Comparison of Different Global Optimal Design Approximations

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Background

Calculation of globally optimal designs require the evaluation of an integral over the complete parameter space. The appearance of the Fisher information matrix in the integrand makes evaluations computationally expensive.

For ED optimal design this integral is given by

$$j^{ED}(x) = \int_{-\infty}^{\infty} p(\alpha) \cdot \left|F(\alpha, x)\right| d\alpha \qquad (1)$$

where x is the vector of design variables, α is the vector of model parameter, $p(\alpha)$ is its probability distribution function (pdf) of the parameters α, F is the Fisher information matrix and |.| denotes the matrix determinant. Several approximations with different properties can be used to evaluate the integral. Despite approximation error and its influence on the optimal design, runtime is of particular importance.

Objective

To compare Monte-Carlo integration and Laplace integral approximation for global optimal design in terms of precision, runtime and best study design. Furthermore, to explore the performance of a new algorithm using the Laplace approximation, but avoiding explicit calculation of 2nd order derivatives.

Methods

In this work we compared the performance of the following four different numerical algorithms in computing ED optimal designs implemented in PopED [1]:

1. **Monte-Carlo integration with random sampling (MC-RS):** The integral in equation (1) is approximated using the definition of the expectation. Given a random variable X with pdf $p_X(x)$ on the set χ, than the expected value of a function g of X is

$$E\left(g\left(X\right)\right) = \int_{x \in \chi} p_X\left(x\right) g\left(x\right) dx \qquad (2)$$

Thus. equation (1) can be approximated by sampling X and computing the mean of g(x) over the sample S_X.

$$j^{ED}(x) = \int_{-\infty}^{\infty} p(\alpha) \cdot \left|F(\alpha, x)\right| d\alpha \approx \frac{1}{n} \sum_{i=1}^{n} \left|F(\alpha_i, x)\right| \qquad (3)$$

2. **Monte-Carlo integration with Latin hypercube sampling (MC-LHS):** Instead of random sampling, stratified Latin hypercube sampling is used to generate S_X. All other calculations are identical to the MC-RS method.
3. **Laplace integral approximation (LAPLACE):** integration is performed by finding the mode of the integrand and performing a second order Taylor expansion around this point

$$j^{ED}(x) = \int_{-\infty}^{\infty} p(\alpha) \cdot \left|F(\alpha, x)\right| d\alpha = \int_{-\infty}^{\infty} e^{-k(\alpha, x)} d\alpha$$

$$k\left(\alpha, x\right) := -\log\left(p(\alpha) \cdot \left|F(\alpha, x)\right|\right) \qquad (4)$$

$$\approx -\frac{1}{\sqrt{\left|2\pi \partial_\alpha^2 k\left(\alpha^m, x\right)\right|}} e^{-k\left(\alpha^m, x\right)} \qquad \alpha^m = \arg\min_\alpha k\left(\alpha, x\right) *$$

4. **Laplace integral approximation with BFGS Hessian (LAPLACE-BFGS):** An approximate Hessian, obtained by employing the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method during the minimization step (*) is used for the Taylor expansion instead of a numerically differentiated Hessian as in LAPLACE. Random effect parameters are automatically log-transformed to allow unconstrained minimization and application of the BFGS method.

Comparison: Performance of the different methods was assessed in terms of optimal sampling points, runtime and objective function value. Variability of Monte-Carlo methods was evaluated by repeating computations for 50 (MC-RS 50, MC-LHS 50) and 500 (MC-RS 500, MC-LHS 500) samples.

Design: A hypothetical experimental design for a drug following a simple one compartment model with IV bolus dosing, 20 individuals and 2 samples per subject was used for the comparison. The model was parameterized in terms of clearance (CL) and volume of distribution (V). Inter-individual variability (IIV) was modeled as being log-normally distributed and an additive model for the residual unexplained variability was used. Log-normal ED uncertainty was assumed for all 4 parameters (CL, V, IIV-CL, IIV-V); for the fixed effects 0.05 and for the random effects 0.09 was used as variance of the uncertainty.

