SOFTWARE FOR OPTIMAL DESIGN IN POPULATION PKPD: A COMPARISON

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OUTLINE

1. Population design
2. Software tools
3. Comparison
4. Conclusions
1. POPULATION DESIGN
Population PK/PD

- Population PK/PD studies increasingly performed during drug development

- Several methods/software for maximum likelihood estimation of population parameters using NonLinear Mixed Effects Models (NLMEM)
  - NONMEM
  - Splus/R: nlme, SAS: Proc NLINMIX
  - MCMC estimation methods: SAEM (MONOLIX), MC-PEM,…

- Problem beforehand: choice of population design
  - number of patients?
  - number of sampling times?
  - sampling times?

- Recommendations on design in the FDA guidance
Statistical estimation

Statistics:

1. Inference
   - hypothesis testing
   - estimation
   - prediction

2. Planning = find ‘optimal’ design given
   - objective (e.g.: estimation)
   - statistical method (e.g.: maximum likelihood)
   - experimental constraints
   - some prior knowledge on expected results (e.g.: models and parameters)
Evaluation of population designs

- Compare designs
  - predicted standard errors of each population parameter

- Optimal design
  - smallest estimation variance
  - greatest information in the data

- Two approaches
  - simulation studies
  - mathematical derivation of the Fisher Information matrix (MF)
    - Cramer-Rao inequality: $\text{MF}^{-1}$ is the lower bound of the estimation variance
Fisher Information Matrix

- Problem in NLMEM because no analytical expression of the likelihood
  - Evaluation of MF using first order linearisation
    - (see other references at the end)

- Since first theoretical work
  - Several statistical developments by different teams
  - Applications in drug development, in clinical pharmacology
  - Several software tools
Population Optimum Design of Experiments (PoDe)

- Creation of a multidisciplinary group: PODE
  - initiated by Barbara Bogacka (School of Mathematical Sciences, University of London)
  - discuss theory of optimum experimental design in NLMEM and their application in drug development
    www.maths.qmul.ac.uk/~bb/PODE/PODE2007.html

- One day workshop
  - May 2006: London, University of London (B. Bogacka)
  - May 2007: Sandwich, Pfizer (P. Johnson)
    - special session on software tools and their statistical methodology
2. SOFTWARE TOOLS
(alphabetical order)
PFIM and PFIM interface

- Developed by Sylvie Retout and France Mentré
  - INSERM & University Paris 7
  - Other participants: Emmanuelle Comets, Hervé Le Nagard, Caroline Bazzoli

- Population Fisher Information Matrix

- Use R

- Available at www.pfim.biostat.fr

- History of PFIM
  - 2001: PFIM 1.1 similar in Splus and Matlab (S. Duffull)
  - 2003: PFIM 2.1 and PFIMOPT 1.0
  - June 2007: PFIM Interface 2.0 (evaluation and optimisation)
  - Soon PFIM 3 (beta version) and PFIM Interface 3
PFIM Interface 2.0

Input Design

- Dose regimen:
  - Identical dose in each elementary design
  - Dose: 100

Initial population design

- Number of groups: 2
- Subjects are given as: Numbers

Initial population design

- 0.0625, 7, 14, 20.58
- 0.0625, 12, 20

Initial proportions or numbers of subjects per group

- 1, 90, 30
Developed by Sergei Leonov
  ● Research Statistics Unit, GlaxoSmithKline
  ● Other participants: Bob Gagnon, Brian McHugh, Valerii Fedorov

- **Sampling Times Allocation - Matlab Platform**
- **Or STand Alone - Matlab Platform**
  ● (no need of Matlab)
  ● free Matlab Component Runtime environment

- Not available outside GSK
PopDes

- Developed by Kayode Ogungbenro, Ivelina Gueorguieva and Leon Aarons
  - CAPKR, University of Manchester

- Population Design

- Matlab platform
- Available at www.capkr.man.ac.uk/PopDes
- Since April 2007 (on website)
PopDes

User Interface:
- **Design Options**
  - Individual
  - Population
  - Uniresponse
  - Multiresponse
  - Local
  - Bayesian
- **Parameters**
  - **Model**
    - Library
      - One compartment IV bolus
    - External
- **Efficiency**
  - Efficiency of a User-Specified Design
    - User Design
  - **Sampling Windows Calculation**
    - % Efficiency
      - Uniform
    - Initial Guess of Sampling Windows Half Length
    - **Optimisers**
      - Exchange step size
      - Hybrid
      - Simplex
  - **Sampling Windows Evaluation**
    - Efficiency of User-Specified Windows
      - User Windows
      - Uniform
    - **Solve & Save**
PopED

