

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

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S. Retout - PODE - 2007

Outline

- **Introduction**
- **Evaluation of population designs with PFIM 3.0**
- **Optimization of population designs with PFIMOPT 3.0**
- **PFIM Interface 2.0**
- **Conclusion**

Introduction

Population Design

- **Definition of a population design Ξ :**

- N: total number of subjects
- Q groups of N_q subjects with elementary designs ξ_q
- Composition of ξ_q
 - n_q sampling times
 - allocation of the sampling times

$$\Xi = \left\{ \begin{array}{l} \xi_1, \dots, \xi_Q \\ N_1, \dots, N_Q \end{array} \right\}$$

- **Determination of a population design**

- for a given total number of samples, determination of
 - the number Q of groups
 - the number N_q of subjects per group
 - the number n_q of samples per group
 - their allocation in time

Choice of a Population Design

- **Empirically**
- **Methods for optimisation / evaluation**
 - simulation
 - criteria based on the the population Fisher information matrix (M_F)
 - extension of the theory used in classical nonlinear regression

Expression of M_F in nonlinear mixed effects models (1)

- $M_F(\Psi, \Xi) = \sum_{q=1}^Q N_q M_F(\Psi, \xi_q)$
 - $M_F(\Psi, \xi_q)$: no analytical expression
 - **Approximation**
 - linearisation of the structural model
 - first order Taylor approximation around the expectation of the random effects
- (F. Mentré, A. Mallet & D. Baccar, *Biometrika*, 1997)
- extension of M_F when σ^2 (parameter for the variance error model) is also estimated
- (S. Retout, S. Duffull & F. Mentré, *Comp Meth Prog Biomed*, 2001)

$$M_F(\Psi, \Xi) = \sum_{q=1}^Q N_q \begin{bmatrix} M_F(\beta, \xi_q) & 0 \\ 0 & M_F(\Omega, \sigma^2, \xi_q) \end{bmatrix}$$

Expression of M_F in nonlinear mixed effects models (2)

- **Evaluation by simulation of the relevance of the proposed expression**
 - use of the population pharmacokinetics (PK) of enoxaparin (S. Retout, R. Bruno & F. Mentré, *Stat Med*, 2002)
- **Extension for more complex models**
 - inter-occasion variability
 - influence of covariates on PK (S. Retout & F. Mentré, *J Biopharm Stat*, 2003)
 - combined variance error models (S. Retout & F. Mentré, *J Pharmacokin Pharmacodyn*, 2003)
- **Recently, evaluation of the same approximation for multiple response models**
 - use of a PK/PD model (C. Bazzoli, S. Retout & F. Mentré. *SFPT*, Toulouse, France, 11-13 April 2007)

Evaluation / Optimization using M_F (1)

- **Implementation of M_F for evaluation**
 - 2001: PFIM 1.0
 - Splus and Matlab (Stephen Duffull) tool
(S. Retout, S. Duffull & F. Mentré, *Comp Meth Prog Biomed*, 2001)
 - 2003: PFIM 1.2
 - Splus and R version
 - inclusion of combined variance error models
- **Implementation of M_F for optimization**
 - 2003: PFIMOPT 1.0
 - Splus and R versions
 - optimization using the Simplex algorithm
- **Context of those implementations**
 - single response model
 - local planification: D-optimality criterion
 - model given under analytical form

Evaluation / Optimization using M_F (2)

Recent works

- Optimization using the Fedorov-Wynn algorithm
- Evaluation and optimization of the power of the Wald test for binary covariates
 - computation of the number of subjects needed to achieve a given power
- Application to the detection of a treatment effect for HIV viral load decrease using bi-exponential model

(S. Retout, E. Comets, A. Samson & F. Mentré. *Stat Med*, in press)

Evaluation of population design with PFIM 3.0

Supported Models (1)

- **Single or multiple response models**
- **Structural model**
 - **Analytical form**
 - analytical derivatives of the model with respect to the parameters
 - **Differential equations system**
 - Use of the Isoda 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 function “fdHess” included in the “nlme” package
 - evaluate an approximate gradient of a scalar function using finite differences

Supported Models (2)

- **Combined variance error model**
 - $\text{Var}(\varepsilon) = (\sigma_{\text{inter}} + \sigma_{\text{slope}}f)^2$
- **Additive or exponential model of the random effects**
- **Diagonal variance of the random effects**

