

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	%

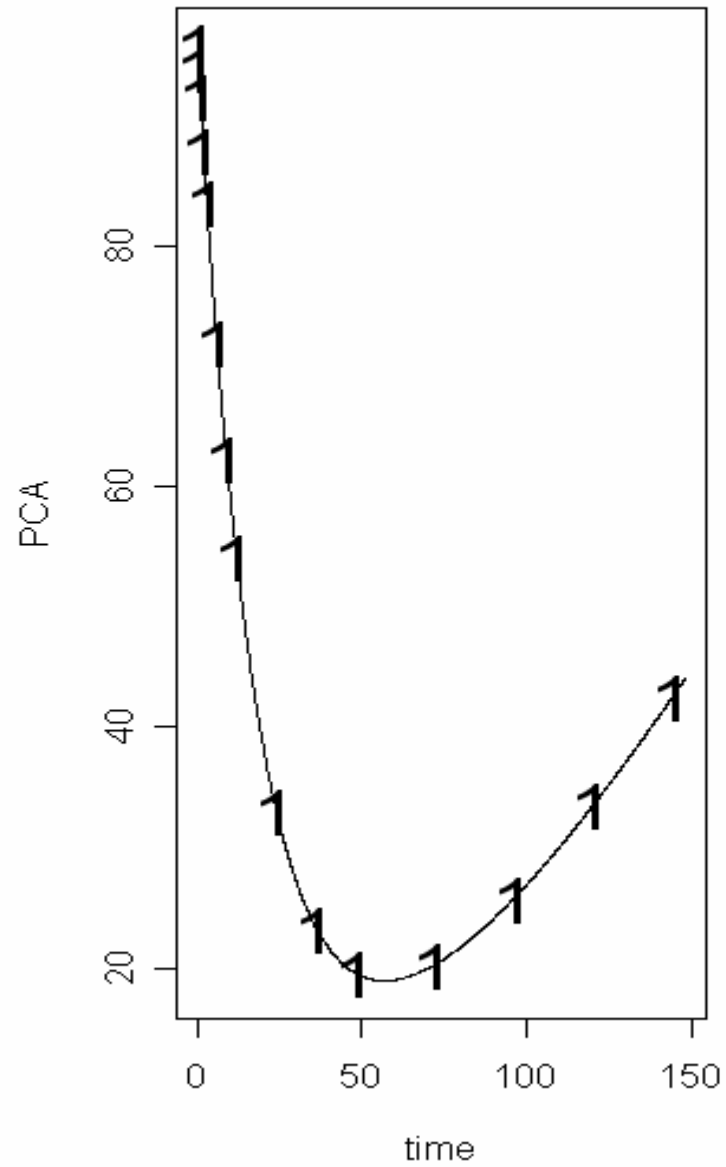
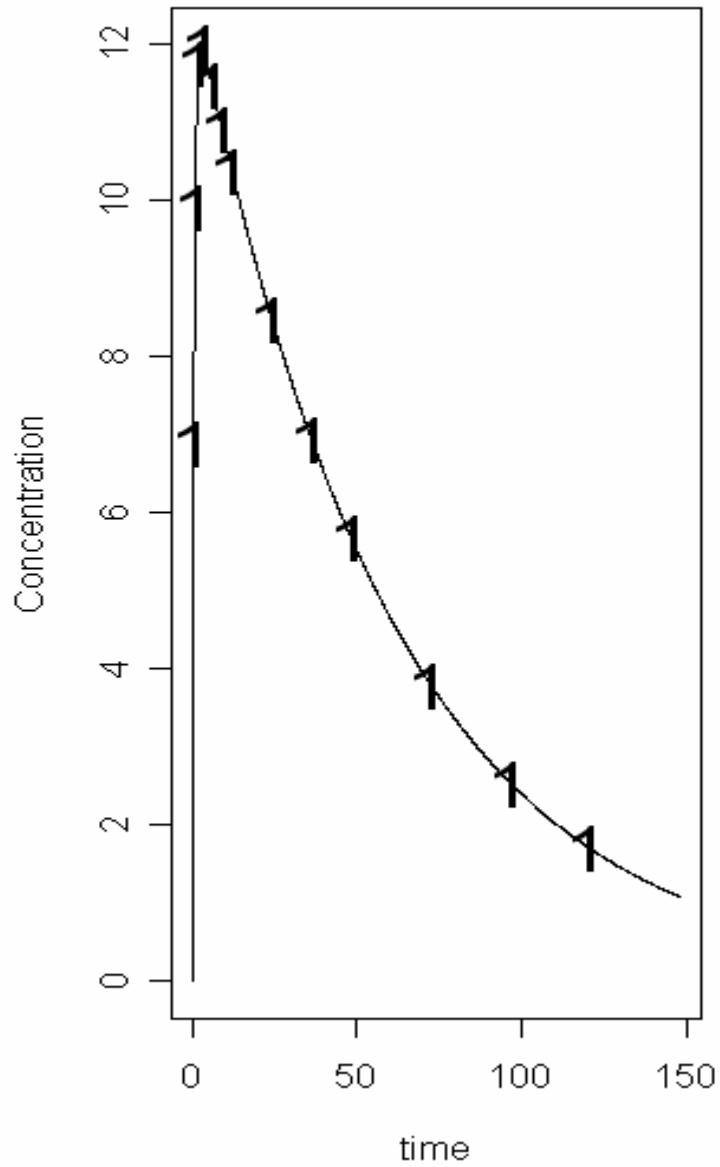
***** DETERMINANT *****

