

An extension of PFIM for optimal design in multiple response nonlinear mixed effects models:



PFIM 3.0

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Context

- ✓ **Models with multiple responses increasingly used in population analyses**
 - * repeated measurements from different responses for one individual
 - * examples:
 - Pharmacokinetics / pharmacodynamics (PK/PD)
 - Parent drug and metabolite(s)
- ✓ **Population design structure → several groups of subjects**
 - * in each group: a number of sampling times and their allocation in time
- ✓ **Population designs evaluation and optimization for single response models**
 - * methodology based on the Fisher Information matrix (M_F)
 - * linearization of M_F using a first order Taylor expansion [1]
 - **Relevance of the use of M_F showed by simulation [2-4]**
 - **Implementation in PFIM 1.2**
 - * a R function → Recent release: PFIM Interface 2.1 with graphical user interface
- ✓ **Extension of M_F for multiple response model [5, 6] using the same linearization as for single response**
 - **Relevance on this extension shown on a PKPD simulation example [7]**

Objectives

- ✓ **To implement the extension of M_F for multiple response model in PFIM**
- ✓ **To improve the specification of the model and the optimization algorithm**
- ✓ **To illustrate this implementation on a PKPD example for warfarin**

Model specifications

- ✓ **Structural model**
 - * analytical form
 - computation of M_F using analytical derivatives of the model
 - * differential equations system
 - use the Isoda function from the "odesolve" package in R
 - numerical derivatives of the model with respect to the parameters
- ✓ **Inclusion of a library of PK models**
 - * 1 or 2 compartments
 - * oral, IV or infusion administration with single, repeated or steady state doses
- ✓ **Combined variance error for each response: $\text{var}(\epsilon) = (\sigma_{\text{inter}} + \sigma_{\text{slope}} f)^2$**
- ✓ **Random effects**
 - * additive or exponential modeling, diagonal variance

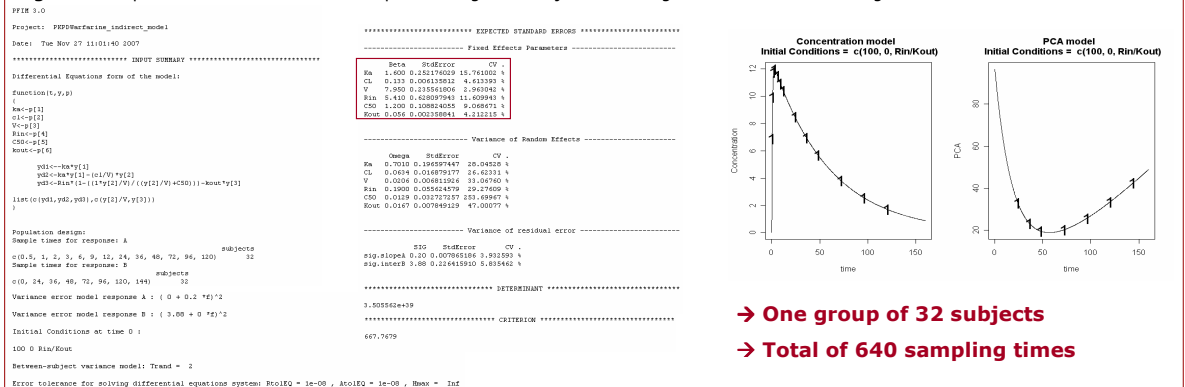
Optimization algorithm

- ✓ **Context**
 - * D-optimality criterion (det of M_F)
 - * optimization for a fixed total number of samples
 - * Simplex or Federov-Wynn algorithm
 - * balanced or unbalanced designs to be optimized
 - same or different numbers of samples and/or sampling times across responses
 - * constraints on sampling times can be different across responses
- ✓ **Simplex algorithm (general algorithm)**
 - * optimization of the sampling times within continuous intervals
 - * exact optimization: for a given group structure, optimization of the sampling times
 - * statistical optimization: optimization of the group structure and the sampling times
- ✓ **Federov-Wynn algorithm (dedicated to statistical design optimization)**
 - * optimization of the sampling times in a given set specified by users
 - more clinically relevant
 - * developed in C and linked with PFIM 3.0 in R using a dynamic library [4]

Design for joint PKPD model of warfarin

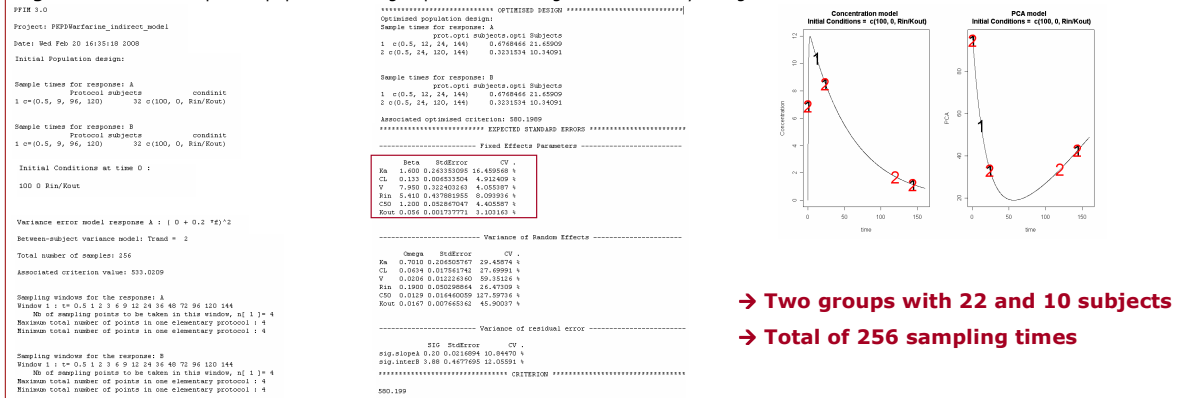
- ✓ **PK: total racemic warfarin plasma concentration**
 - * single oral dose of 100 mg
 - * one compartment model, first order absorption and elimination
 - * exponential modeling of the random effects
 - * proportional error
- ✓ **PD: effect on prothrombin complex activity (PCA)**
 - * turnover model with inhibition of the input
 - * exponential modeling of the random effects
 - * additive error
- ✓ **Evaluation of an empirical design**
 - * one group of 32 subjects with 13 sampling times for PK and 7 sampling times for PD
- ✓ **Design optimization with the Federov-Wynn algorithm under constraints**
 - * only 4 sampling times per subject common to both responses performed into 32 subjects

Figure 1. Output of the evaluation of the empirical design for the joint modeling of PKPD of warfarin using PFIM 3.0.



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

Figure 2. PFIM 3.0 output for population design optimization using the Federov-Wynn algorithm.



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

→ 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

- ✓ Population design evaluation and optimization tools widely used → several software [8]
- ✓ PFIM 3.0 for multiple responses is freely available at www.pfim.biostat.fr (with recent release: PFIM Interface 2.1)
- ✓ Perspective: PFIM Interface 3.0 for multiple response models

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[8]. Mentré F et al. *PAGE* (abstr 1179), 2007