PFIM 4.0

PFIM Group

IAME UMR1137, INSERM and Université Paris Diderot, Paris, France

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www.pfim.biostat.fr

Examples

Written by Giulia Lestini

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PFIM 4.0 is free library of functions.
The Université Paris Diderot and INSERM are the co-owners of this library of functions.

Contact: pfim@inserm.fr

Members of the PFIM Group

Pr France Mentré (Chair)
Caroline Bazzoli (active member)
Julie Bertrand
Emmanuelle Comets (active member)
Anne Dubois
Cyrielle Dumont (active member)
Hervé Le Nagard (active member)
Giulia Lestini (active member)
Thu Thuy Nguyen (active member)
Sylvie Retout

This documentation contains a series of examples for **EVALUATION** (first section) and **OPTIMISATION** (second section) of design in pharmacokinetics (PK) and pharmacodynamics (PD).

We have tried to illustrate all the features of PFIM 4.0 in this choice of examples. In example 1 of each section we have more specifically illustrated all the new features in this version 4.0 of PFIM.

All the input, model and output codes used for this example are available when PFIM is downloaded. In this document we have copied the specific part of the code on the illustrated features.
Please remember to update the directories in the `PFIM.R` file before running each example.

EVALUATION

1. Example 1: PK Model

The purpose is to evaluate a design for a one compartment first order absorption PK model with parameters `ka`, `V` and `k` after single dose administration.

1.1. Model Files

Four possible and exchangeable ways for defining models are available in PFIM. These are listed below:

A. Model Library
B. Expression
C. User-defined Model
D. Ordinary Differential Equations (ODE)

For completeness, this model was written in the four available forms.

A. Model Library:

```
source(file.path(directory.program,"LibraryPK.r"))

formA<-oral1_1cpt_kaVk()[[1]]

form<-c(formA)
```

B. Expression:

```
formA <-expression(dose/V*ka/(ka-k)*(exp(-k*t)-exp(-ka*t)))

form<-c(formA)
```

C. User-defined 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)
}
```

D. choiceODE:

```
formED<-function(t,y,p)
{
ka<-p[1]
k<-p[2]
V <-p[3]
yd1<-ka*y[2]-k*y[1]
yd2<--ka*y[2]
list(c(yd1,yd2),c(y[1]/V))
}
```

NB 1: **Derivatives**

A new feature for specifying the derivatives is available under the Analytical Model Option (in the "stdin.R" file). This option is available only if the model is written as a function using User-defined Model form. The code for this feature in the stdin.R file is:

```
#Numerical derivatives  (Yes=T, No=F)

#If 'Yes', specify the model function "form" in the model file

#If 'No', specify the object "form" which is a vector of expressions in the model
file

#-------------------------------------------------------------

NUM<-F
```

NB 2: **Graphs**

Another new feature allows one to display graphs of the simulated model and sensitivity functions without evaluation of the Fisher Information Matrix (FIM). This can help for a better initial understanding of the case study and to check the model code.

In order to do this, one can set in the stdin.R file the "`graph.only`" option equals to true ("T"). Then for the evaluation of FIM it is necessary to switch the `graphic.only` option back to false and re-run PFIM.

1.2. Population Fisher Information Matrix (P-FIM)

Evaluation of the Population Fisher information matrix (P-FIM) for several designs, all patient have a a dose of 100.

1.2.1. One group with Elementary Design ξ_1

200 subjects who have the same elementary design composed of 4 sampling times:

$$\xi_1 = (0.33, 1.5, 5, 12)$$

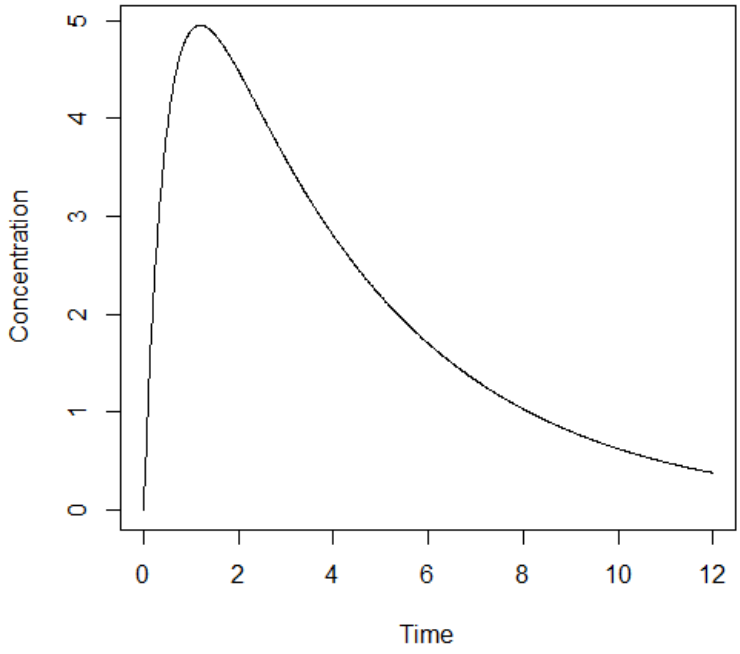
For this first example, we report the PFIM input files (stdin.R) for each possible model form (see section 1.1). We therefore repeated the example four times, using four input files. Note that all the outputs are identical so only one is given.

For other features in EXAMPLE 1, the model was written always in the “User-Defined” form.

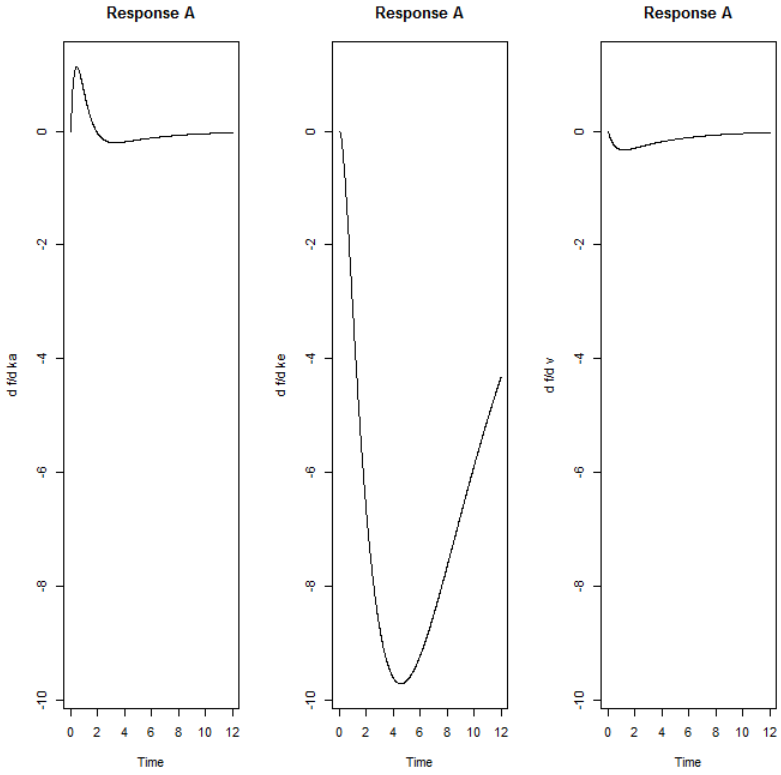
Graphs pre-evaluation

Graphs were obtained using the graphical option “`graphic.only`” showed in section 1.1.

Simulated model



Sensitivity functions with respect to each parameter



INPUT FILE; model called from the library

```
##############################################################################
##                      INPUT FILE FOR PFIM 4.0                             ##
##############################################################################


#Name of the project
#--------------------
project<-"1.1_ModLibrary_1.2.1"

#Name of the file containing the PK or PD model
#-----------------------------------------------
file.model<-"model.R"

#Name of the output file for the results and for the Fisher information matrix
#--------------------------------------
output<-"Stdout.r";
outputFIM<-"FIM.txt";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-----------------------------------------------------
previous.FIM<-""
```

```
#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"EVAL"

#To display only  graphs of models and/or sensitivity functions before computing
the Fisher Information matrix
graph.only<-F

#Block diagonal Fisher information matrix (option<-1) or complete Fisher
information matrix (option<-2)
#-----------------------------------------------------------
option<-1

#Number of responses
#-------------------------------------------------------------------
nr<-1

################## MODEL OPTION ##########################

#Model form: Differential equations (DE) or analytical form (AF)
#-----------------------------------------------------------------

modelform<-"AF"

###### ANALYTICAL MODEL OPTION ############################
############################################################

#Identical dose in each elementary design (Yes=T, No=F)
#-------------------------------------------------------------
dose.identical<-T

# If 'Yes', enter the value of the dose,
# else, enter the vector of the dose values for each elementary design
#-------------------------------------------------------------------
dose<-c(100)

#Vector of the times intervals of each expression
#-----------------------------------------------------------
boundA<-list(c(0,Inf))

#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-----------------------------------------------------------
NUM<-F

###### END ANALYTICAL MODEL OPTION ########################
#Name of the fixed effects parameters
#-------------------------------------
parameters<-c("ka","k","V")

#Fixed effects parameters values
#-------------------------------
beta<-c(2,0.25,15)

#Some parameters may not be estimated (not estimated = T, estimated = F)
```

```
#-------------------------------
beta.fixed<-c(F,F,F)

#Number of occasions
#-------------------------------------------------------------------------
n_occ<-1

#Random effect model (1) = additive  (2) = exponential
#-----------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#-------------------------------------------------
omega<-diag(c(1,0.25,0.1))

#Diagonal Matrix of variance for inter-occasion random effects:
#-------------------------------------------------
gamma<-diag(c(0,0,0))

#Standard deviation of residual error (sig.inter+sig.slope*f)^2:
#-----------------------------------------------------------------
sig.interA<-0.5
sig.slopeA<-0.15


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.33,1.5,5,12))

#Vector of initial proportions or numbers of subjects for each elementary design
#-----------------------------------------------------------------
subjects<-c(200)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1

#If 'proportions of subjects' give the total number of samples
#-----------------------------------------------------------
#Ntot<-40
############## GRAPH SPECIFICATION OPTION ###############

#graphical representation of the model (Yes=T, No=F)
#-----------------------------------
graph.logical<-T

#graphical representation of sensitivity functions (Yes=T, No=F)
#-----------------------------------
graphsensi.logical<-T


#Vector of Names on X axes for each response
#--------------------------------
names.datax<-c("Time")

#Vector of Names on Y axes for each response
#--------------------------------
```

```
names.datay<-c("Concentration")

#Controls logarithmic axes for the graphical representation of the model
#Values "xy", "x", or "y" produce log-log or log-x or log-y axes.
#(For standard graphic, log.logical<-F)
#-------------------------------------------------------------
log.logical<-F
#log.logical<-'y'

#Vector of lower and upper sampling times for the graphical representations
#-----------------------------------------------------------------------
graph.infA<-c(0)
graph.supA<-c(16)

#Vector of lower and upper concentration for the graphical representations
#-----------------------------------------------------------------------
y.rangeA<-NULL # default range
#y.rangeA<-c(1,10)
```

INPUT FILE; model written in expression form

Same stdin.R as in the sub-section above, where the model is called from the library.

```
#Name of the project
#--------------------
project<-"1.1_ExpressionMod_1.2.1"
```

INPUT FILE; model written in User-defined model form

```
#Name of the project
#--------------------
project<-"1.1_UserDefMod_1.2.1"
```

Change in the stdin.R code

```
#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-------------------------------------------------------------
NUM<-T
```

INPUT FILE; ODE Model

```
#Name of the project
#--------------------
project<-"1.1_ModeOde_1.2.1"



################### MODEL OPTION ############################
```

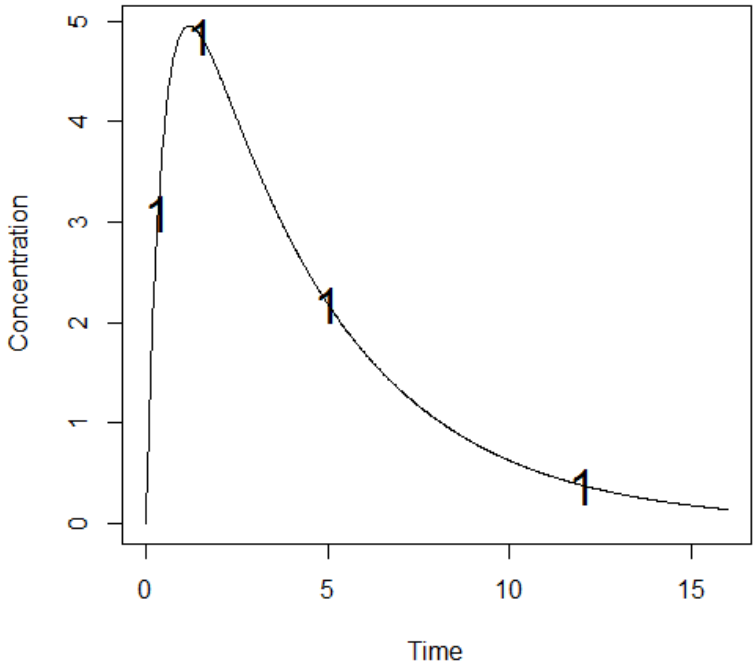
```
#Model form: Differential equations (DE) or analytical form (AF)
#-------------------------------------------------------------

modelform<-"DE"
###### DIFFERENTIAL EQUATION OPTION ##########################
#############################################################

#Initial time for which initial conditions are given
#---------------------------------------------------
time.condinit<-0

#Identical initial conditions in each elementary design (Yes=T, No=F)
#-------------------------------------------------------------
condinit.identical<-T

# If 'Yes', enter once the expression of the initial values of the system at the
initial time
# else, enter the vectors of the initial conditions for each elementary design
# If initial values depend on the parameters to be estimated,
# enter this parameter into the expression without any quotation marks
#-----------------------------------------------------
condinit<-expression(c(0,100))

# Error tolerance for solving differential equations
#---------------------------------------------------

RtolEQ<-1e-08
AtolEQ<-1e-08
Hmax<-Inf

###### END DIFFERENTIAL EQUATION OPTION ###################################
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.1_ModeOde_1.2.1

Date:  Mon Jan 27 13:34:58 2014



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

Differential Equations form of the model:

function(t,y,p)
{
ka<-p[1]
k<-p[2]
V <-p[3]
yd1<-ka*y[2]-k*y[1]
yd2<--ka*y[2]
list(c(yd1,yd2),c(y[1]/V))
}


Design:
Sample times for response: A
```

```
               times subjects
1 c(0.33, 1.5, 5, 12)      200


Initial Conditions at time 0 :

0 100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Error tolerance for solving differential equations system: RtolEQ = 1e-08 , AtolEQ
= 1e-08 , Hmax =  Inf

Computation of the Population Fisher information matrix: option =  1

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

         [,1]       [,2]      [,3]      [,4]       [,5]       [,6]       [,7]
[1,] 38.46761   82.86692 -3.770150  0.000000   0.000000    0.00000    0.00000
[2,] 82.86692 8310.88573 77.977974  0.000000   0.000000    0.00000    0.00000
[3,] -3.77015   77.97797  4.938229  0.000000   0.000000    0.00000    0.00000
[4,]  0.00000    0.00000  0.000000 59.190272   4.291829   31.98157   28.15945
[5,]  0.00000    0.00000  0.000000  4.291829 674.519743  213.76984  193.67427
[6,]  0.00000    0.00000  0.000000 31.981572 213.769845 3086.36662  295.74231
[7,]  0.00000    0.00000  0.000000 28.159451 193.674273  295.74231 1208.60605
[8,]  0.00000    0.00000  0.000000 85.786203 226.638153 1167.39334 1544.00251
          [,8]
[1,]    0.0000
[2,]    0.0000
[3,]    0.0000
[4,]   85.7862
[5,]  226.6382
[6,] 1167.3933
[7,] 1544.0025
[8,] 4118.3997


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

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

    Beta   StdError      RSE
ka  2.00 0.17480763 8.740382 %
k   0.25 0.01239415 4.957658 %
V  15.00 0.52291111 3.486074 %

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

   omega²   StdError      RSE
ka   1.00 0.13203570 13.20357 %
k    0.25 0.03977275 15.90910 %
V    0.10 0.01933249 19.33249 %
```

```
------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04077340  8.154681 %
sig.slopeA  0.15 0.02293716 15.291443 %


****************************** DETERMINANT *********************************

2.930398e+20

****************************** CRITERION ***********************************

361.7144



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************

        FixedEffects VarianceComponents
min      2490.782065           3.598669
max      8312.446904         702.614499
max/min     3.337284         195.242883


****************** CORRELATION MATRIX *****************

           [,1]       [,2]       [,3]          [,4]          [,5]        [,6]
[1,]  1.0000000 -0.2836925  0.3614018  0.0000000000  0.0000000000  0.00000000
[2,] -0.2836925  1.0000000 -0.4466787  0.0000000000  0.0000000000  0.00000000
[3,]  0.3614018 -0.4466787  1.0000000  0.0000000000  0.0000000000  0.00000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000000  0.0008945392 -0.01707707
[5,]  0.0000000  0.0000000  0.0000000  0.0008945392  1.0000000000 -0.13147269
[6,]  0.0000000  0.0000000  0.0000000 -0.0170770725 -0.1314726865  1.00000000
[7,]  0.0000000  0.0000000  0.0000000  0.0186040065 -0.1824110351  0.12863649
[8,]  0.0000000  0.0000000  0.0000000 -0.1283096902  0.0574454505 -0.31004595
            [,7]        [,8]
[1,]  0.00000000  0.00000000
[2,]  0.00000000  0.00000000
[3,]  0.00000000  0.00000000
[4,]  0.01860401 -0.12830969
[5,] -0.18241104  0.05744545
[6,]  0.12863649 -0.31004595
[7,]  1.00000000 -0.68199073
[8,] -0.68199073  1.00000000



Time difference of 0.539031 secs
```



1.2.2. One group with Elementary Design ξ_2

200 subjects who have the same elementary design composed of 3 sampling times:

$$\xi_2 = (1, 3, 8)$$

INPUT FILE

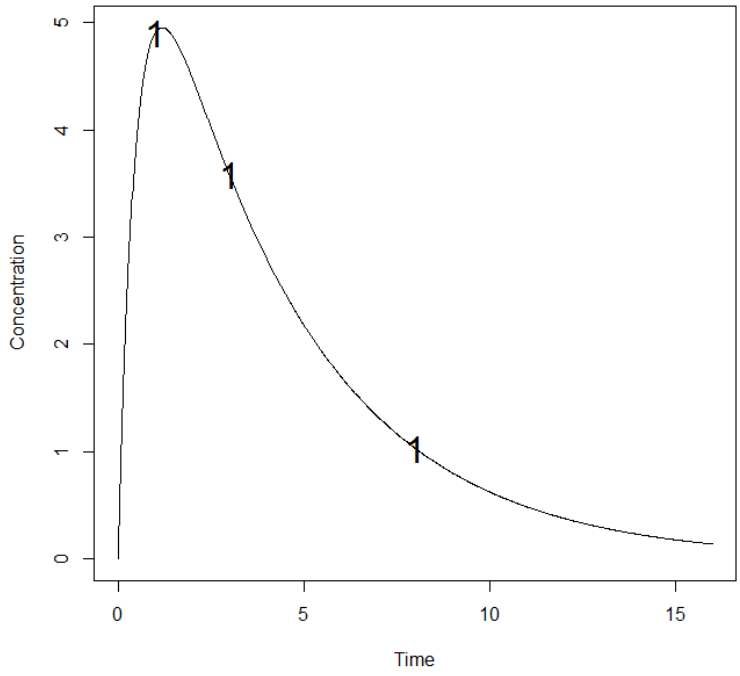
```
#Name of the project
#--------------------
project<-"1.2.2"