- Developed by Andy Hooker, Joakim Nyberg, Mats Karlsson
  - Uppsala University
- Population optimal Experimental Design
- Matlab platform
  - O-matrix with previous versions (University of Washington, Paolo Vicini)
- Matlab version available
  - by request andrew.hooker@farmbio.uu.se
  - soon (July 2007) from www.sourceforge.net
- Previous O-matrix version available
  - depts.washington.edu/rfpk/rd/software_popED.html
  - since March 2003
PopED

**Optimization settings**
- Optimization method: D-Optimal
- Search Type:
  - Random Search
  - Stochastic Gradient
  - Line Search

**Design parameters**
- Use grouping
- Number of groups: 3
- Max number of samples/group: 3
- Min number of samples/group: 1
- Num individuals in each group:
  - Group 1: 4
  - Group 2: 4
  - Group 3: 4

**Tasks to optimize**
- Samples per Subject
- Sampling Schedule
- Number of individuals per group
- Covariates
- Other variables

**Model size**
- Number of Pop in model: 3
- Number of random effects in model: 3
- Number of covariates in model: 1
- Number of other design-variables in model: 0

**Model name**:
Theophylline Time and Dose

**Model description**:
Optimization of Theophylline (1 comp model with linear absorption). Optimizing on Dose and Time at the same time. Only PK optimization.
POPT and WinPOPT

- Developed by Stephen Duffull
  - University of Otago (NZ), University of Queensland, Johnson & Johnson
  - Other participants: Nick Denman, Hui Kimko, John Eccleston
- Matlab platform
- For WinPOPT:
  - stand alone version (no need of Matlab)
  - free Matlab Component Runtime environment
- Available at www.winpopt.com
- POPT: since July 2003
- WinPOPT: since March 2006
WinPOPT
3. COMPARISON

Summary done by France Mentré from slides at PoDe2007 based on currently available versions (June 2007)
### Language, availability, interface, models...

<table>
<thead>
<tr>
<th></th>
<th>PFIM</th>
<th>PFIM Int.</th>
<th>PkStaMP</th>
<th>PopDes</th>
<th>PopED</th>
<th>POPT</th>
<th>WinPOPT</th>
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<tbody>
<tr>
<td><strong>Authors</strong></td>
<td>Retout</td>
<td>Retout</td>
<td>Leonov</td>
<td>Ogungbeno ro</td>
<td>Hooker</td>
<td>Duffull</td>
<td>Duffull</td>
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<td><strong>Language</strong></td>
<td>R</td>
<td>R</td>
<td>Matlab CR</td>
<td>Matlab</td>
<td>Matlab O matrix</td>
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<td>Matlab CR</td>
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<td><strong>GUI</strong></td>
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<td><strong>Library of PK models</strong></td>
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<td>No*</td>
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## Evaluation of information matrix

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<td><strong>Analytical derivatives</strong></td>
<td><strong>Yes</strong></td>
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<tr>
<td><strong>Off-diagonal terms in MF</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
<td><strong>Yes</strong></td>
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<td><strong>Yes</strong></td>
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<td><strong>Full covariance matrix $\Omega$</strong></td>
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<td><strong>Designs differ across responses</strong></td>
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<td><strong>Yes</strong></td>
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### Optimisation

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<tbody>
<tr>
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<td>Sampling Windows</td>
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<td>No</td>
<td>Yes</td>
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Future developments

- All software tools have ongoing development that should fill the gap with the others.
- Some have other specific features:
  - See documentation or slides at PoDe2007.
- Other statistical developments:
  - Models with covariates.
  - Models with inter-occasion variability.
  - …
- Main limitation:
  - First-order approximation:
    - Simulation results: closer to FOCE and SAEM than to FO.
  - Exact evaluation of MF: stochastic approach or Gaussian quadrature.
4. CONCLUSIONS
1. Start a distribution list: PopDesign
   - organised by S. Duffull
   - to register: http://lists.otago.ac.nz/listinfo/popdesign
   - to send an email: popdesign@lists.otago.ac.nz
   - any questions/comments on design in NLMEM and software tools
   - answers by all members of PoDe

2. Start a discussion ‘Would it be possible to combine all software tools in one for future developments?’
   - to be organised by A. Hooker & F. Mentré
   - role of nlme consortium?
Conclusion

- Results of population PK/PD analyses increasingly used
  - in drug labeling
  - in test of covariates
  - for clinical trial simulation
  ➔ Informative studies with small estimation error

- Evaluation and comparison of population designs without simulation using statistical approach

- Results show that design may CONSIDERABLY affect precision of estimation

SPARSE-SAMPLING DESIGN = BEST INFORMATION NEEDED

- Several software tools available: no excuses!
  - define good population designs (ethical/financial reasons)
  - anticipate fatal population designs
Several Methodological References (1)

PFIM

Several Methodological References (2)

- **PkStaMP**
Several Methodological References (3)

PopDES

Several Methodological References (4)

PopED

Several Methodological References (5)

- **POPT/ WinPOPT**