Example: Joint modeling of PK/PD of Warfarin

- **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
 - $CL=0.133$; $V=7.95$; $Ka=1.6$; $\omega_{CL}=0.0634$; $\omega_V=0.0206$; $\omega_{KA}=0.701$
 - exponential modelling of the random effects
 - $\text{Var}(\varepsilon)=(0.2 f)^2$
- **A priori PD knowledge**
 - turnover model with inhibition of the input
 - $I_{max}=1(\text{FIX})$; $R_{in}=5.41$; $C_{50}=1.2$; $K_{out}=0.056$; $\omega_{R_{in}}=0.19$; $\omega_{K_{out}}=0.0167$; $\omega_{C_{50}}=0.0129$
 - exponential modelling of the random effects
 - $\text{Var}(\varepsilon)=3.88$
- **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)
 - 16 PD sampling times at (0, 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144)

PFIM 3.0
Project: Exercice 3.1
Date: Thu May 03 14:06:04 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]
    Kout<-p[5]
    C50<-p[6]

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

    list(c(yd1,yd2,yd3))
}
```

Compartments of interest: (2,3)

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, 0.5, 1, 2, 3, 6, 9, 12, 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	0.251793942	15.737121	%
Cl	0.133	0.006129620	4.608737	%
V	7.950	0.233343361	2.935137	%
Rin	5.410	0.426109877	7.876338	%
Kout	0.056	0.001505852	2.689021	%
C50	1.200	0.038000600	3.166717	%

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

	Omega	StdError	CV	.
ka	0.7010	0.196529125	28.03554	%