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(1,3,8))
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.2.2

Date:  Mon Jan 27 15:05:21 2014



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

Analytical function models :
```

```
 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)
}


Design:
Sample times for response: A
       times subjects doses
1 c(1, 3, 8)      200   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Population Fisher information matrix: option =  1

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

          [,1]       [,2]      [,3]       [,4]       [,5]       [,6]       [,7]      [,8]
[1,]  24.824352  114.28686 -3.961996   0.000000   0.000000    0.00000   0.00000    0.0000
[2,] 114.286857 8098.01333 80.527748   0.000000   0.000000    0.00000   0.00000    0.0000
[3,]  -3.961996   80.52775  5.116281   0.000000   0.000000    0.00000   0.00000    0.0000
[4,]   0.000000    0.00000  0.000000  24.649938   8.163429   35.31918  33.35118  147.8426
[5,]   0.000000    0.00000  0.000000   8.163429 640.408398  227.97837 186.69165  204.3552
[6,]   0.000000    0.00000  0.000000  35.319180 227.978372 3312.94177 284.04661 1079.4933
[7,]   0.000000    0.00000  0.000000  33.351180 186.691652  284.04661 455.36961  971.8908
[8,]   0.000000    0.00000  0.000000 147.842611 204.355180 1079.49330 971.89080 2577.3614


************************* 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 %


****************************** DETERMINANT ********************************

1.230099e+18

****************************** 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


****************** CORRELATION MATRIX *****************

           [,1]       [,2]       [,3]       [,4]       [,5]       [,6]       [,7]       [,8]
[1,]  1.0000000 -0.4582328  0.5094178  0.0000000  0.0000000  0.0000000  0.0000000  0.0000000
[2,] -0.4582328  1.0000000 -0.5360254  0.0000000  0.0000000  0.0000000  0.0000000  0.0000000
[3,]  0.5094178 -0.5360254  1.0000000  0.0000000  0.0000000  0.0000000  0.0000000  0.0000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000 -0.4660810  0.4704245  0.7368611 -0.8188563
[5,]  0.0000000  0.0000000  0.0000000 -0.4660810  1.0000000 -0.4194565 -0.6482711  0.5995498
[6,]  0.0000000  0.0000000  0.0000000  0.4704245 -0.4194565  1.0000000  0.5456326 -0.6075711
[7,]  0.0000000  0.0000000  0.0000000  0.7368611 -0.6482711  0.5456326  1.0000000 -0.9589960
[8,]  0.0000000  0.0000000  0.0000000 -0.8188563  0.5995498 -0.6075711 -0.9589960  1.0000000



Time difference of 0.02700186 secs
```



1.2.3. Two Groups Design

Two group population design of 400 subjects: 200 with elementary designs ξ_1 and 200 with elementary design ξ_2.

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.2.3"


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-------------------------------------------------------------------
protA<- list(c(0.33,1.5,5,12),c(1,3,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(200,200)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-----------------------------------------------------------------------------
subjects.input<-1
```

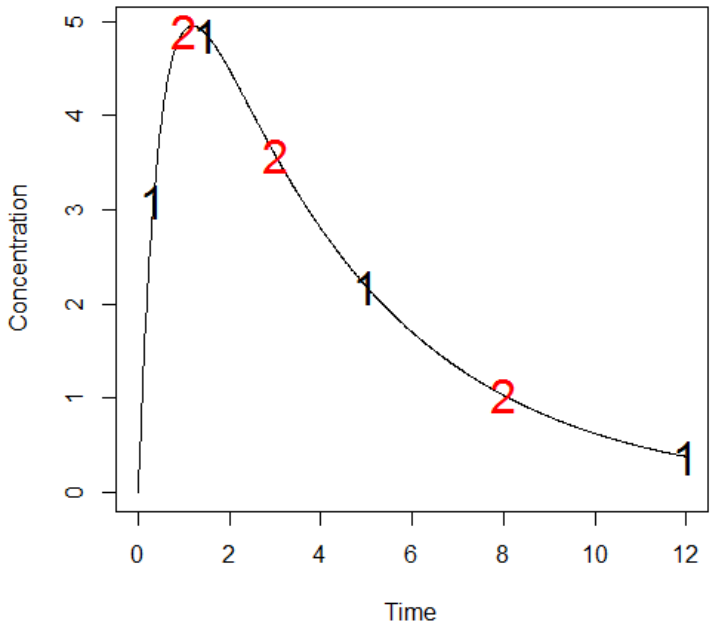
OUTPUT FILE

```
PFIM 4.0

Project:  1.2.3

Date:  Mon Jan 27 15:37:15 2014
```

```
*************************** INPUT SUMMARY *******************************

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)      200   100
2          c(1, 3, 8)      200   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Population Fisher information matrix: option =  1

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

           [,1]       [,2]       [,3]      [,4]       [,5]       [,6]
[1,]  63.291953   197.1538  -7.732147   0.00000    0.00000    0.00000
[2,] 197.153796 16408.8991 158.505718   0.00000    0.00000    0.00000
[3,]  -7.732147   158.5057  10.054510   0.00000    0.00000    0.00000
[4,]   0.000000     0.0000   0.000000  83.84019   12.45526   67.30076
[5,]   0.000000     0.0000   0.000000  12.45526 1314.92814  441.74820
[6,]   0.000000     0.0000   0.000000  67.30076  441.74820 6399.30871
[7,]   0.000000     0.0000   0.000000  61.51064  380.36592  579.78890
[8,]   0.000000     0.0000   0.000000 233.62885  430.99333 2246.88658
           [,7]       [,8]
[1,]    0.00000    0.0000
[2,]    0.00000    0.0000
[3,]    0.00000    0.0000
[4,]   61.51064  233.6288
[5,]  380.36592  430.9933
[6,]  579.78890 2246.8866
[7,] 1663.97567 2515.8934
[8,] 2515.89337 6695.7614


************************ 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 %


****************************** DETERMINANT *********************************

1.665585e+22

****************************** CRITERION ***********************************

599.3712



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      4693.602414           6.806441
max     16412.806404        1313.606918
max/min     3.496846         192.994680


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]        [,4]        [,5]        [,6]
[1,]  1.0000000 -0.3572238  0.4228893  0.00000000  0.00000000  0.00000000
[2,] -0.3572238  1.0000000 -0.4813562  0.00000000  0.00000000  0.00000000
[3,]  0.4228893 -0.4813562  1.0000000  0.00000000  0.00000000  0.00000000
[4,]  0.0000000  0.0000000  0.0000000  1.00000000 -0.02281874  0.03522493
[5,]  0.0000000  0.0000000  0.0000000 -0.02281874  1.00000000 -0.14572956
[6,]  0.0000000  0.0000000  0.0000000  0.03522493 -0.14572956  1.00000000
[7,]  0.0000000  0.0000000  0.0000000  0.11792720 -0.24609424  0.16443852
[8,]  0.0000000  0.0000000  0.0000000 -0.28514144  0.12142535 -0.33126615
           [,7]       [,8]
[1,]  0.0000000  0.0000000
[2,]  0.0000000  0.0000000
[3,]  0.0000000  0.0000000
[4,]  0.1179272 -0.2851414
[5,] -0.2460942  0.1214254
[6,]  0.1644385 -0.3312662
```

```
[7,]  1.0000000 -0.7482048
[8,] -0.7482048  1.0000000


Time difference of 0.04000306 secs
```



1.2.4. Previous Information on PFIM

A new feature in v4.0 is the possibility to evaluate a population design with previous information stored in a file. Here we evaluate a design with 200 subjects with elementary design ξ_2 in addition to a previous information stored in the file "`FIM_Prev_Info.txt`". This file was produced from the example in section 1.2.1(with the name of "`FIM.txt`") which corresponds to the FIM evaluated for 200 subjects with the elementary design ξ_1.

INPUT FILE

```
#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-------------------------------------------------------
previous.FIM<-"FIM_Prev_Info.txt"


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-------------------------------------------------------------------
protA<-list(c(1,3,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(200)
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.2.4

Date:  Mon Jan 27 16:23:13 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
       times subjects doses
1 c(1, 3, 8)      200   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Population Fisher information matrix: option =  1

Previous FIM from file FIM_Prev_Info.txt

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

             V1         V2         V3        V4         V5         V6
[1,]  63.291953   197.1538  -7.732147   0.00000    0.00000    0.00000
[2,] 197.153796 16408.8991 158.505718   0.00000    0.00000    0.00000
[3,]  -7.732147   158.5057  10.054510   0.00000    0.00000    0.00000
[4,]   0.000000     0.0000   0.000000  83.84019   12.45526   67.30076
[5,]   0.000000     0.0000   0.000000  12.45526 1314.92814  441.74820
[6,]   0.000000     0.0000   0.000000  67.30076  441.74820 6399.30871
[7,]   0.000000     0.0000   0.000000  61.51064  380.36592  579.78890
[8,]   0.000000     0.0000   0.000000 233.62885  430.99333 2246.88658
             V7        V8
[1,]    0.00000    0.0000
[2,]    0.00000    0.0000
[3,]    0.00000    0.0000
[4,]   61.51064  233.6288
[5,]  380.36592  430.9933
```

```
[6,]  579.78890 2246.8866
[7,] 1663.97567 2515.8934
[8,] 2515.89337 6695.7614


************************* 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 %


****************************** DETERMINANT ********************************

1.665585e+22

******************************** CRITERION ********************************

599.3712



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      4693.602414           6.806441
max     16412.806404        1313.606918
max/min     3.496846         192.994680


****************** CORRELATION MATRIX ******************

         [,1]       [,2]       [,3]        [,4]        [,5]        [,6]
V1  1.0000000 -0.3572238  0.4228893  0.00000000  0.00000000  0.00000000
V2 -0.3572238  1.0000000 -0.4813562  0.00000000  0.00000000  0.00000000
V3  0.4228893 -0.4813562  1.0000000  0.00000000  0.00000000  0.00000000
V4  0.0000000  0.0000000  0.0000000  1.00000000 -0.02281874  0.03522493
V5  0.0000000  0.0000000  0.0000000 -0.02281874  1.00000000 -0.14572956
V6  0.0000000  0.0000000  0.0000000  0.03522493 -0.14572956  1.00000000
V7  0.0000000  0.0000000  0.0000000  0.11792720 -0.24609424  0.16443852
V8  0.0000000  0.0000000  0.0000000 -0.28514144  0.12142535 -0.33126615
```

```
          [,7]       [,8]
V1   0.0000000  0.0000000
V2   0.0000000  0.0000000
V3   0.0000000  0.0000000
V4   0.1179272 -0.2851414
V5  -0.2460942  0.1214254
V6   0.1644385 -0.3312662
V7   1.0000000 -0.7482048
V8  -0.7482048  1.0000000



Time difference of 0.1180069 secs
```

Comment on results

When comparing the results from the output with those obtained in section 1.2.2, it is noticeable that the criterion increased when prior information on FIM is used. It increased from 182.5 to 599.3. There are evident improvements also in the RSE of both fixed and random effects, which are lower here than in point 1.2.2.

Comparing the output of one group design using prior information with the output of the two groups design in section 1.2.3, it is evident that results are the same. Indeed, the prior information on FIM used was the FIM obtained for the first group design, group that was evaluated in section 1.2.1.

1.3. Individual Fisher Information Matrix (I-FIM)

Evaluation of the Individual Fisher Information Matrix for the elementary design ξ_1 and then ξ_2.

1.3.1. Elementary Design ξ_1

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.3.1"

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"I"


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.33,1.5,5,12))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(1)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.3.1

Date:  Mon Jan 27 16:33:26 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)        1   100


Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Individual Fisher information matrix

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX ******************

           [,1]       [,2]       [,3]     [,4]     [,5]
[1,]  1.3302192   1.159014 -0.2522055  0.00000  0.00000
[2,]  1.1590137 214.546128  3.6213766  0.00000  0.00000
[3,] -0.2522055   3.621377  0.1479803  0.00000  0.00000
[4,]  0.0000000   0.000000  0.0000000 12.85799 21.91468
[5,]  0.0000000   0.000000  0.0000000 21.91468 66.59115


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

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

    Beta  StdError      RSE
ka  2.00 1.4531150 72.65575 %
k   0.25 0.1228738 49.14952 %
V  15.00 5.6733768 37.82251 %


------------------------ Standard deviation of residual error ----------------------
```

```
           Sigma  StdError       RSE
sig.interA  0.50 0.4208513  84.17025 %
sig.slopeA  0.15 0.1849298 123.28655 %


****************************** DETERMINANT ******************************

3317.958

****************************** CRITERION ******************************

5.060276



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min         5.053743         0.02977512
max       214.613529         1.38102331
max/min    42.466252        46.38178541


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]       [,5]
[1,]  1.0000000 -0.6884871  0.8014327  0.0000000  0.0000000
[2,] -0.6884871  1.0000000 -0.8305558  0.0000000  0.0000000
[3,]  0.8014327 -0.8305558  1.0000000  0.0000000  0.0000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000 -0.7489284
[5,]  0.0000000  0.0000000  0.0000000 -0.7489284  1.0000000



Time difference of 0.02400112 secs
```

1.3.2. Elementary Design ξ_2

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.3.2"


#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"I"

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#------------------------------------------------------------------
protA<-list(c(1,3,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(1)
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.3.2

Date:  Mon Jan 27 17:02:58 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
       times subjects doses
1 c(1, 3, 8)        1   100


Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Individual Fisher information matrix

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX ******************

            [,1]       [,2]        [,3]      [,4]     [,5]
[1,]  0.35331883   1.538575 -0.08983448  0.000000  0.00000
[2,]  1.53857495 214.538102  3.84156478  0.000000  0.00000
[3,] -0.08983448   3.841565  0.13399054  0.000000  0.00000
[4,]  0.00000000   0.000000  0.00000000  7.836682 17.89450
[5,]  0.00000000   0.000000  0.00000000 17.894502 60.29574


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

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

    Beta  StdError       RSE
ka  2.00 2.7633469 138.16734 %
k   0.25 0.1464156  58.56623 %
V  15.00 6.3313534  42.20902 %


------------------------ Standard deviation of residual error ----------------------
```

```
           Sigma  StdError      RSE
sig.interA  0.50 0.6291957 125.8391 %
sig.slopeA  0.15 0.2268342 151.2228 %


****************************** DETERMINANT ******************************

279.0063

****************************** CRITERION ******************************

3.08406



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min         2.314023         0.02215148
max       214.617932         0.38532766
max/min    92.746652        17.39511865


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]       [,5]
[1,]  1.0000000 -0.7437627  0.7857500  0.0000000  0.0000000
[2,] -0.7437627  1.0000000 -0.8806589  0.0000000  0.0000000
[3,]  0.7857500 -0.8806589  1.0000000  0.0000000  0.0000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000 -0.8232092
[5,]  0.0000000  0.0000000  0.0000000 -0.8232092  1.0000000



Time difference of 0.02400088 secs
```

1.4. Bayesian Fisher Information Matrix (B-FIM)

Evaluation of the Bayesian Fisher Information Matrix for the elementary design ξ_1 and then ξ_2.

1.4.1. Elementary Design ξ_1

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.4.1"


#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"B"


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.33,1.5,5,12))
```

```
#Vector of initial proportions or numbers of subjects for each elementary design
#-----------------------------------------------------------------
subjects<-c(1)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.4.1

Date:  Mon Jan 27 17:09:24 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)        1   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2




Computation of the Bayesian Fisher information matrix

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

           [,1]       [,2]       [,3]
[1,]  1.5802192   1.159014 -0.2522055
[2,]  1.1590137 278.546128  3.6213766
[3,] -0.2522055   3.621377  0.1924248


************************ 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 %

****************************** DETERMINANT *******************************

43.88159

****************************** CRITERION *********************************

3.527179



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     9.700529e-02                NA
max     2.785981e+02                NA
max/min 2.871988e+03                NA


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]
[1,]  1.0000000 -0.3642010  0.5585526
[2,] -0.3642010  1.0000000 -0.5855403
[3,]  0.5585526 -0.5855403  1.0000000



Time difference of 0.02100205 secs
```

1.4.2. Elementary Design ξ_2

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.4.2"


#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"B"

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(1,3,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(1)
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.4.2

Date:  Tue Jan 28 08:26:36 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
       times subjects doses
1 c(1, 3, 8)        1   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Computation of the Bayesian Fisher information matrix

FIM saved in FIM.txt

****************** FISHER INFORMATION MATRIX *****************

            [,1]       [,2]        [,3]
[1,]  0.60331883   1.538575 -0.08983448
[2,]  1.53857495 278.538102  3.84156478
[3,] -0.08983448   3.841565  0.17843498


************************* 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 %

******************************* DETERMINANT *******************************

17.34976
```

```
******************************** CRITERION *********************************

2.588796



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************

        FixedEffects VarianceComponents
min        0.1004813                NA
max      278.5996083                NA
max/min 2772.6525284                NA


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]
[1,]  1.0000000 -0.3321737  0.4065396
[2,] -0.3321737  1.0000000 -0.6046221
[3,]  0.4065396 -0.6046221  1.0000000



Time difference of 0.02000093 secs
```

Comment on results

Comparing examples 1.3 and 1.4, it is noticeable that the evaluation of B-FIM leads to smaller RSE particularly for the parameter ka, which in the evaluation of I-FIM is very high, above all for the second elementary design, reaching the value of 138 %.

Comparing the two elementary designs, for both I-FIM and B-FIM, results are overall better with ξ_1 than with ξ_2,as the variability on ka is kept lower and the criterion is slightly higher. For B-FIM, shrinkage values are provided and they show that with ξ_1 it is obtained more information than with ξ_2.

1.5. Delta Method

Using the delta method available in the R package "car", we can compute the standard error (SE) of any derived parameters.

Here we evaluate the SE of the Clearance (Cl= k*V) for the Population, Individual and Bayesian Fisher Matrix using design ξ_1. We use M_F stored in the `outputFIM` for each of these three cases, or the one directly obtained in R console after running PFIM().

1.5.1. P-FIM

```
setwd("C:\\Users\\Guilia\\Desktop\\ExamplesPFIM4\\EVALUATION\\EXAMPLE
1\\1.1_UserDefMod_1.2.1")

Beta<-c(2,0.25,15) # provided from the stdin.r file in example
#1.1_UserDefMod_1.2.1.
names(Beta) <- c("ka","k","V")

fishmat <- read.table("FIM.txt",sep="")
```

```
colnames(fishmat) <- paste(1:8)

varcov<-solve(fishmat)[1:3,1:3]#we only include the columns of the fix effects

DMcl <- deltaMethod(Beta,"k*V",vcov.=varcov)
> DMcl
      Estimate        SE
k * V     3.75 0.1730348
```

1.5.2. I-FIM

```
directory<-"C:\\Users\\Guilia\\Desktop\\ExamplesPFIM4\\EVALUATION\\EXAMPLE
1\\1.3.1"
directory.program<-"C:\\Users\\Guilia\\Documents\\PFIM4.0\\Program"

result<-PFIM()
fishmat<-result$mfisher
colnames(fishmat) <- paste(1:5)

varcov<-solve(fishmat)[1:3,1:3]
DMcl <- deltaMethod(Beta,"k*V",vcov.=varcov)
> DMcl
      Estimate       SE
k * V     3.75 1.032634
```

1.5.3. B-FIM

```
directory<-"C:\\Users\\Guilia\\Desktop\\ExamplesPFIM4\\EVALUATION\\EXAMPLE
1\\1.4.1"

colnames(fishmat) <- paste(1:3)

varcov<-solve(fishmat)[1:3,1:3]
DMcl <- deltaMethod(Beta,"k*V",vcov.=varcov)
> DMcl
      Estimate        SE
k * V     3.75 0.9110153
```

1.6. Evaluation of FIM with Fixed Parameter

Another new feature of v4.0 is to assume that a parameter is known (fixed) and not estimated.

