Sparse sampling design in population PK/PD studies

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Outline

- Introduction
- Methodology for population design evaluation and optimisation
- Software
- Example of evaluation and optimisation with PFIM
- Conclusion

Introduction

Population pharmacokinetics (Pop PK)

- **Increasingly used in drug development**
  - estimation of the mean parameters and of inter-patient variabilities
  - quantification of the influence of covariates
  - allows sparse data

- **Method**
  - nonlinear mixed effects models (NLME)
  - maximum likelihood estimation: now well known methodology

- **Several available software**
  - NONMEM, WinNonmix, Monolix
  - SAS (NLINMIX)
  - Splus (nlme)
  - …

Design for POP PK analyses (1)

- **Increasingly important task for pharmacologist**
- **Importance of the choice**
  - influence the precision of parameters estimation
  - poor design can lead to unreliable studies
  - all the more important in pediatric studies
    - severe limitations on the number of samples to be taken
    - ethical and physiological reasons
- **FDA Guideline for population PK (1999)**
  - "Optimizing the sampling times becomes particularly important when severe limitations exist on the number of subjects and / or samples per subject (e.g., in pediatric patients or the elderly). Use of informative designs for population PK studies is encouraged… "
- **EMEA Guideline for PK in the paediatric population (2006)**
  - "Population pharmacokinetic analysis, using non-linear mixed effects models, is an appropriate methodology for obtaining pharmacokinetic information in paediatric trials both from a practical and ethical point of view.

    The population approach may replace conventionally designed pharmacokinetic studies with rich sampling. Simulations or theoretical optimal design approaches, based on prior knowledge should be considered as tools for the selection of sampling times and number of subjects…"

Design for population PK analyses (2)

Classical PK: recall

- **Estimation of the p parameters of one subject**
  - nonlinear regression
- **Choice of n sampling times with n≥p**
- **Theory of evaluation / optimisation in nonlinear regression**
  - based on the Fisher information matrix M_F
  - Rao-Cramer inequality: M_F^{-1} is the lower bound of the estimation variance-covariance matrix
- **Tool for helping to the design choice**
  - ADAPT II (D'Argenio & Schumitzky, BMSR, 1997)
  - evaluates and optimises individual design based on M_F

Design for population PK analyses (3)

Population PK

- **Estimation of the vector of the population parameters from N subjects**
  - fixed effects (p)
  - variance of the random effects (≤p)
  - parameters for the error model (1 or 2)

- **Choice of N?**
- **Same number of samples for everybody ?**
- **Same sampling times?…**
- **Different groups of subjects?**

Methodology for population design evaluation and optimisation

Evaluation of a population design

- **Two approaches**
  - simulation studies: cumbersome!
  - methodology based on the Fisher Information matrix in NLME
    - extension of the theory in nonlinear regression
- **Expression of M_F for population PK**
  - complex
  - based on a linearisation of the model around the fixed effects

(Mentré, Mallet & Baccar. Biometrika,1997) (Retout, Mentré & Bruno. Stat Med, 2002)

- **Principle**
  - to compute M_F and its inverse for each population design to be evaluated
    - from the population model
    - from a priori value of the population parameters
  - expected standard errors on the parameters = root mean square of the diagonal of M_F^{-1}
- **Design comparisons**
  - objective : to have the “smallest” M_F^{-1} or the “largest” M_F
  - criteria for matrix comparison
    - D-optimality, the most usual one: det (M_F)

Optimisation of population design

- **Maximisation of det(M_F)**
  - find the best design for a given value of the population parameters

- **Design variables**
  - real variables for the sampling times
  - discrete variables for the structure of the design
    - number of groups
    - number of subjects per group
    - number of samples per groups

- **Optimisation of exact or statistical designs**
  - exact design
    - fixed group structure (number of groups, subjects per group, samples per subject)
    - optimization of the sampling times in each group
    - general algorithms: simplex, simulated annealing, NARS, …
  - statistical designs
    - optimization of both the sampling times and the group structure
    - Fedorov-Wynn (specific algorithm), Simplex algorithm…

Software for population designs evaluation and optimisation

Langage, availability, interface, models…

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT	WinPOPT
Authors	Retout	Retout	Leonov	Ogungbenro	Hooker	Duffull	Duffull
Langage	R	R	Matlab	Matlab	O matrix	Matlab	Matlab RC
Available on website	Yes	Yes	No	Yes	Yes	Yes	Yes
GUI	No	Yes	Yes	Yes	Yes	No	Yes
Library of PK models	No	Yes	Yes	Yes	Yes	Yes	Yes
Multi response models	No	No	No	Yes	Yes	Yes	Yes