Cl	0.0634	0.016665162	26.28574	%
V	0.0206	0.006803023	33.02439	%
Rin	0.1900	0.049032559	25.80661	%
Kout	0.0167	0.005660916	33.89770	%
C50	0.0129	0.007879900	61.08450	%

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

	SIG	StdError	CV	.
sig.slopeA	0.20	0.007839017	3.919509	%
sig.interB	3.88	0.141035529	3.634936	%

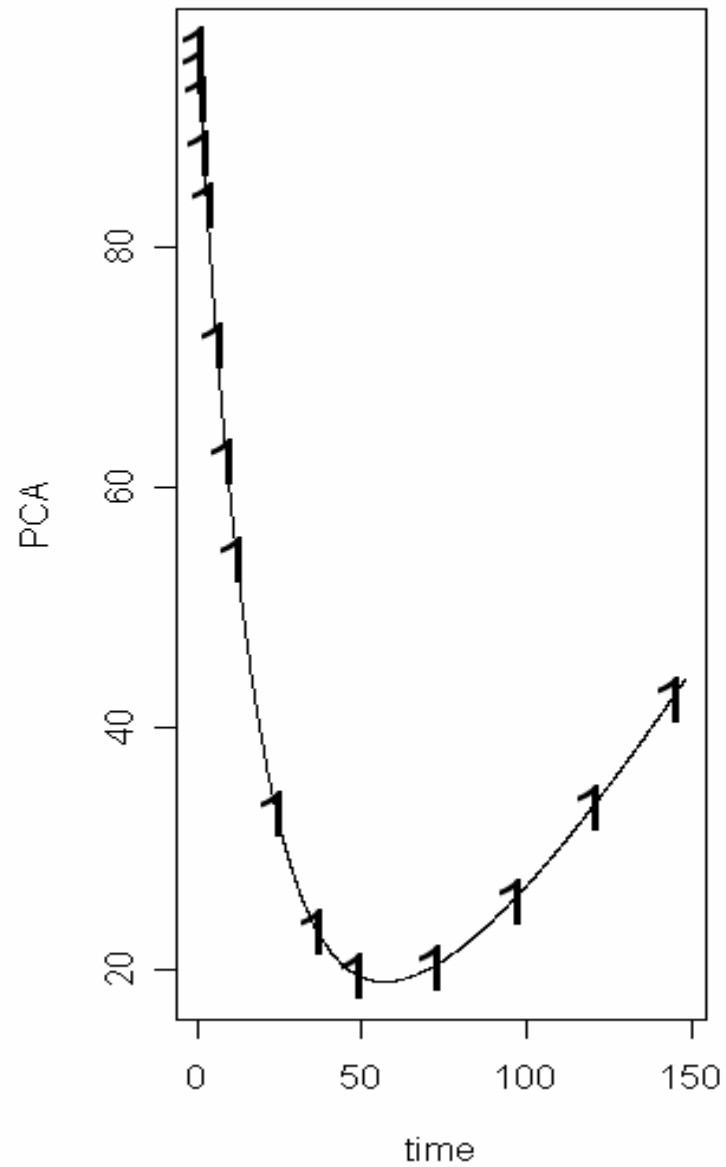
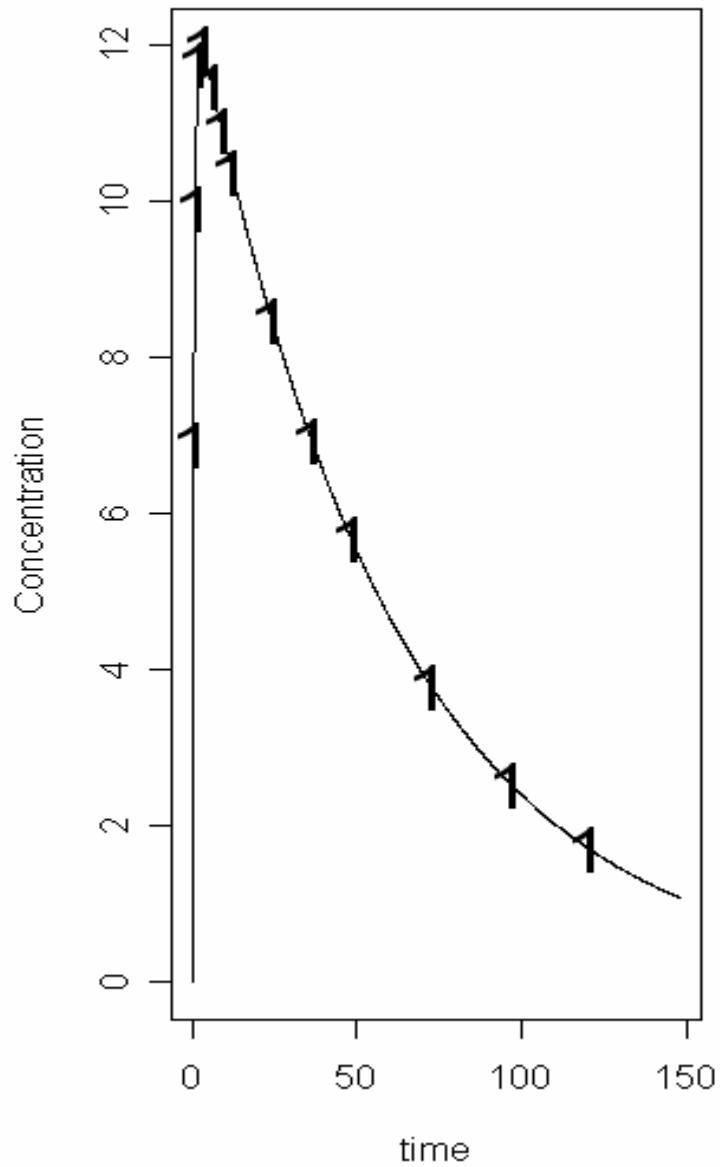
***** DETERMINANT *****

4.828546e+42

***** CRITERION *****

1119.036

Concentration model Initial Conditions = $c(100, 0, Rin/Ko)$ **PCA model** Initial Conditions = $c(100, 0, Rin/Ko)$



Optimisation with PFIMOPT 3.0

Context

- **Optimisation for a fixed total number of samples (n_{tot})**
 - fix $n_{\text{tot}} = \sum N_q n_q$
 - fix N_q and n_q
- **Simplex and Fedorov-Wynn algorithms**
- **Case of multiple response model**
 - balanced or unbalanced designs can be optimized
 - same or 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

Algorithms in PFIMOPT 3.0 (1)

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 optimisation
 - for a given group structure: optimisation of sampling times ξ_q
 - statistical optimisation
 - optimisation of the proportion of subjects $\alpha_q (=N_q/N)$ and of sampling times ξ_q

PFIMOPT Output – Simplex

```
Analytical function model:
100/V * ka/(ka - Cl/V) * (exp(-Cl/V * t) - exp(-ka * t))

Variance error model response A : ( 0 + 0.2 *f)^2
Between-subject variance model: Trand = 2

