Bayesian Estimation of Optimal Sampling Times for Pharmacokinetic Models

Stephen Duffull[1,2], Gordon Graham[3], Kerrie Mengersen[4]

[1]School of Pharmacy, University of Otago, Dunedin, New Zealand; [2]School of Pharmacy, University of Queensland, Brisbane, Australia, [3]Pfizer, Sandwich, UK; [4]QUT, Brisbane, Australia

Introduction

- Optimal design techniques are gaining acceptance as a tool for designing PK and PKPD studies [1,2].
- These designs are based on finding the maximum of a scalar function of the information matrix (usually the determinant) – this provides the optimum sampling times for a given set of models and parameter values.
- Clinical acceptability of an optimized design requires that windows are provided around the optimal sampling times [1,2].
- These sampling windows are designed to provide regions of acceptable sub-optimality.

Aim

- To explore the use of an MCMC approach for estimating sampling windows

Theory

- A fully Bayesian method is described that involves defining:
  - priors on the sampling times and the parameter values
  - a utility function
- The posterior distributions for the sampling times are obtained using MCMC

Prior for parameters

- The prior on the parameter space was assumed to be given by a lognormal distribution where,

$$p(\boldsymbol{\theta}) \sim N_p\left(\begin{bmatrix}\ln(\mu_1)\\ \vdots \\ \ln(\mu_p)\end{bmatrix}, \begin{bmatrix}\omega_{1,1} & \cdots & \omega_{1,p}\\ \vdots & \ddots & \vdots \\ \omega_{p,1} & \cdots & \omega_{p,p}\end{bmatrix}\right)$$

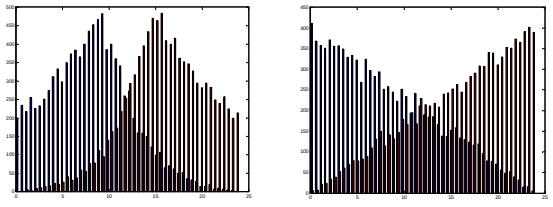
Prior for sampling times

- The prior for the n sampling times on the design space is given by

$$p(\mathbf{X}_i) = Unif(a_i, b_i),\ a_i > a_{i-1}, b_i > b_{i-1}, b_i > a_i \text{ for all } i$$

- Two priors were considered, a mixture of uniforms or ordered uniforms
- For *n* = 2 sampling times these provide the following prior (Figure 1)

Figure 1: Prior



Mixture of uniforms Ordered uniforms

Utility function

- The utility (*U*) was given by the inverse square of the product of the relative standard errors (*i* denotes the i^{th} iteration of the MCMC algorithm), and *M* the Fisher information matrix

$$U(\mathbf{X}^i, \boldsymbol{\theta}^i) = prod((diag((M^{-1}(\mathbf{X}^i, \boldsymbol{\theta}^i))^{0.5}(\boldsymbol{\theta}^i)^{-1}))^{-2})$$

Posterior

- The (pre-) posterior distribution of the sampling times was obtained by integrating the following expression using the Metropolis Hastings algorithm

$$p(U(\mathbf{X}, \boldsymbol{\theta})) = \int p(U(\mathbf{X}, \boldsymbol{\theta}) \mid \boldsymbol{\theta}, \mathbf{X}) p(\boldsymbol{\theta}) p(\mathbf{X}) d\boldsymbol{\theta} d\mathbf{X}$$

- The sampling windows were defined as the 95% credible interval of the posterior distribution of the sampling times

Application

- The model was a first order input and first order output, one-compartment model, given by:

$$C(t) = Dka(V(ka-k))^{-1}(\exp(-kt) - \exp(-kat)), \quad \boldsymbol{\theta} = [\log(V), \log(ka), \log(k)]'$$

- The parameters were assumed to be lognormally distributed, where $\boldsymbol{\theta}$ = [ln(20), ln(1), ln(0.1)] and ω_{ii} = 0.1 for all *i*
- The dose was 400 units and an additive residual variance model with a variance of 0.1 was assumed.
- Three sampling times were considered (data for mixture of uniforms prior is shown).
- Histograms of the sampling windows are provided in Figure 2, and for the asymptotic estimates of the expected standard error in Figure 3.

Figure 2: Sampling Times

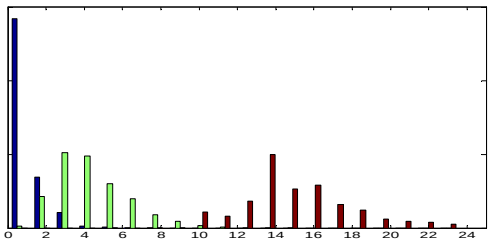
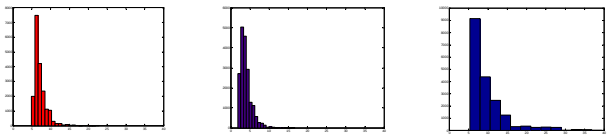


Figure 3 Standard Errors (%)



V *Ka* *K*

- The posterior mode of the sampling times were 0.46, 2.7 and 15 hours
- The optimal sampling windows were (0.08, 3.1) (1.9, 8.9), (9.6, 21.8) hours
- The two priors gave comparable estimates of the windows
- The 97.5th percentile of the expected standard errors of the parameters were less than 30%

Conclusions

- A fully Bayesian method has been described for determining the full posterior distribution of optimal sampling times from which specific sampling times can be chosen and sampling windows defined
- The method is convenient (in terms of computation effort) and appears robust to our choice of the prior on the sampling times

References: 1. Waterhouse et al. JPKPD 2006;32:521-545. **2.** Hennig et al. PAGE 15(2006) Abstr 970 [www.page-meeting.org/?abstract=970]