Accelerating Monte-Carlo Power Studies through Parametric Power Estimation

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Objectives

To evaluate the performance of a novel parametric power estimation (PPE) algorithm for faster sample size calculations and to compare it to sample size calculations through standard Monte-Carlo simulations and estimations (MC).

Methods

Both algorithms rely on Monte-Carlo simulations and estimations as well as the log-likelihood ratio (LLR) test statistic to estimate the power π for sample size s of the planned study.

MC algorithm:

For each study size s:

Simulate N_{MC} datasets from full model

For each dataset:

Re-estimate with full & reduced model

Determine LLR test statistic t

π_S =Number of $t \in T$ where $t < \chi_{\alpha,k}$

PPE algorithm: The PPE algorithm utilizes the theoretical non-central chi-square distribution[1] of the LLR test statistic under the null hypothesis and estimates the non-centrality parameter λ from a sample of LLR values. Furthermore, the algorithm exploits the linear relationship between sample size and λ to derive a full power curve.

Simulate N_{PPE} datasets of study size s_0

For each dataset:

Re-estimate with full & reduced model

Determine LLR test statistic t

$$\hat{\lambda} = \arg\max_{\lambda} \sum_{t \in T} \log f_{\chi^2}(t, k, \lambda)$$

$$\pi(s) = 1 - F_{\chi^2}\left(\chi^2_{\alpha,k}, k, \frac{s}{s_0} \cdot \hat{\lambda}\right)$$