Initial population design:
Sample times for response: A
                subjects.prop doses
c(2, 6, 48, 120)          32      1

Total number of samples (nr responses): 128
Associated criterion value: 253.2057

Window of the allowed optimised sampling times:
Upper and lower admissible samples times for the response A : [ 0.5 : 120 ]

Minimum delay between two sampling times: 0
Optimisation of the proportions of subjects: FALSE

***** OPTIMISED DESIGN *****
Number of iterations: 265
Number of function evaluations: 357
Convergence Achieved

        Optimised population design :
Sample times for response: A
                subjects.prop subjects doses
c(0.528, 13.832, 4.571, 120)          1      32      1

Associated optimised criterion: 466.0648
```

Algorithms in PFIMOPT 3.0 (2)

Fedorov-Wynn algorithm

- **Specific algorithm dedicated to statistical design optimisation**
- **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**

PFIMOPT Output – Fedorov-Wynn

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

Analytical **function** model:

$100/V * ka / (ka - Cl/V) * (\exp(-Cl/V * t) - \exp(-ka * t))$

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

Between-subject variance model: $\text{Trand} = 2$

Initial population design:

Sample times **for** response: A

	Protocol	subjects	doses
1	c(2, 6, 48, 120)	32	1

Total number of samples: 128

Associated criterion value: 253.2057

Sampling **windows for** the response: A

Window 1 : $t = 0.5$ 1 2 3 4 5 6 9 12 24 36 48 72 96 120

Nb of sampling **points** to be taken **in** this **window**, $n[1] = 3$ 4

Maximum total number of **points in** one elementary protocol : 4

Minimum total number of **points in** one elementary protocol : 3

***** OPTIMISED DESIGN *****

Optimised population design:

Sample times **for** response: A

	prot.opti	subjects.opti	Subjects	doses
1	c(0.5, 4, 5, 120)	0.8320670	27.792983	1
2	c(0.5, 5, 120)	0.1679330	5.609356	1

Associated optimised criterion: 474.8826

PFIMOPT Output – Fedorov-Wynn

Project: PKPDwarfarine_optimisation_indirect_model

Date: Wed May 02 15:09:29 2007

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

...

Initial Population design:

Sample times for response: A

Protocol subjects

1 c(0.5, 6, 48, 96) 32

Sample times for response: B

Protocol subjects

1 c(0.5, 6, 48, 96) 32

Initial Conditions at time 0 : 100 0 Rin/kout

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

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

Between-subject variance model: Trand = 2

Total number of samples: 256

Associated criterion value: 494.1647

Sampling windows for the response: A

Window 1 : t= 0.5 1 2 3 6 9 12 24 36 48 72 96 120 144

Nb of sampling points to be taken in this window, n[1]= 4

Maximum total number of points in one elementary protocol : 4

Minimum total number of points in one elementary protocol : 4

Sampling windows for the response: B

Window 1 : t= 0.5 1 2 3 6 9 12 24 36 48 72 96 120 144

Nb of sampling points to be taken in this window, n[1]= 4

Maximum total number of points in one elementary protocol : 4

Minimum total number of points in one elementary protocol : 4

PFIMOPT Output – Fedorov-Wynn