(Mentré, Duffull, Gueorguieva, Hooker, Leonov, Ogungbenro & Retout. PAGE 2007, 13-15 June 2007)

PFIM

- **Freely available at www.pfim.biostat.fr**
- **First version in 2001: PFIM 1.1**
  - Splus and Matlab (S. Duffull) code
- **PFIM in April 2008**
  - evaluation and optimisation for single response models
    - PFIM 2.1 and PFIMOPT 1.0

    (Retout, Mentré. J Pharmacokin Pharmacodyn, 2003)
    - PFIM Interface 2.1 (graphical user interface)

    (Retout, Bazzoli, Comets, Le Nagard, Mentré. PAGE 2007, June 2007)
- **PFIM Interface 2.1**
  - includes a library of pharmacokinetic models
  - design optimisation
    - Simplex algorithm: optimisation of the sampling times in continuous intervals
    - Fedorov Wynn algorithm: optimisation of both the group structure and the sampling times in a user-defined set of possible times
- **May 2008: PFIM 3.0**
  - evaluation and optimisation for multiple response models

  (Bazzoli, Retout, Mentré. PODE 2007, May 2007)

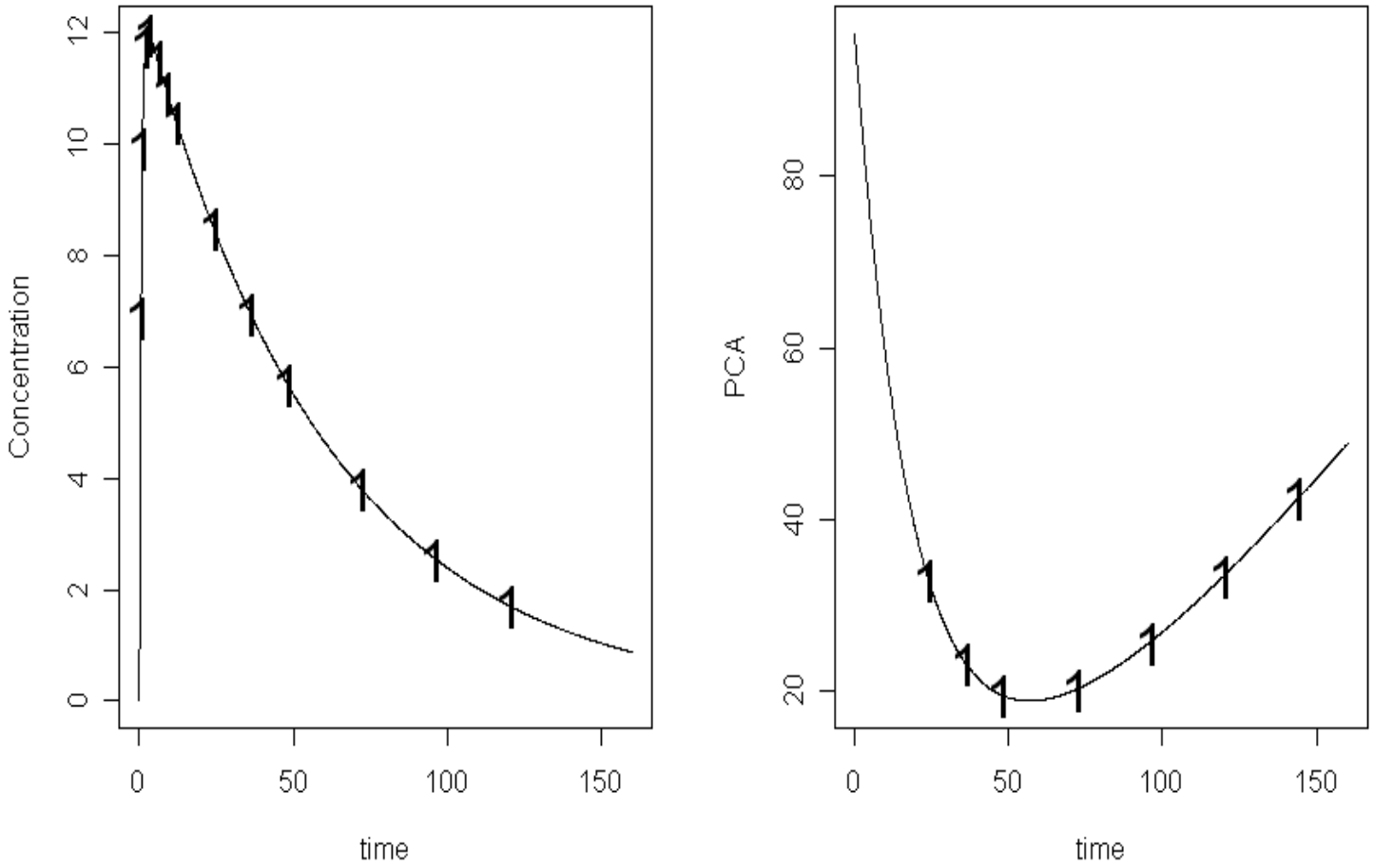
Example of evaluation and optimisation with PFIM