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

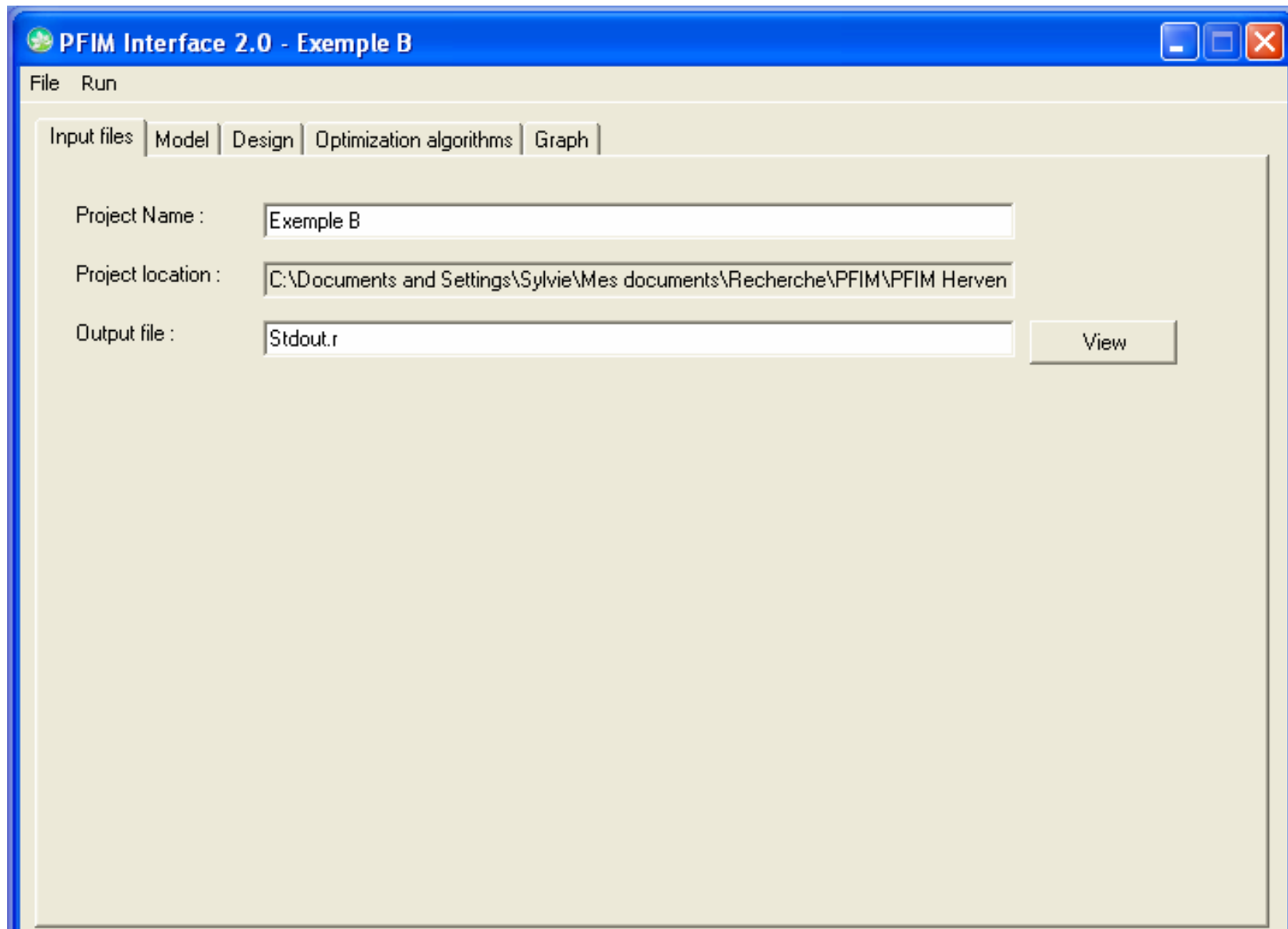
```
Associated optimised criterion: 580.1989
```

