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

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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

$$\Xi = \left\{ \begin{matrix} \xi_1, \ldots, \xi_Q \\ N_1, \ldots, N_Q \end{matrix} \right\}$$

- **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 lsoda 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)

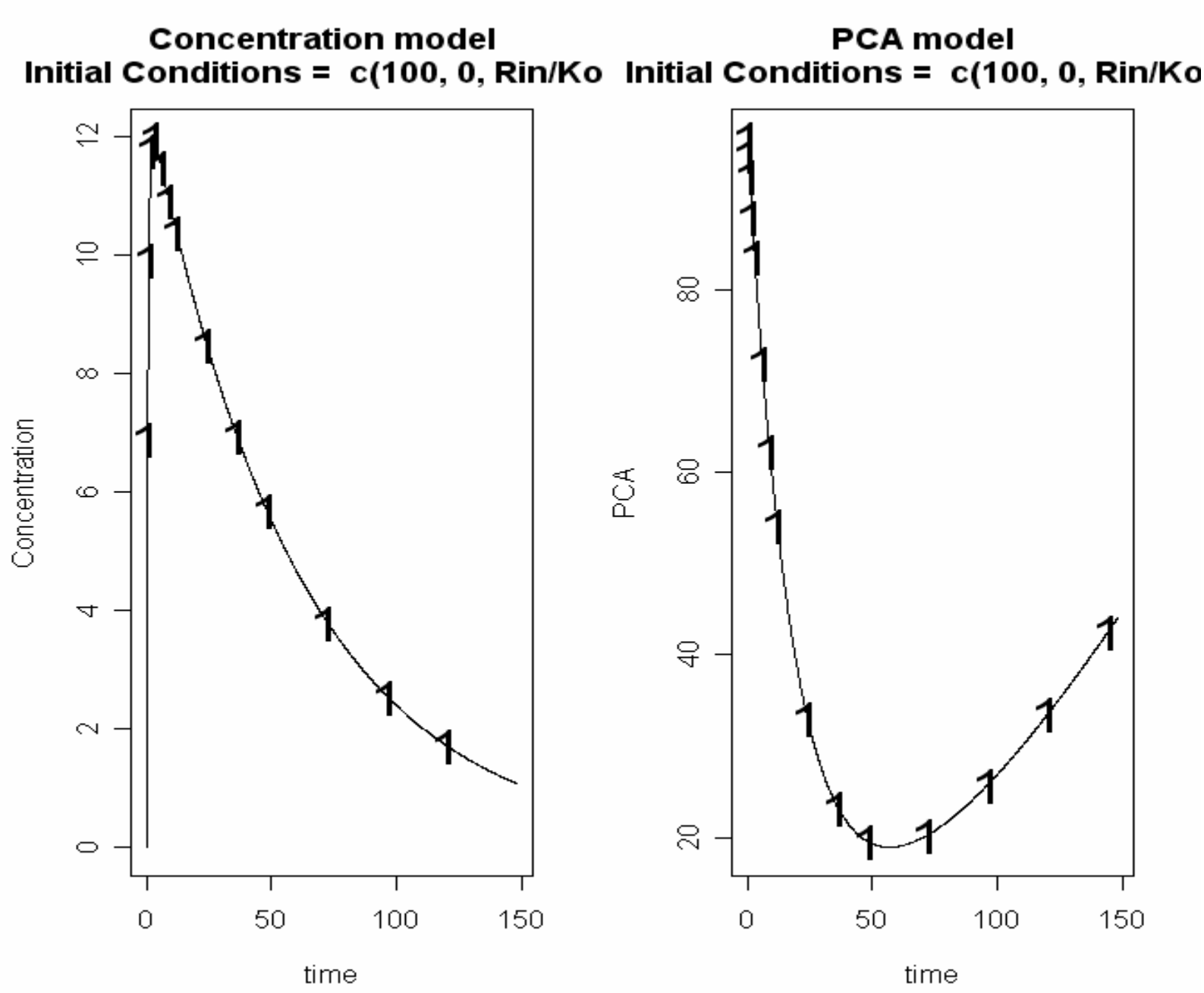
- **Combined variance error model**
  - $Var(\varepsilon)=(\sigma_{inter}+\sigma_{slope}f)^2$
- **Additive or exponential model of the random effects**
- **Diagonal variance of the random effects**

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; ω_{CL}=0.0634; ω_{V}=0.0206; ω_{KA}=0.701