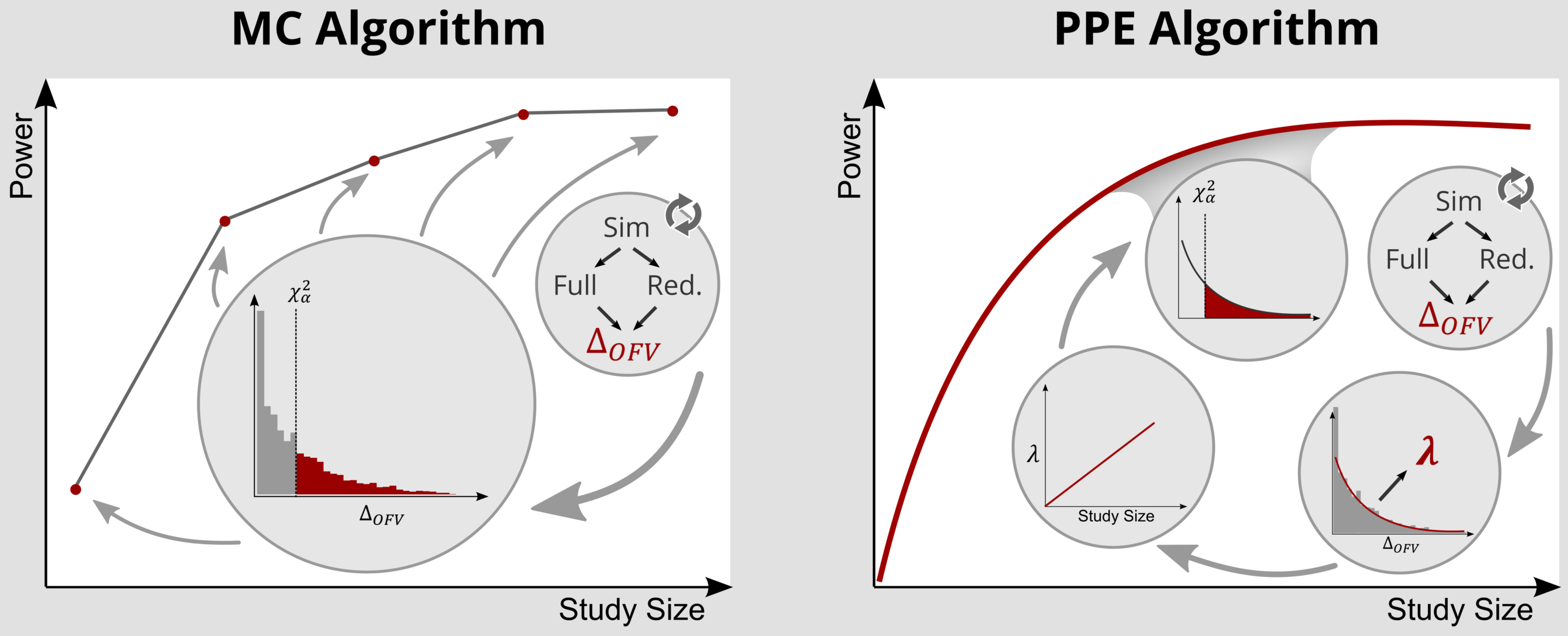

Fig.1: Schematic representation of the MC and the PPE algorithms

Algorithms comparison: Power versus sample size curves from both algorithms were compared to a reference obtained with the MC algorithm and 10,000 Monte-Carlo samples. Furthermore, the range (max – min) of power estimates using differing number of Monte-Carlo samples was compared. The evaluation was performed for the following three scenarios:

PK auto-induction[2] model for different compliance levels:

$$\frac{dA_1}{dt} = -k_{ai}A_1 \quad \frac{dA_2}{dt} = k_{ai}A_1 - \frac{CL_i}{V_i}EA_2$$

$$\frac{dE}{dt} = k_{enz}\left(1 + \boldsymbol{\alpha}\frac{A_2}{V_i}\right) - k_{enz}E$$

Disease progression[3] model for different study lengths:

$$y_{ij} = S_{0i} + \alpha_i(1 - \boldsymbol{\gamma} \cdot trt)t + A\left(e^{-k_{off}t} - e^{-k_{on}t}\right) + \varepsilon_{ij}$$

Count model for different doses:

$$P(Y_{ij} = k) = \frac{\lambda e^{-\lambda k}}{k!} \qquad \lambda = \lambda_{0i}\left(1 - \frac{\boldsymbol{E_{max}}D}{D + ED_{50}}\right)$$

(Highlighted parameters were assumed 0 in the null hypothesis, parameters with subscript i were modeled as subject specific)

Results

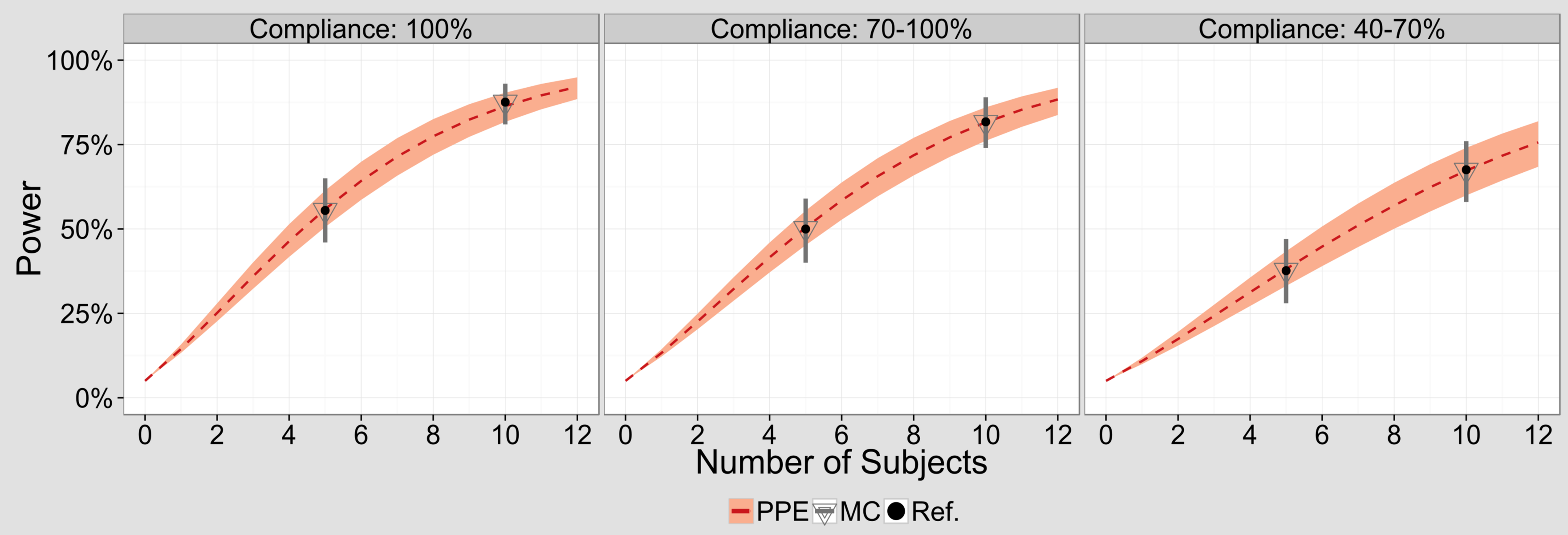

Fig. 2: Power obtained from both algorithms (100 Monte-Carlo samples) and reference power for the PK auto-induction model.