PFIM Interface 2.0

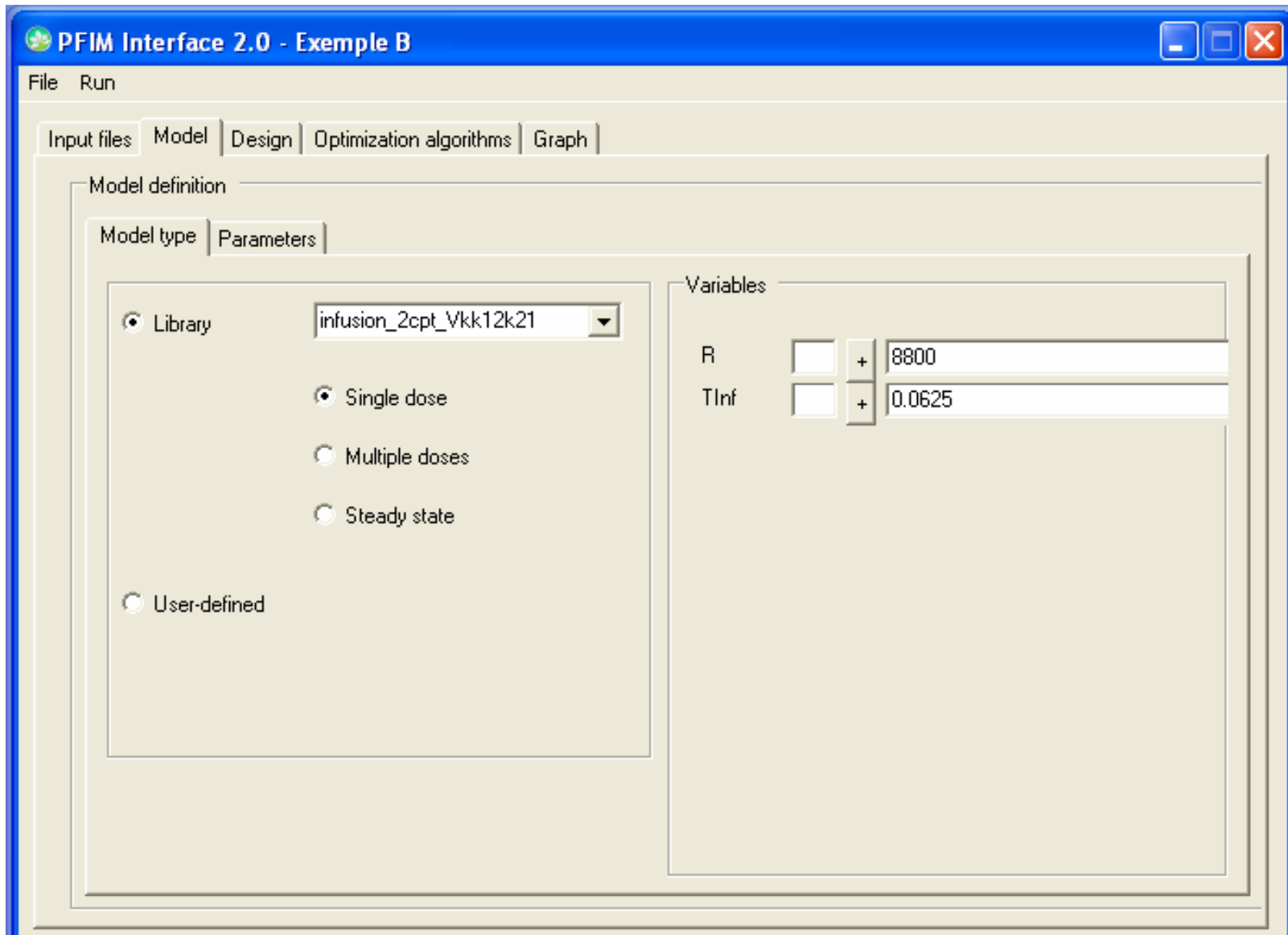
PFIM Interface 2.0

- 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: 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:' field 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 two rows of data: '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 is titled "PFIM Interface 2.0 - Exemple B" and 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 %

