Development of a Bayesian Adaptive Sampling Time Strategy for PK Studies with Constrained Number of Samples to Ensure Accurate Estimates

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INTRODUCTION AND BACKGROUND

Objective: To ensure credible estimation of model parameters under uncertainty

Constraints: Ethical constraints on the number of patients (typical scenario: a paediatric study)

Proposal: Utilize Bayesian Adaptive Sampling Times in which sample times are optimally defined according to updated PK information available from preceding patients

METHODS

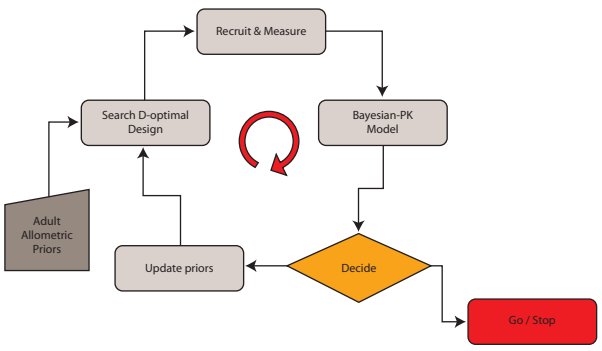
Bayesian Adaptive Sampling Times (BAST) Strategy

The adaptive strategy is:

1. First, priors on the PK parameters are established based on previous data or information (i.e. adult data).
2. Based on these priors, a D-optimal design for non linear mixed-effect models is determined using PFIM 1.2 software (*Retout, S. and Mentré, F., 2003*).
3. After determined collection of concentration values on a patient or a cohort of patients, a Bayesian PK model is fit to the data using the model and the priors elicited previously (with WinBUGS software version 1.4.3).
4. The posteriors from the Bayesian fit are then used as prior for finding the optimal design for the next cohort of patients. Back to step 2.

This process is iterated each time a patient is recruited until confidence on parameter estimates is deemed satisfactory (**Figure 1**)

Figure 1: BAST process



Bayesian PK model

The following Bayesian one-compartmental oral model was used to fit the PK profile:

$$Y \sim \text{Lognorm}(C, \tau)$$

$$C = \ln\left(\frac{D}{\exp(\alpha)} \frac{\exp(\beta)}{\exp(\beta)-\exp(\gamma)} (\exp(-\exp(\gamma)*t) - \exp(-\exp(\beta)*t))\right)$$

$$\Theta \sim \text{Mnorm}(\mu, R) \text{ with } \Theta = (\alpha,\beta,\gamma)$$

$$\mu \sim \text{Mnorm}(M,P)$$

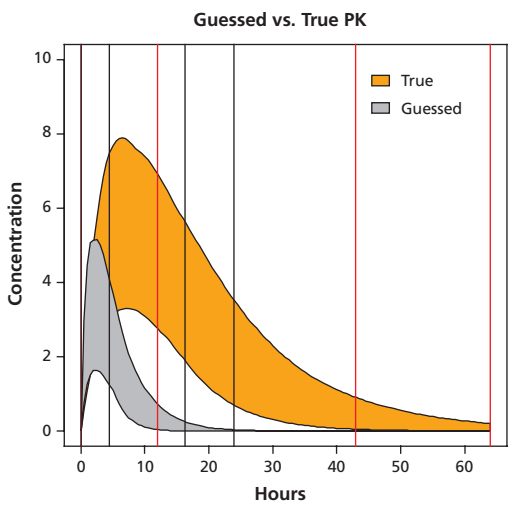
$$R \sim \text{Wish}(\Omega,3)$$

$$\tau \sim \text{Gamma}(a,b)$$

Assumptions

- The functional form of PK is assumed known.
- Allometric scaling given adult data gives the "grey" profile and its corresponding optimal design (black lines) (**Figure 2**).
- In order to test the robustness of this approach, we assumed the following scenario which deviates significantly from the hypothesized one: we consider that volume and elimination are "smaller" than anticipated (yellow profile on **Figure 2**) since, for children under 1 year of age, pharmacokinetics can drift non-linearly.

Figure 2: Hypothesized (grey) versus True (yellow) PK profile



Simulations

Simulations are performed with the following considerations:

- Phase I Single Dose data are simulated according to the yellow profile (**Figure 2**).
- Focus is on accuracy of PK parameter estimates.
- A priori is at least moderately informative since adult data were available.
- For ethical reasons, we have maximum 4 D-optimal sampling times per patient.
- We have 2 patients per cohort, maximum of 6 cohorts.
- Bayesian Hierarchical PK model (1-compartment, oral) with informative prior from adults or from previous cohorts.
- Trial could stop when accuracy on PK parameters satisfactory, but 12 patients is the stopping rule.

We will compare the adaptive procedure previously explained with non-adaptive study designs based upon

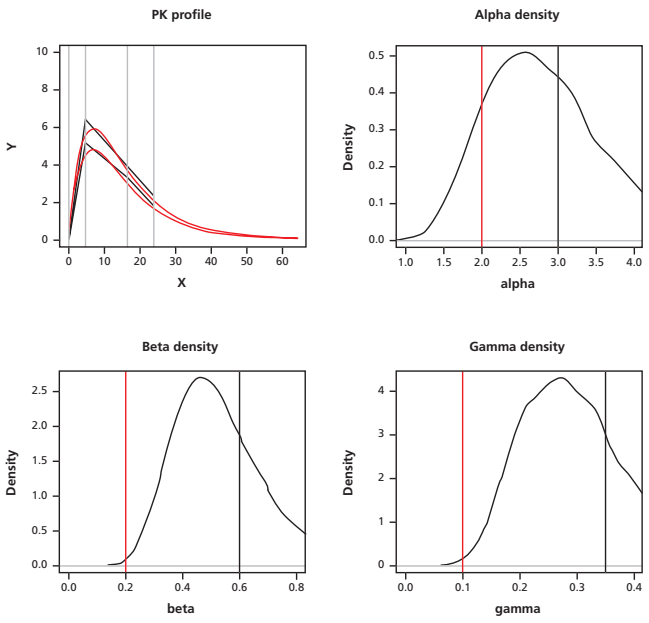
- the correct scenario
- the hypothesized (wrong) situation