Here we evaluated Population, Individual and Bayesian Fisher Information Matrix for the design ξ_1 assuming that the parameter k_a is fixed (and has no variability).

1.6.1. P-FIM

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.6.1"


#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"
```

```
#Name of the fixed effects parameters
#-------------------------------------
parameters<-c("ka","k","V")

#Fixed effects parameters values
#-------------------------------
beta<-c(2,0.25,15)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#--------------------------------
beta.fixed<-c(T,F,F)
omega<-diag(c(0,0.25,0.1))
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.6.1

Date:  Mon Jan 27 17:15:03 2014

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

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)      200   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Computation of the Population Fisher information matrix: option =  1

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

           [,1]     [,2]      [,3]       [,4]      [,5]      [,6]
[1,] 8906.33251 50.88726   0.00000    0.00000    0.0000    0.0000
[2,]   50.88726  6.17076   0.00000    0.00000    0.0000    0.0000
[3,]    0.00000  0.00000 774.63632   91.03759  212.6390  298.6706
[4,]    0.00000  0.00000  91.03759 4819.28232  362.6152 1318.2543
[5,]    0.00000  0.00000 212.63905  362.61524 1502.9442 2413.8017
[6,]    0.00000  0.00000 298.67055 1318.25428 2413.8017 6880.7738
```

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

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

   Beta   StdError      RSE
k  0.25 0.01085503 4.342010 %
V 15.00 0.41239269 2.749285 %


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

  omega²   StdError      RSE
k   0.25 0.03667690 14.67076 %
V   0.10 0.01482801 14.82801 %


------------------------ Standard deviation of residual error --------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.03957486  7.914972 %
sig.slopeA  0.15 0.01861316 12.408776 %


******************************** DETERMINANT *********************************

8.000286e+17

******************************** CRITERION ***********************************

963.4982

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      8350.060448           5.879818
max      8906.623447         795.196613
max/min     1.066654         135.241698


****************** CORRELATION MATRIX ******************

           [,1]       [,2]        [,3]        [,4]        [,5]        [,6]
[1,]  1.0000000 -0.2170653  0.00000000  0.00000000  0.00000000  0.00000000
[2,] -0.2170653  1.0000000  0.00000000  0.00000000  0.00000000  0.00000000
[3,]  0.0000000  0.0000000  1.00000000 -0.02729577 -0.15390246  0.03342554
[4,]  0.0000000  0.0000000 -0.02729577  1.00000000  0.06116443 -0.19591071
[5,]  0.0000000  0.0000000 -0.15390246  0.06116443  1.00000000 -0.74204223
[6,]  0.0000000  0.0000000  0.03342554 -0.19591071 -0.74204223  1.00000000


Time difference of 0.02500105 secs
```

Comment on results

Comparing the output of this example with the one in section 1.2.1, we can see that the standard errors are slightly reduced in this example.

1.6.2. I-FIM

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.6.2"

outputFIM<-"FIM.txt";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#---------------------------------------
FIM<-"I"

###### END ANALYTICAL MODEL OPTION ########################
#Name of the fixed effects parameters
#-----------------------------------
parameters<-c("ka","k","V")

#Fixed effects parameters values
#-------------------------------
beta<-c(2,0.25,15)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(T,F,F)
```

OUTPUT FILE

```
PFIM 4.0

Project:  1.6.2

Date:  Mon Jan 27 17:21:44 2014




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

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)        1   100


Variance error model response A : ( 0.5 + 0.15 *f)^2
```

```
Computation of the Individual Fisher information matrix

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX *****************

           [,1]      [,2]     [,3]     [,4]
[1,] 214.546128 3.6213766  0.00000  0.00000
[2,]   3.621377 0.1479803  0.00000  0.00000
[3,]   0.000000 0.0000000 12.85799 21.91468
[4,]   0.000000 0.0000000 21.91468 66.59115


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

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

   Beta   StdError      RSE
k  0.25 0.08911405 35.64562 %
V 15.00 3.39316156 22.62108 %


------------------------ Standard deviation of residual error ----------------------

           Sigma  StdError       RSE
sig.interA  0.50 0.4208513  84.17025 %
sig.slopeA  0.15 0.1849298 123.28655 %


****************************** DETERMINANT ******************************

7006.011

******************************** CRITERION ********************************

9.148875



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min        74.395393         0.08682947
max       214.607279         0.08682947
max/min     2.884685         1.00000000


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]
[1,]  1.0000000 -0.6427045  0.0000000  0.0000000
[2,] -0.6427045  1.0000000  0.0000000  0.
[3,]  0.0000000  0.0000000  1.0000000 -0.74892840000000
[4,]  0.0000000  0.0000000 -0.7489284  1.0000000


Time difference of 0.02300096 secs
```

Comments on the results

As for PFIM, fixing ka resulted in slight improvements of the Relative Standard Errors with respect to the results in section 1.3.1.

1.6.3. B-FIM

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.6.3"


#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"B"



#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(T,F,F)
```

OUPTUT FILE

```
PFIM 4.0

Project:  1.6.3

Date:  Mon Jan 27 17:27:30 2014



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

Analytical function models :

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)
}


Design:
Sample times for response: A
                times subjects doses
1 c(0.33, 1.5, 5, 12)        1   100


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2
```

```
Computation of the Bayesian Fisher information matrix

FIM saved in FIM.txt


****************** FISHER INFORMATION MATRIX ******************

           [,1]      [,2]
[1,] 278.546128 3.6213766
[2,]   3.621377 0.1924248


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

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

   Beta   StdError      RSE   Shrinkage
k  0.25 0.06894209 27.57684 %  30.41928 %
V 15.00 2.62302564 17.48684 %  30.57895 %


****************************** DETERMINANT ********************************

40.48481

****************************** CRITERION **********************************

6.362767









****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min        0.1453187                NA
max      278.5932338                NA
max/min 1917.1190240                NA


****************** CORRELATION MATRIX ******************

           [,1]       [,2]
[1,]  1.0000000 -0.4946462
[2,] -0.4946462  1.0000000


Time difference of 0.02200103 secs
```

2. Example 2: PK and immediate response PD model using the libraries of PK and PD Models (ODE)

The purpose is to evaluate a population design using a PKPD model. The PK model is a one compartment model with an infusion of 1 hour and a Michaelis-Menten elimination. The PD model is an immediate response model with linear drug action and no baseline. The PKPD model is described by a differential equation system using the function create_formED implemented in the file CreateModel_PKPDdesign.r.

The design to be evaluated is composed of one group of 100 subjects with a dose of 100 and sampling times at 0.5, 2, 30, 49, 180 for the PK and 0.5, 2, 14, 110, 150 for the PD.

2.1. Model File

```
source(file.path(directory.program,"CreateModel_PKPDdesign.r"))
create_formED(infusion_1cpt_VVmkm,immed_lin_null,dose=100,TInf=1)
# The differential equation system is created in the file model_created.r
```

2.2. Input File (P-FIM)

```
##############################################################################
##                      INPUT FILE FOR PFIM 4.0                             ##
##############################################################################


#Name of the project
#--------------------
project<-"EXAMPLE 2"

#Name of the file containing the PK or PD model
#-----------------------------------------------
file.model<-"model.R"

#Name of the output file for the results and for the Fisher information matrix
#--------------------------------------
output<-"Stdout.r";
outputFIM<-"";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#---------------------------------------
FIM<-"P"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-------------------------------------------------------
previous.FIM<-""

#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"EVAL"

#To display only  graphs of models and/or sensitivity functions before evaluating
the Fisher Information matrix
graph.only<-F
```

```
#Block diagonal Fisher information matrix (option<-1) or complete Fisher
information matrix (option<-2)
#-------------------------------------------------------
option<-1

#Number of responses
#-----------------------------------------------------------------
nr<-2



################## MODEL OPTION ############################

#Model form: Differential equations (DE) or analytical form (AF)
#-------------------------------------------------------------

modelform<-"DE"
###### DIFFERENTIAL EQUATION OPTION ########################
############################################################

#Initial time for which initial conditions are given
#---------------------------------------------------
time.condinit<-0

#Identical initial conditions in each elementary design (Yes=T, No=F)
#-------------------------------------------------------------
condinit.identical<-T

# If 'Yes', enter once the expression of the initial values of the system at the
initial time
# else, enter the vectors of the initial conditions for each elementary design
# If initial values depend on the parameters to be estimated,
# enter this parameter into the expression without any quotation marks
#-----------------------------------------------------------
condinit<-expression(c(0,0))

# Error tolerance for solving differential equations
#---------------------------------------------------

RtolEQ<-1e-08
AtolEQ<-1e-08
Hmax<-Inf

###### END DIFFERENTIAL EQUATION OPTION ###################################



#Name of the fixed effects parameters
#------------------------------------
parameters<-c("V","Vm","km","Alin")

#Fixed effects parameters values
#-------------------------------
beta<-c(12.2,0.082,0.37,0.1)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(F,F,F)
```

```
#Number of occasions
#-------------------------------------------------------------------------
n_occ<-1

#Random effect model (1) = additive  (2) = exponential
#-----------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#-------------------------------------------------
omega<-diag(c(0.25,0.25,0,0.25))

#Diagonal Matrix of variance for inter-occasion random effects:
#-------------------------------------------------
gamma<-diag(c(0,0,0))

#Standard deviation of residual error (sig.inter+sig.slope*f)^2:
#-----------------------------------------------------------------
sig.interA<-0
sig.slopeA<-0.2

sig.interB<-0.1
sig.slopeB<-0

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5, 2, 30, 49, 180))
protB<-list(c(0.5, 2, 14, 110, 150))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(100)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1

#If 'proportions of subjects' give the total number of samples
#-------------------------------------------------------------
#Ntot<-40
############### GRAPH SPECIFICATION OPTION ###############

#graphical representation (Yes=T, No=F)
#-------------------------------------
graph.logical<-T

#Vector of Names on Y axes for each response
#----------------------------------
names.datax<-c("Time","Time")

#Vector of Names on Y axes for each response
#----------------------------------
names.datay<-c("Concentration","Effet")

#Controls logarithmic axes for the graphical representation.
#Values "xy", "x", or "y" produce log-log or log-x or log-y axes.
```

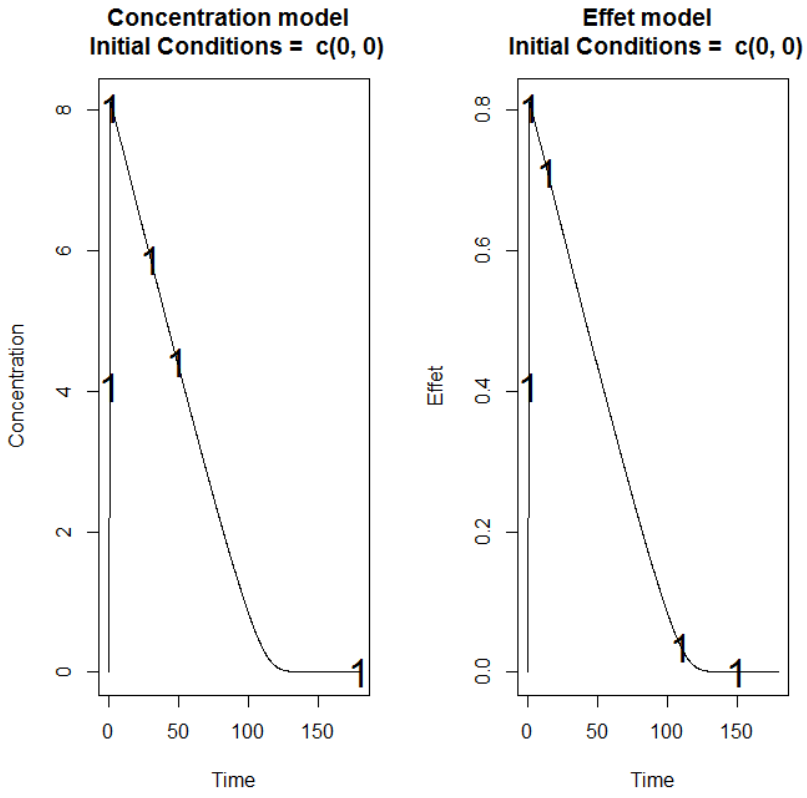
```
#(For standard graphic, log.logical<-F)
#---------------------------------------------------------------
#log.logical<-'y'
log.logical<-F

#Vector of lower and upper sampling times for the graphical representation
#-------------------------------------------------------------------------
graph.infA<-c(0)
graph.supA<-c(180)
graph.infB<-c(0)
graph.supB<-c(180)

#Vector of lower and upper concentration for the graphical representation
#-----------------------------------------------------------------------
y.rangeA<-NULL # default range
#y.range<-c(0,10)

############## END OF GRAPH SPECIFICATION OPTION ###############
```

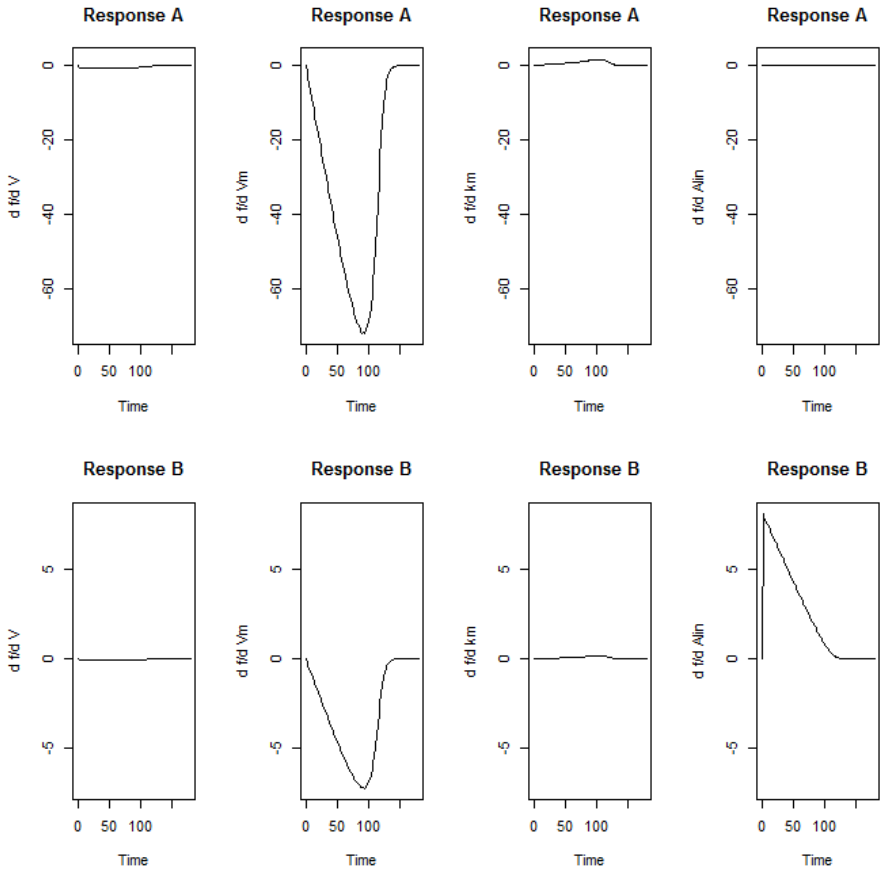
2.3. Output File

```
PFIM 4.0

Project:  EXAMPLE 2

Date:  Fri Mar 21 15:57:00 2014



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

Differential Equations form of the model:

function(t,y,p){
V<-p[1]
Vm<-p[2]
km<-p[3]
Alin<-p[4]
pk<-y[1:1]
pd<-y[2:2]
conc<-y[1]
if(t<=1){
dpk1<-(100/(1*V))+(-Vm)*pk[1]/(km+pk[1])}
else{
dpk1<-(-Vm)*pk[1]/(km+pk[1])}
dpd1<-0
pdIm<-Alin*conc
return(list(c(dpk1,dpd1),c(pk[1],pdIm)))
}


Design:
Sample times for response: A
                    times subjects
1 c(0.5, 2, 30, 49, 180)      100


Sample times for response: B
                     times subjects
1 c(0.5, 2, 14, 110, 150)      100
```

```
Initial Conditions at time 0 :

0 0

Random effect model: Trand =  2

Variance error model response A : ( 0 + 0.2 *f)^2
Variance error model response B : ( 0.1 + 0 *f)^2


Error tolerance for solving differential equations system: RtolEQ = 1e-08 , AtolEQ
= 1e-08 , Hmax =  Inf

Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX ******************

           [,1]        [,2]       [,3]         [,4]        [,5]       [,6]         [,7]        [,8]         [,9]
 [1,]   2.6770341    9.444202   -57.39048    -0.7254162 0.000000e+00   0.0000000 0.000000e+00 0.000000e+00     0.000000
 [2,]   9.4442023 50919.213161  7982.73905   657.4076389 0.000000e+00   0.0000000 0.000000e+00 0.000000e+00     0.000000
 [3,] -57.3904833  7982.739050 33057.82792 -6714.1078293 0.000000e+00   0.0000000 0.000000e+00 0.000000e+00     0.000000
 [4,]  -0.7254162   657.407639 -6714.10783 38772.8151987 0.000000e+00   0.0000000 0.000000e+00 0.000000e+00     0.000000
 [5,]   0.0000000     0.000000     0.00000     0.0000000 7.938111e+02   0.4463216 3.916193e-03 2.546794e+00     8.097541
 [6,]   0.0000000     0.000000     0.00000     0.0000000 4.463216e-01 586.1230244 1.453005e-01 9.449987e+01   301.234913
 [7,]   0.0000000     0.000000     0.00000     0.0000000 3.916193e-03   0.1453005 7.516656e+02 8.332548e-01   116.540931
 [8,]   0.0000000     0.000000     0.00000     0.0000000 2.546794e+00  94.4998735 8.332548e-01 1.725786e+04  1714.876645
 [9,]   0.0000000     0.000000     0.00000     0.0000000 8.097541e+00 301.2349133 1.165409e+02 1.714877e+03 64572.948196


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

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

       Beta    StdError      RSE
V    12.200 0.624822332 5.121495 %
Vm    0.082 0.004534793 5.530235 %
km    0.370 0.005841524 1.578790 %
Alin  0.100 0.005182493 5.182493 %


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

     omega²   StdError      RSE
V      0.25 0.03549293 14.19717 %
Vm     0.25 0.04137028 16.54811 %
Alin   0.25 0.03647948 14.59179 %


------------------------ Standard deviation of residual error ---------------------

           Sigma    StdError      RSE
sig.slopeA   0.2 0.007625037 3.812519 %
sig.interB   0.1 0.003945487 3.945487 %


****************************** DETERMINANT *******************************

5.994606e+31

******************************** CRITERION *********************************

3395.176
```

```
 ******************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************

        FixedEffects VarianceComponents
min      26521.376944           2.561446
max      64636.681018       17196.209993
max/min      2.437154        6713.478513


******************** CORRELATION MATRIX ******************

            [,1]        [,2]       [,3]        [,4]          [,5]          [,6]          [,7]          [,8]         [,9]
 [1,]  1.00000000 -0.06785010  0.2062542  0.04352023  0.000000e+00  0.0000000000  0.000000e+00  0.0000000000  0.000000000
 [2,] -0.06785010  1.00000000 -0.2101514 -0.05600795  0.000000e+00  0.0000000000  0.000000e+00  0.0000000000  0.000000000
 [3,]  0.20625422 -0.21015142  1.0000000  0.19876898  0.000000e+00  0.0000000000  0.000000e+00  0.0000000000  0.000000000
 [4,]  0.04352023 -0.05600795  0.1987690  1.00000000  0.000000e+00  0.0000000000  0.000000e+00  0.0000000000  0.000000000
 [5,]  0.00000000  0.00000000  0.0000000  0.00000000  1.000000e+00 -0.0005826757  1.311462e-05 -0.0006146867 -0.001068259
 [6,]  0.00000000  0.00000000  0.0000000  0.00000000 -5.826757e-04  1.0000000000  5.840399e-04 -0.0272653545 -0.047524772
 [7,]  0.00000000  0.00000000  0.0000000  0.00000000  1.311462e-05  0.0005840399  1.000000e+00  0.0006127203 -0.016746938
 [8,]  0.00000000  0.00000000  0.0000000  0.00000000 -6.146867e-04 -0.0272653545  6.127203e-04  1.0000000000 -0.050000216
 [9,]  0.00000000  0.00000000  0.0000000  0.00000000 -1.068259e-03 -0.0475247719 -1.674694e-02 -0.0500002164  1.000000000


Time difference of 3.551203 secs
```





3. Example 3: PK model with inter-occasion variability

The purpose of this example is to evaluate a design for a PK model including inter-occasion variability. The PK model is a one compartment oral model with first order absorption and first order elimination. The inter-occasion variability was 15% for the three parameters. The design to be evaluated is composed of one group of 40 subjects with a dose of 30 and sampling times at 0.5, 2, 4, 8.