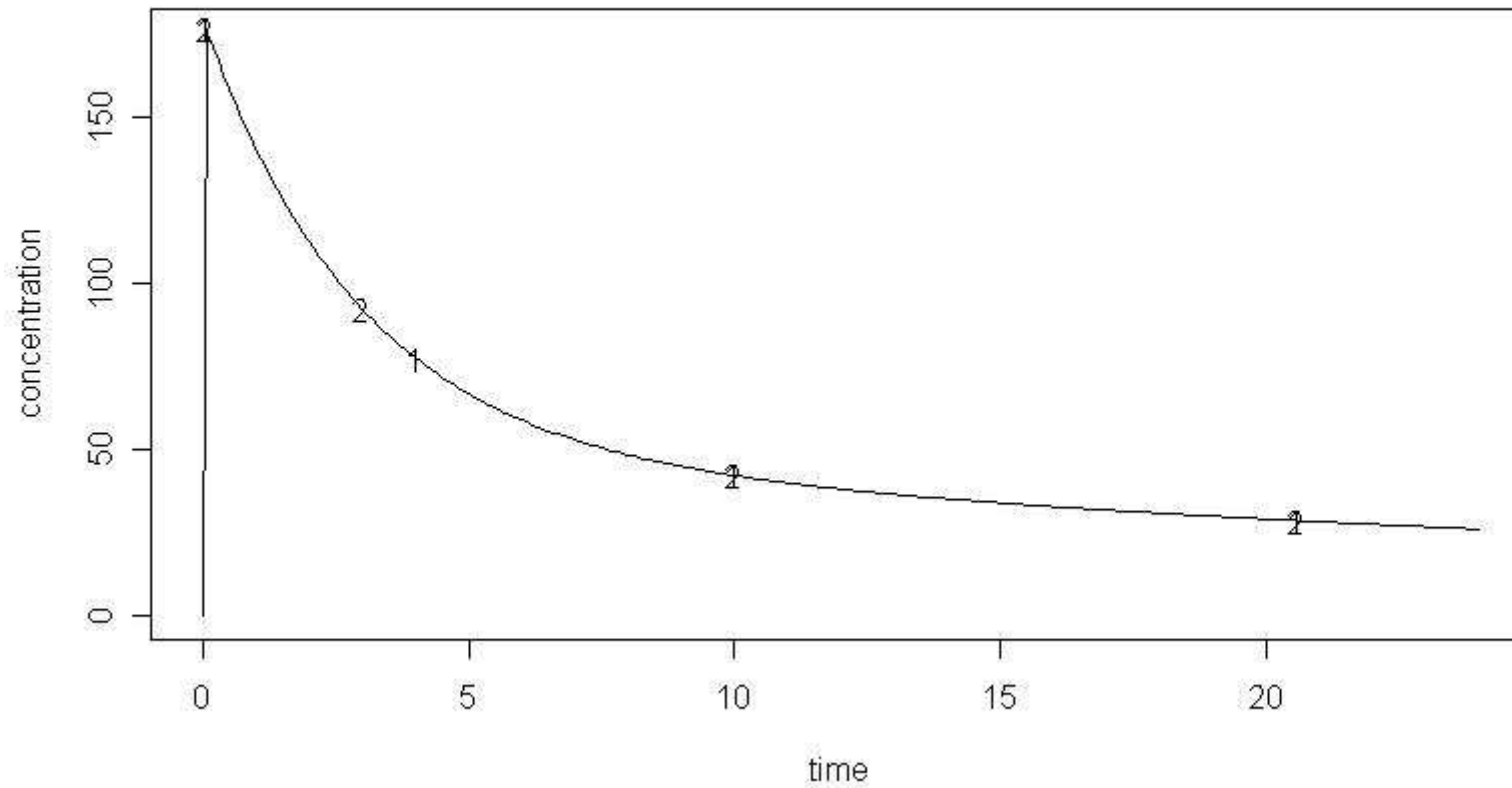
----- Variance of residual error -----

      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 input fields for sampling parameters. The first field, 'Allowed sampling times for each sampling window', contains the list '0.0625, 1, 2, 3, 4, 6, 7, 10, 14, 18, 20.58'. The second field, 'Allowed numbers of points to be taken from each sampling window', contains the list '4, 3'. At the bottom, the 'Number of sampling windows' is set to 1, and the 'Total number of sampling times per subject' is set to 3, with a 'Min' value of 3 and a 'Max' value of 4.