  - exponential modelling of the random effects
  - Var(ε)=(0.2 f)²
- **A priori PD knowledge**
  - turnover model with inhibition of the input
  - Imax=1(FIX); Rin=5.41; C_{50}=1.2; Kout=0.056; ω_{Rin}=0.19; ω_{Kout}=0.0167; ω_{C50}=0.0129
  - exponential modelling of the random effects
  - Var(ε)=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
Concentration
0
2
4
6
8
10
12
0
50
100
150
time
PCA model
Initial Conditions = c(100, 0, Rin/Ko
PCA
20
40
60
80
0
50
100
150
time

Optimisation with PFIMOPT 3.0

Context

- **Optimisation for a fixed total number of samples (n_{tot})**
  - fix $n_{tot} = \Sigma N_q n_q$
  - 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 α_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: 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

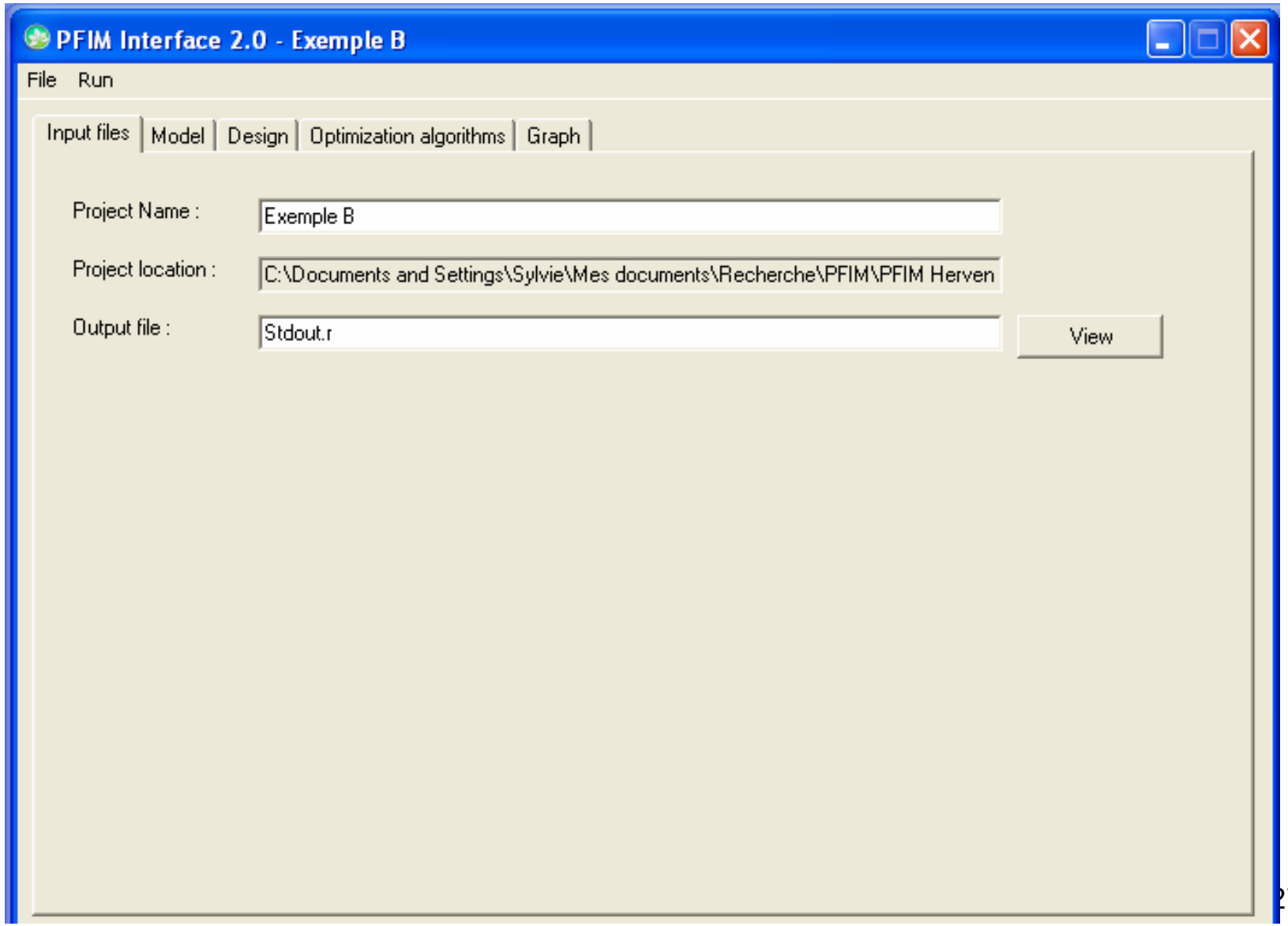
```
****************************** OPTIMISED DESIGN ********************************

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

