Population designs evaluation and optimization in R: the PFIM function and its new features

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Introduction

- Population analyses often based on limited sampling strategy
  - ethical and / or financial reasons
- Population design: N subjects divided in Q groups of N_q subjects with the same elementary design ξ_q
  - $\xi_q = (t_1, t_2, \ldots, t_{nq})$: n_q samples and their allocation in time
- Methodology developed over the last decade to ensure informative population design
  - based on the Fisher information matrix (M_F)
  - expression of M_F using a first order Taylor expansion of the model [1]
- Relevance of the use of M_F showed by simulation [2-3] and on real data
- Implementation in PFIM
  - R function for population design evaluation and optimization

History of PFIM

- Implementation of M_F for evaluation
  - 2001: PFIM 1.0
    - Splus and Matlab function (Stephen Duffull) [4]
  - 2003: PFIM 1.2
    - Splus and R version
    - inclusion of combined variance error models
- Implementation of M_F for optimizationn
  - 2003: PFIMOPT 1.0 [5]
    - Splus and R versions
    - optimization using the Simplex algorithm
- Features of those implementations: single response model, local planification (D-optimality), model given under analytical form

Objectives

To describe the new features of PFIM and to present the new extension for multiple responses model

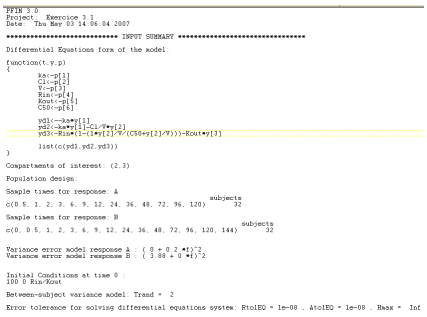
Models supported in PFIM 3.0 and PFIMOPT 3.0

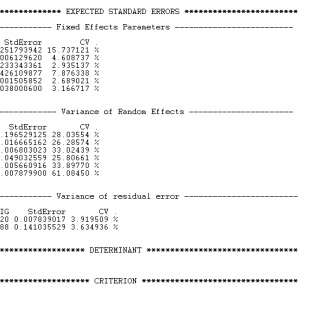
- Single or multiple response models (new development and evaluation using a first order expansion [6])
- Structural model
  - analytical form
    - computation of M_F using analytical derivatives of the model
  - differential equations system
    - use of the lsoda function from the "odesolve" package in R
      - method of Adams for non stiff systems
      - method "Backward Differentiation Formula" for stiff systems
    - numerical derivatives of the model with respect to the parameters
      - use of the functions "fdHess" in the "nlme" package
      - evaluate an approximate gradient of a scalar function using finite differences
- Inclusion of a library of pharmacokinetic models
  - 1 or 2 compartments
  - oral, IV or infusion administration
  - single or repeated doses or steady state
- Combined variance error model
  - $var(\varepsilon)=(\sigma_{inter}+\sigma_{slope}f)^2$
- Random effects
  - additive or exponential modelling
  - diagonal variance

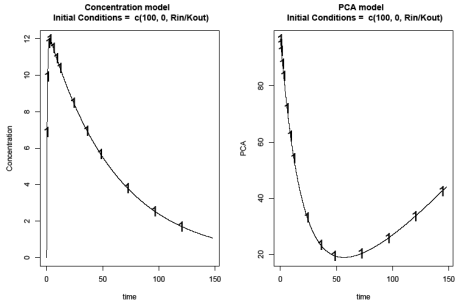
Example: Joint modelling of PK/PD of Warfarin

- PK: time course of total racemic warfarin plasma concentration
  - 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 random effects
  - var(ε)=(0.2 f)²
- PD: effect on prothrombin complex activity (PCA)
  - 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 modeling of the random effects
  - var(ε)=3.88

Figure 1. Evaluation of a population design for the joint modeling of PK/PD of Warfarin using PFIM 3.0. Design to be evaluated: one group of 32 subjects, 13 PK sampling times at (0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120) and 16 PD sampling times at (0, 0.5,1, 2, 3, 6, 9,12, 24, 36, 48, 72, 96, 120, 144)







Optimization with PFIMOPT 3.0

Context

- Optimization for a fixed total number of samples (n_{tot})
  - fix $n_{tot} = \Sigma N_q * n_q$
  - fix N_q and n_q
- Simplex or Fedorov-Wynn algorithm
- Case of multiple response model
  - balanced or unbalanced designs to be optimized
    - same of different numbers of samples across responses
    - same or different sampling times across responses
  - constraint on sampling times can be different for each type of response