```
***** 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
```


PFIM Interface 2.0

PFIM Interface 2.0

- Graphical user interface
- Use 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 a library of PK models
 - 1 or 2 compartments
 - oral, IV or infusion administration
 - single / repeated doses or steady state
- **Optimisation**
 - Simplex or Fedorov-Wynn algorithm

PFIM Interface 2.0

PFIM Interface 2.0 - Exemple B

File Run

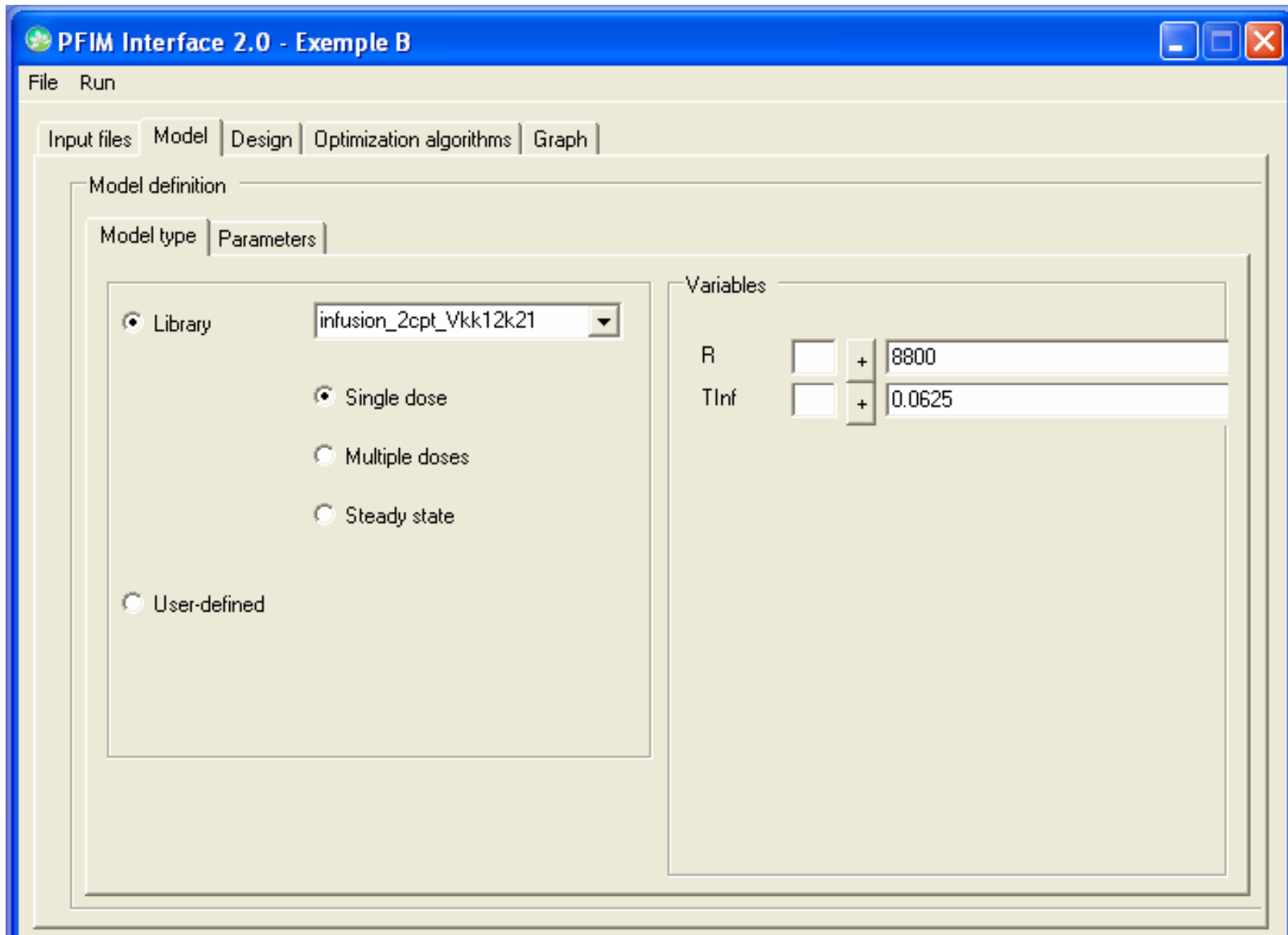
Input files | Model | Design | Optimization algorithms | Graph

Project Name :

Project location :

Output file :

PFIM Interface 2.0: Model type



PFIM Interface 2.0: Parameters

PFIM Interface 2.0 - Exemple B

File Run

Input files Model Design Optimization algorithms Graph

Model definition

Model type Parameters

Population parameters

	Mean	Variance
V	3.08	0.1
k	0.0808	0.2
k12	0.175	0.3
k21	0.116	0.1

Between-subject variance model

Exponential

Standard deviation of the residual error

Inter : 0 Slope : 0.25

PFIM Interface 2.0: Design

The screenshot shows the 'PFIM Interface 2.0 - Exemple B' window with the 'Design' tab selected. The interface includes a menu bar with 'File' and 'Run', and a tabbed navigation system with 'Input files', 'Model', 'Design', 'Optimization algorithms', and 'Graph'. The 'Design' section is divided into three main areas:

- Dose regimen:** A dropdown menu is set to 'Identical dose in each elementary design'. Below it, the 'Dose:' field is set to '100'.
- Initial population design:** The 'Number of groups:' is set to '2'. Under 'Subjects are given as:', the 'numbers' radio button is selected, and the 'proportions' radio button is unselected.
- Initial population design (table):** A table with two columns and two rows. The first column contains an empty input field, a '+' sign, and another empty input field. The second column contains the text '0.0625, 7, 14, 20.58' and '0.0625, 12, 20'. Navigation arrows are present between the columns.
- Initial proportions or numbers of subjects per group:** A table with two columns and one row. The first column contains an empty input field, a '+' sign, and another empty input field. The second column contains the text '90, 30'.

PFIM Interface 2.0: Evaluation (1)

PFIM Interface 2.0 - Exemple B

File Run

Evaluation
Optimization

Design Optimization algorithms Graph

Dose regimen
Identical dose in each elementary design

Dose: 100

Initial population design

Number of groups: 2

Subjects are given as: numbers proportions

Initial population design

	+		>	0.0625, 7, 14, 20.58
			<	0.0625, 12, 20

Initial proportions or numbers of subjects per group

	+	90, 30
--	---	--------

PFIM Interface 2.0: Evaluation (2)

The screenshot displays the PFIM Interface 2.0 software. The main window, titled "PFIM Interface 2.0 - Exemple B", has a menu bar with "File" and "Run". Below the menu bar are tabs for "Input files", "Model", "Design", "Optimization algorithms", and "Graph". The "Design" tab is active, showing a "Dose regimen" dropdown menu set to "Identical dose in each elementary design" and a "Dose:" input field with the value "100".

An "Output" window is overlaid on the main interface, displaying the following text:

```
[6.] 19.05475 132.92633 373.1271
[7.] 94.30110 22.09768 285.6027
[8.] 22.09768 63.48998 147.7415
[9.] 285.60269 147.74154 5897.1541

$determinant
[1] 1.671819e+26

$crit
[1] 819.7618

$se
[1] 0.11371932 0.01191466 0.01981884 0.03085408 0.01921437 0.08659374 0.11908397
[8] 0.22957550 0.01468703

$cv
[1] 3.692186 14.745868 11.325050 26.598342 19.214368 43.296868 39.694656
[8] 229.575501 5.874812

>
```

At the bottom of the "Output" window, there are three buttons: "View output file", "Show graph", and "Close".

PFIM Interface 2.0: Stdout

```
Stdout - Bloc-notes
Fichier Edition Format Affichage ?
PFIM Interface 3.0
Project: Exemple B
Date: Fri Apr 20 10:44:55 2007

***** INPUT SUMMARY *****
Analytical function model:
8800 * (1 * (((k + k21 + k12) + sqrt((k + k21 + k12)^2 - 4 * k * k21))/2) - k21)/(v * (((k + k21 + k12) + sqrt((k + k21 + k12)
-8800 * (1 * (((k + k21 + k12) + sqrt((k + k21 + k12)^2 - 4 * k * k21))/2) - k21)/(v * (((k + k21 + k12) + sqrt((k + k21 + k12)

Population design:
                subjects dose
c(0.0625, 7, 14, 20.58)      90 100
c(0.0625, 12, 20)           30 100