Example: Joint PK/PD modeling of Warfarin

(Bazzoli, Retout, Mentré, *American Conference on Pharmacometrics (ACOP)*, Mars 2008)

- **PK: time course of total racemic warfarin plasma concentration**
- **PD: effect on prothrombin complex activity (PCA)**
- **A priori PK knowledge**
  - single oral dose of 100 mg
  - 1 compartment model, 1st order absorption and elimination
  - CL=0.133; V=7.95; Ka=1.6; ω_{CL}=0.0634; ω_{V}=0.0206; ω_{KA}=0.701
  - exponential modelling of the random effects
  - Var(ε)=(0.2 f)^2
- **A priori PD knowledge**
  - turnover model with inhibition of the input
  - Imax=1(FIX); Rin=5.41; C_{50}=1.2; Kout=0.056; ω_{Rin}=0.19; ω_{Kout}=0.0167; ω_{C50}=0.0129
  - exponential modelling of the random effects
  - var(ε)=3.88
- **Evaluation of an empirical design**
  - one group of 32 subjects
  - 13 sampling times for PK and 7 sampling times for PD
- **Design optimisation with the Federov-Wynn algorithm under constraints**
  - only 4 sampling times per subject common to both responses performed into 32 subjects

Evaluation of the pop PK design with PFIM 3.0 (1)



→ One group of 32 subjects
→ Total of 640 sampling times

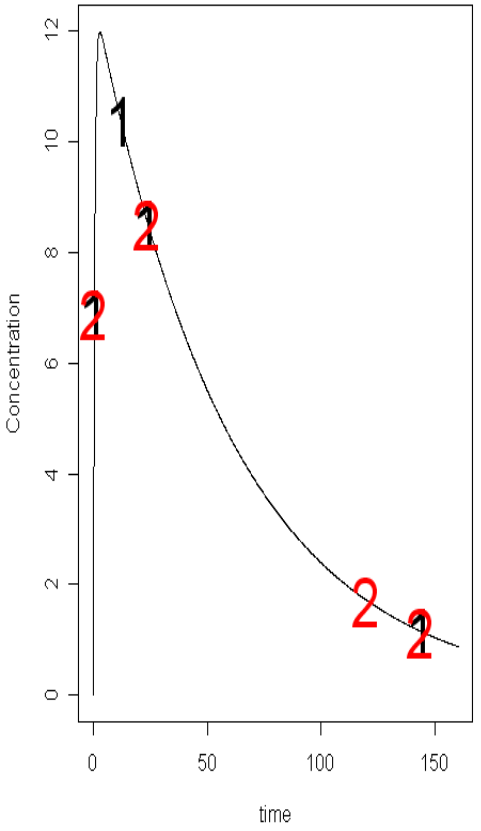
Evaluation of the pop PK design with PFIM 3.0 (2)