RESULTS

Results with BAST after cohort 1 and interim 1 (2 patients)

- Sampling times (grey vertical lines) are not appropriate given the observed profiles
- Posterior distribution on parameters are migrating toward true values (red lines) but are still intermediate between these and the hypothesized situation (black lines)

Figure 3 : Results after Cohort 1, with adaptive design



CONCLUSIONS

- This approach was found to be very efficient for estimating the parameters of a pharmacokinetic model under uncertainty.
- When the guesses about the priors are wrong or very uninformative, then the BAST provides significantly more accurate estimates of the parameters than those derived from a fixed design based upon the same (wrong) assumptions.
- When the guess is correct, then the BAST doesn't impact the original optimal plan and estimates are as accurate as the fixed design without loss of power.
- The BAST method also appears to converge rapidly to the optimal sampling schedule.
- There are several potential usesto be an and developments of Adaptive Sampling-times:

- Use in TK studies where dose-proportionality is always challenged, to obtain better estimates for PBPK and allometric scaling
- First-In-Man trial (Single Dose) & Repeated Doses trials based on animal priors from PBPK or allometric models
- PK studies in special population or diseases.
- Extend to ODE to allow advanced PK/PD
- Staggered designs

The only requirement is to have a bio-analytical lab that works in "real-time": possible with new technologies.

Reference:

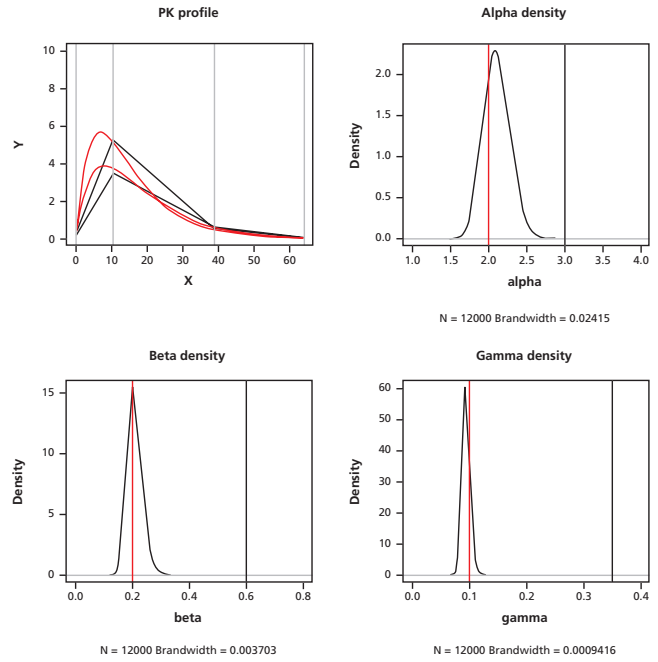
Retout S, Mentré F. Optimisation of individual and population designs using Splus, *Journal of Pharmacokinetic and Pharmacodynamics*, 2003, 30: 417-443.

Comparative analysis after 6 cohorts or 12 patients

1. BAST

- Posterior distributions for beta and gamma PK parameters are satisfactory, estimates are accurate (unbiased and precise).
- Posterior distribution on alpha may require more data in order to alleviate bias.

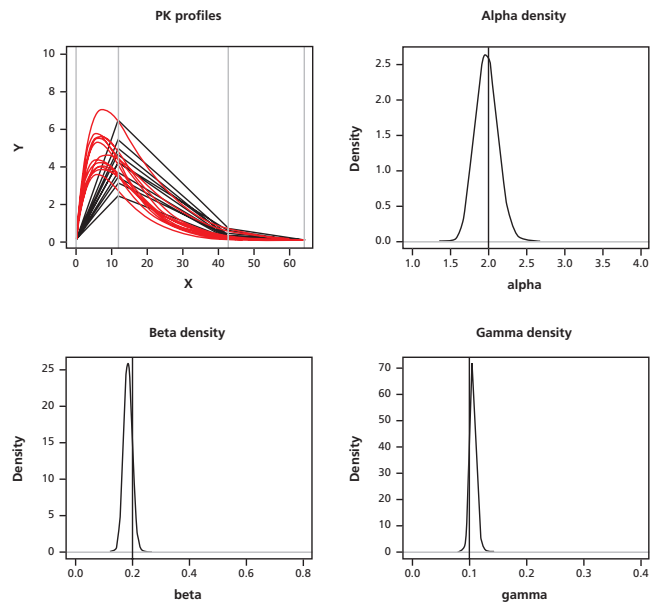
Figure 4: Results after 6 cohorts, with adaptive design



2. Fixed design and correct guess

- With or without adaptation on sampling times: results are the same when the guess is correct.

Figure 5: Results with 12 patients, no adaptation, correct guess



3. Fixed design and incorrect guess

- Estimates are less accurate
- Bias caused by the sub-optimal sampling-times design
- Inappropriate estimates for dose prediction and regimen optimization.

Figure 6: Results with 12 patients, no adaptation, incorrect guess