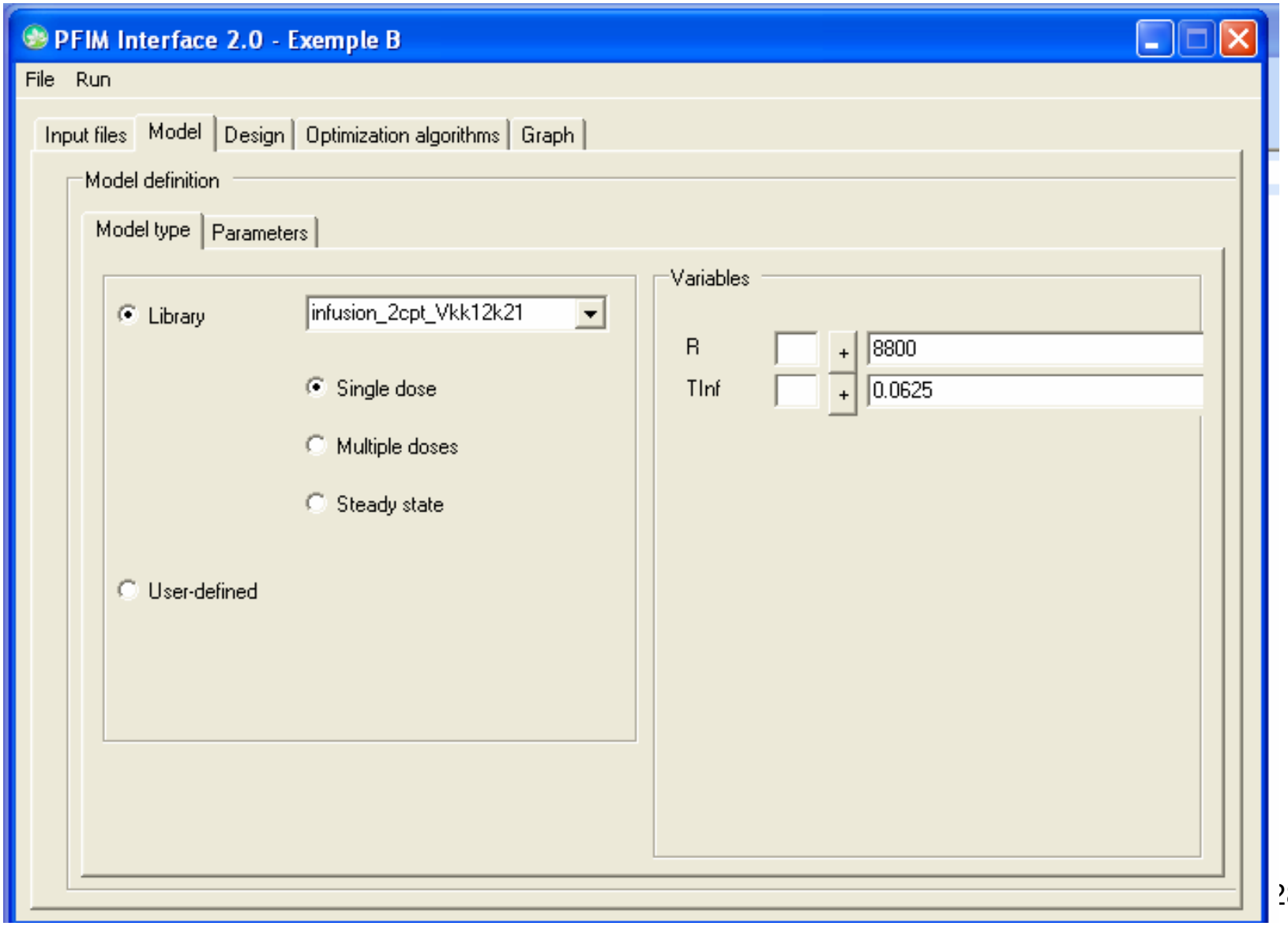
PFIM Interface 2.0

- **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

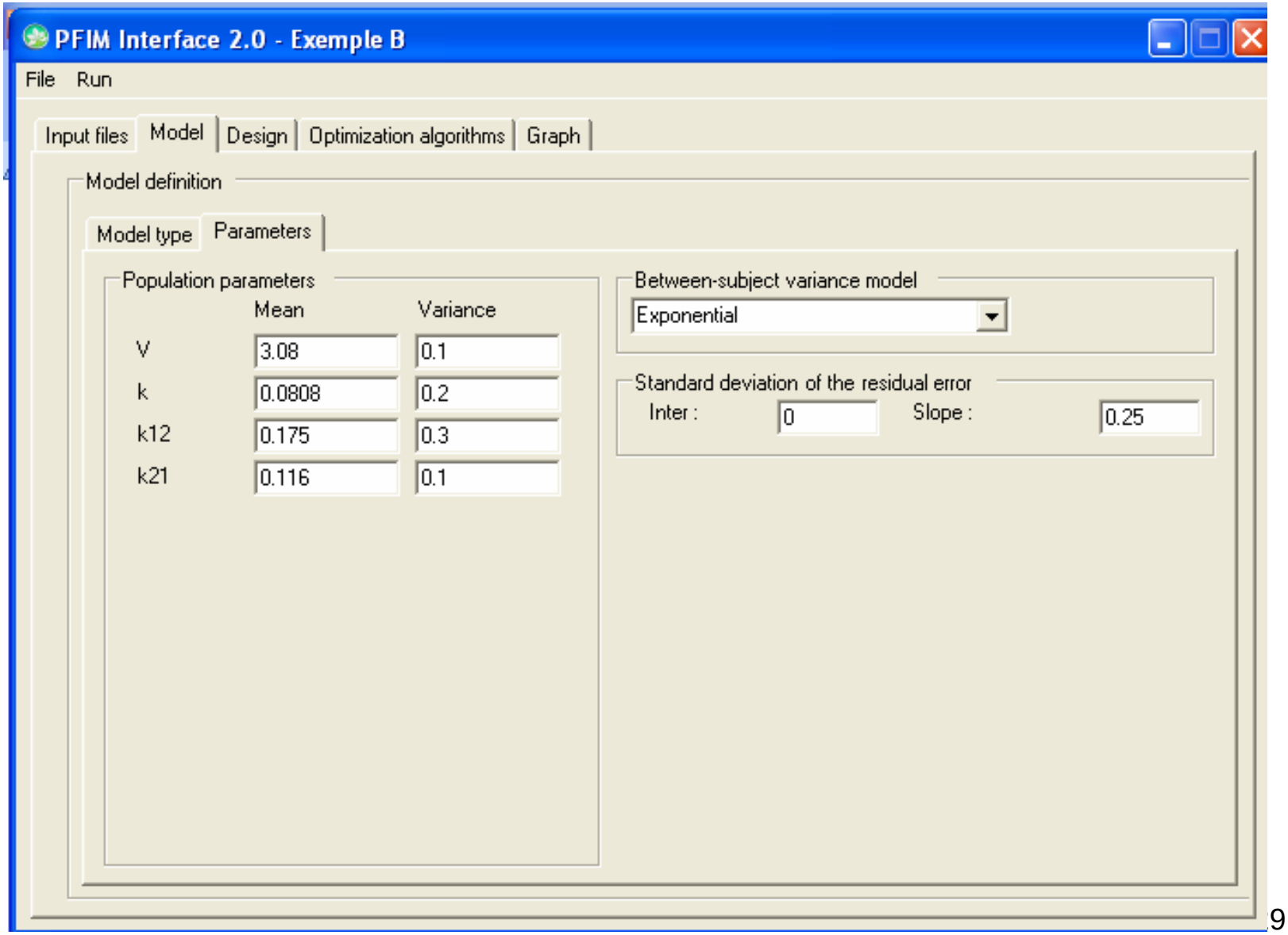
PFIM Interface 2.0



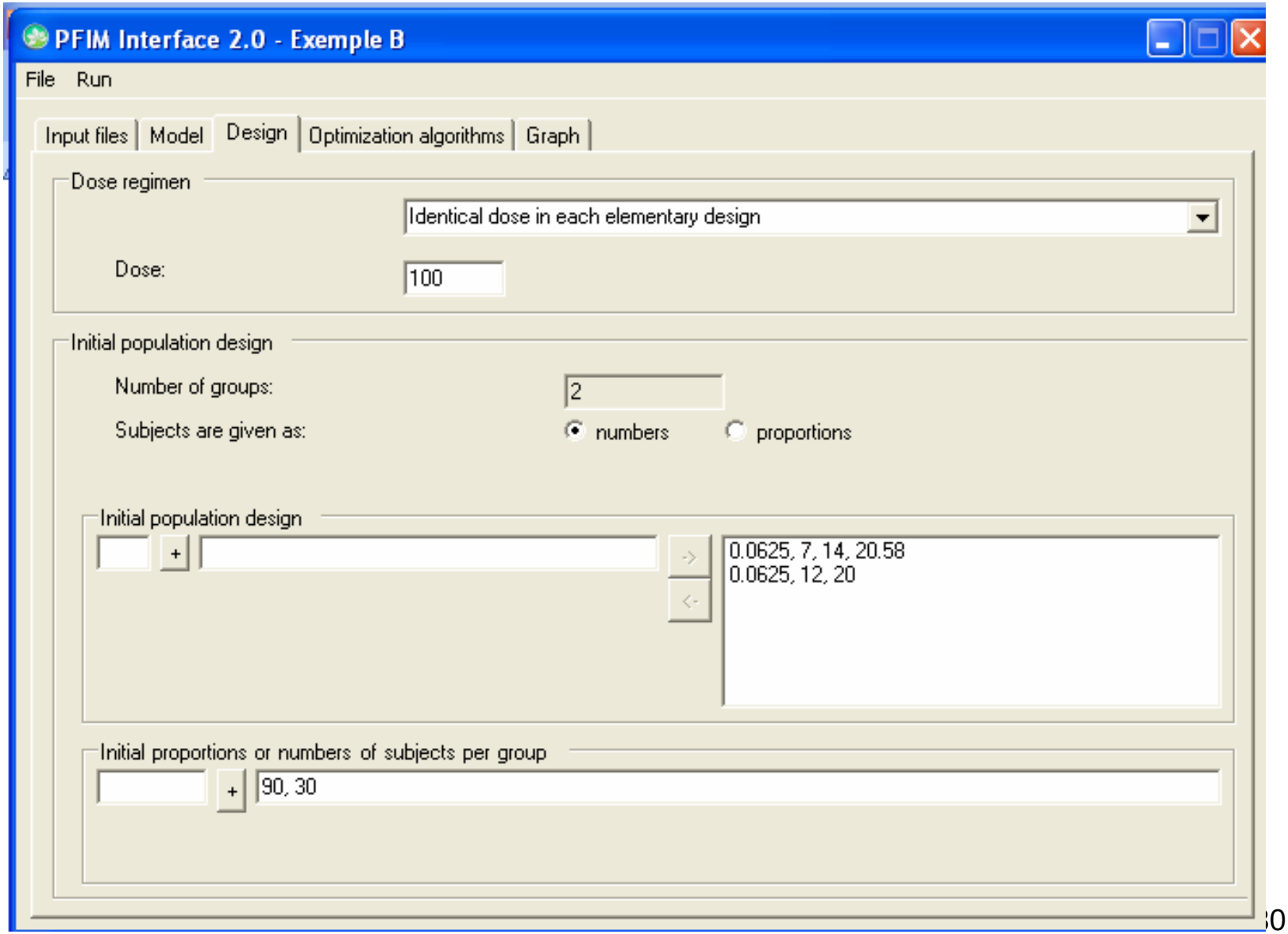
PFIM Interface 2.0: Model type



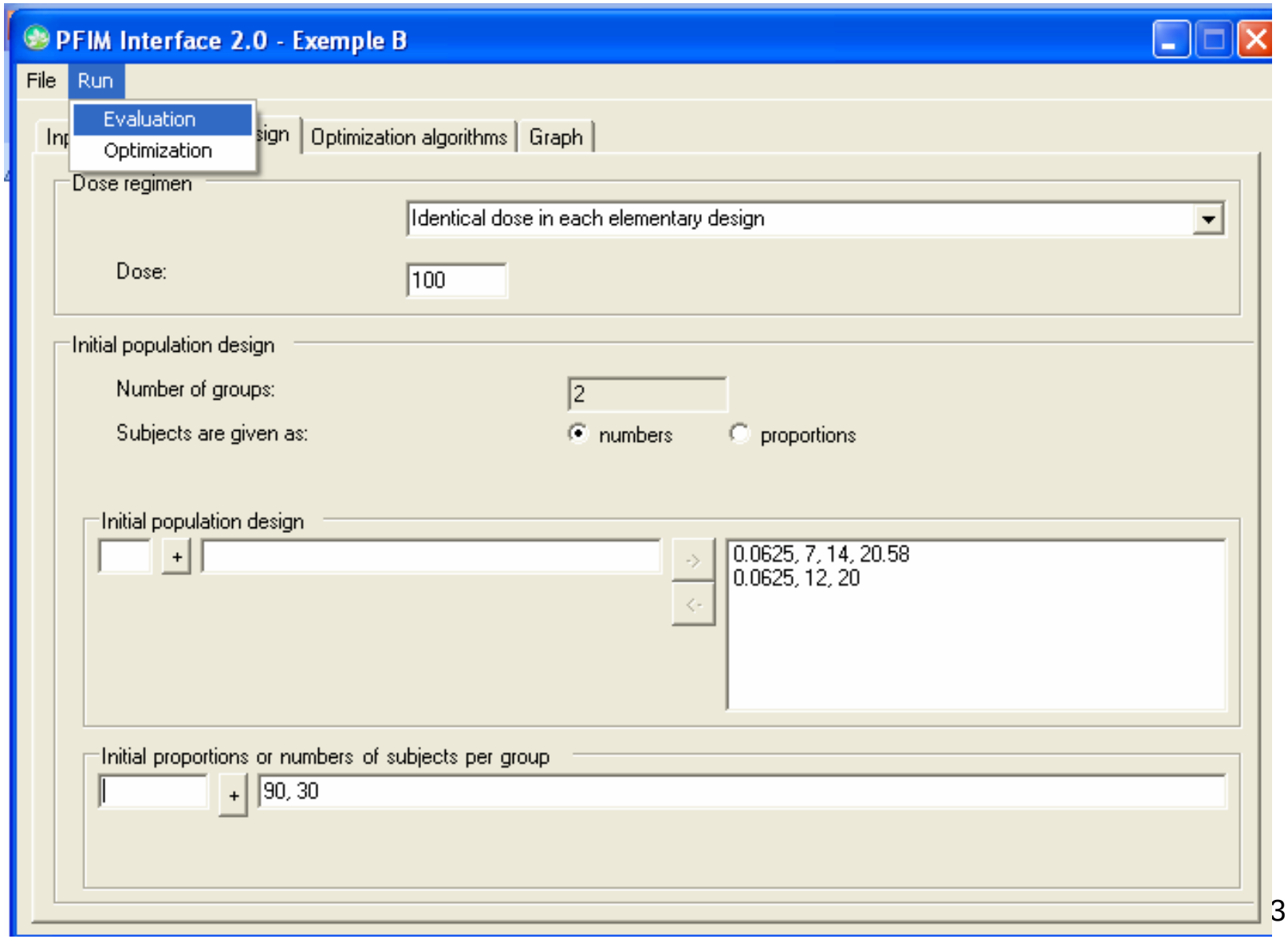
PFIM Interface 2.0: Parameters