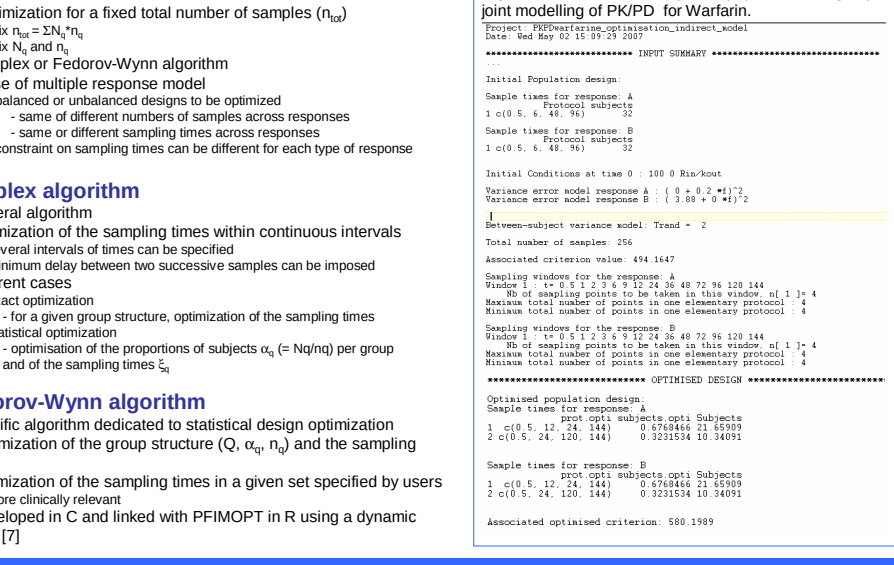
Simplex algorithm

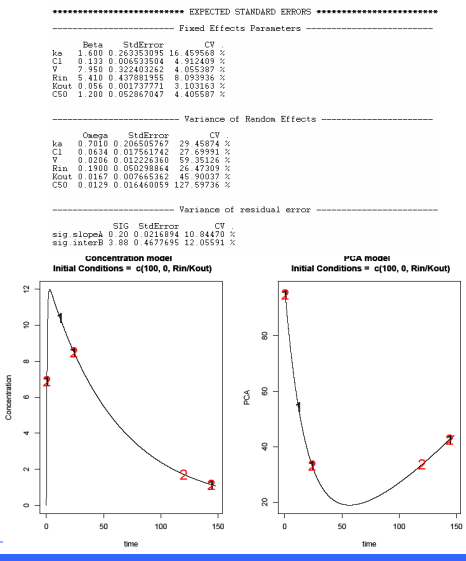
- General algorithm
- Optimization of the sampling times within continuous intervals
  - several intervals of times can be specified
  - minimum delay between two successive samples can be imposed
- Different cases
  - exact optimization
    - for a given group structure, optimization of the sampling times
  - statistical optimization
    - optimisation of the proportions of subjects α_q (= Nq/nq) per group and of the sampling times ξ_q

Fedorov-Wynn algorithm

- Specific algorithm dedicated to statistical design optimization
- Optimization of the group structure (Q, α_q, n_q) and the sampling times
- Optimization of the sampling times in a given set specified by users
  - more clinically relevant
- Developed in C and linked with PFIMOPT in R using a dynamic library [7]

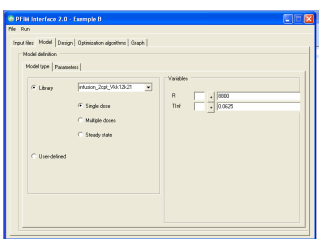
Figure 2. PFIMOPT 3.0 output for population design optimization using the Fedorov-Wynn algorithm on the example of the joint modelling of PK/PD for Warfarin.

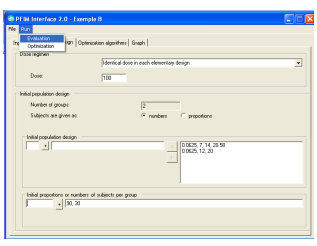


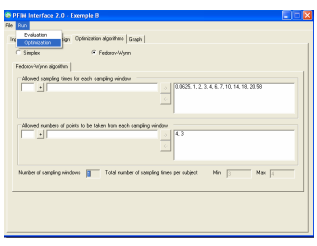


PFIM Interface 2.0

- Graphical user interface
- Requires R version 2.4.1
- Windows 2000 / XP platform
- Same features as PFIM / PFIMOPT 3.0 but only for single response model
- Model
  - analytical form or differential equations system
  - inclusion of the library of PK models
- Optimisation
  - Simplex or Fedorov-Wynn algorithm







Conclusion

- PFIM Interface 2.0 freely available at www.pfim.biostat.fr (with PFIM 1.2 and PFIMOPT 1.0)
- PFIM 3.0 and PFIMOPT 3.0 for multiple responses model: beta version under evaluation
- Perspective: PFIM Interface 3.0 for multiple response models

References

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