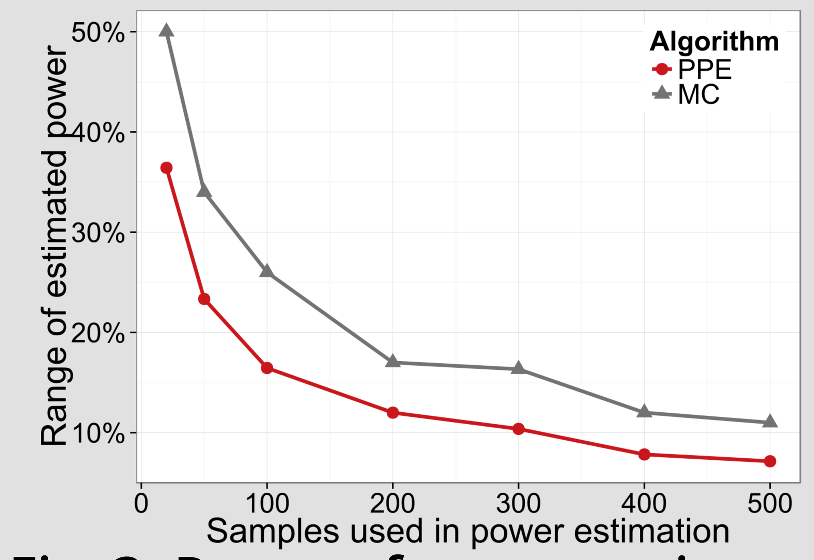

Fig. 3: Range of power estimates versus number of Monte-Carlo samples from both algorithms for the auto-induction model.

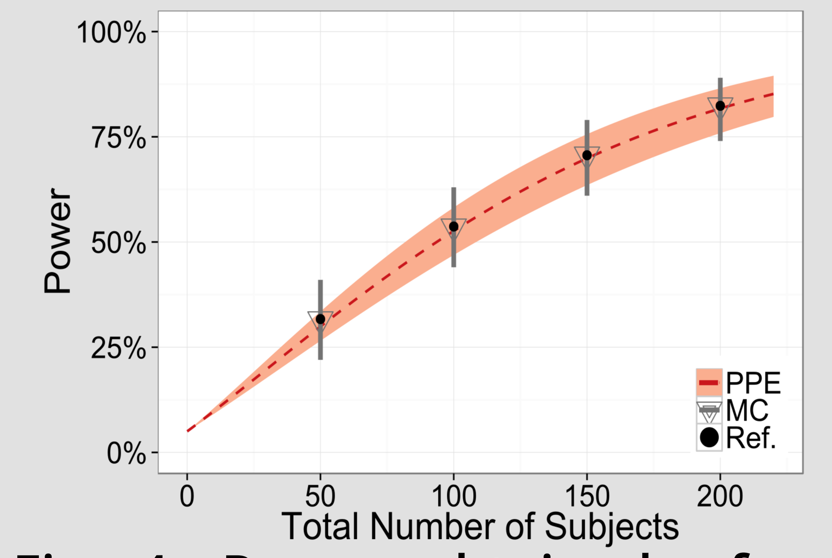

Fig. 4: Power obtained from both algorithms and reference power (100 samples) for the disease progression model.

Dose	MC	PPE	Ref.
10 mg	13% [7-20]	10.0% [6.3-14.8]	13.0%
25 mg	64% [55-74]	62.2% [54-69.4]	63.7%
50 mg	98% [95-100]	96.5% [95-97.5]	98.2%

Tab. 1: Median estimated power and 95% confidence interval (CI) for different dose levels for the count model.