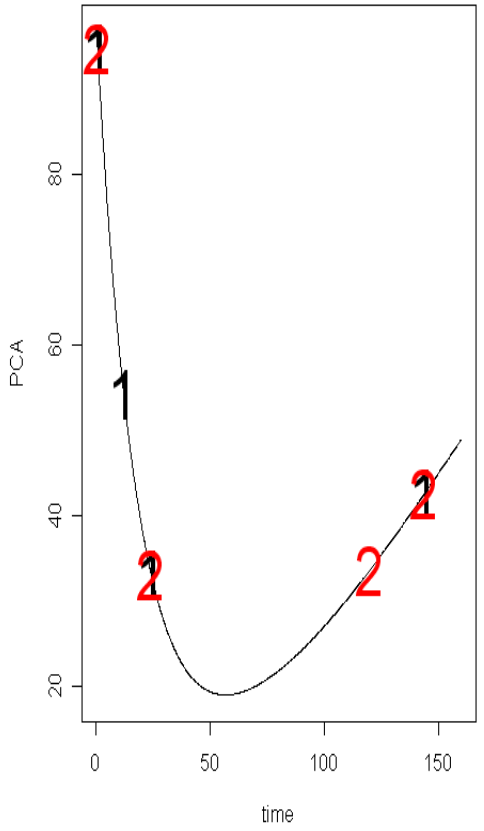
```
PFIM 3.0

Project:  PKPDWarfarine_indirect_model

Date:  Tue Nov 27 11:01:40 2007

**************************** INPUT SUMMARY *********************************

Differential Equations form of the model:

function(t,y,p)
{
ka<-p[1]
cl<-p[2]
V<-p[3]
Rin<-p[4]
C50<-p[5]
kout<-p[6]

      yd1<--ka*y[1]
      yd2<-ka*y[1]-(cl/V)*y[2]
      yd3<-Rin*(1-((1*y[2]/V)/((y[2]/V)+C50)))-kout*y[3]

list(c(yd1,yd2,yd3),c(y[2]/V,y[3]))
}


Population design:
Sample times for response: A
                                                    subjects
c(0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120)       32
Sample times for response: B
                                  subjects
c(0, 24, 36, 48, 72, 96, 120, 144)       32

 Variance error model response A : ( 0 + 0.2 *f)^2

 Variance error model response B : ( 3.88 + 0 *f)^2

 Initial Conditions at time 0 :

 100 0 Rin/Kout

 Between-subject variance model: Trand =  2

 Error tolerance for solving differential equations system: RtolEQ = 1e-08 , AtolEQ = 1e-08 , Hmax =  Inf
```

```
************************** EXPECTED STANDARD ERRORS *********

------------------------ Fixed Effects Parameters -----------

      Beta    StdError        CV .
Ka    1.600 0.252176029 15.761002 %
CL    0.133 0.006135812  4.613393 %
V     7.950 0.235561806  2.963042 %
Rin   5.410 0.628097943 11.609943 %
C50   1.200 0.108824055  9.068671 %
Kout 0.056 0.002358841  4.212215 %


-------------------------- Variance of Random Effects --------

      Omega    StdError        CV .
Ka    0.7010 0.196597447  28.04528 %
CL    0.0634 0.016879177  26.62331 %
V     0.0206 0.006811926  33.06760 %
Rin   0.1900 0.055624579  29.27609 %
C50   0.0129 0.032727257 253.69967 %
Kout 0.0167 0.007849129  47.00077 %


------------------------ Variance of residual error ---------

           SIG    StdError        CV .
sig.slopeA 0.20 0.007865186 3.932593 %
sig.interB 3.88 0.226415910 5.835462 %


******************************** DETERMINANT *****************

3.505562e+39
```

Optimisation of a pop PK design with PFIM 3.0

```
**************************** OPTIMISED DESIGN ************
Optimised population design:
Sample times for response: A
              prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091


Sample times for response: B
              prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091

Associated optimised criterion: 580.1989

************************* EXPECTED STANDARD ERRORS *********

------------------------- Fixed Effects Parameters -----------

      Beta     StdError         CV .
Ka    1.600 0.263353095 16.459568 %
CL    0.133 0.006533504  4.912409 %
V     7.950 0.322403263  4.055387 %
Rin   5.410 0.437881955  8.093936 %
C50   1.200 0.052867047  4.405587 %
Kout 0.056 0.001737771  3.103163 %


------------------------- Variance of Random Effects --------

      Omega     StdError         CV .
Ka   0.7010 0.206505767  29.45874 %
CL   0.0634 0.017561742  27.69991 %
V    0.0206 0.012226360  59.35126 %
Rin  0.1900 0.050298864  26.47309 %
C50  0.0129 0.016460059 127.59736 %
Kout 0.0167 0.007665362  45.90037 %


------------------------- Variance of residual error ---------

            SIG  StdError       CV .
sig.slopeA 0.20 0.0216894 10.84470 %
sig.interB 3.88 0.4677695 12.05591 %
```





→ Two groups with 22 and 10 subjects
→ Total of 256 sampling times

Example: comparison empirical / optimal designs

- Relative standard errors of estimation in the same range for the fixed effects
- 2.5 less measurements with the optimal design compare to the empirical design

Conclusion (1)

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

- **Importance of design evaluation and optimisation in pediatrics**
  - limited number of PK PD studies by ethical and physiological reasons
  - need reduced number of sampling times but informative !
  - need a priori knowledge of the population parameters
    - extrapolation from adults to children as for dose finding?
    - ex: mizolastine in children

    (Mentré, Dubruc, Thénot, J Pharmacokin Pharmacodyn, 2001)

- **Several software tools available: no excuse!**
  - PFIM : www.pfim.biostat.fr
  - help in the definition of good population designs
  - anticipate fatal population designs

Conclusion (2)

- **Creation of a multidisciplinary group: PoDe**
  - initiated by Barbara Bogacka (School of Mathematical Sciences, University of London)
  - discuss theory of optimum experimental design in population analyses and their application in drug development

  www.maths.qmul.ac.uk/~bb/PODE/PODE2007.html
  - several investigations ongoing
    - sampling windows
    - sequential designs
    - tests of covariates
    - cost functions
    - …

- **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 population designs and software tools
  - answers by all members of PoDe