3.1. Model File

```
source(file.path(directory.program,"LibraryPK.r"))

formA<-oral1_1cpt_kaVCl()[[1]]

form<-c(formA)
```

3.2. Input File (P-FIM)

```
########################################################################
##                  INPUT FILE FOR PFIM 4.0                           ##
########################################################################


#Name of the project
#--------------------
```

```
project<-"EXAMPLE 3"

#Name of the file containing the PK or PD model
#----------------------------------------
file.model<-"model.R"

#Name of the output file for the results and for the Fisher information matrix
#-------------------------------------
output<-"Stdout.r";
outputFIM<-"";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-----------------------------------------------------
previous.FIM<-""

#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"EVAL"

#To display only  graphs of models and/or sensitivity functions before evaluating
the Fisher Information matrix
graph.only<-F

#Block diagonal Fisher information matrix (option<-1) or complete Fisher
information matrix (option<-2)
#-----------------------------------------------------
option<-1

#Number of responses
#-----------------------------------------------------------------
nr<-1



################## MODEL OPTION ##########################

#Model form: Differential equations (DE) or analytical form (AF)
#-----------------------------------------------------------

modelform<-"AF"

###### ANALYTICAL MODEL OPTION ############################
##########################################################

#Identical dose in each elementary design (Yes=T, No=F)
#-----------------------------------------------------------
dose.identical<-T

# If 'Yes', enter the value of the dose,
# else, enter the vector of the dose values for each elementary design
#-----------------------------------------------------------------
dose<-c(30)
#Vector of the times intervals of each expression
```

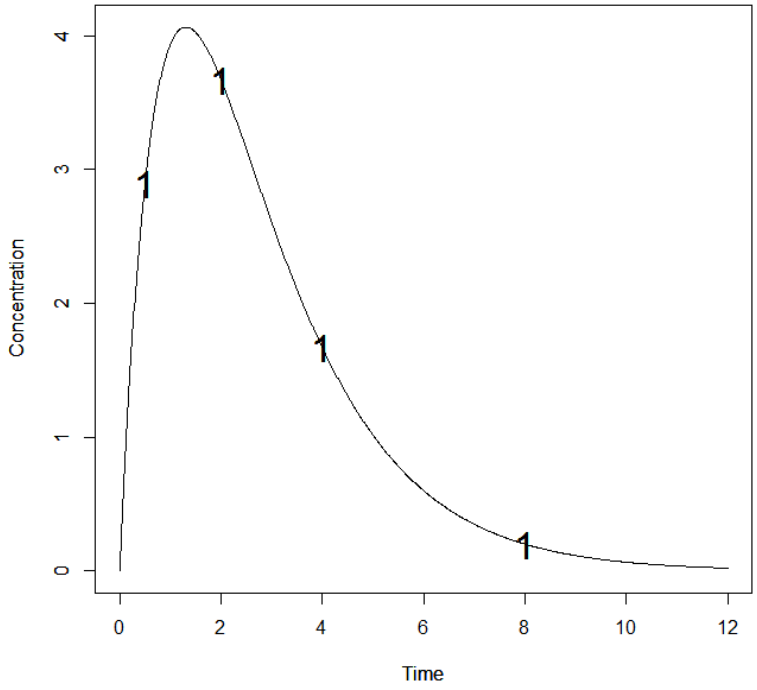
```
#-----------------------------------------------------------
boundA<-list(c(0,Inf))

#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-----------------------------------------------------------
NUM<-F
###### END ANALYTICAL MODEL OPTION ########################
#Name of the fixed effects parameters
#-----------------------------------
parameters<-c("ka","V","Cl")

#Fixed effects parameters values
#-------------------------------
beta<-c(1,3.5,2)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(F,F,F)

#Number of occasions
#-------------------------------------------------------------------------
n_occ<-2

#Random effect model (1) = additive  (2) = exponential
#-----------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#-----------------------------------------------------
omega<-diag(c(0.09,0.09,0.09))

#Diagonal Matrix of variance for inter-occasion random effects:
#-----------------------------------------------------
gamma<-diag(c(0.0225,0.0225,0.0225))

#Standard deviation of residual error (sig.inter+sig.slope*f)^2:
#-----------------------------------------------------------------
sig.interA<-0.1
sig.slopeA<-0

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5,2,4,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-----------------------------------------------------------
subjects<-c(40)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1
#If 'proportions of subjects' give the total number of samples
#-------------------------------------------------------------
#Ntot<-40
```

3.3. Output File

```
PFIM 4.0

Project:  EXAMPLE 3

Date:  Tue Jan 28 11:40:35 2014



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

Analytical function models :

dose/V * ka/(ka - (Cl/V)) * (exp(-(Cl/V) * t) - exp(-ka * t))

Design:
Sample times for response: A
            times subjects doses
1 c(0.5, 2, 4, 8)       40    30


Number of occasions: 2

Random effect model: Trand =  2

Variance error model response A : ( 0.1 + 0 *f)^2



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

            [,1]        [,2]       [,3]         [,4]         [,5]         [,6]
 [1,] 326.376227 -15.9864218  3.8839055    0.0000000    0.0000000    0.0000000
 [2,] -15.986422  28.3366743  0.9574449    0.0000000    0.0000000    0.0000000
 [3,]   3.883905   0.9574449 98.1347183    0.0000000    0.0000000    0.0000000
 [4,]   0.000000   0.0000000  0.0000000 1331.5180159   39.1334952    0.7542361
 [5,]   0.000000   0.0000000  0.0000000   39.1334952 1506.1906549    0.5614793
 [6,]   0.000000   0.0000000  0.0000000    0.7542361    0.5614793 1926.0845868
 [7,]   0.000000   0.0000000  0.0000000  665.7590079   19.5667476    0.3771180
 [8,]   0.000000   0.0000000  0.0000000   19.5667476  753.0953275    0.2807396
 [9,]   0.000000   0.0000000  0.0000000    0.3771180    0.2807396  963.0422934
[10,]   0.000000   0.0000000  0.0000000  486.6656278  340.8242080   22.4031198
              [,7]         [,8]         [,9]       [,10]
 [1,]     0.000000 0.000000e+00 0.000000e+00     0.00000
 [2,]     0.000000 0.000000e+00 0.000000e+00     0.00000
 [3,]     0.000000 0.000000e+00 0.000000e+00     0.00000
 [4,]   665.759008 1.956675e+01 3.771180e-01   486.66563
 [5,]    19.566748 7.530953e+02 2.807396e-01   340.82421
 [6,]     0.377118 2.807396e-01 9.630423e+02    22.40312
 [7,] 11180.419592 5.410321e+03 9.653853e+01  2203.93606
 [8,]  5410.320690 1.766938e+04 8.459735e+01  1682.30579
 [9,]    96.538535 8.459735e+01 3.679038e+04   634.05703
[10,]  2203.936057 1.682306e+03 6.340570e+02 21694.43805


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

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

   Beta   StdError      RSE
ka  1.0 0.05615162 5.615162 %
V   3.5 0.19055327 5.444379 %
Cl  2.0 0.10099429 5.049714 %


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

   omega²   StdError      RSE
ka   0.09 0.02797418 31.08242 %
V    0.09 0.02614241 29.04712 %
Cl   0.09 0.02293631 25.48479 %


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

   gamma²    StdError      RSE
ka 0.0225 0.010507710 46.70093 %
V  0.0225 0.008278751 36.79445 %
Cl 0.0225 0.005249319 23.33031 %


------------------------ Standard deviation of residual error ---------------------

           Sigma    StdError      RSE
sig.interA   0.1 0.006890589 6.890589 %


****************************** DETERMINANT *******************************

4.122587e+32

****************************** CRITERION *********************************

1826.068



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     18665.494014           27.46247
max     36847.167079         8088.68560
max/min     1.974079          294.53599


****************** CORRELATION MATRIX ******************

             [,1]        [,2]        [,3]          [,4]          [,5]
 [1,]  1.00000000  0.16669388 -0.02507303  0.0000000000  0.0000000000
 [2,]  0.16669388  1.00000000 -0.02207619  0.0000000000  0.0000000000
 [3,] -0.02507303 -0.02207619  1.00000000  0.0000000000  0.0000000000
 [4,]  0.00000000  0.00000000  0.00000000  1.0000000000 -0.0347716680
 [5,]  0.00000000  0.00000000  0.00000000 -0.0347716680  1.0000000000
 [6,]  0.00000000  0.00000000  0.00000000 -0.0004678731 -0.0002900774
 [7,]  0.00000000  0.00000000  0.00000000 -0.1783934889  0.0676233782
```

```
 [8,]  0.00000000  0.00000000  0.00000000  0.0756870609 -0.1565953140
 [9,]  0.00000000  0.00000000  0.00000000  0.0022115605  0.0013941467
[10,]  0.00000000  0.00000000  0.00000000 -0.0684619703 -0.0523532439
                [,6]           [,7]           [,8]           [,9]          [,10]
 [1,]  0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
 [2,]  0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
 [3,]  0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
 [4,] -0.0004678731 -0.1783934889  0.0756870609  0.0022115605 -0.0684619703
 [5,] -0.0002900774  0.0676233782 -0.1565953140  0.0013941467 -0.0523532439
 [6,]  1.0000000000  0.0005358684  0.0002096836 -0.1143575380 -0.0009338365
 [7,]  0.0005358684  1.0000000000 -0.3886303379 -0.0014888252 -0.1064630705
 [8,]  0.0002096836 -0.3886303379  1.0000000000 -0.0009173038 -0.0305013497
 [9,] -0.1143575380 -0.0014888252 -0.0009173038  1.0000000000 -0.0218405019
[10,] -0.0009338365 -0.1064630705 -0.0305013497 -0.0218405019  1.0000000000

Time difference of 0.04000306 secs
```



4. Example 4: PK model with inter-occasion variability and covariate effects (Equivalence test)

The purpose of this example is to evaluate a design for a crossover PK trial with two periods, two sequences: 20 subjects receive treatment A at period 1 then treatment B at period 2; 20 subjects receive treatment B at period 1 then treatment A at period 2. The PK model is a one compartment oral model with first order absorption and first order elimination. We add a gender effect which does not change with the occasion on the volume of distribution (V) and a treatment effect changing with the occasion on the clearance (Cl). The dose is fixed to 30 for the 40 subjects with the same sampling times at 0.5, 2, 6 and 8. With alpha=0.05, we then compute the expected power of the Wald test for

equivalence on the interval [ln(0.8) and ln(1.25)] and the number of subjects needed for a given power of 0.9.

4.1. Model File

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

4.2. Input File (P-FIM)

```
#####################################################################
##                  INPUT FILE FOR PFIM 4.0                        ##
#####################################################################


#Name of the project
#--------------------
project<-"EXAMPLE 4"

#Name of the file containing the PK or PD model
#-----------------------------------------
file.model<-"model.R"

#Name of the output file for the results and for the Fisher information matrix
#-------------------------------------
output<-"Stdout.r";
outputFIM<-"";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-----------------------------------------------------
previous.FIM<-""

#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"EVAL"

#To display only  graphs of models and/or sensitivity functions before evaluating
the Fisher Information matrix
graph.only<-F

#Block diagonal Fisher information matrix (option<-1) or complete Fisher
information matrix (option<-2)
#-----------------------------------------------------
option<-1

#Number of responses
#-------------------------------------------------------------------
nr<-1
```

```
################### MODEL OPTION ############################

#Model form: Differential equations (DE) or analytical form (AF)
#-------------------------------------------------------------

modelform<-"AF"

###### ANALYTICAL MODEL OPTION ############################
############################################################

#Identical dose in each elementary design (Yes=T, No=F)
#-----------------------------------------------------------
dose.identical<-T

# If 'Yes', enter the value of the dose,
# else, enter the vector of the dose values for each elementary design
#-------------------------------------------------------------------
dose<-c(30)

#Vector of the times intervals of each expression
#-----------------------------------------------------------
boundA<-list(c(0,Inf))

#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-----------------------------------------------------------
NUM<-T

###### END ANALYTICAL MODEL OPTION ########################
#Name of the fixed effects parameters
#-------------------------------------
parameters<-c("ka","V","Cl")

#Fixed effects parameters values
#-------------------------------
beta<-c(1,3.5,2)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#--------------------------------
beta.fixed<-c(F,F,F)

#Number of occasions
#-----------------------------------------------------------------------------
n_occ<-2

#Random effect model (1) = additive  (2) = exponential
#-------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#-------------------------------------------------
omega<-diag(c(0.09,0.09,0.09))

#Diagonal Matrix of variance for inter-occasion random effects:
#-------------------------------------------------
gamma<-diag(c(0.0225,0.0225,0.0225))
```

```
#Standard deviation of residual error (sig.inter+sig.slope*f)^2:
#-----------------------------------------------------------------
sig.interA<-0.1
sig.slopeA<-0


#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5,2,4,6,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(40)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-------------------------------------------------------------------------
subjects.input<-1

#If 'proportions of subjects' give the total number of samples
#-------------------------------------------------------------
#Ntot<-40




#####################################################################
#                                                                   #
#                        Covariate model                            #
#                                                                   #
#####################################################################

########################################
# Covariates not changing with occasion  #
########################################

#Add covariate to the model  (Yes==T No==F)
#-----------------------------------------------------------------------------
covariate.model<-T

#Vector of covariates
#--------------------------------------------------------------------
covariate.name<-list(c("Sex"))

#Categories for each covariate (the first category is the reference)
#-------------------------------------------------------------------------
covariate.category<-list(Sex=c("M","F"))

#Proportions of subjects in each category
#----------------------------------------------------------------------
covariate.proportions<-list(Sex=c(0.5,0.5))

#Parameter(s) associated with each covariate
#-------------------------------------------------------------------
parameter.associated<-list(Sex=c("V"))

# Values of covariate parameters in covariate model
```

```
# (values of parameters for all other categories than the reference category (for
which beta=0)
# covariate is additive on parameter if additive random effect model (Trand=1)
# covariate is additive on log parameters if exponential random effect model
(Trand=2)
#------------------------------------------------------------------
beta.covariate<-list(Sex=list(c(log(1.2))))



####################################
#Covariates changing with occasion  #
####################################


#Add covariate to the model   (Yes==T No==F)
#-------------------------------------------------------------------------
covariate_occ.model<-T

#Vector of covariates depending on the occasion
#-------------------------------------------------------------------
covariate_occ.name<-list(  c("Treat") )

#Categories for each covariate (the first category is the reference)
#-------------------------------------------------------------------
covariate_occ.category<-list(  Treat=c("A","B") )

#Sequences of values of covariates at each occasion
#Specify as many values in each sequence as number of occasions (n_occ) for each
covariate
#-----------------------------------------------------------------------------------

covariate_occ.sequence<-list(  Treat=list(c("A","B"),c("B","A"))  )

#Proportions of elementary designs corresponding to each sequence of covariate
values
#Specify as many values of proportion as number of sequences defined in
covariate_occ.sequence for each covariate
#-----------------------------------------------------------------------------------
-------------------------------
covariate_occ.proportions<-list(  Treat=c(0.5,0.5)  )

#Parameter(s) associated with each covariate
#-------------------------------------------------------------------
parameter_occ.associated<-list(  Treat=c("Cl")  )

# Values of covariate parameters in covariate model
# (values of parameters for all other categories than the reference category (for
which beta=0)
# covariate is additive on parameter if additive random effect model (Trand=1)
# covariate is additive on log parameters if exponential random effect model
(Trand=2)
#------------------------------------------------------------------
beta.covariate_occ<-list(  Treat=list(c(log(1.1)))  )

#Type one error alpha
#-------------------------------------------------------------------------
alpha<-0.05
```

```
#Compute expected power for comparison test (Yes=T, No=F)
#-------------------------------------------------------------------------
compute.power<-F

#Compute the number of subjects needed for a given power for comparison test(Yes=T,
No=F)
#-------------------------------------------------------------------------
compute.nni<-F

#Equivalence interval
interval_eq<-c(log(0.8),log(1.25))

#Compute expected power for equivalence test (Yes=T, No=F)
#-------------------------------------------------------------------------
compute.power_eq<-T

#Compute the number of subjects needed for a given power for equivalence test
(Yes=T, No=F)
#-------------------------------------------------------------------------
compute.nni_eq<-T

#Set value the given power
#-------------------------------------------------------------------------
given.power<-0.9
```