PFIM Interface 2.0 - Exemple B

File Run

Input files | Model | Design | Optimization algorithms | Graph

Simplex Fedorov-Wynn

Fedorov-Wynn algorithm

Allowed sampling times for each sampling window

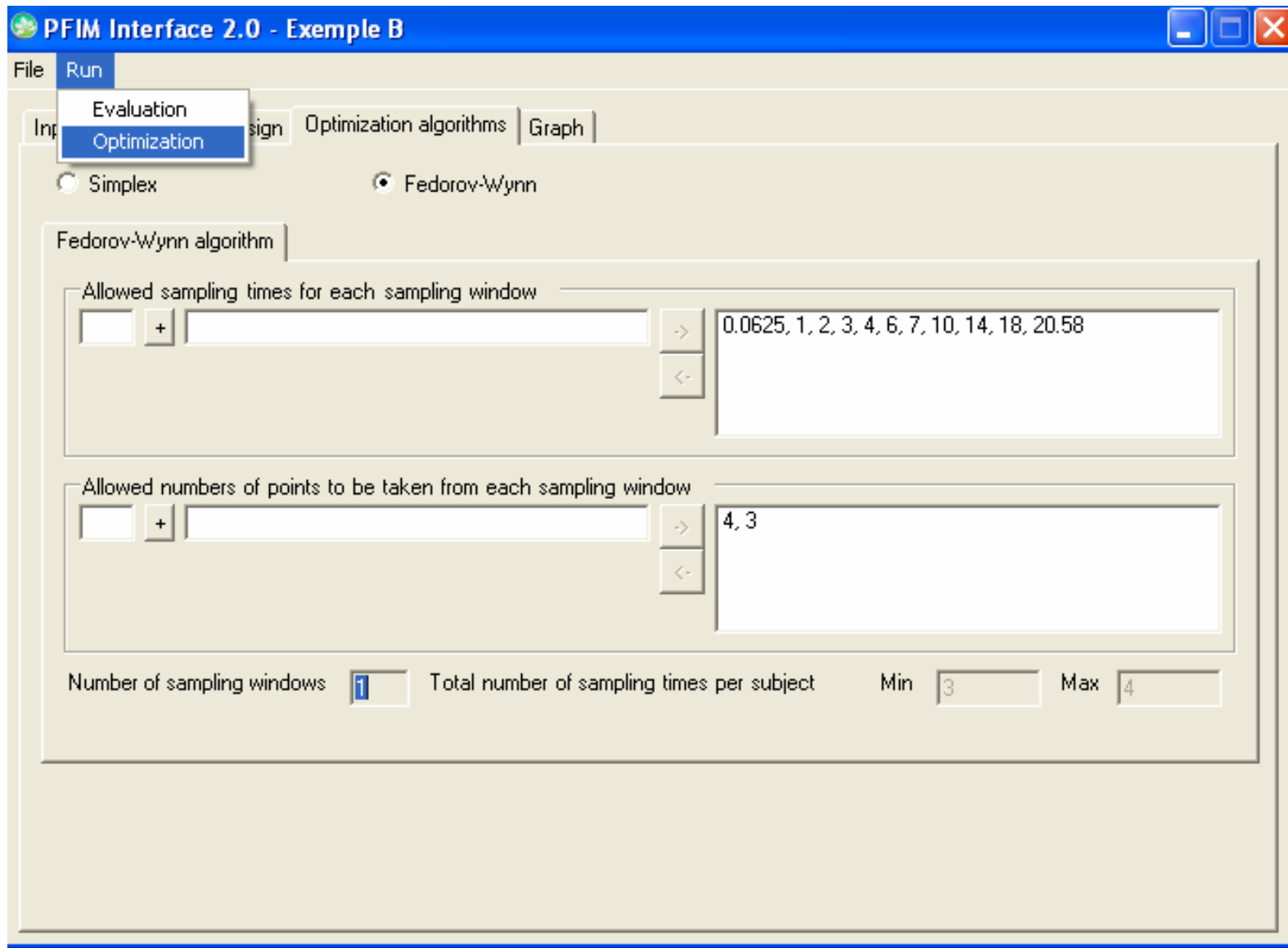
+ > 0.0625, 1, 2, 3, 4, 6, 7, 10, 14, 18, 20.58 <-

Allowed numbers of points to be taken from each sampling window

+ > 4, 3 <-

Number of sampling windows Total number of sampling times per subject Min Max

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