# New features for population design evaluation and optimization with R functions: PFIM Interface 3.1 and PFIM 3.2

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## INTRODUCTION

- **Nonlinear mixed effect modeling or population analysis**
  - pharmacokinetic (PK) /pharmacodynamic (PD) data
- **Population analyses often based on limited sampling strategy**
  - ethical and / or financial reasons
- **Methodology developed to ensure informative population design**
  - based on the Fisher information matrix (MF)
  - expression of MF using a first order Taylor expansion of the model
- **Implementation in a R function PFIM** [1]
  - R function for population design evaluation and optimization

- **Recent extensions of PFIM (released in March 2011)**
  - for multiple response models [2]
    → **Implementation in a new interface version PFIM Interface 3.1**
  - for models with parameters quantifying influence of discrete covariates [3]
  - for models including within-subject variability [4]
    → **Implementation in a new R script version PFIM 3.2 (last version PFIM 3.2.2)**
    **=> Other features for both versions**
    - inclusion of libraries of PK and PD models with their documentation
    - computation of the block or the complete MF

## OBJECTIVES

**To illustrate the use of PFIM Interface 3.1 and PFIM 3.2 on warfarin PKPD**

## 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
- **PD: effect on prothrombin complex activity (PCA)**
  - turnover model with inhibition of the input
  - exponential modeling of the random effects

## PFIM Interface 3.1

### Joint PKPD design on warfarin

- **Evaluation of the empirical design**
  - one group of 32 subjects
  - 13 sampling times for PK and 7 sampling times for PD
- **Design optimization with the Federov-Wynn algorithm**
  - 32 subjects with only 5 sampling times per subject (common to both responses)
  - sampling times from empirical design (PK + PD)

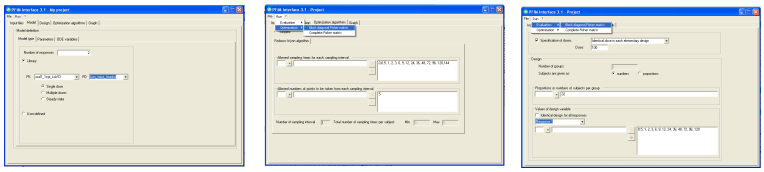


Figure 1. Empirical design versus optimal design

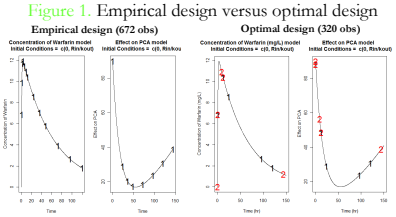
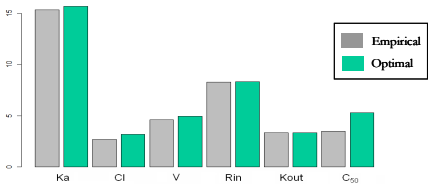



Figure 2. Comparison of predicted RSE for fixed effects (%)




→ **Relative standard errors (RSE) in the same range for the fixed effects**

→ **2.1 less samples with optimal design than empirical design**

## PFIM 3.2

### Pharmacogenetic on warfarin PK

- **Single nucleotide polymorphism (SNP) CYP2C9**
  - SNP on the gene of a cytochrome involved in the warfarin metabolism
  - influence of the genetic covariate on the clearance
    - clearance decrease of 50% for subjects with a mutant genotype
- **Evaluation of the optimized PK/PD design with the effect of the genetic covariate on clearance**
  - predicted power of the comparison Wald test (type I error=5%)
  - number of subjects needed (given power=90%)

Table 1. Covariate effect parameters

| Covariate | Parameter Associated | Categories | Proportions of subjects in each category (%) | β |
|---|---|---|---|---|
| CYP2C9 | CL | Wild genotype (ref) | 60 | log(0.5)=-0.69 or log(0.8)=-0.22 |
| | | Mutant genotypes | 40 | |

Figure 3. Empirical design evaluation output

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Covariate model :

        NB: Covariates are additive on log parameters

                Covariate 1 : CYP ( Cl )
   Categories References Proportions
(1)          W          *         0.6
(2)          M                    0.4