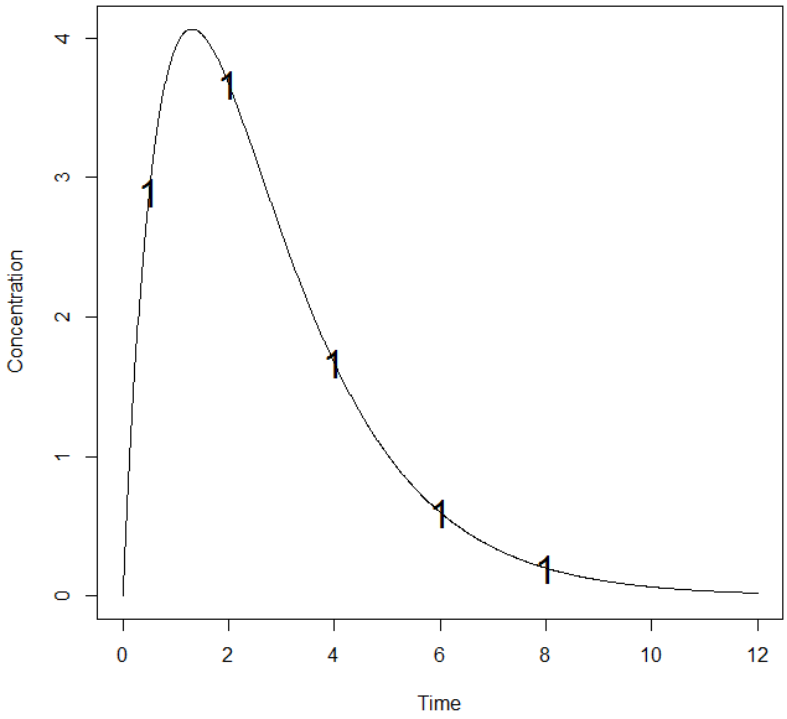
4.3. Output File

```
PFIM 4.0

Project:  EXAMPLE 4

Date:  Tue Jan 28 11:59:42 2014



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

Analytical function models :

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


Design:
Sample times for response: A
              times subjects doses
1 c(0.5, 2, 4, 6, 8)       40    30


Number of occasions: 2

Random effect model: Trand =  2

Variance error model response A : ( 0.1 + 0 *f)^2
```

```
 Covariate model :

      NB: Covariates are additive on log parameters

      Covariates not changing with occasion

      Covariate 1 : Sex ( V )
    Categories References Proportions
(1)          M          *         0.5
(2)          F                    0.5


      Covariates changing with occasion

      Covariate  1 : Treat ( Cl )
    Categories References
(1)          A          *
(2)          B


    Sequences Proportions
(1)       A B         0.5
(2)       B A         0.5




Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

                                                 s2
   339.888866 -12.1244029  2.2403232 -17.9762700   1.8294873    0.0000000
   -12.124403  29.3831440  0.5085979  52.3319426   0.4561115    0.0000000
     2.240323   0.5085979 98.2790307   0.8587853  98.1435338    0.0000000
s2 -17.976270  52.3319426  0.8587853 183.1617993   0.8270805    0.0000000
     1.829487   0.4561115 98.1435338   0.8270805 953.4932901    0.0000000
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000 1444.4800034
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000   23.0348957
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000    0.2509671
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000  736.6832299
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000   34.0127520
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000   32.8694695
     0.000000   0.0000000  0.0000000   0.0000000   0.0000000  423.7018814

      0.000000    0.0000000 0.000000e+00 0.000000e+00     0.00000     0.00000
      0.000000    0.0000000 0.000000e+00 0.000000e+00     0.00000     0.00000
      0.000000    0.0000000 0.000000e+00 0.000000e+00     0.00000     0.00000
s2    0.000000    0.0000000 0.000000e+00 0.000000e+00     0.00000     0.00000
      0.000000    0.0000000 0.000000e+00 0.000000e+00     0.00000     0.00000
     23.034896    0.2509671 7.366832e+02 3.401275e+01    32.86947   423.70188
   1620.000487    0.1586320 2.250149e+01 8.207294e+02    33.13093   269.48022
      0.158632 1931.7539827 1.103168e-01 4.364955e-01   966.47638    18.52264
     22.501490    0.1103168 1.214320e+04 4.704703e+03   189.35871  2594.79722
    820.729393    0.4364955 4.704703e+03 2.268081e+04   281.84596  2441.16633
     33.130931  966.4763757 1.893587e+02 2.818460e+02 39310.95582  1152.57041
    269.480223   18.5226438 2.594797e+03 2.441166e+03  1152.57041 36667.05676
```

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

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

                     Beta   StdError       RSE
ka              1.00000000 0.05466202  5.466202 %
V               3.50000000 0.26457492  7.559283 %
Cl              2.00000000 0.10650676  5.325338 %
beta_V_Sex_F    0.18232156 0.10545703 57.841231 %
beta_Cl_Treat_B 0.09531018 0.03418960 35.871924 %


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

   omega²   StdError      RSE
ka   0.09 0.02678397 29.75997 %
V    0.09 0.02510621 27.89579 %
Cl   0.09 0.02289350 25.43722 %


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

   gamma²    StdError      RSE
ka 0.0225 0.009674645 42.99842 %
V  0.0225 0.007009914 31.15517 %
Cl 0.0225 0.005077443 22.56641 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError     RSE
sig.interA   0.1 0.00527779 5.27779 %


****************************** DETERMINANT *******************************

1.124604e+38

****************************** CRITERION *********************************

1482.234




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

                     Beta       90 % CI   exp(Beta)       90 % CI
beta_V_Sex_F    0.18232156 [0.009;0.356]         1.2 [1.009;1.427]
beta_Cl_Treat_B 0.09531018 [0.039;0.152]         1.1  [1.04;1.164]


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_V_Sex_F         0.1042397                2286.08074
beta_Cl_Treat_B      0.9818745                  24.50351
```

```
****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min       1906.77601           13.14078
max      39940.96957        10311.16801
max/min     20.94686          784.66932


****************** CORRELATION MATRIX ******************

                                                        s2
    1.0000000000  0.1001424653 -0.0130648058 -0.0208510685  0.0008066425
    0.1001424653  1.0000000000 -0.0080189689 -0.7116799991  0.0004664293
   -0.0130648058 -0.0080189689  1.0000000000  0.0008174403 -0.3205794817
s2 -0.0208510685 -0.7116799991  0.0008174403  1.0000000000 -0.0002392205
    0.0008066425  0.0004664293 -0.3205794817 -0.0002392205  1.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000

    0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
s2  0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
    1.0000000000 -0.0200347674  0.0001617218 -0.177542015  0.0509009583
   -0.0200347674  1.0000000000  0.0002346615  0.040695390 -0.1389520685
    0.0001617218  0.0002346615  1.0000000000  0.000553334  0.0006633813
   -0.1775420153  0.0406953900  0.0005533340  1.000000000 -0.2827635331
    0.0509009583 -0.1389520685  0.0006633813 -0.282763533  1.0000000000
   -0.0020201992 -0.0022890742 -0.1108965657 -0.002912419 -0.0055072134
   -0.0393506869 -0.0267091218  0.0010141798 -0.095641750 -0.0497080067

    0.000000000  0.00000000
    0.000000000  0.00000000
    0.000000000  0.00000000
s2  0.000000000  0.00000000
    0.000000000  0.00000000
   -0.002020199 -0.03935069
   -0.002289074 -0.02670912
   -0.110896566  0.00101418
   -0.002912419 -0.09564175
   -0.005507213 -0.04970801
    1.000000000 -0.02893390
   -0.028933901  1.00000000



Time difference of 0.09300518 secs
```


Concentration
Time
0
1
2
3
4
0
2
4
6
8
10
12
1
1
1
1
1

OPTIMISATION

We illustrate optimisation algorithms with the same examples used in the Evaluation section. As for Evaluation, Example 1 is more detailed with all the new features. For Example 2, 3 and 4, optimisation was performed only with Federow-Wynn (FW) algorithm. We therefore paste in the INPUT FILE only the part concerning optimisation.

1. Example 1: PK Model

1.1. Population Fisher Information Matrix (P-FIM)

Optimize a design for 200 subjects with a dose of 100.

1.1.1. Simplex algorithm

- Initial sampling times vector: $\xi_1 = (0.33, 1.5, 5, 12)$
- Time interval for the optimisation: (0,12)

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.1.1"
#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#----------------------------------------------------
run<-"OPT"

############ONLY FOR OPTIMISATION ###############################

#Identical sampling times for each response
# (only if you do not have sampling times==NULL)
#-------------------------------------------------------------------------------
identical.times<-F

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-----------------------------------------

algo.option<-"SIMP"


########################
#SIMPLEX SPECIFICATION #
########################

#Optimisation of the proportions of subjects: (Yes=T, No=F)
#-----------------------------------------------------------

subjects.opt<-T

#Vector of lower and upper admissible sampling times
#---------------------------------------------------
```

```
lowerA<-c(0)
upperA<-c(12)

#Minimum delay between two sampling times
#-----------------------------------------

delta.time<-0

#Print iteration step (Yes=T, No=F)
#---------------------------------

iter.print<-T


#Parameter for initial simplex building (%)
#-----------------------------------------

simplex.parameter<-20


#Maximum iteration number
#-----------------------

Max.iter<-5000


#Relative convergence tolerance
#-----------------------------
Rctol<-1e-6
```

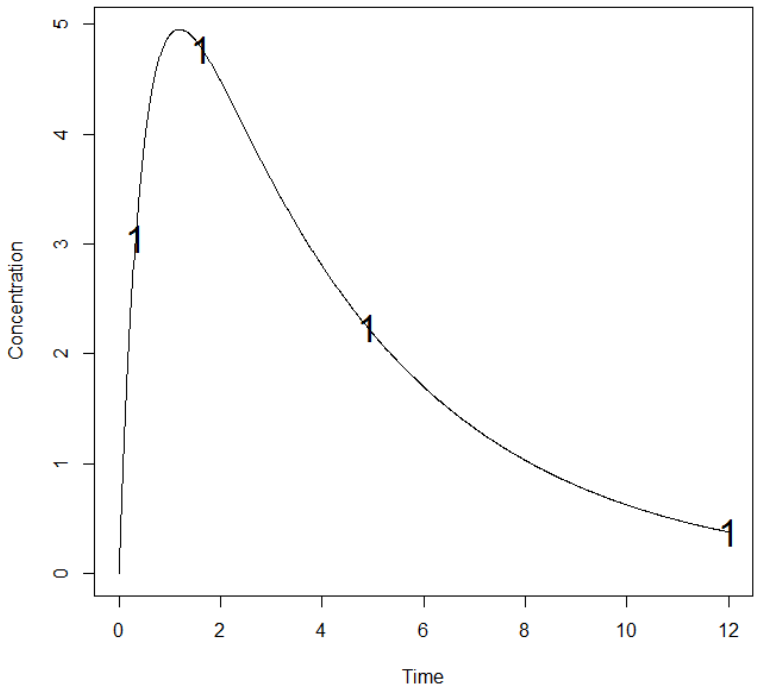
OUTPUT FILE

```
PFIM 4.0

Option 1

Project: 1.1.1

Date: Wed Apr 02 11:28:22 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
                times subjects.prop doses
```

```
1 c(0.33, 1.5, 5, 12)           200   100



Total number of samples (nr responses): 800

Associated criterion value: 361.7144


Window of the allowed optimised sampling times:

Upper and lower admissible samples times for the response A : [ 0 : 12 ]


Minimum delay between two sampling times: 0

Optimisation of the proportions of subjects: TRUE


Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


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

Number of iterations: 80
Number of function evaluations: 105
Convergence Achieved


Design:


Sample times for response: A
                     times subjects.prop subjects
1 c(0.325, 1.632, 4.9, 12)             1      200



Associated optimised criterion: 362.4325


Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX ******************

          [,1]       [,2]      [,3]      [,4]       [,5]       [,6]       [,7]
[1,] 38.769206   82.24941 -3.519151  0.000000   0.000000    0.00000    0.00000
[2,] 82.249405 8247.39675 79.157847  0.000000   0.000000    0.00000    0.00000
[3,] -3.519151   79.15785  5.006781  0.000000   0.000000    0.00000    0.00000
[4,]  0.000000    0.00000  0.000000 60.122052   4.228103   27.86495   28.36476
[5,]  0.000000    0.00000  0.000000  4.228103 664.253448  220.28782  194.26206
```

```
[6,]  0.000000    0.00000  0.000000 27.864947 220.287825 3172.65027  302.74176
[7,]  0.000000    0.00000  0.000000 28.364762 194.262062  302.74176 1200.08551
[8,]  0.000000    0.00000  0.000000 86.421975 224.605138 1165.00625 1538.20498
           [,8]
[1,]    0.00000
[2,]    0.00000
[3,]    0.00000
[4,]   86.42197
[5,]  224.60514
[6,] 1165.00625
[7,] 1538.20498
[8,] 4050.28122




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

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

    Beta   StdError      RSE
ka  2.00 0.17257305 8.628652 %
k   0.25 0.01243021 4.972085 %
V  15.00 0.51585801 3.439053 %


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

   omega2   StdError      RSE
ka   1.00 0.13103070 13.10307 %
k    0.25 0.04013111 16.05244 %
V    0.10 0.01905418 19.05418 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04125377  8.250754 %
sig.slopeA  0.15 0.02329525 15.530170 %


****************************** DETERMINANT ******************************

2.977264e+20

******************************** CRITERION ********************************

362.4325



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      2543.534911           3.704497
max      8248.980105         691.463321
max/min     3.243117         186.655122
```

```
****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]          [,4]          [,5]         [,6]
[1,]  1.0000000 -0.2736378  0.3393837  0.0000000000  0.0000000000  0.000000000
[2,] -0.2736378  1.0000000 -0.4453064  0.0000000000  0.0000000000  0.000000000
[3,]  0.3393837 -0.4453064  1.0000000  0.0000000000  0.0000000000  0.000000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000000 -0.0005031654 -0.004823983
[5,]  0.0000000  0.0000000  0.0000000 -0.0005031654  1.0000000000 -0.135409227
[6,]  0.0000000  0.0000000  0.0000000 -0.0048239829 -0.1354092271  1.000000000
[7,]  0.0000000  0.0000000  0.0000000  0.0225623149 -0.1862954540  0.127956169
[8,]  0.0000000  0.0000000  0.0000000 -0.1340088049  0.0616794121 -0.307811878
           [,7]        [,8]
[1,]  0.00000000  0.00000000
[2,]  0.00000000  0.00000000
[3,]  0.00000000  0.00000000
[4,]  0.02256231 -0.13400880
[5,] -0.18629545  0.06167941
[6,]  0.12795617 -0.30781188
[7,]  1.00000000 -0.68756593
[8,] -0.68756593  1.00000000

Time difference of 0.6150351 secs
sys.self
    0.03
```



Comment on results

The criterion associated with the initial times (ξ_1) was 361.7.

When optimizing with Simplex algorithm, the criterion associated to the optimal times (0.325, 1.632, 4.9, 12) improved of about 1 point, (362.4).

1.1.2. Fedorov-Wynn algorithm

- Allowed sampling times: 0.33,1,1.5,3,5,8,12
- Maximum total number of points in one elementary protocol: 4

Compare the result with the one obtained with Simplex algorithm.

INPUT FILE

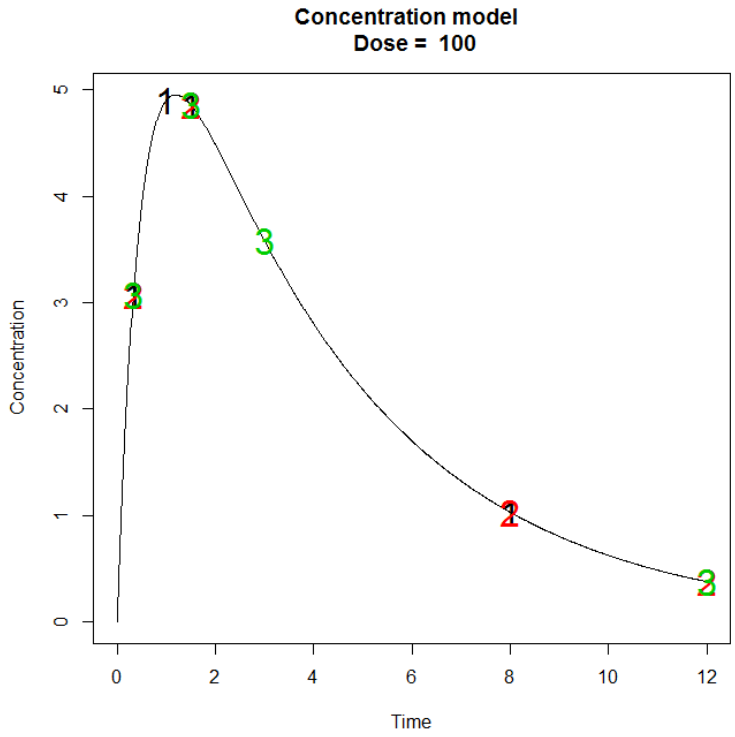
```
#Name of the project
#--------------------
project<-"1.1.2"

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.33,1.5,5,12))

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#----------------------------------------

algo.option<-"FW"
############################
#FEDOROV-WYNN SPECIFICATION #
############################

#Number of sampling windows
#--------------------------
nwindA<-1

#List of vector of the allowed sampling times for each sampling window
#---------------------------------------------------------------------

sampwinA<-list(c(0.33,1,1.5,3,5,8,12))

#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#---------------------------------------------------------------------
fixed.timesA<-c()

#List of vector of allowed number of points to be taken from each sampling window
#--------------------------------------------------------------------------------

nsampA<-list(c(4))

#Maximum total number of sampling times per subject
#--------------------------------------------------

nmaxptsA<-4

#Minimum total number of sampling times per subject
#--------------------------------------------------

nminptsA<-4
############# END OF OPTIMISATION ALGORITHM OPTION ###############
```

OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.1.2

Date: Tue Jan 28 13:56:35 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)      200   100


Total number of samples: 800

Associated criterion value: 361.7144

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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



Now evaluating the Fisher Information Matrix for the 35 protocols generated


BEST ONE GROUP PROTOCOL:
```

```
Sample times for response: A
                times freq Subjects doses
1 c(0.33, 1.5, 5, 12)    1      200   100


Associated criterion: 361.7144



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

Optimised design:
Sample times for response: A
                times       freq   Subjects doses
1  c(0.33, 1, 1.5, 8) 0.35271097  70.542193   100
2 c(0.33, 1.5, 8, 12) 0.61581304 123.162608   100
3 c(0.33, 1.5, 3, 12) 0.03147599   6.295199   100


Associated optimised criterion: 371.3125



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX ******************

          [,1]       [,2]      [,3]     [,4]      [,5]       [,6]       [,7]
[1,] 37.939211   64.62921 -4.169241  0.00000   0.00000    0.00000    0.00000
[2,] 64.629208 8560.77091 62.570273  0.00000   0.00000    0.00000    0.00000
[3,] -4.169241   62.57027  4.976251  0.00000   0.00000    0.00000    0.00000
[4,]  0.000000    0.00000  0.000000 57.57818   2.61675   39.23578   28.01875
[5,]  0.000000    0.00000  0.000000  2.61675 718.59967  138.15673  225.75506
[6,]  0.000000    0.00000  0.000000 39.23578 138.15673 3144.16863  286.25131
[7,]  0.000000    0.00000  0.000000 28.01875 225.75506  286.25131 1080.19191
[8,]  0.000000    0.00000  0.000000 89.57049 200.03981 1334.31438 1543.24600
           [,8]
[1,]    0.00000
[2,]    0.00000
[3,]    0.00000
[4,]   89.57049
[5,]  200.03981
[6,] 1334.31438
[7,] 1543.24600
[8,] 4822.65968


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

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

    Beta   StdError      RSE
ka  2.00 0.17491805 8.745902 %
k   0.25 0.01164345 4.657380 %
V  15.00 0.50355898 3.357060 %
```

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

   omega²   StdError      RSE
ka   1.00 0.13382715 13.38272 %
k    0.25 0.03891768 15.56707 %
V    0.10 0.01919088 19.19088 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04302074  8.604149 %
sig.slopeA  0.15 0.02094322 13.962147 %


****************************** DETERMINANT *********************************

3.613401e+20

****************************** CRITERION ***********************************

371.3125


****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      2520.328902           3.876959
max      8561.718019        2520.328902
max/min     3.397064         650.078745


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]         [,4]         [,5]        [,6]
[1,]  1.0000000 -0.2261971  0.3567942  0.000000000  0.000000000  0.00000000
[2,] -0.2261971  1.0000000 -0.3565652  0.000000000  0.000000000  0.00000000
[3,]  0.3567942 -0.3565652  1.0000000  0.000000000  0.000000000  0.00000000
[4,]  0.0000000  0.0000000  0.0000000  1.000000000  0.008100681 -0.03710528
[5,]  0.0000000  0.0000000  0.0000000  0.008100681  1.000000000 -0.09027489
[6,]  0.0000000  0.0000000  0.0000000 -0.037105280 -0.090274892  1.00000000
[7,]  0.0000000  0.0000000  0.0000000 -0.002578939 -0.259173157  0.12946239
[8,]  0.0000000  0.0000000  0.0000000 -0.108202443  0.115209250 -0.32726371
             [,7]       [,8]
[1,]  0.000000000  0.0000000
[2,]  0.000000000  0.0000000
[3,]  0.000000000  0.0000000
[4,] -0.002578939 -0.1082024
[5,] -0.259173157  0.1152093
[6,]  0.129462393 -0.3272637
[7,]  1.000000000 -0.6698686
[8,] -0.669868635  1.0000000

Time difference of 1.401081 secs
sys.self
    0.13
```



For this example, the optimisation with Fedorov-Wynn (FW) algorithm led to a criterion of 371.3, higher than the one obtained with the Simplex algorithm (362.4) in point 1.1.1. Relative standard errors are acceptable in both cases (below 20%).