Variance error model: ( 0 + 0.25 *f)^2
Between-subject variance model: Trand = 2

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

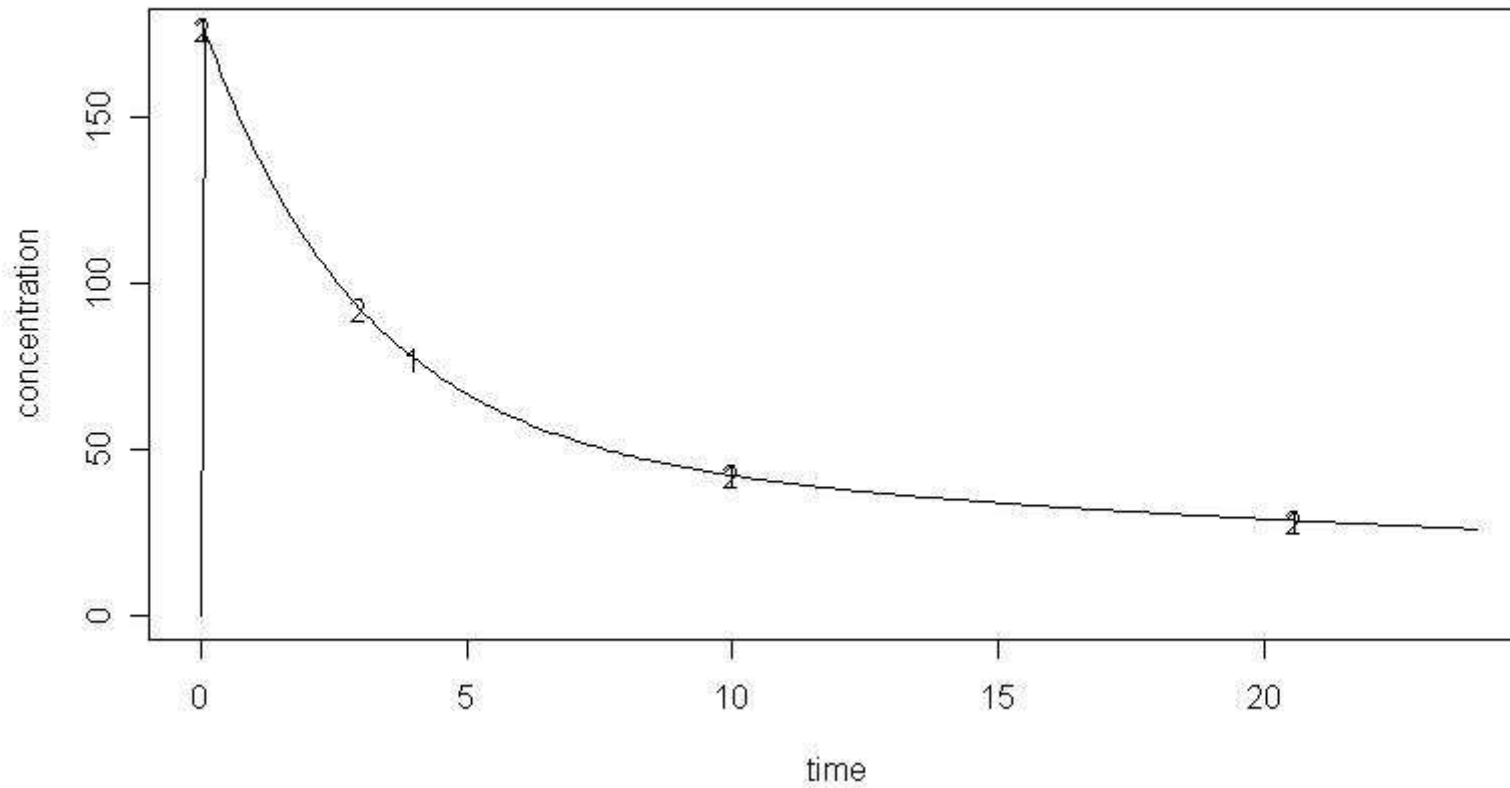
----- Fixed Effects Parameters -----
      Beta  StdError      CV .
v  3.0800  0.11371932  3.692186 %
k   0.0808  0.01191466 14.745868 %
k12 0.1750  0.01981884 11.325050 %
k21 0.1160  0.03085408 26.598342 %

----- Variance of Random Effects -----
      Omega  StdError      CV .
v   0.1  0.01921437 19.21437 %
k   0.2  0.08659374 43.29687 %
k12 0.3  0.11908397 39.69466 %
k21 0.1  0.22957550 229.57550 %

----- Variance of residual error -----
      SIG  StdError      CV .
sig.slope 0.25  0.01468703 5.874812 %

