Bayesian Adaptive Sampling Time Design for Constrained PK Studies
Phase I Single Dose study in young children:
- 1 month to 4 years

Focus is on accuracy of PK parameter estimates:
- to be used for predictions
- dose/regimen optimization

A priori rather informative:
- numerous data in adults (16y to 70y)
- experience in allometric scaling.

Ethics:
- kids are not small adults, need to be robust against this potential issue
- maximum 3 or 4 samples per kid.
Accuracy on parameter estimates is linked on sampling time choice.

D-optimality criteria is not independent of the parameters in nonlinear (hierarchical) model:
- design is only locally optimal around preliminary estimates or guesses
- if guesses about parameters are wrong, then the design is not optimal with respect to the true value of the parameter

How to overcome these difficulties?
A Bayesian adaptive framework based on D-optimality and prior information on parameters.
I. BAST: How it works?

II. Practical case: pediatric population PK study

III. Conclusion & further work
Goal:

An Adaptive Sampling-Time Design trial is investigated to guide the sampling times in single-dose and multiple-dose studies

Main ideas:

- Given (updated) a priori information on parameters, a D-optimal design for non-linear mixed effect model is derived at each interim.
  NB: not a Bayesian D-optimal design, too computer intensive
- A Bayesian hierarchical PK model has been applied to update information on the parameters
The Design:

1. 2/3/4 patients per cohort, maximum of 6 cohorts
2. 3/4/5 sampling times obtain using the D-optimality criterion given prior information
3. Bayesian Hierarchical PK model with informative prior from adults and allometric scaling
4. Posteriors on parameters are used to find the D-optimal design for the next cohort.
5. Posteriors are used as priors for the Bayesian model at the next interim
6. Trial could stop when accuracy on parameters satisfactory, but 12 patients is the stopping rule.
Non-linear mixed effects model

For $q = 1, \ldots, Q$,

$$y^q = f(\theta, \gamma^q, \xi^q) + \varepsilon^q \circ \left(\sigma_{\text{inter}} + \sigma_{\text{slope}} f(\theta, \gamma^q, \xi^q)\right)$$

The assumptions:
- $\gamma^q \sim \mathcal{N}_p(0, \Omega)$,
- $\varepsilon^q \sim \mathcal{N}_{n_q}(0, I_{n_q})$,
- Independence between $\gamma^q$ and $\varepsilon^q$.

The parameter to estimate is the vector $\Psi = (\theta^T, \omega^T, \sigma^T)^T$, with:
- $\theta = (\theta_1, \ldots, \theta_p)^T$ the vector of fixed effects,
- $\omega = (\omega_1, \ldots, \omega_p)^T$ the variance of random effects,
- $\sigma = (\sigma_{\text{inter}}, \sigma_{\text{slope}})^T$ for the structure of the variance of residual error.
Definition

An experimental plan is defined by:

\[ \Xi = \left\{ \xi^1, \ldots, \xi^Q \right\} \]

Fisher Information Matrix

\[ M_F(\Psi, \Xi) = E\left( -\frac{\partial^2 l(\Psi, y)}{\partial \Psi \partial \Psi^T} \right) \]

The \textit{D-}optimality criterion:

\[ \Phi(\Xi) = \left| M_F(\Psi, \Xi) \right|^{1/l_\Psi} \]

Goal: find \( \Xi \) that maximize the criterion \( \Phi \)

Software & functions:

– software \texttt{R},

– functions \texttt{PFIM} \& \texttt{PFIMOPT} (Sylvie Retout & France Mentré)
**Model for the data:**

\[
\ln(y_j) = \ln(C(\Psi^i, \xi_j)) + \varepsilon_j \sim \mathcal{N}(0, \tau^{-1})
\]

**Model for the inter-individual variability:**

\[
\Psi^i \sim \mathcal{N}_p(\Psi, R^{-1})
\]

**Priors:**

\[
\tau \sim \mathcal{Ga}(a, b) \\
\Psi \sim \mathcal{N}_p(\mu, \Sigma^{-1}) \\
R \sim \mathcal{Wi}_p((\rho \Omega)^{-1}, \rho)
\]
## Priors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$</td>
<td>$\sim\text{Ga}(a, b)$</td>
</tr>
<tr>
<td>$\Psi$</td>
<td>$\sim\mathcal{N}_p(\mu, \Sigma^{-1})$</td>
</tr>
<tr>
<td>$R$</td>
<td>$\sim\mathcal{W}_p((\rho\Omega)^{-1}, \rho)$</td>
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</tbody>
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## Updates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expression</th>
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</thead>
<tbody>
<tr>
<td>$a$</td>
<td>$\frac{E^2(\tau_{\text{post}})}{\text{Var}(\tau_{\text{post}})}$</td>
</tr>
<tr>
<td>$b$</td>
<td>$\frac{E(\tau_{\text{post}})}{\text{Var}(\tau_{\text{post}})}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$E(\Psi_{\text{post}})$</td>
</tr>
<tr>
<td>$\Sigma$</td>
<td>$\left(\text{Var}(\Psi_{\text{post}})\right)^{-1}$</td>
</tr>
<tr>
<td>$\Omega$</td>
<td>$\left(\frac{E(\tau_{\text{post}})}{\text{Var}(\tau_{\text{post}})}\right)^{-1}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>$\frac{2\left(\frac{E^2(\tau_{\text{post}})}{\text{Var}(\tau_{\text{post}})}\right)<em>{kk}}{\left(\text{Var}(\tau</em>{\text{post}})\right)_{kk}}$</td>
</tr>
</tbody>
</table>
BAST: How it works?
Practical case: pediatric population PK study
Conclusion