1.1.3. Fixed Parameter

Optimize the design in 1.1 keeping the parameter k_a fixed (assuming no variability on k_a) using the constrains as in 1.1.1 and 1.1.2.

1.1.3.1. Simplex algorithm

INPUT FILE

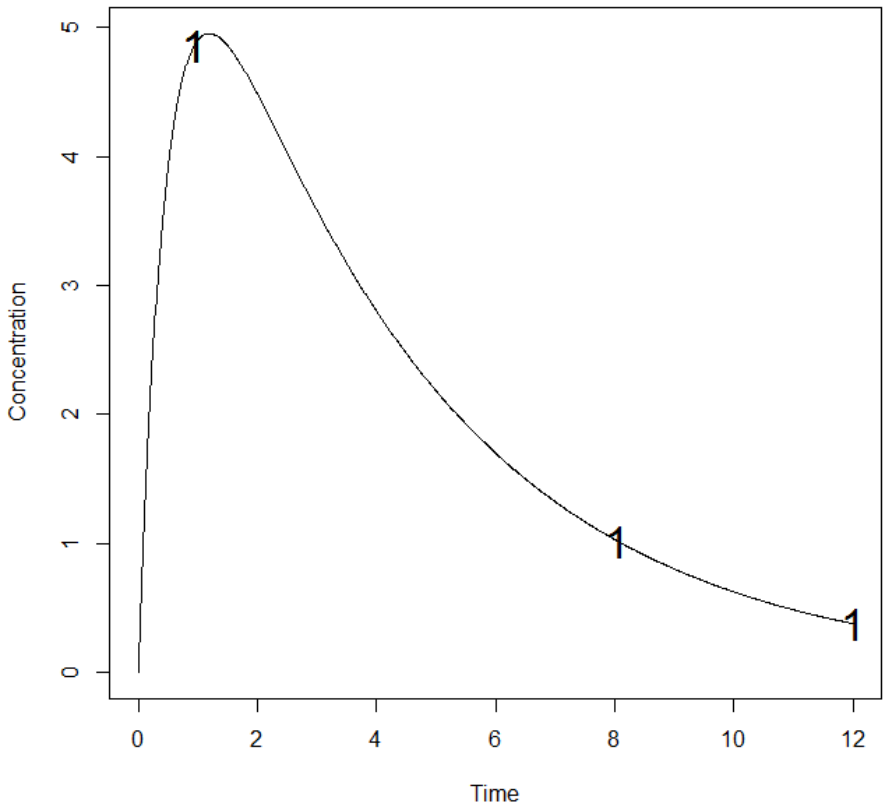
```
#Name of the project
#--------------------
project<-"1.1.3.1"
#-------------------------------------
parameters<-c("ka","k","V")

#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(T,F,F)
omega<-diag(c(0,0.25,0.1))

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#----------------------------------------
algo.option<-"SIMP"
```

OUTPUT FILE

```
PFIM 4.0

Option 1

Project: 1.1.3.1

Date: Thu Apr 17 15:50:27 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
                times subjects.prop doses
1 c(0.33, 1.5, 5, 12)           200   100




Total number of samples (nr responses): 800

Associated criterion value: 963.4982



Window of the allowed optimised sampling times:

Upper and lower admissible samples times for the response A : [ 0 : 12 ]


Minimum delay between two sampling times: 0

Optimisation of the proportions of subjects: TRUE



Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


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

Number of iterations: 111
```

```
Number of function evaluations: 146
Convergence Achieved



Design:


Sample times for response: A
                      times subjects.prop subjects
1 c(0.939, 0.942, 8.038, 12)             1      200




Associated optimised criterion: 1081.782



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

           [,1]      [,2]      [,3]       [,4]      [,5]      [,6]
[1,] 9265.40922 35.103559   0.00000    0.00000    0.0000    0.0000
[2,]   35.10356  6.528763   0.00000    0.00000    0.0000    0.0000
[3,]    0.00000  0.000000 838.35750   43.32164  241.6202  202.8993
[4,]    0.00000  0.000000  43.32164 5394.69421  304.1137 1442.1010
[5,]    0.00000  0.000000 241.62021  304.11367 1544.1300 2123.2272
[6,]    0.00000  0.000000 202.89928 1442.10098 2123.2272 7237.6960







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

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

   Beta   StdError      RSE
k  0.25 0.01049631 4.198526 %
V 15.00 0.39541549 2.636103 %


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

  omega2   StdError      RSE
k   0.25 0.03543207 14.17283 %
V   0.10 0.01401500 14.01500 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.03373599  6.747199 %
sig.slopeA  0.15 0.01561541 10.410275 %
```

```
******************************** DETERMINANT ********************************

1.60265e+18

******************************** CRITERION **********************************

1081.782



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************

        FixedEffects VarianceComponents
min      8618.806407           6.395675
max      9265.542306         995.276798
max/min     1.075038         155.617157


****************** CORRELATION MATRIX *****************

           [,1]       [,2]        [,3]        [,4]        [,5]        [,6]
[1,]  1.0000000 -0.1427261  0.00000000  0.00000000  0.00000000  0.00000000
[2,] -0.1427261  1.0000000  0.00000000  0.00000000  0.00000000  0.00000000
[3,]  0.0000000  0.0000000  1.00000000 -0.01310911 -0.20830125  0.07075104
[4,]  0.0000000  0.0000000 -0.01310911  1.00000000  0.05635404 -0.21370973
[5,]  0.0000000  0.0000000 -0.20830125  0.05635404  1.00000000 -0.63060423
[6,]  0.0000000  0.0000000  0.07075104 -0.21370973 -0.63060423  1.00000000

Time difference of 0.8560491 secs
sys.self
       0
```



1.1.3.2. Fedorov-Wynn algorithm

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.1.3.2"

#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(T,F,F)

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#----------------------------------------

algo.option<-"FW"
```

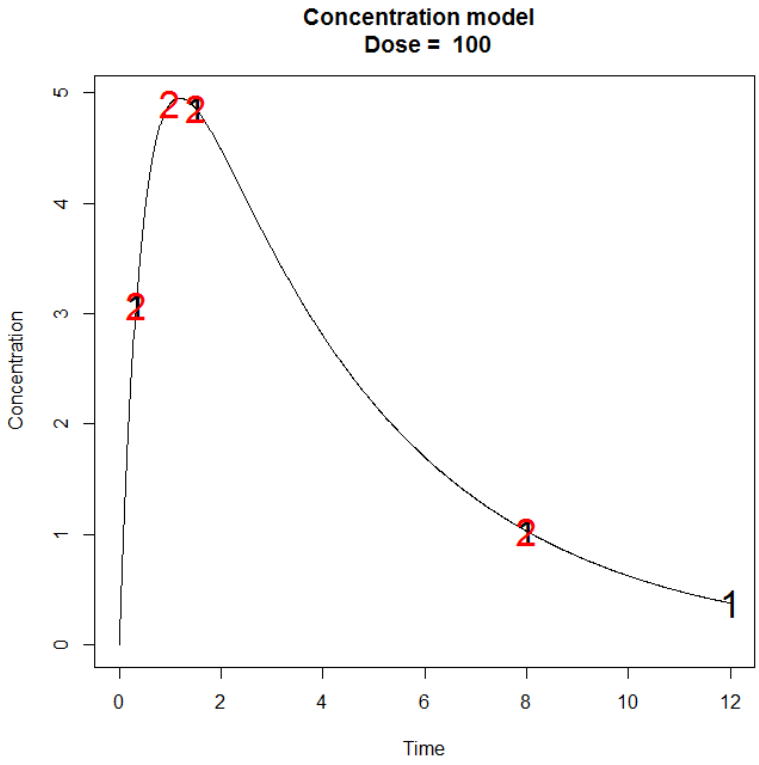
OUTPUT FILE

```
PFIM 4.0

Option: 1
```

```
Project: 1.1.3.2
Date: Tue Jan 28 15:07:15 2014



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

Analytical function model:

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)
}
Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)      200   100


Total number of samples: 800

Associated criterion value: 963.4982

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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



Now evaluating the Fisher Information Matrix for the 35 protocols generated


BEST ONE GROUP PROTOCOL:

Sample times for response: A
                times freq Subjects doses
1 c(0.33, 1.5, 8, 12)    1      200   100


Associated criterion: 713.2923
```

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



Optimised design:
Sample times for response: A
                times      freq  Subjects doses
1 c(0.33, 1.5, 8, 12) 0.8620492 172.40984   100
2  c(0.33, 1, 1.5, 8) 0.1379508  27.59016   100


Associated optimised criterion: 1003.861



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

           [,1]      [,2]      [,3]       [,4]      [,5]     [,6]
[1,] 9164.75153 39.514527   0.00000    0.00000    0.0000    0.000
[2,]   39.51453  6.256111   0.00000    0.00000    0.0000    0.000
[3,]    0.00000  0.000000 821.25546   54.89381  237.7609  215.400
[4,]    0.00000  0.000000  54.89381 4961.58304  359.2888 1388.113
[5,]    0.00000  0.000000 237.76094  359.28876 1546.0399 2284.918
[6,]    0.00000  0.000000 215.40005 1388.11316 2284.9178 6651.617




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

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

   Beta   StdError      RSE
k  0.25 0.01059096 4.236382 %
V 15.00 0.40536223 2.702415 %




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

  omega²   StdError      RSE
k   0.25 0.03583385 14.33354 %
V   0.10 0.01466132 14.66132 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.03713537  7.427074 %
sig.slopeA  0.15 0.01795893 11.972620 %


****************************** DETERMINANT ******************************

1.023392e+18
```

```
******************************** CRITERION *********************************
1003.861

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min       8171.126965           6.085627
max       9164.922016        8171.126965
max/min      1.121623        1342.692610


****************** CORRELATION MATRIX ******************

            [,1]       [,2]        [,3]        [,4]        [,5]        [,6]
[1,]  1.0000000 -0.1650229  0.00000000  0.00000000  0.00000000  0.00000000
[2,] -0.1650229  1.0000000  0.00000000  0.00000000  0.00000000  0.00000000
[3,]  0.0000000  0.0000000  1.00000000 -0.01850452 -0.20874886  0.08681517
[4,]  0.0000000  0.0000000 -0.01850452  1.00000000  0.06481377 -0.21521132
[5,]  0.0000000  0.0000000 -0.20874886  0.06481377  1.00000000 -0.70786839
[6,]  0.0000000  0.0000000  0.08681517 -0.21521132 -0.70786839  1.00000000


Time difference of 0.714041 secs
sys.self
    0.13
```



1.1.4. *Fixed Sampling Times*

Optimize the design in 1.1 with the Fedorov-Wynn algorithm keeping fixed two sampling times $(0.33, 1.5)$, using the constrains as in 1.1.1 and 1.1.2.

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.1.4"
######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#----------------------------------------

algo.option<-"FW"

#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#-------------------------------------------------------------------
fixed.timesA<-c(0.33,1.5)
############## END OF OPTIMISATION ALGORITHM OPTION ###############
```

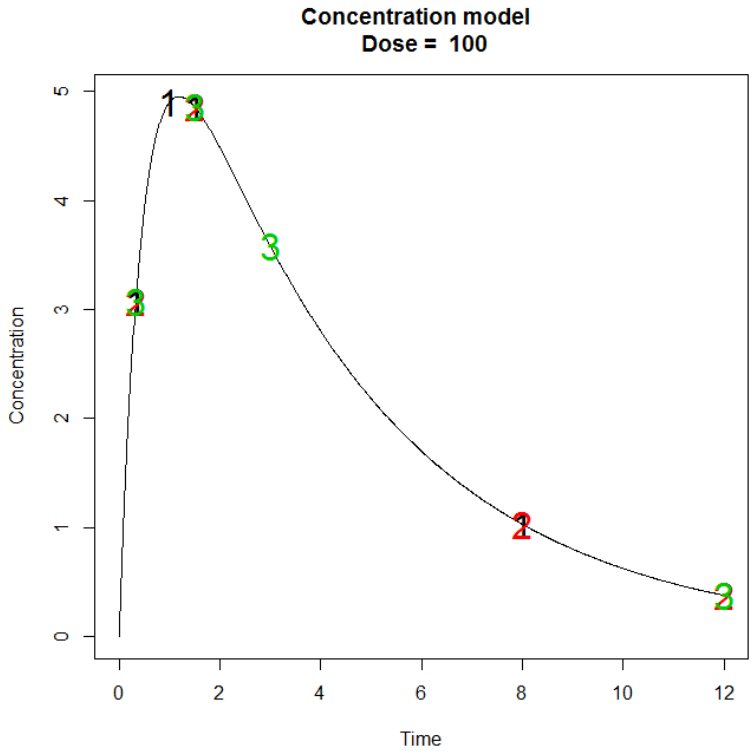
OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.1.4.2

Date: Tue Apr 22 15:30:37 2014



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

Analytical function model:

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)
}




Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)      200   100
```

```
Total number of samples: 800

Associated criterion value: 361.7144

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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



Now evaluating the Fisher Information Matrix for the 10 protocols generated


BEST ONE GROUP PROTOCOL:

Sample times for response: A
                times freq Subjects doses
1 c(0.33, 1.5, 5, 12)    1      200   100


Associated criterion: 361.7144



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



Optimised design:
Sample times for response: A
                times       freq   Subjects doses
1  c(0.33, 1, 1.5, 8) 0.35271097  70.542193   100
2 c(0.33, 1.5, 8, 12) 0.61581304 123.162608   100
3 c(0.33, 1.5, 3, 12) 0.03147599   6.295199   100



Associated optimised criterion: 371.3125



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

          [,1]       [,2]      [,3]     [,4]      [,5]       [,6]       [,7]
[1,] 37.939211   64.62921 -4.169241  0.00000   0.00000    0.00000    0.00000
[2,] 64.629208 8560.77091 62.570273  0.00000   0.00000    0.00000    0.00000
```

```
[3,] -4.169241   62.57027  4.976251  0.00000   0.00000    0.00000    0.00000
[4,]  0.000000    0.00000  0.000000 57.57818   2.61675   39.23578   28.01875
[5,]  0.000000    0.00000  0.000000  2.61675 718.59967  138.15673  225.75506
[6,]  0.000000    0.00000  0.000000 39.23578 138.15673 3144.16863  286.25131
[7,]  0.000000    0.00000  0.000000 28.01875 225.75506  286.25131 1080.19191
[8,]  0.000000    0.00000  0.000000 89.57049 200.03981 1334.31438 1543.24600
           [,8]
[1,]    0.00000
[2,]    0.00000
[3,]    0.00000
[4,]   89.57049
[5,]  200.03981
[6,] 1334.31438
[7,] 1543.24600
[8,] 4822.65968



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

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

    Beta   StdError      RSE
ka  2.00 0.17491805 8.745902 %
k   0.25 0.01164345 4.657380 %
V  15.00 0.50355898 3.357060 %

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

   omega2   StdError      RSE
ka   1.00 0.13382715 13.38272 %
k    0.25 0.03891768 15.56707 %
V    0.10 0.01919088 19.19088 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04302074  8.604149 %
sig.slopeA  0.15 0.02094322 13.962147 %


****************************** DETERMINANT ******************************

3.613401e+20

******************************** CRITERION ********************************

371.3125

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min      2520.328902           3.876959
max      8561.718019        2520.328902
max/min     3.397064         650.078745
```

```
****************** CORRELATION MATRIX ******************

            [,1]        [,2]        [,3]         [,4]         [,5]         [,6]
[1,]  1.0000000 -0.2261971  0.3567942  0.000000000  0.000000000  0.00000000
[2,] -0.2261971  1.0000000 -0.3565652  0.000000000  0.000000000  0.00000000
[3,]  0.3567942 -0.3565652  1.0000000  0.000000000  0.000000000  0.00000000
[4,]  0.0000000  0.0000000  0.0000000  1.000000000  0.008100681 -0.03710528
[5,]  0.0000000  0.0000000  0.0000000  0.008100681  1.000000000 -0.09027489
[6,]  0.0000000  0.0000000  0.0000000 -0.037105280 -0.090274892  1.00000000
[7,]  0.0000000  0.0000000  0.0000000 -0.002578939 -0.259173157  0.12946239
[8,]  0.0000000  0.0000000  0.0000000 -0.108202443  0.115209250 -0.32726371
              [,7]        [,8]
[1,]  0.000000000  0.0000000
[2,]  0.000000000  0.0000000
[3,]  0.000000000  0.0000000
[4,] -0.002578939 -0.1082024
[5,] -0.259173157  0.1152093
[6,]  0.129462393 -0.3272637
[7,]  1.000000000 -0.6698686
[8,] -0.669868635  1.0000000



Time difference of 0.2184012 secs
sys.self
    0.06
```



1.1.5. Fixed Parameter and Fixed Sampling Times

Optimize P-FIM using the Fedorov-Wynn algorithm keeping the parameter k_a fixed (assuming no variability on k_a) and keeping fixed 2 sampling times $(0.33, 1.5)$.