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

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

                  Beta     StdError       RSE
ka          1.6000000 0.250716480 15.669780 %
V           8.0000000 0.254637830  3.182973 %
Cl          0.1300000 0.008119389  6.245684 %
Rin         5.4000000 0.450093467  8.335064 %
kout        0.0600000 0.001999504  3.332506 %
C50         1.2000000 0.059443091  4.953591 %
beta_Cl_CYP_M -0.6931472 0.101924601 14.704612 %

****************************** COMPARISON TEST *******************************

                  Beta         95 % CI   exp(Beta)        95 % CI
beta_Cl_CYP_M -0.6931472 [-0.893;-0.493]         0.5 [0.409;0.611]

Type I error = 0.05

                Expected_power Number_subjects_needed (for a given power=0.9)
beta_Cl_CYP_M        0.999999                 7.270317
```

Covariate model

(W=wild, M=mutant)

Standard error and RSE of the genetic covariate effect on clearance

95% confidence interval of the covariate effect

Expected power and number of subjects needed for the comparison Wald test

Table 2. Results on genetic covariate effect

| β | SE (RSE %) | 95% CI(β) | exp(β) | 95% CI(exp(β)) | Expected power | Number of subjects needed |
|---|---|---|---|---|---|---|
| -0.69 | 0.10 (15) | [-0.89; -0.49] | 0.50 | [0.41; 0.61] | 1 | 8 |
| -0.22 | 0.10 (43) | [-0.41; -0.03] | 0.80 | [0.66; 0.97] | 0.63 | 64 |

### Interaction of drug X on warfarin PK in crossover trial

**Planification of a new study to assess the absence of interaction of drug X on warfarin ka**

- two-period, two-sequence balanced crossover trial
- inter-occasion variability on ka: $\gamma^2_{ka}$=0.3 (CV=55%)
- expected effect of the co-medication on ka: β=log(1)=0

- **Evaluation of the empirical PK design**
  - 32 subjects
  - sampling times
    - 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96 and 120 hours
  - Predicted power of the bioequivalence Wald test (type I error=5%)
  - Number of subjects needed (given power=90%)

Figure 4. Empirical design evaluation output

```
Covariate model :

        NB: Covariates are additive on log parameters

        Covariates changing with occasion

              Covariate  1 : Comed ( ka )
   categories References
(1)          W          *
(2)          X

   Sequences Proportions
(1)       W X         0.5
(2)       X W         0.5

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

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

                  Beta     StdError       RSE
ka          1.60  0.288960018 18.060001 %
V           8.00  0.208783108  2.609789 %
Cl          0.13  0.005832788  4.479837 %
beta_ka_Comed_X  0.00  0.144882923       Inf %

------------------------ Variance of Inter-Subject Random Effects ------------

   Omega     StdError       RSE
ka  0.70 0.221683522 31.66907 %
V   0.02 0.005448212 27.24106 %
Cl  0.06 0.016066907 26.77818 %

------------------------ Variance of Inter-Occasion Random Effects -----------

   Gamma    StdError       RSE
ka   0.3 0.07139004 23.79668 %

****************************** EQUIVALENCE TEST ******************************

                  Beta         90 % CI   exp(Beta)        90 % CI
beta_ka_Comed_X      0 [-0.238;0.238]           1 [0.788;1.269]

Type I error = 0.05
Equivalence interval = [log(0.8),log(1.25)]

                Expected_power Number_subjects_needed (for a given power=0.9)
beta_ka_Comed_X      0.4583113                115.5273
```

Covariate model

(W=warfarin, X=warfarin+drug X)

Standard error and RSE of the co-medication covariate effect on ka

Standard error and RSE of the inter-occasion variability

90% confidence interval of the covariate effect

Expected power and number of subjects needed for the bioequivalence Wald test

## CONCLUSION

- **PFIM Interface 3.1 and PFIM 3.2 freely available at** www.pfim.biostat.fr
- **Great potential of these tools to evaluate and/or optimize designs :**
  - for multiple response models
  - for more complex models quantifying the influence of discrete covariate and/or inter-occasion variability.

## REFERENCES

[1] www.pfim.biostat.fr
[2] Bazzoli C, Retout S and Mentré F. *Computer Methods and Programs in Biomedicine*. 98: 55-65, 2010.
[3] Retout S, Comets E, Samson A and Mentré F. *Statistics in Medicine*. 26: 5162-5179, 2007.
[4] Nguyen TT, Bazzoli C and Mentré F. *American Conference in Pharmacometrics*, Mashantucket, United-States, 2009.