Results

Method	OFV·10^{21} [95% CI]	
MC-RS 50	3.27	[2.2-5.0]
MC-RS 500	3.33	[2.8-3.8]
MC-LHS 50	3.24	[2.2-4.6]
MC-LHS 500	3.22	[2.9-3.7]
LAPLACE	2.95	
LAPLACE-BFGS	3.01	

Tab 1. Comparison of integration results obtained by evaluating the example model with a fixed design. Values shown are mean OFV (ED integral) and 95% non-parametric confidence interval from 100 integrations for the MC methods.

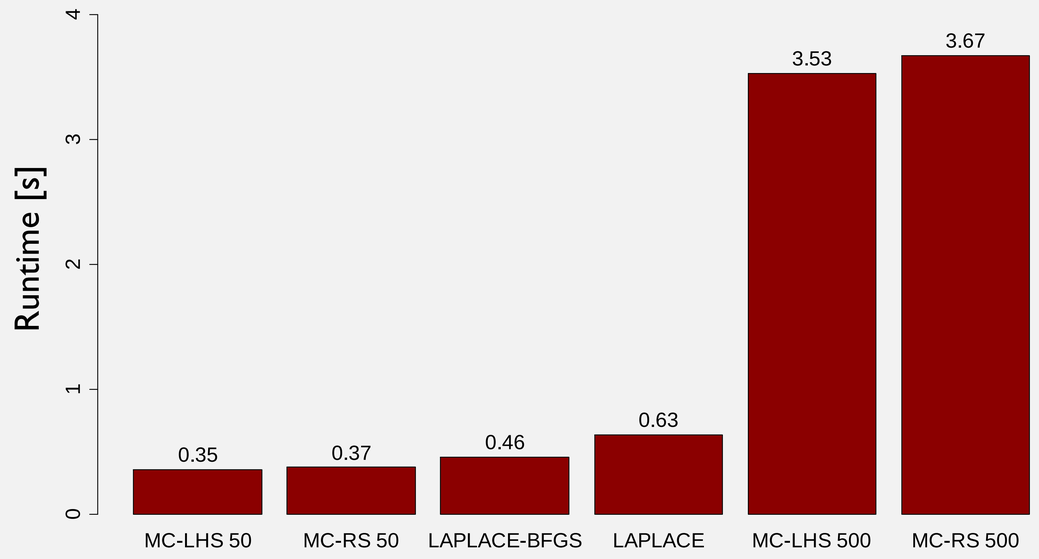

Fig 1. Runtime in seconds averaged over 100 integrations

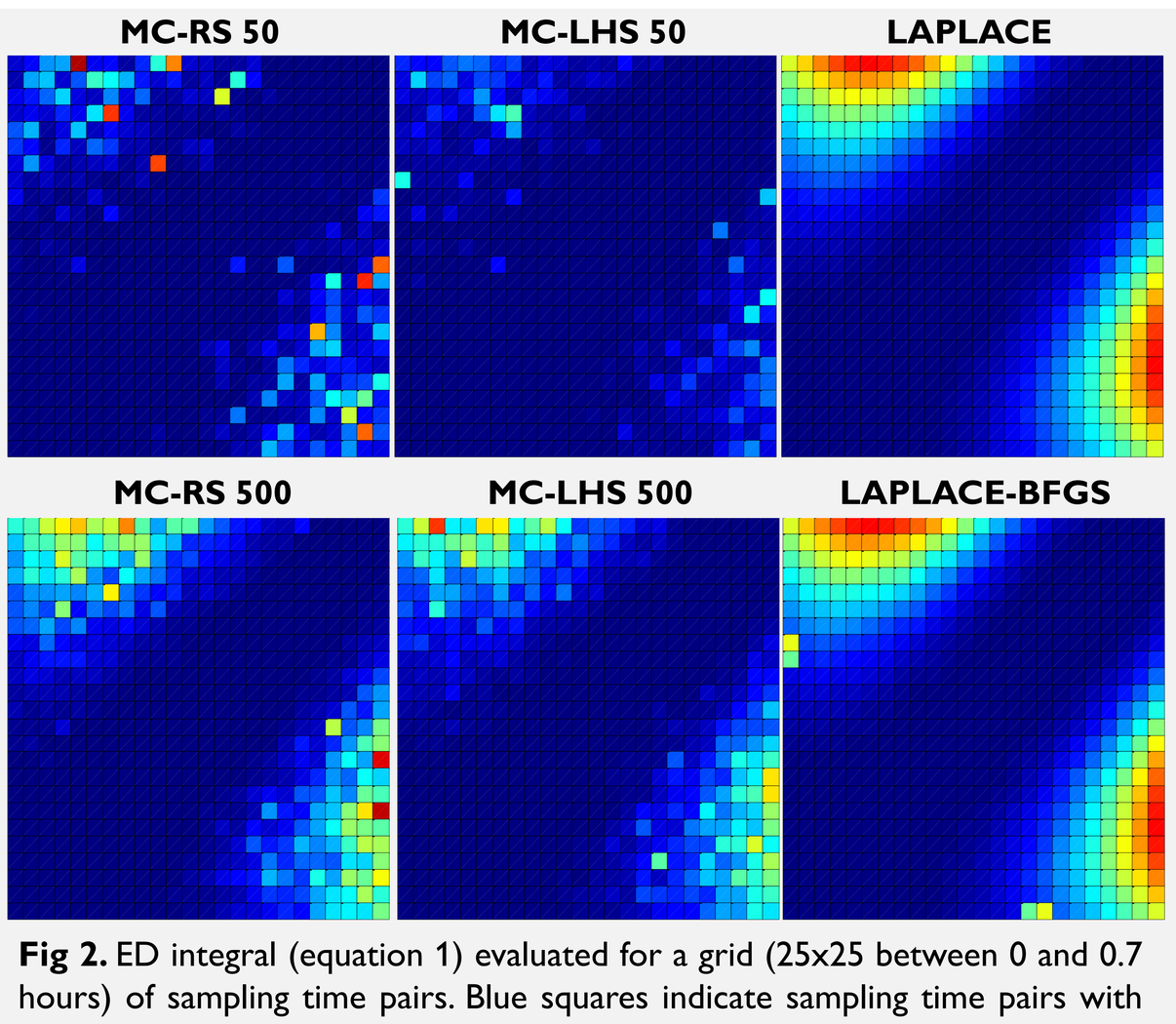

Fig 2. ED integral (equation 1) evaluated for a grid (25x25 between 0 and 0.7 hours) of sampling time pairs. Blue squares indicate sampling time pairs with low, red squares time pairs with high information.

Conclusions

- ❖ All methods tested were implemented in PopED 2.11
- ❖ Monte-Carlo methods are easy and flexible but need high number of samples to give stable results
- ❖ Laplace approximation constitutes fast alternative for priors with continuous probability distribution function
- ❖ Laplace integral approximation with BFGS Hessian gave same sampling times with approx. 30% shorter runtimes

[1] Foracchia M, Hooker A, Vicini P & Ruggeri A: POPED, a software for optimal experiment design in population kinetics, Computer Methods and Programs in Biomedicine, vol. 74, Apr. 2004, pp. 29-46.
[2] Dodds M, Hooker A & Vicini P: Robust Population Pharmacokinetic Experiment Design, Journal of Pharmacokinetics and Pharmacodynamics, vol. 32, Feb. 2005, pp. 33-64.
[3] C.G. Broyden: The Convergence of a Class of Double-rank Minimization Algorithms 1. General Considerations, IMA J Appl Math, vol. 6, Mar. 1970, pp. 76-90.