INPUT FILE

```
##############################################################################
##                        INPUT FILE FOR PFIM 4.0                           ##
##############################################################################
#Name of the project
#--------------------
project<-"1.1.5"


beta.fixed<-c(T,F,F)



######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:

#      "FW" for the Fedorov-Wynn algorithm

#      "SIMP" for the Simplex algorithm

#----------------------------------------



algo.option<-"FW"

#############################

#FEDOROV-WYNN SPECIFICATION #

#############################

#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)

#-------------------------------------------------------------------

fixed.timesA<-c(0.33,1.5)
```

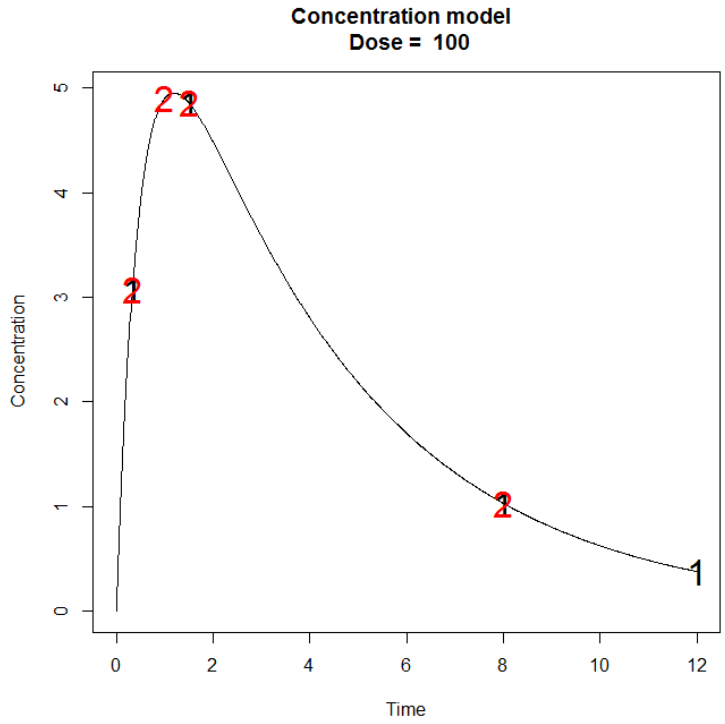
OUPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.1.5

Date: Tue Apr 22 15:37:32 2014



*************************** INPUT SUMMARY *******************************
```

```
Analytical function model:

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)
}



Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)      200   100


Total number of samples: 800

Associated criterion value: 963.4982

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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



Now evaluating the Fisher Information Matrix for the 10 protocols generated


BEST ONE GROUP PROTOCOL:

Sample times for response: A
                times freq Subjects doses
1 c(0.33, 1.5, 8, 12)    1      200   100


Associated criterion: 999.542



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

```
Optimised design:
Sample times for response: A
                times      freq  Subjects doses
1 c(0.33, 1.5, 8, 12) 0.8542171 170.84342   100
2  c(0.33, 1, 1.5, 8) 0.1457829  29.15658   100



Associated optimised criterion: 1003.871



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

          [,1]      [,2]      [,3]       [,4]      [,5]      [,6]
[1,] 9157.4312 39.518203   0.00000    0.00000    0.0000    0.0000
[2,]   39.5182  6.261843   0.00000    0.00000    0.0000    0.0000
[3,]    0.0000  0.000000 819.99351   54.90407  237.9162  216.0253
[4,]    0.0000  0.000000  54.90407 4971.04579  358.6388 1386.2277
[5,]    0.0000  0.000000 237.91618  358.63875 1539.3337 2289.9023
[6,]    0.0000  0.000000 216.02528 1386.22774 2289.9023 6693.1956


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

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

   Beta  StdError      RSE
k  0.25 0.0105952 4.238079 %
V 15.00 0.4051770 2.701180 %


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

  omega2   StdError      RSE
k   0.25 0.03587088 14.34835 %
V   0.10 0.01464165 14.64165 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.03727137  7.454275 %
sig.slopeA  0.15 0.01792088 11.947254 %


****************************** DETERMINANT *******************************

1.023455e+18

****************************** CRITERION *******************************

1003.871



****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************
```

```
        FixedEffects VarianceComponents
min       8203.777970           6.091192
max       9157.601823        8203.777970
max/min      1.116266        1346.826382


****************** CORRELATION MATRIX ******************

           [,1]       [,2]        [,3]        [,4]        [,5]        [,6]
[1,]  1.0000000 -0.1650286  0.00000000  0.00000000  0.00000000  0.00000000
[2,] -0.1650286  1.0000000  0.00000000  0.00000000  0.00000000  0.00000000
[3,]  0.0000000  0.0000000  1.00000000 -0.01850719 -0.20992982  0.08790201
[4,]  0.0000000  0.0000000 -0.01850719  1.00000000  0.06395325 -0.21352190
[5,]  0.0000000  0.0000000 -0.20992982  0.06395325  1.00000000 -0.70879981
[6,]  0.0000000  0.0000000  0.08790201 -0.21352190 -0.70879981  1.00000000


Time difference of 0.2028 secs
sys.self
    0.03
```



1.1.6. Previous information on PFIM

1.1.6.1. Simplex algorithm

For the optimization with previous information, it was used the prior FIM "`priorFIM.txt`" created in the "priorInfo" folder, stored in the folder of this example.

This prior FIM was created on purpose giving early initial times: (0.33, 1, 1.5).

INPUT FILE

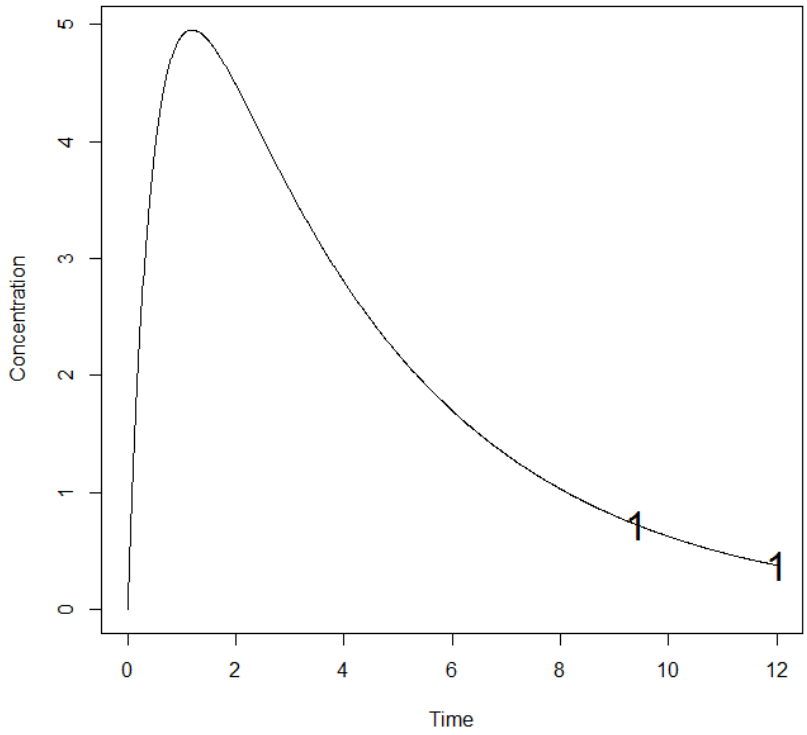
```
#Name of the project
#--------------------
project<-"1.1.6.1"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-------------------------------------------------------
previous.FIM<-"priorFIM.txt"

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(1.5,8))
#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(100)
```

OUTPUT FILE

```
PFIM 4.0

Option 1

Project: 1.1.6.1

Date: Thu Apr 17 14:00:37 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
      times subjects.prop doses
1 c(1.5, 8)           100   100

Total number of samples (nr responses): 200

Associated criterion value: 148.6897
```

```
Window of the allowed optimised sampling times:

Upper and lower admissible samples times for the response A : [ 0 : 12 ]


Minimum delay between two sampling times: 0

Optimisation of the proportions of subjects: TRUE



Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


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

Number of iterations: 55
Number of function evaluations: 71
Convergence Achieved

Design:

Sample times for response: A
         times subjects.prop subjects
1 c(9.395, 12)             1      100


Associated optimised criterion: 215.3191


Computation of the Population Fisher information matrix: option =  1

Previous FIM from file priorFIM.txt

****************** FISHER INFORMATION MATRIX *****************

            V1         V2        V3        V4         V5         V6         V7
[1,] 19.138168   49.07954 -1.908044  0.000000   0.000000    0.00000    0.00000
[2,] 49.079541 5092.04238 68.482856  0.000000   0.000000    0.00000    0.00000
[3,] -1.908044   68.48286  2.868817  0.000000   0.000000    0.00000    0.00000
[4,]  0.000000    0.00000  0.000000 28.530155   1.668454   20.98622   14.72601
[5,]  0.000000    0.00000  0.000000  1.668454 386.741448  166.91230  134.56302
[6,]  0.000000    0.00000  0.000000 20.986224 166.912299 1785.26280  145.47772
[7,]  0.000000    0.00000  0.000000 14.726007 134.563018  145.47772  813.66712
[8,]  0.000000    0.00000  0.000000 47.319224 139.206982  601.75932 1099.59528
             V8
[1,]    0.00000
[2,]    0.00000
[3,]    0.00000
[4,]   47.31922
[5,]  139.20698
[6,]  601.75932
[7,] 1099.59528
[8,] 3764.97222
************************* EXPECTED STANDARD ERRORS **********************
```

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

    Beta   StdError       RSE
ka  2.00 0.25582962 12.791481 %
k   0.25 0.01839233  7.356932 %
V  15.00 0.79194479  5.279632 %

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

   omega2   StdError      RSE
ka   1.00 0.18959249 18.95925 %
k    0.25 0.05343693 21.37477 %
V    0.10 0.02485754 24.85754 %

----------------------- Standard deviation of residual error --------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04629044  9.258087 %
sig.slopeA  0.15 0.02156098 14.373985 %

****************************** DETERMINANT *******************************

4.620192e+18

******************************** CRITERION *******************************

215.3191

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************

        FixedEffects VarianceComponents
min      1645.644667           1.561834
max      5093.437880         503.888117
max/min     3.095102         322.625898

****************** CORRELATION MATRIX *****************

         [,1]       [,2]       [,3]        [,4]        [,5]        [,6]
V1  1.0000000 -0.3807142  0.4259198  0.00000000  0.00000000  0.00000000
V2 -0.3807142  1.0000000 -0.6361945  0.00000000  0.00000000  0.00000000
V3  0.4259198 -0.6361945  1.0000000  0.00000000  0.00000000  0.00000000
V4  0.0000000  0.0000000  0.0000000  1.00000000  0.01474447 -0.06375773
V5  0.0000000  0.0000000  0.0000000  0.01474447  1.00000000 -0.19257026
V6  0.0000000  0.0000000  0.0000000 -0.06375773 -0.19257026  1.00000000
V7  0.0000000  0.0000000  0.0000000 -0.01288362 -0.22656742  0.07587018
V8  0.0000000  0.0000000  0.0000000 -0.09204095  0.08428419 -0.20714892
          [,7]        [,8]
V1  0.00000000  0.00000000
V2  0.00000000  0.00000000
V3  0.00000000  0.00000000
V4 -0.01288362 -0.09204095
V5 -0.22656742  0.08428419
V6  0.07587018 -0.20714892
V7  1.00000000 -0.61883269
V8 -0.61883269  1.00000000

Time difference of 0.5510318 secs
sys.self
       0
```



1.1.6.2. Best One Group design

INPUT FILE

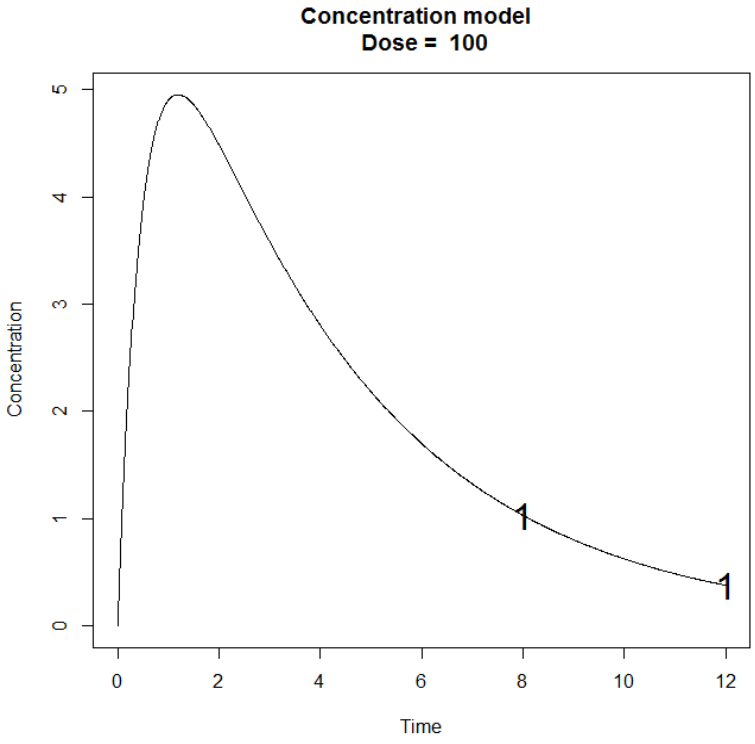
```
#Name of the project
#--------------------
project<-"1.1.6.2"

#Previous information for population design (FIM<-"P") only:
#If previous information is available, please specify below the file name;
#otherwise leave it as the default
#-----------------------------------------------------
previous.FIM<-"priorFIM.txt"

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-------------------------------------------------------------
protA<-list(c(1.5,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(100)
```

OUTPUT FILE

```
PFIM 4.0

Option: 1

Project: 1.1.6.2

Date: Thu Apr 17 10:00:15 2014


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

Analytical function model:

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)
}

Initial design:


Sample times for response: A
    Protocol subjects doses
1 c=(1.5, 8)      100   100


Total number of samples: 200

Associated criterion value: 148.6897

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    Nb of sampling points to be taken in this window, n[ 1 ]= 2
Maximum total number of points in one elementary protocol : 2
Minimum total number of points in one elementary protocol : 2


BEST ONE GROUP PROTOCOL:

Sample times for response: A
     times freq Subjects doses
1 c(8, 12)    1      100   100


Associated criterion: 214.2912
```

```
Previous FIM from file priorFIM.txt

Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

           V1         V2        V3        V4         V5         V6         V7
[1,] 19.25130   54.34133 -1.802420  0.000000   0.000000    0.00000    0.00000
[2,] 54.34133 5159.92461 73.396138  0.000000   0.000000    0.00000    0.00000
[3,] -1.80242   73.39614  2.967429  0.000000   0.000000    0.00000    0.00000
[4,]  0.00000    0.00000  0.000000 28.535801   2.132073   21.26297   14.92574
[5,]  0.00000    0.00000  0.000000  2.132073 398.485186  189.64107  117.76653
[6,]  0.00000    0.00000  0.000000 21.262967 189.641070 1798.82796  155.27405
[7,]  0.00000    0.00000  0.000000 14.925744 117.766531  155.27405  777.68829
[8,]  0.00000    0.00000  0.000000 47.680745 147.847133  619.48320 1115.37779
             V8
[1,]    0.00000
[2,]    0.00000
[3,]    0.00000
[4,]   47.68074
[5,]  147.84713
[6,]  619.48320
[7,] 1115.37779
[8,] 3804.74812



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

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

    Beta   StdError       RSE
ka  2.00 0.25623615 12.811807 %
k   0.25 0.01887938  7.551752 %
V  15.00 0.79850925  5.323395 %

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

   omega2   StdError      RSE
ka   1.00 0.18957978 18.95798 %
k    0.25 0.05245918 20.98367 %
V    0.10 0.02489123 24.89123 %

------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError       RSE
sig.interA  0.50 0.04797421  9.594842 %
sig.slopeA  0.15 0.02187599 14.583994 %


******************************* DETERMINANT *******************************

4.446667e+18

******************************** CRITERION ********************************

214.2912
 ****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****************
```

```
        FixedEffects VarianceComponents
min       1655.303411           1.536137
max       5161.542600        1655.303411
max/min      3.118185        1077.575115

****************** CORRELATION MATRIX ******************

          [,1]       [,2]       [,3]        [,4]        [,5]        [,6]
V1  1.0000000 -0.4014290  0.4296629  0.00000000  0.00000000  0.00000000
V2 -0.4014290  1.0000000 -0.6630338  0.00000000  0.00000000  0.00000000
V3  0.4296629 -0.6630338  1.0000000  0.00000000  0.00000000  0.00000000
V4  0.0000000  0.0000000  0.0000000  1.00000000  0.01228004 -0.06344937
V5  0.0000000  0.0000000  0.0000000  0.01228004  1.00000000 -0.21184140
V6  0.0000000  0.0000000  0.0000000 -0.06344937 -0.21184140  1.00000000
V7  0.0000000  0.0000000  0.0000000 -0.01245173 -0.18708739  0.06908877
V8  0.0000000  0.0000000  0.0000000 -0.08998746  0.06500474 -0.20304566
           [,7]        [,8]
V1  0.00000000  0.00000000
V2  0.00000000  0.00000000
V3  0.00000000  0.00000000
V4 -0.01245173 -0.08998746
V5 -0.18708739  0.06500474
V6  0.06908877 -0.20304566
V7  1.00000000 -0.63690284
V8 -0.63690284  1.00000000

Time difference of 0.4670269 secs
sys.self
    0.04
```



1.2. Individual Fisher Information Matrix (I-FIM)

Optimize the design in 1.1 this time for the Individual Fisher Information Matrix (I-FIM). Use same constraints in 1.1.1 and 1.1.2.

1.2.1. Simplex algorithm

INPUT FILE

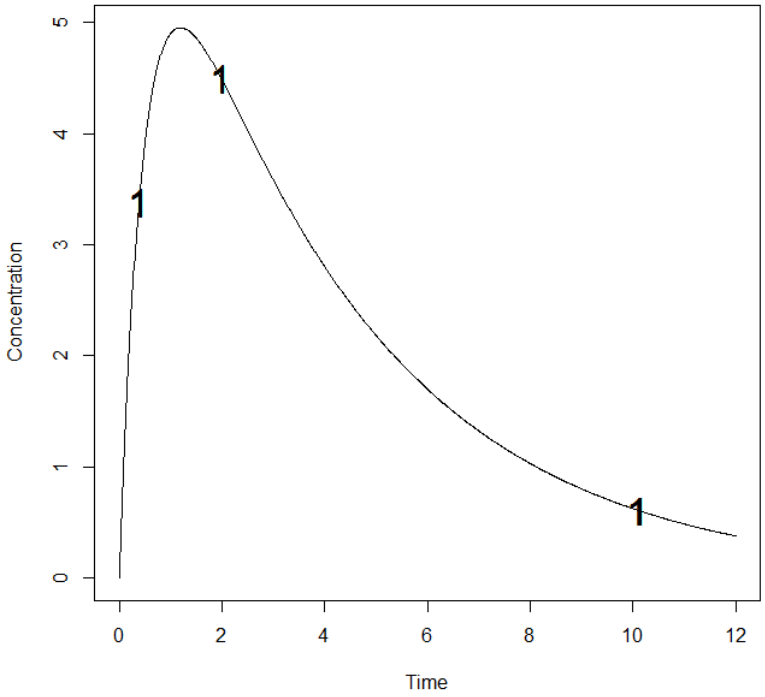
```
#Name of the project
#--------------------
project<-"1.2.1"

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"I"
subjects<-c(1)
############ONLY FOR OPTIMISATION ##############################

#Identical sampling times for each response
# (only if you do not have sampling times==NULL)
#-------------------------------------------------------------------------------
identical.times<-F

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-----------------------------------------

algo.option<-"SIMP"
```

OUTPUT FILE

```
PFIM 4.0

Option 1

Project: 1.2.1

Date: Fri Apr 04 09:53:14 2014



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

Analytical function model:

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)
}
```

```
Initial design:


Sample times for response: A
                times subjects.prop doses
1 c(0.33, 1.5, 5, 12)             1   100

Total number of samples (nr responses): 4

Associated criterion value: 5.0603


Window of the allowed optimised sampling times:

Upper and lower admissible samples times for the response A : [ 0 : 12 ]


Minimum delay between two sampling times: 0

Optimisation of the proportions of subjects: FALSE



Variance error model response A : ( 0.5 + 0.15 *f)^2


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

Number of iterations: 64
Number of function evaluations: 113
Convergence Achieved



Design:


Sample times for response: A
                            times subjects.prop subjects
1 c(0.388, 1.984, 10.109, 10.103)             1        1


Associated optimised criterion: 5.4114

Computation of the Individual Fisher information matrix




****************** FISHER INFORMATION MATRIX ******************

           [,1]        [,2]       [,3]     [,4]     [,5]
[1,]  1.2325747   0.8128637 -0.2303858  0.00000  0.00000
[2,]  0.8128637 225.3364445  2.9541561  0.00000  0.00000
[3,] -0.2303858   2.9541561  0.1250120  0.00000  0.00000
[4,]  0.0000000   0.0000000  0.0000000 14.84573 20.15214
[5,]  0.0000000   0.0000000  0.0000000 20.15214 56.25539
```

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

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

    Beta   StdError      RSE
ka  2.00 1.34079039 67.03952 %
k   0.25 0.09664122 38.65649 %
V  15.00 5.06159668 33.74398 %


----------------------- Standard deviation of residual error ---------------------

           Sigma  StdError       RSE
sig.interA  0.50 0.3621023  72.42046 %
sig.slopeA  0.15 0.1860159 124.01058 %


****************************** DETERMINANT *******************************

4640.201

******************************** CRITERION *********************************

5.411372

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min         6.657679         0.03753734
max       225.378114         1.27838008
max/min    33.852356        34.05622730


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]       [,5]
[1,]  1.0000000 -0.5581703  0.7400163  0.0000000  0.0000000
[2,] -0.5581703  1.0000000 -0.7236730  0.0000000  0.0000000
[3,]  0.7400163 -0.7236730  1.0000000  0.0000000  0.0000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000 -0.6973299
[5,]  0.0000000  0.0000000  0.0000000 -0.6973299  1.0000000

Time difference of 0.5850329 secs
sys.self
       0
```



