Evaluating the Predictive Power of the Fisher Information Matrix in Population Optimal Experimental Design

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Objectives

In previous work, we evaluated computed population optimal designs via simulation studies [1]. Others have evaluated optimal designs without simulation by looking directly at the Fisher information matrix (FIM) and the predicted parameter variances (the diagonal elements of the FIM) [2]. However, the FIM is only an asymptotic lower bound on the covariance matrix of the model parameter values and it is not clear how well the FIM predicts experimentally measured variances in studies where the number of samples and number of individuals are not close to the asymptotic limit. In this work, we compare population D-optimal pharmacokinetic (PK) designs using both the asymptotic Fisher information matrix (FIM) predicted model parameter variances and model parameter variances derived from simulation studies. Previous work has looked at this problem for one specific model [3], here we expand this comparison and look at three separate models.

Background and Theory

Why is optimal design important?

- Models are complex
- Parameters are hard to estimate
- Data is often quite sparse
- Poor designs lead to poor parameter estimates
- In drug development, costs are huge:
  - $500-$800 Million per new chemical entity.

What is optimal design?

- Optimal design means the resulting experiment will lead to the most accurate model parameter estimates $\hat{\theta}$.
- The Cramer-Rao inequality tells us that an asymptotic lower bound on parameter variances is the *Fisher Information Matrix (FIM):*

$$\mathrm{Cov}\left[\hat{\theta}\right] \geq \left(FIM(t,\theta,a)\right)^{-1}$$

Time; Best guess of parameter values; Covariates

- Given the log-likelihood of a particular model L(θ), prior information of parameter values, and specific design criteria, the FIM can be caluculated, after linearizing the model about its random effect parameters, as:

$$FIM(t,\theta,a) = E_y\left[\partial_\theta L(\theta)^T \;\; \partial_\theta L(\theta)\right]$$

- Using D-optimality we minimize the FIM with respect to time and/or covariates to get a minimal *asymptotic* lower bound

$$\mathrm{argmin}_{t,a}\left(\mathrm{Det}\left[\,\mathrm{FIM}(t,\theta,a)^{-1}\right]\right)$$

What do optimal design calculations tell us?

- Optimal design calculations result in asymptotic values for the model parameter covariances (the optimal FIM).
- Population PK-PD studies are generally not close to the asymptotic limit of samples per individual and number of individuals.
- So what can these asymptotic values tell us?
- To test this we compare the asymptotic covariance values to parameter covariances computed from replicate simulation studies.

Methods

- Computed 5-7 different optimal designs for each of three separate population PK models taken from the literature.
- From each optimal design computed, we calculate the predicted asymptotic percent coefficients of variation (CVs) for all model parameters, θ, from the FIM:

$$CV_{A,\theta_k} = \frac{\sqrt{FIM_{k,k}}}{\theta_k^{true}} \cdot 100\%$$

- Next, using NONMEM, we simulate numerous replicate experiments from the optimal designs and compute the simulated parameter CVs for each optimal design.

$$CV_{S,\theta_k} = \frac{\sqrt{Var(\hat{\theta}_k)}}{\theta_k^{true}} \cdot 100\%$$

where

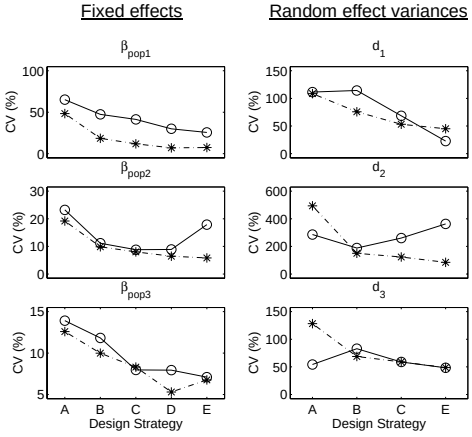
$$Var(\hat{\theta}_k) = \frac{1}{N_e - 1}\sum_{i=1}^{N_e}\left(\hat{\theta}_{k,i} - Mean(\hat{\theta}_k)\right)^2$$

- We treat the simulated CVs as the true values that the asymptotic CVs are trying to predict.

Results

Theophylline

- Model is one-compartment with linear absorption and constant measurement error variance (Beal and Sheiner 1992).
- Population parameters are log-normally distributed.
- Samples per individual in different design strategies: A-1, B-2, C-3, D-3, E-11

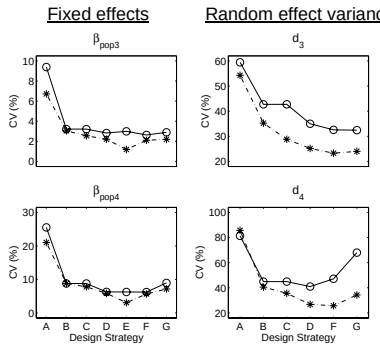


- General trends for asymptotic (*) and Simulated (O) CV values are similar.

HIV viral load model

$$y(t,\theta) = \log_{10}\left(e^{\theta_1 - \theta_2 t} + e^{\theta_3 - \theta_4 t}\right) + \varepsilon$$

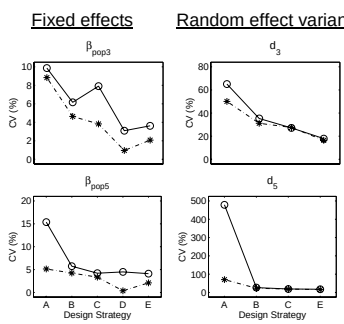
- Model comes from Wu and Ding, 1999.
- Population parameters are normally distributed.
- Samples per individual in different design strategies: A-1, B-2, C-3, D-4, E-4, F-(3-9), G-(3-9)



- Asymptotic CV values (*) tend to underestimate the CV values of simulation experiments (O) in both the fixed and random effects.

Ketorolac

- Model is two-compartment with first-order absorption and proportional measurement error variance (Mandema and Stanski, 1996).
- Population parameters are log-normally distributed.
- Samples per individual in different design strategies: A-1, B-2, C-3, D-5, E-15



- Asymptotic CV values (*) in designs with only one sample per individual (strategy A) can greatly underestimate the CV values of simulation experiments (O).

Conclusions

- Using the asymptotic FIM to ***compare*** different designs is possible.
- However, using the asymptotic FIM to predict actual values (not the trends) of estimated parameter variances may not be reliable.
- Asymptotic variance values should be used as a guide to investigate designs.
- Conclusions should be drawn from a combination of asymptotic variance values and simulation studies.
- Note that the asymptotic FIM variance values can give us no information about the likely bias in the parameter estimates; simulation studies must be done to examine bias.
- Previous work found no difference between asymptotic FIM and simulation for fixed effects [3]. Differences found here are assumed to be model and design dependent.

References

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[3] S. Retout, F. Mentré, and R. Bruno. Fisher information matrix for non-linear mixed-effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. Stat. Med., 21:2623–2639, 2002.

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