearance BSV (26%) for both healthy volunteers and patients, the number of patients required to give 90% power to detect a patient bioavailability of 27% (compared to 38% in healthy volunteers) is predicted to be 4.
- A higher clearance BSV (50%) in the patient population increases the required sample size to 8.
- For all sample sizes and low/high clearance variability, the estimates for the healthy volunteer and patient bioavailability are distinct and in line with their true values (see Table).

Predicted power to detect a covariate on bioavailability versus number of patients: SSE (red cross) and MCMP (black circle) comparison



Bioavailability estimates for the healthy volunteer and patient population, for the different clearance and sample size scenarios.

Patient CL BSV	# Simulated Patients	Population	Median Estimate
Low (27%)	5	Healthy Vol. Patients	0.380 ± 0.5% 0.263 ± 10.4%
Low (27%)	8	Healthy Vol. Patients	0.380 ± 0.5% 0.259 ± 6.6%
Low (27%)	12	Healthy Vol. Patients	0.380 ± 0.6% 0.261 ± 6.2%
High (50%)	5	Healthy Vol. Patients	0.379 ± 0.3% 0.261 ± 14.2%
High (50%)	8	Healthy Vol. Patients	0.379 ± 0.4% 0.268 ± 11.1%
High (50%)	12	Healthy Vol. Patients	0.379 ± 0.3% 0.258 ± 8.9%

Conclusions

- The SSR and extended MCMP methods were successfully implemented to estimate the minimum number of subjects required to detect a difference in the bioavailability, for a monoclonal antibody using observed PK data and a sparse PK study design in the population of interest.
- The results from the SSR and MCMP methods were in agreement, showing that the MCMP method is a fast but reliable method to calculate power for study design purposes.

References

[1] Vong C1, Bergstrand M, Nyberg J, Karlsson MO. Rapid sample size calculations for a defined likelihood ratio test-based power in mixed-effects models. AAPS J. 2012 Jun;14(2):176-86. doi: 10.1208/s12248-012-9327-8. Epub 2012 Feb 17.

[2] Lindbom L, Ribbing J, Jonsson EN. Perl¬speaks¬NONMEM (PsN) -a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 75(2):85¬94

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