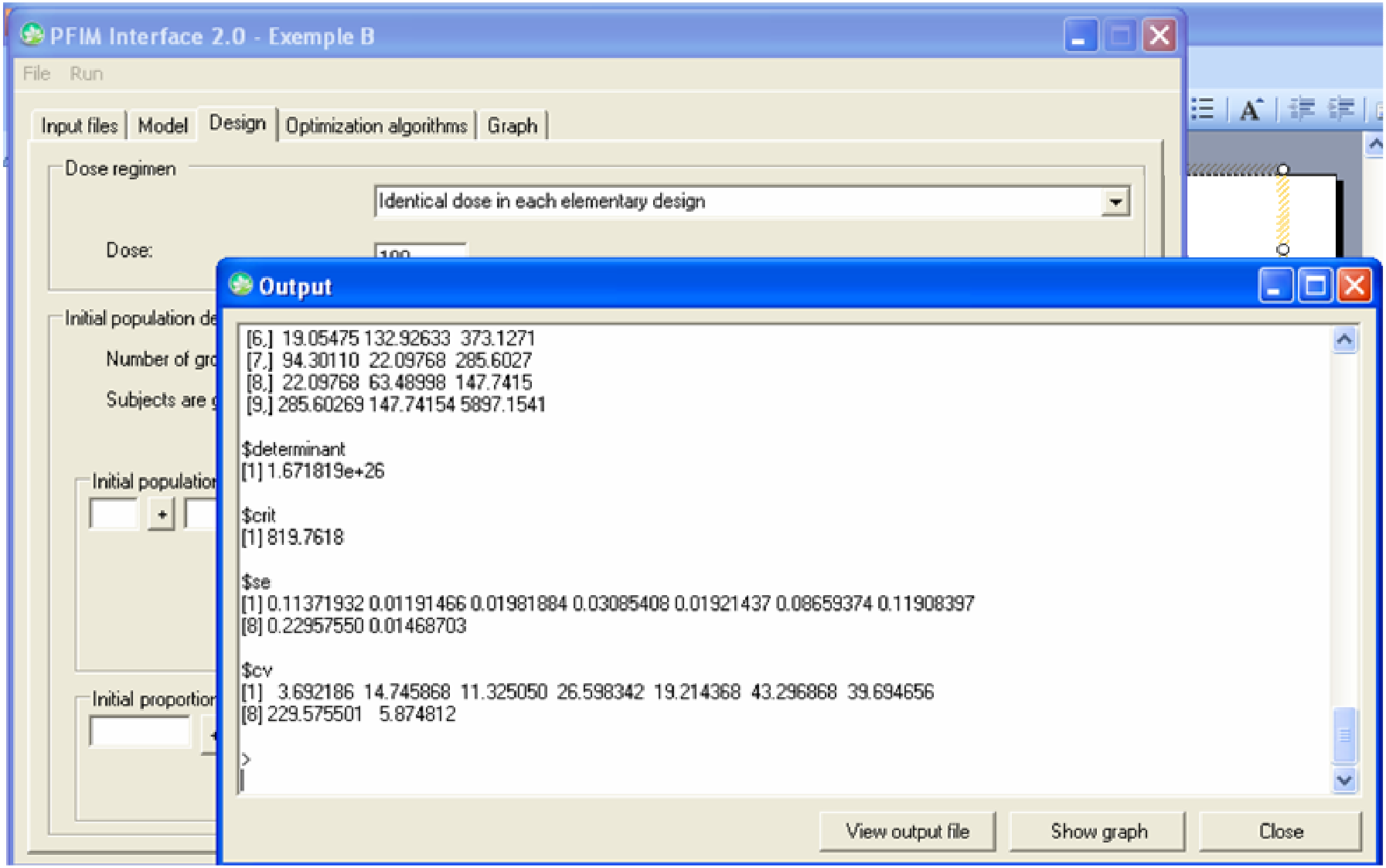
PFIM Interface 2.0: Design



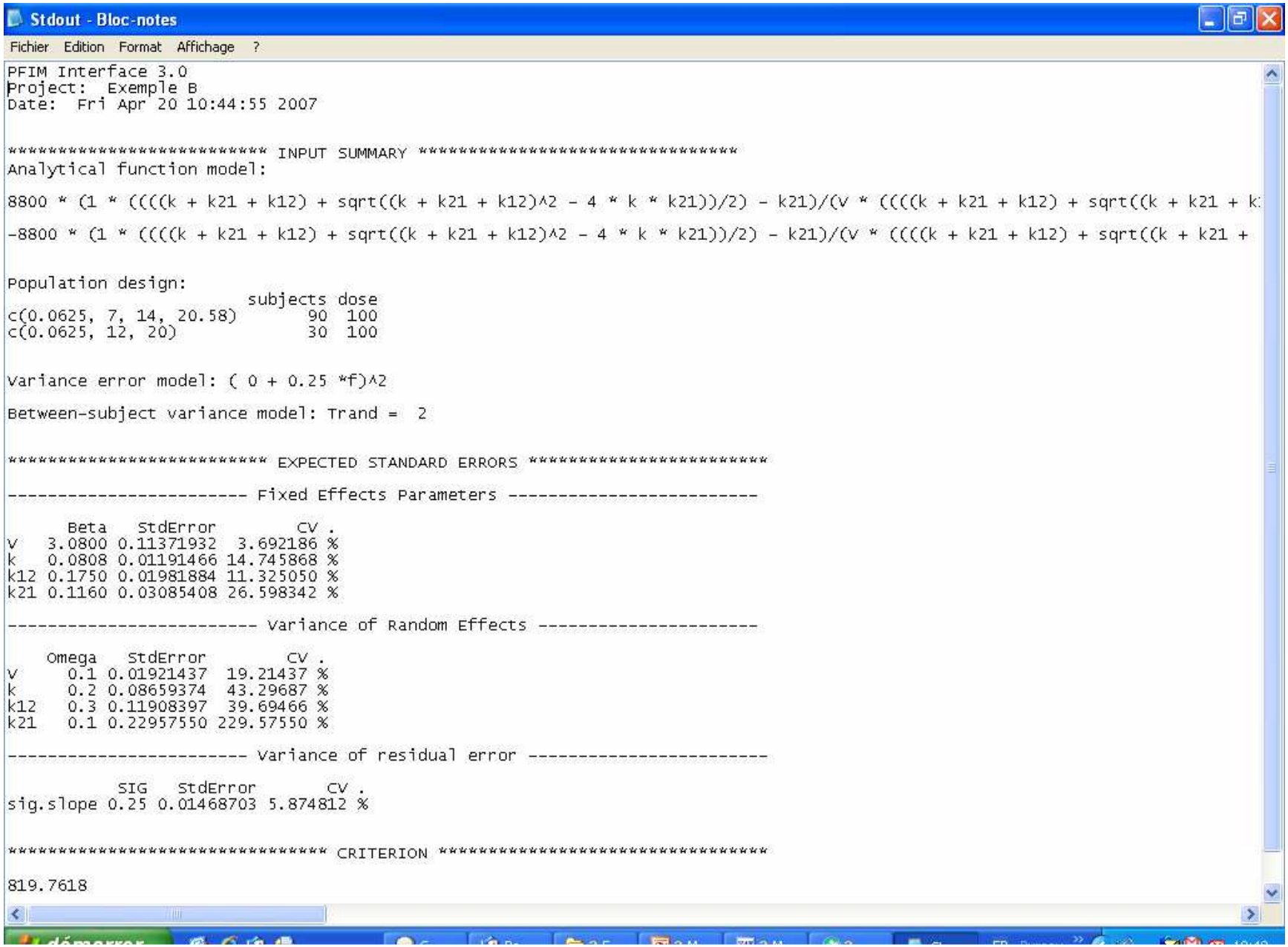
PFIM Interface 2.0: Evaluation (1)



PFIM Interface 2.0: Evaluation (2)



PFIM Interface 2.0: Stdout

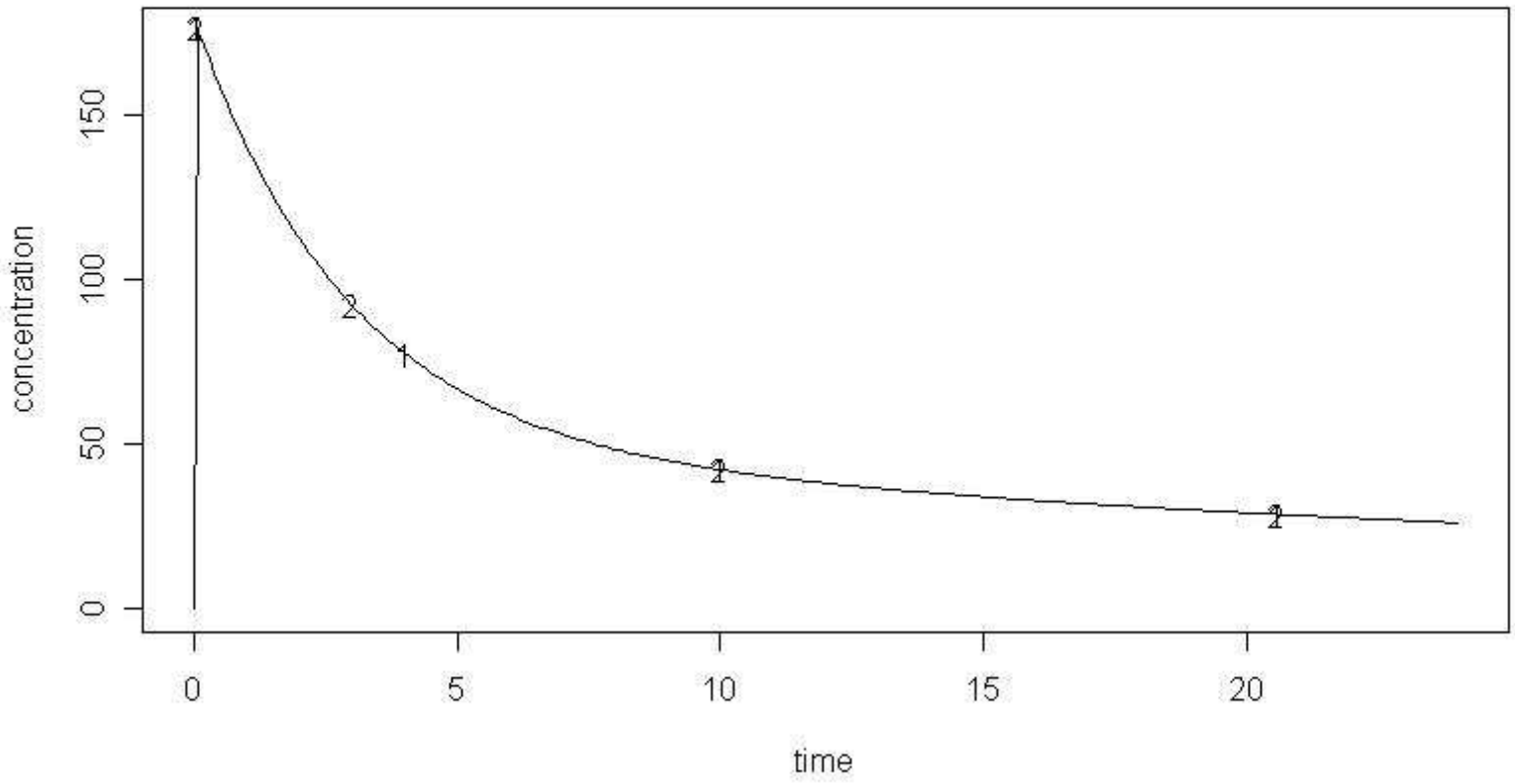


Stdout - Bloc-notes

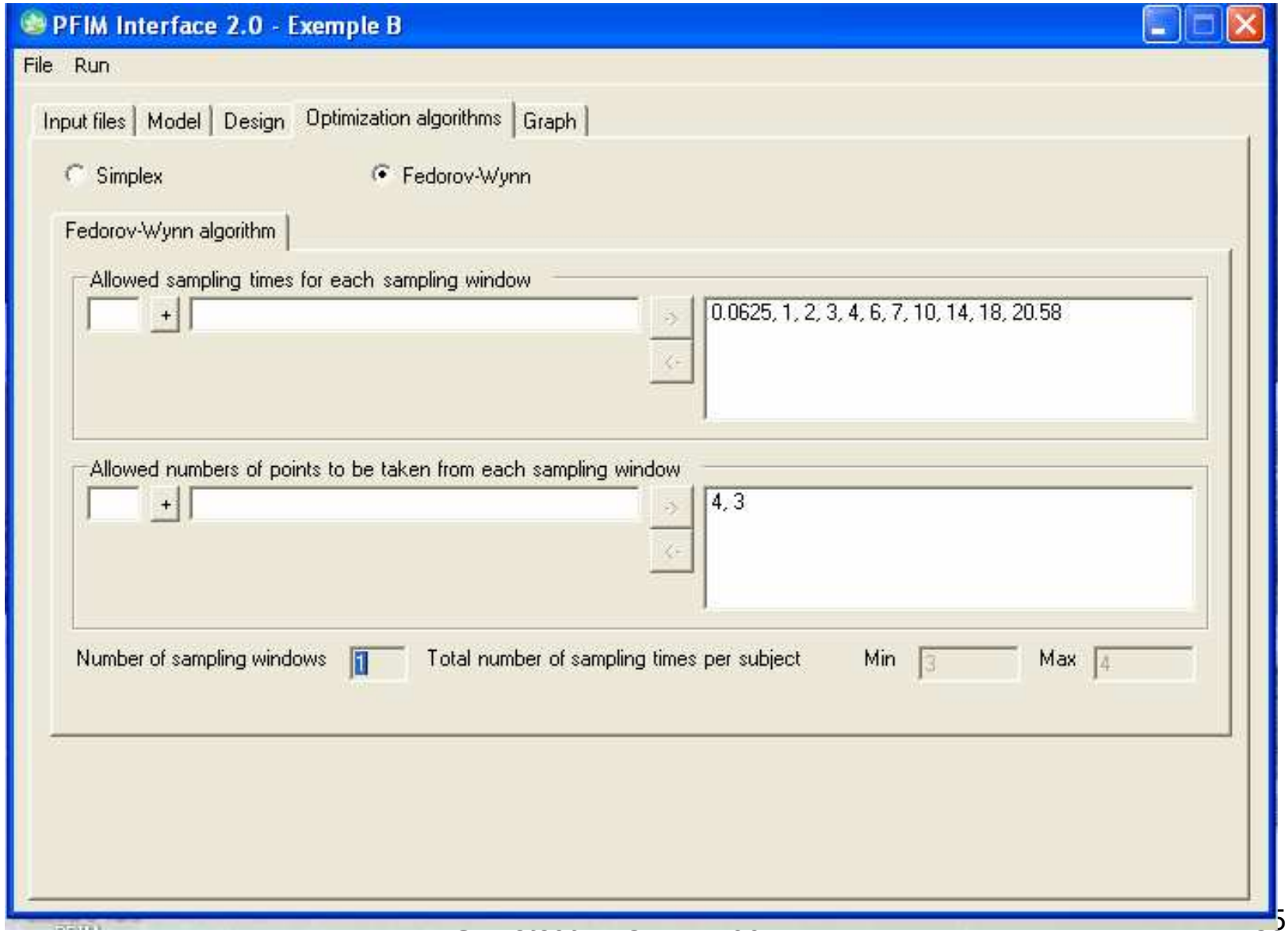
Fichier Edition Format Affichage ?