Application example: Impact of study length

The PPE algorithm was used to calculate power versus sample size curves for different study lengths of a disease progression study from only 100 Monte-Carlo samples. Diagnostic plots (e.g. fig. 5) provide information about the validity of the underlying assumptions.

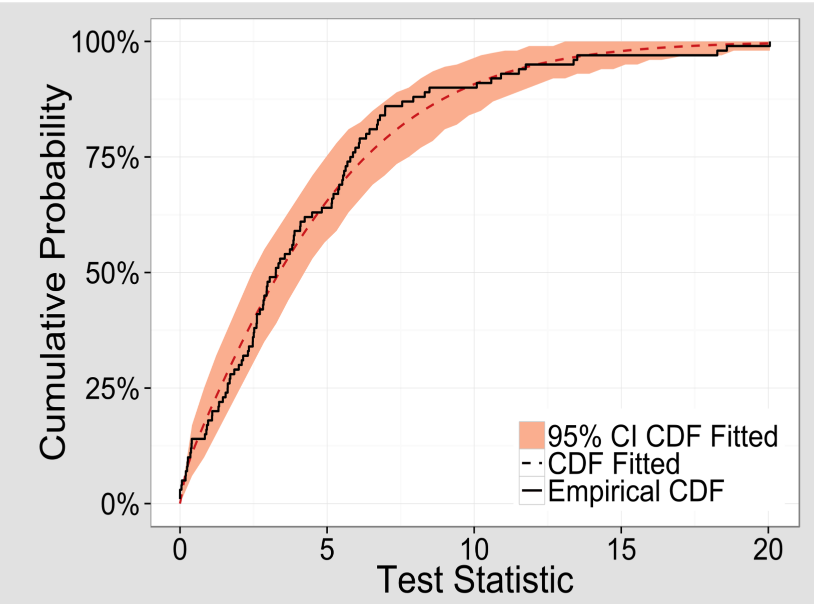

Fig.5: Diagnostic plot comparing the empirical and fitted cumulative distribution function (CDF) of the LLR statistic.

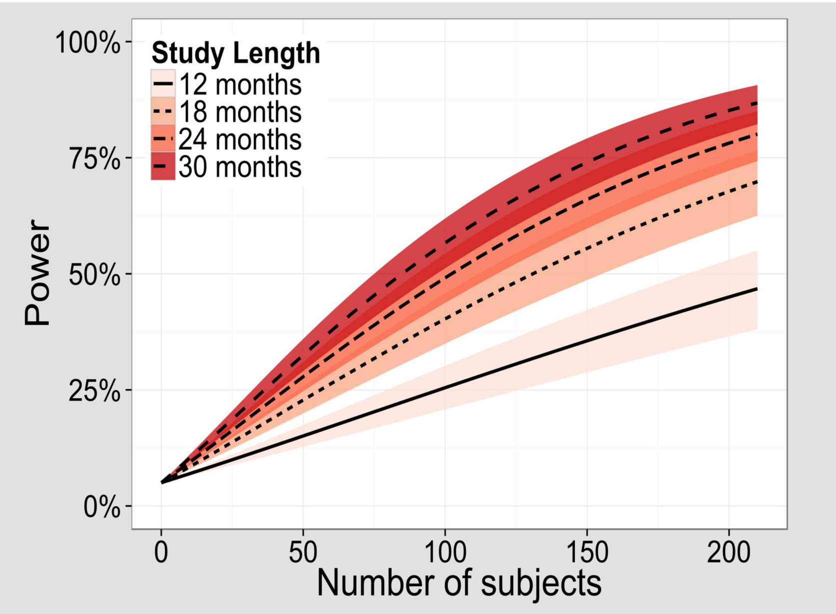

Fig.6: Power to detect a drug effect and 95% CI (shaded area) for different study lengths.

Conclusions

Parametric power estimation algorithm:

- Delivers full power versus sample size curves based on a few hundred Monte-Carlo samples
- Reduces computational effort drastically compared to pure Monte-Carlo simulations and estimations
- Allows quick and effective communication of trial design impact

References:

1. R. F. Engle et al., Elsevier, 1984.
2. Wilkins et al., PAGE, 2004
3. Ito et al., Alzheimer's and Dementia 2011.

Acknowledgement:
This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement no 602552.