***** CRITERION *****
819.7618
```

PFIM Interface 2.0: Graph



PFIM Interface 2.0: Optimisation (1)

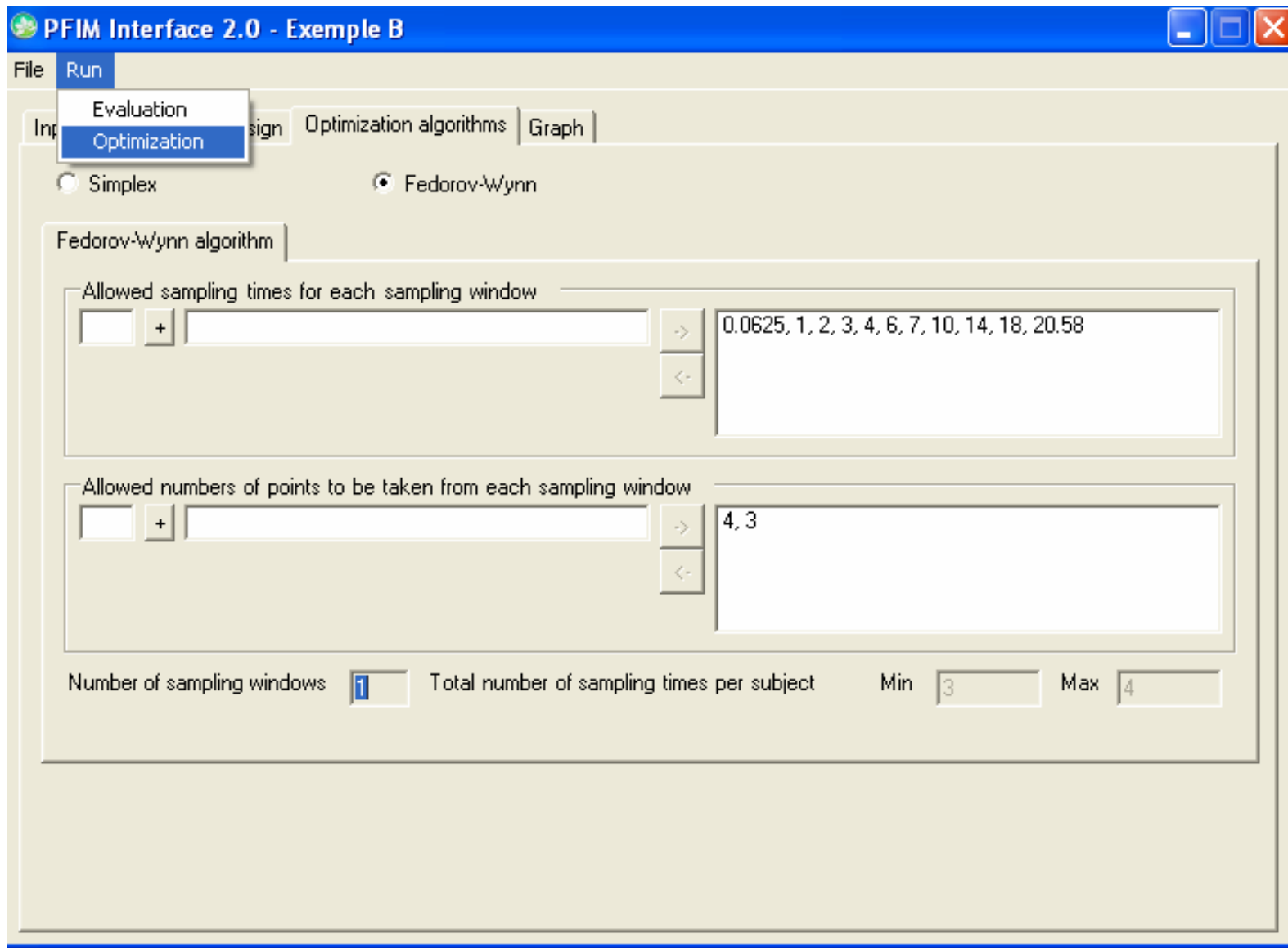
The screenshot shows the 'PFIM Interface 2.0 - Exemple B' window. The 'Optimization algorithms' tab is selected, and the 'Fedorov-Wynn' radio button is chosen. The 'Fedorov-Wynn algorithm' section contains two main input areas:

- Allowed sampling times for each sampling window:** A list box containing the values 0.0625, 1, 2, 3, 4, 6, 7, 10, 14, 18, 20.58.
- Allowed numbers of points to be taken from each sampling window:** A list box containing the values 4, 3.

At the bottom of the window, there are three input fields:

- Number of sampling windows:** A text box with the value 1.
- Total number of sampling times per subject:** A text box with the value 3.
- Min:** A text box with the value 3.
- Max:** A text box with the value 4.

PFIM Interface 2.0: Optimisation (2)



Conclusion

PFIM and PFIMOPT in 2007

- PFIM 1.2 and PFIMOPT 1.0
 - freely available at <http://www.bichat.inserm.fr/equipes/Emi0357/download.html>
- PFIM Interface 2.0
 - available before June 2007
- PFIM 3.0 and PFIMOPT 3.0 for multiple responses model
 - beta version under evaluation

Software Perspectives

- PFIM Interface 3.0 for multiple response models
- Discrete covariates