```
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 + k:

-8800 * (1 * ((((k + k21 + k12) + sqrt((k + k21 + k12)^2 - 4 * k * k21))/2) - k21)/(V * ((((k + k21 + k12) + sqrt((k + k21 +


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
```

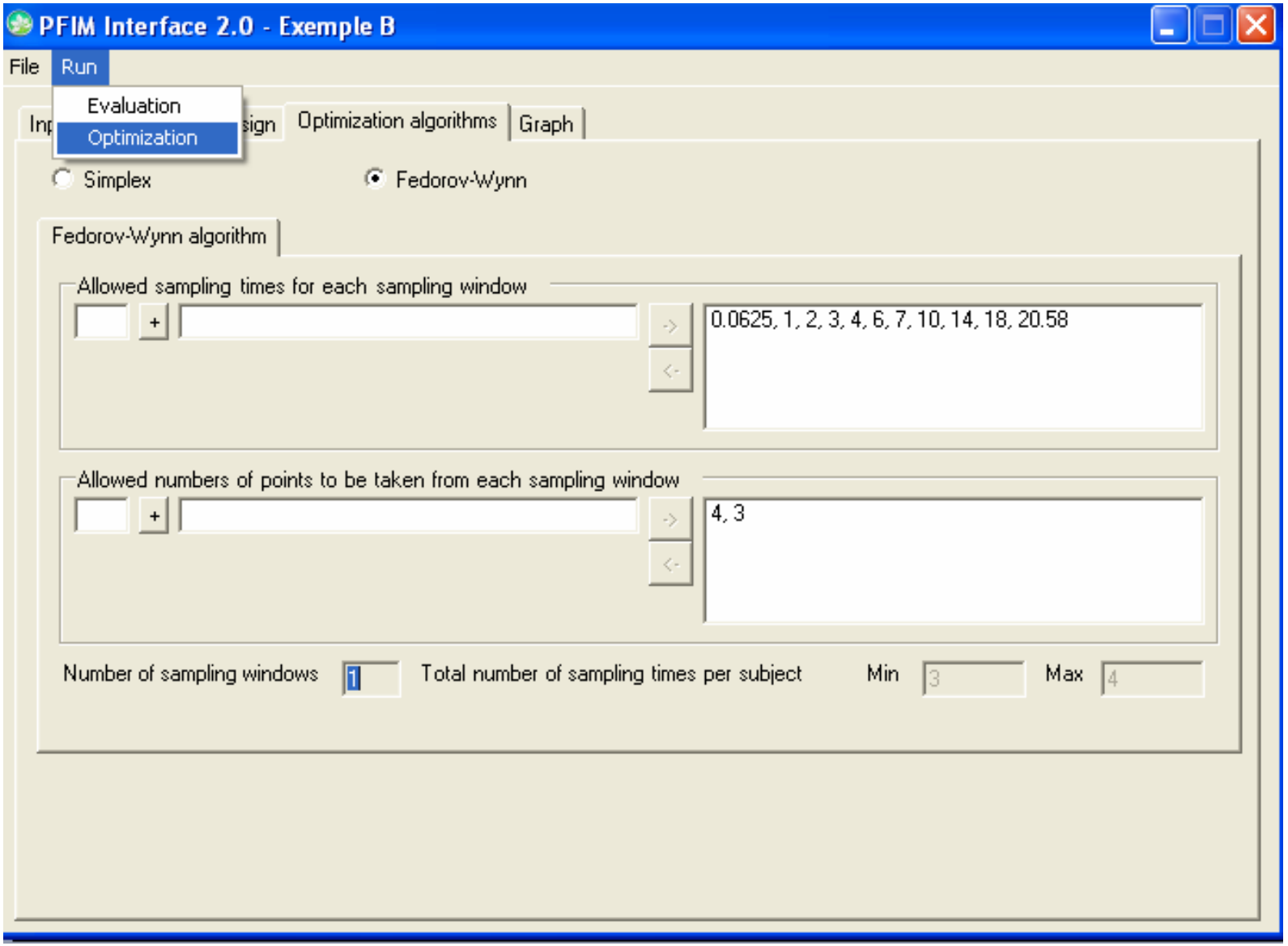
PFIM Interface 2.0: Graph



PFIM Interface 2.0: Optimisation (1)



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