- The BAST procedure
- Model and D-optimal design
- Bayesian hierarchical PK model
- Updates of priors
- Adaptive upper time search

Flowchart:
- Priors
- Upper time \( P(C > LLOQ) > 0.5 \)
- \( D \)-optimal Design
- Recruitment & Measures
- Bayesian PK-model
- Decision
- Go/Stop
- Update of priors
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Concentration for a one compartment model:

\[ C(V, k_a, k_e, \xi) = \frac{D}{V} \times \frac{k_a}{k_a - k_e} \times (e^{-k_e \xi} - e^{-k_a \xi}) \]

With:
- \( D \) the oral dose,
- \( k_a \) and \( k_e \) the absorption & elimination constant,
- \( V \) the volume of the compartment.

Parameterization with \( \log(V) \), \( \log(k_a) \) and \( \log(k_e) \).
WinBUGS code

model {
  for(i in 1:M) {
    for(j in 1:N) {
      log.y[i,j] ~ dnorm(log.C[i,j],tau)
      log.C[i,j] <- log(D/
        exp(psi[i,1])*
        exp(psi[i,2])/
        (exp(psi[i,2])-exp(psi[i,3]))*
        (exp(-exp(psi[i,3])*xi[i,j])-
          exp(-exp(psi[i,2])*xi[i,j])))
    }
    psi[i,1:3] ~ dmnorm(mean_psi[,R[,]])
  }
  mean_psi[1:3] ~ dmnorm(mu[,prec[,]])
  R[1:3,1:3] ~ dwish(rho_omega[,], rho)
  tau ~ dgamma(a,b)
}

Jonathan Jaeger, Astrid Jullion, Bruno Boulanger
Different sizes for cohorts

Different number of sampling times

Prior values for the first cohort

Interest for the configuration:
- 6 cohorts of 2 patients
- 4 sampling times per subject

2, 3, 4 & 12 patients per cohort

3, 4 & 5 sampling times

good guess or wrong guess
After the 1\textsuperscript{st} cohort

**PK profiles**

- Concentration over time for different cohorts.
- LLOQ (Lower Limit of Quantitation).

**log(V)**

- Distribution of the log-transformed volume of distribution (V).
- A PRIORI distribution compared to TRUE distribution.

**log(k_a)**

- Distribution of the log-transformed absorption rate constant (k_a).

**log(k_e)**

- Distribution of the log-transformed elimination rate constant (k_e).
After the 2\textsuperscript{nd} cohort

**PK profiles**

- Concentration over time for the 2\textsuperscript{nd} cohort.

**log(\(V\))**

- Distribution of the log-transformed volume of distribution.

**log(\(k_a\))**

- Distribution of the log-transformed absorption rate constant.

**log(\(k_e\))**

- Distribution of the log-transformed elimination rate constant.
After the 6th cohort

PK profiles

log(V)

log(\(k_a\))

log(\(k_e\))
After 12 patients, fixed design & correct a priori

PK profiles

log(V)

log(k_a)

log(k_e)
BAST vs. Fixed design & wrong guess:

- reduction of MSE,
- dispersion of relative bias less important,
- reduction of bias for log($k_e$).

BAST vs. Fixed design & good guess:

- similar results,
- MSE slightly lower,
- relative bias similar,
- reduction of the dispersion for log($k_e$).
BAST vs. Fixed designs (3 sampling times)
- BAST rapidly converges to the Fixed Design with correct a priori
- After 12 patients, both BAST and Fixed Design with correct a priori provide similar quality.
- BAST convergence is, within limits, robust against a prioris, correct or incorrect.

Proportion of simulations with 95% of joint posterior distribution on parameters included within [-20%, 20%] of true values
Influence of the number of patients per cohort

Configuration:
– 2, 3, 4 & 12 patients per cohort,
– A total of 12 patients,
– 4 sampling times.

Results:
– Reduction of the relative bias for \( \log(k_e) \),
– Reduction of the dispersion of relative bias,
– Limited gain to the passage of 3 to 2 patients,
– The less patients by cohort, the faster the adaptation.
Influence of the number of sampling time:

Configuration:

– 2 patients per cohort,
– 6 cohorts,
– 3, 4 & 5 sampling time.

Results:

– **Reduction** of the relative bias for log($k_a$),
– Reduction of the dispersion of the bias,
– **Gain** for the passage of 4 to 5 times.
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When a priori are wrong
BAST design with 12 patients provides parameter estimates more accurate (less bias, more precision) than a fixed design with 12 patients.

When a priori are right
BAST design with 12 patients provides parameter estimates as accurate than a fixed design with 12 patients.

How are you sure about a priori information?

Adaptive Design, in particular "sampling-times" adaptive design provides PK/PD models with accurate "fit-for-purpose" estimates. Accurate estimates permit better predictions and therefore more accurate dose and regimen optimization.

