PFIM 4.0: new features for optimal design in nonlinear mixed effects models using R

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ABSTRACT

Model based optimal design approaches are increasingly used in population pharmacokinetic / pharmacodynamics (PKPD) [1]. These approaches rely on the Fisher information matrix (FIM) for nonlinear mixed effect models and are a good alternative to clinical trial simulation. Several software tools are available and were recently compared [2]. They all incorporate a PKPD library of models and model defined by differential equations.

PFIM (www.pfim.biostat.fr), developed in our group, was the first tool in R. It is available since 2001 and was extended in version 3 to multi-response models, inter-occasion variability, discrete covariates with prediction of power of Wald test [3]. We released in April 2014 the version 4 of PFIM with several new features that we applied on several PKPD examples.

For population designs, optimization can be done with fixed parameters or fixed sampling times. Previous information already obtained can be assumed and loaded through a predicted or an observed FIM. This is crucial to performed adaptive designs which are a strong requirement in drug industry and one of the task of the DDMoRe project [4].

Additional features for design in Bayesian estimation of individual parameters were added. The Bayesian information matrix was implemented. Design for Maximum A Posteriori (MAP) estimation can be evaluated or optimized [5]. The predicted shrinkage is also reported [5]. There is a clear influence of design on shrinkage. This new feature is useful to select informative sampling times in therapeutic drug monitoring.

This new version of PFIM fulfilled some of the needs expressed in industry [1]. The examples again showed the importance of model based optimal design to predict good studies and anticipate 'fatal' ones.

1] Mentré F, Chenel M, Comets E, Grevel J, Hooker A, Karlsson MO, Lavielle M, Gueorguieva I. Current use and developments needed for optimal design in pharmacometrics: a study performed amongst DDMoRe's EFPIA members. *CPT Pharmacometrics Syst Pharmacol.*, 2013;2:e46.
[2] Nyberg J, Bazzoli C, Ogungbenro K, Aliev A, Leonov S, Dufull S, Hooker A, Mentré F. Methods and software tools for design evaluation in population pharmacokinetics-pharmacodynamics. *Br J Clin Pharmacol*, 2014; in press.
[3] Bazzoli C, Retout S, Mentré F. Design evaluation and optimization in multiple response nonlinear mixed effect models: PFIM 3.0. *Comput Methods Programs Biomed*, 2010; 98:55-65.
[4] Harnisch L, Matthews I, Chard J, Karlsson MO. Drug and disease model resources: a consortium to create standards and tools to enhance model-based drug development. *CPT Pharmacometrics Syst Pharmacol*, 2013;2:e34.
[5] Combes F, Retout S, Frey N, Mentré F. Prediction of shrinkage of individual parameters using the Bayesian information matrix in nonlinear mixed-effect models with application in pharmacokinetics. *Pharm Res*, 2013; 30:2355-67.

PFIM 3 & PFIM 4

PFIM 3

- R functions for population designs evaluation and optimisation
- Analytical form/ Differential equation model
- Library of PK and PD models
- Multiple response model
- Combined error models
- Optimisation: Simplex algorithm/ Fedorov-Wynn algorithm
- Within subject variability (IOV)
- Discrete covariates
- Computation of the predicted power for the Wald test of comparison or equivalence
- Computation of the number of subjects needed

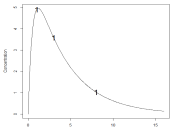
PFIM 4: additional features

- Simpler expression for user defined models
- Fixed parameters and/or fixed sampling times
- New outputs
  - Graph of sensitivity functions
  - Eigenvalues and condition numbers
  - Correlation matrix
- Individual design
- Bayesian design for MAP with predicted shrinkage
- Previous Information Matrix for adaptive designs

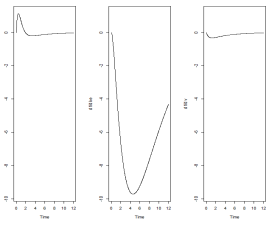
MODELS AND GRAPHS

General function for user model

```
form<-function(t,p,X){
ka<-p[1]
k<-p[2]
V<-p[3]
y<-(X/V*ka/(ka-k)*(exp(-k*t)-exp(-ka*t)))
return(y)
}
```



Graph of sensitivity functions



OUTPUT: BAYESIAN DESIGN EVALUATION FOR MAP & PREDICTION OF SHRINKAGE [5]

```
Design:
              times      subjects doses
1   c(0.33, 1.5, 5, 12)      1   100

Bayesian Fisher information matrix
** EXPECTED STANDARD ERRORS ***********
 ------ Fixed Effects Parameters ------

    Beta StdError      RSE      Shrinkage
ka  2.00 0.96051649 48.02582 %  23.06480 %
k   0.25 0.07402618 29.61047 %  35.07121 %
V  15.00 3.16229457 21.08196 %  44.44492 %

******** CRITERION ********************
3.527179
```

```
Design:
       times    subjects doses
1   c(1, 3, 8)        1   100

Bayesian Fisher information matrix
** EXPECTED STANDARD ERRORS ***********
 ------ Fixed Effects Parameters -----

    Beta StdError   RSE      Shrinkage
ka  2.00 1.419173 70.95865 %  50.35130 %
k   0.25 0.075761 30.30440 %  36.73427 %
V  15.00 3.090213 20.60142 %  42.44184 %

******** CRITERION ******************
2.588796
```

OUTPUT: POPULATION DESIGN EVALUATION

```
Design:
      times subjects doses
1    c(1, 3, 8)      200   100

Computation of the Population Fisher information matrix
************************* EXPECTED STANDARD ERRORS ************************
------------------------ Fixed Effects Parameters -------------------------

    Beta   StdError       RSE
ka  2.00 0.24120620 12.060310 %
k   0.25 0.01361296  5.445183 %
V  15.00 0.55940163  3.729344 %
------------------------- Variance of Inter-Subject Random Effects --------------

   omega²   StdError      RSE
ka   1.00 0.37079715 37.07971 %
k    0.25 0.05288198 21.15279 %
V    0.10 0.02260288 22.60288 %
------------------------ Standard deviation of residual error ------------------

           Sigma   StdError      RSE
sig.interA  0.50 0.18804055 37.60811 %
sig.slopeA  0.15 0.09283442 61.88961 %

******************************** CRITERION *********************************
182.4914
****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ***************

        FixedEffects VarianceComponents
min      2020.201440          3.027094
max      8100.430663        627.104778
max/min     4.009714        207.163955
```

OUTPUT: WITH PREVIOUS INFORMATION

```
Previous FIM from file FIM_Prev_Info.txt; Observed FIM from a fit or Predicted FIM
         ; here 200 patients with design c(0.33,1.5,5,12)
Design:
      times subjects doses
1    c(1, 3, 8)      200   100

Computation of the Population Fisher information matrix
************************* EXPECTED STANDARD ERRORS ************************
------------------------ Fixed Effects Parameters -------------------------

    Beta    StdError      RSE
ka  2.00 0.141381876 7.069094 %
k   0.25 0.009077767 3.631107 %
V  15.00 0.377988684 2.519925 %
------------------------- Variance of Inter-Subject Random Effects -------------
   omega²   StdError      RSE
ka   1.00 0.11577052 11.57705 %
k    0.25 0.02893401 11.57360 %
V    0.10 0.01357748 13.57748 %
------------------------ Standard deviation of residual error ------------------
          Sigma   StdError       RSE
sig.interA  0.50 0.03908612  7.817223 %
sig.slopeA  0.15 0.02065427 13.769511 %

******************************** CRITERION *********************************
 599.3712
```

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