1.2.2. Fedorov-Wynn algorithm

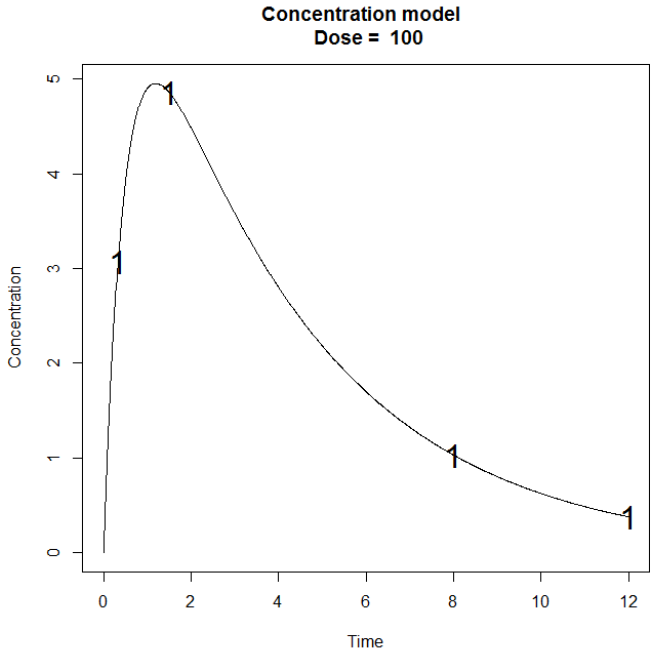
```
#Name of the project
#--------------------
project<-"1.2.2"
#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"I"

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-----------------------------------------

algo.option<-"FW"
############# END OF OPTIMISATION ALGORITHM OPTION ###############
```

OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.2.2

Date: Tue Jan 28 16:09:34 2014



**************************** INPUT SUMMARY *******************************
```

```
Analytical function model:

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)
}



Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)        1   100


Total number of samples: 4

Associated criterion value: 5.0603

Identical sampling times for each response: FALSE

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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




BEST ONE GROUP PROTOCOL:

Sample times for response: A
               times freq Subjects doses
1 c(0.33, 1.5, 8, 12)    1        1   100


Associated criterion: 5.2451



Computation of the Individual Fisher information matrix
```

```
****************** FISHER INFORMATION MATRIX *****************

           [,1]        [,2]       [,3]     [,4]     [,5]
[1,]  1.3081545   0.2980722 -0.2731617  0.00000  0.00000
[2,]  0.2980722 214.9216449  2.7951498  0.00000  0.00000
[3,] -0.2731617   2.7951498  0.1280792  0.00000  0.00000
[4,]  0.0000000   0.0000000  0.0000000 14.60286 20.34989
[5,]  0.0000000   0.0000000  0.0000000 20.34989 57.63562



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

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

    Beta  StdError      RSE
ka  2.00 1.4570744 72.85372 %
k   0.25 0.1000394 40.01575 %
V  15.00 5.5016631 36.67775 %



----------------------- Standard deviation of residual error ---------------------

           Sigma StdError      RSE
sig.interA  0.50 0.367167  73.4334 %
sig.slopeA  0.15 0.184815 123.2100 %


****************************** DETERMINANT *******************************

3969.882

****************************** CRITERION *******************************

5.245121

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min         6.503832         0.03157995
max       214.958418         6.50383230
max/min    33.051040       205.94814148


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]       [,5]
[1,]  1.0000000 -0.5923083  0.7998900  0.0000000  0.0000000
[2,] -0.5923083  1.0000000 -0.7313914  0.0000000  0.0000000
[3,]  0.7998900 -0.7313914  1.0000000  0.0000000  0.0000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000 -0.7014513
[5,]  0.0000000  0.0000000  0.0000000 -0.7014513  1.0000000

Time difference of 0.6250348 secs
sys.self
    0.09
```



1.2.3. *Fixed Parameter and Fixed Sampling Times*

Optimize I-FIM using the Fedorov-Wynn algorithm keeping the parameter k_a fixed (assuming no variability on k_a) and keeping fixed 2 sampling times $(0.33, 1.5)$.

INPUT FILE

```
#Name of the project
#--------------------
project<-"1.2.3"
#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"I"
#Some parameters may not be estimated (not estimated = T, estimated = F)
#--------------------------------
beta.fixed<-c(T,F,F)
#Diagonal Matrix of variance for inter-subject random effects:
#-------------------------------------------------
############ONLY FOR OPTIMISATION ################################

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#----------------------------------------

algo.option<-"FW"
############################
#FEDOROV-WYNN SPECIFICATION #
############################
```

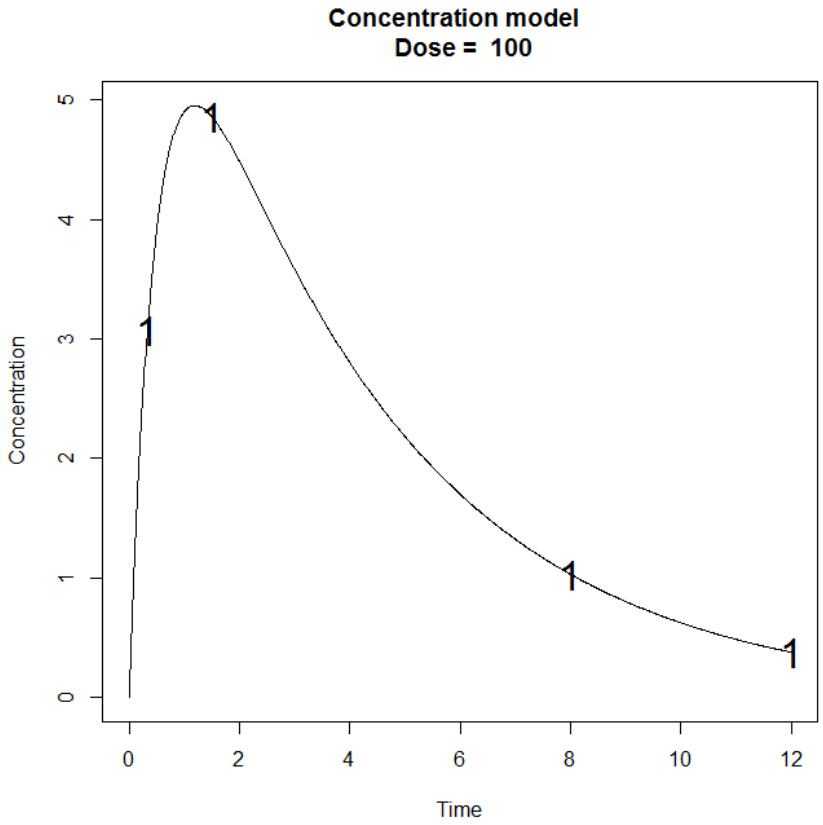
```
#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#---------------------------------------------------------------------
fixed.timesA<-c(0.33,1.5)
```

OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.2.3

Date: Tue Apr 22 15:20:04 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)        1   100


Total number of samples: 4

Associated criterion value: 9.1489

Identical sampling times for each response: FALSE

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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
```

```
BEST ONE GROUP PROTOCOL:

Sample times for response: A
                times freq Subjects doses
1 c(0.33, 1.5, 8, 12)    1        1   100


Associated criterion: 9.5815


Computation of the Individual Fisher information matrix

****************** FISHER INFORMATION MATRIX *****************

          [,1]      [,2]     [,3]     [,4]
[1,] 214.92164 2.7951498  0.00000  0.00000
[2,]   2.79515 0.1280792  0.00000  0.00000
[3,]   0.00000 0.0000000 14.60286 20.34989
[4,]   0.00000 0.0000000 20.34989 57.63562



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

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

   Beta   StdError      RSE
k  0.25 0.08060287 32.24115 %
V 15.00 3.30180471 22.01203 %



------------------------ Standard deviation of residual error ----------------------

           Sigma StdError      RSE
sig.interA  0.50 0.367167  73.4334 %
sig.slopeA  0.15 0.184815 123.2100 %


******************************* DETERMINANT *******************************

8428.321

******************************** CRITERION ********************************

9.581539

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min        65.734649         0.09171149
max       214.958013        65.73464882
max/min     3.270087       716.75477518
```

```
****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]       [,4]
[1,]  1.0000000 -0.5327529  0.0000000  0.0000000
[2,] -0.5327529  1.0000000  0.0000000  0.0000000
[3,]  0.0000000  0.0000000  1.0000000 -0.7014513
[4,]  0.0000000  0.0000000 -0.7014513  1.0000000

Time difference of 0.2652011 secs
sys.self
    0.03
```



1.3. Bayesian Fisher Information Matrix (B-FIM)

Optimize the design in 1.1 this time for the Bayesian Fisher Information Matrix (B-FIM). Use same constraints in 1.1.1 and 1.1.2.

1.3.1. Simplex algorithm

INPUT FILE

```
##############################################################################
##                          INPUT FILE FOR PFIM 4.0                         ##
##############################################################################


#Name of the project
#--------------------
project<-"1.3.1"
```

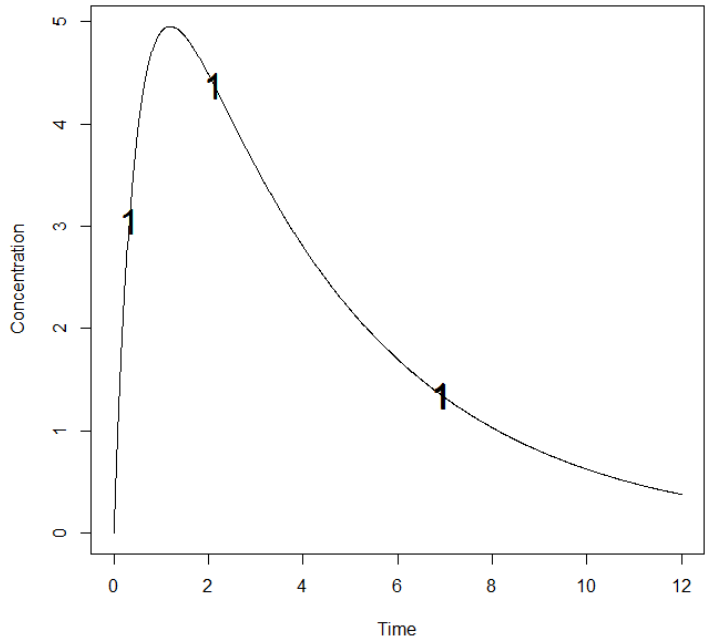
```
#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#---------------------------------------
FIM<-"B"

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-----------------------------------------

algo.option<-"SIMP"
```

OUTPUT FILE

```
PFIM 4.0

Option 1

Project: 1.3.1

Date: Thu Apr 17 15:06:38 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
                times subjects.prop doses
1 c(0.33, 1.5, 5, 12)             1   100




Total number of samples (nr responses): 4

Associated criterion value: 3.5272



Window of the allowed optimised sampling times:

Upper and lower admissible samples times for the response A : [ 0 : 12 ]
```

```
Minimum delay between two sampling times: 0

Optimisation of the proportions of subjects: FALSE



Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2


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

Number of iterations: 70
Number of function evaluations: 122
Convergence Achieved



Design:


Sample times for response: A
                         times subjects.prop subjects
1 c(0.332, 2.13, 6.537, 6.538)             1        1


Associated optimised criterion: 3.8917



Computation of the Bayesian Fisher information matrix

****************** FISHER INFORMATION MATRIX ******************

           [,1]       [,2]       [,3]
[1,]  1.5579242   3.378667 -0.1817856
[2,]  3.3786674 402.310191  5.0219864
[3,] -0.1817856   5.021986  0.1912682

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

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

    Beta   StdError      RSE   Shrinkage
ka  2.00 0.93681117 46.84056 %  21.94038 %
k   0.25 0.06704337 26.81735 %  28.76681 %
V  15.00 3.23108382 21.54056 %  46.39957 %


******************************* DETERMINANT *******************************

58.94244

******************************** CRITERION ********************************

3.89173
```

```
****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     9.363022e-02                NA
max     4.024013e+02                NA
max/min 4.297772e+03                NA

****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]
[1,]  1.0000000 -0.4211662  0.5050159
[2,] -0.4211662  1.0000000 -0.6608620
[3,]  0.5050159 -0.6608620  1.0000000

Time difference of 0.6450372 secs
sys.self
       0
```



1.3.2. Fedorov-Wynn algorithm

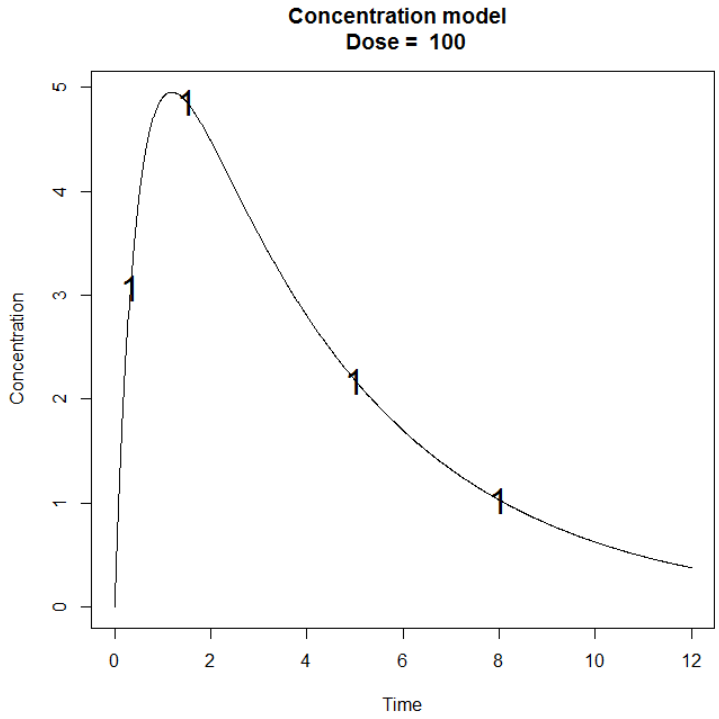
INPUT FILE

```
#Name of the project
#--------------------
project<-"1.3.2"
#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"B"
######## OPTIMISATION ALGORITHM OPTION ###############
#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-------------------------------------
algo.option<-"FW"
```

OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.3.2

Date: Tue Jan 28 16:45:40 2014



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

Analytical function model:

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)
}




Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)        1   100


Total number of samples: 4

Associated criterion value: 3.5272

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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

BEST ONE GROUP PROTOCOL:

Sample times for response: A
               times freq Subjects doses
```

```
1 c(0.33, 1.5, 5, 8)    1        1   100


Associated criterion: 3.8066


Computation of the Bayesian Fisher information matrix

****************** FISHER INFORMATION MATRIX ******************

          [,1]       [,2]       [,3]
[1,]  1.590507   2.096455 -0.2426030
[2,]  2.096455 354.843266  4.4964361
[3,] -0.242603   4.496436  0.2013882


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

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

    Beta  StdError      RSE   Shrinkage
ka  2.00 0.9638509 48.19255 %  23.22522 %
k   0.25 0.0688475 27.53900 %  30.33586 %
V  15.00 3.1862487 21.24166 %  45.12080 %

******************************** DETERMINANT ********************************

55.15913

******************************** CRITERION ********************************

3.806617

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     9.552493e-02                NA
max     3.549127e+02                NA
max/min 3.715393e+03                NA


****************** CORRELATION MATRIX ******************

           [,1]       [,2]       [,3]
[1,]  1.0000000 -0.4133690  0.5638373
[2,] -0.4133690  1.0000000 -0.6330761
[3,]  0.5638373 -0.6330761  1.0000000


Time difference of 0.7720439 secs
sys.self
    0.09
```



1.3.3. Fixed Parameter and Fixed Sampling Times

Optimize B-FIM using the Fedorov-Wynn algorithm keeping the parameter k_a fixed (assuming no variability on k_a) and keeping fixed 2 sampling times $(0.33, 1.5)$.

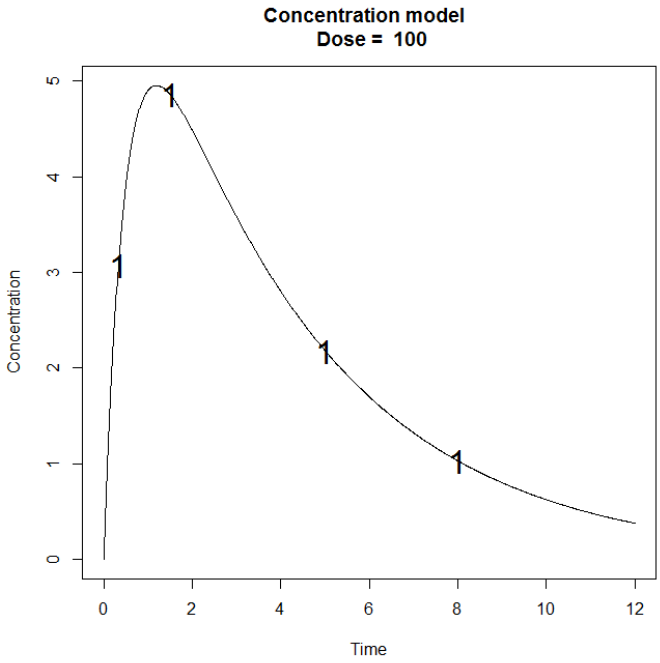
INPUT FILE

```
#Name of the project
#--------------------
project<-"1.3.3"

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"B"
#Some parameters may not be estimated (not estimated = T, estimated = F)
#-------------------------------
beta.fixed<-c(T,F,F)
#Diagonal Matrix of variance for inter-subject random effects:
#-----------------------------------------------------
omega<-diag(c(0,0.25,0.1))

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#---------------------------------------

algo.option<-"FW"
#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#-----------------------------------------------------------------------
fixed.timesA<-c(0.33,1.5)
```

OUTPUT FILE

```
PFIM 4.0

Option: 1


Project: 1.3.3

Date: Tue Apr 22 15:24:41 2014



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

Analytical function model:

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)
}


Initial design:


Sample times for response: A
              Protocol subjects doses
1 c=(0.33, 1.5, 5, 12)        1   100


Total number of samples: 4

Associated criterion value: 6.3628

Identical sampling times for each response: FALSE

Random effect model: Trand =  2

Variance error model response A : ( 0.5 + 0.15 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.33 1 1.5 3 5 8 12
    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




BEST ONE GROUP PROTOCOL:

Sample times for response: A
```

```
              times freq Subjects doses
1 c(0.33, 1.5, 5, 8)    1        1   100


Associated criterion: 7.1584



Computation of the Bayesian Fisher information matrix

****************** FISHER INFORMATION MATRIX *****************

           [,1]      [,2]
[1,] 354.843266 4.4964361
[2,]   4.496436 0.2013882




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

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

   Beta   StdError      RSE   Shrinkage
k  0.25 0.06269002 25.07601 %  25.15225 %
V 15.00 2.63147786 17.54319 %  30.77634 %


****************************** DETERMINANT ******************************

51.2433

******************************** CRITERION ********************************

7.158443


****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min        0.1443879                NA
max      354.9002664                NA
max/min 2457.9640320                NA


****************** CORRELATION MATRIX *****************

           [,1]       [,2]
[1,]  1.0000000 -0.5319039
[2,] -0.5319039  1.0000000



Time difference of 0.1715999 secs
sys.self
    0.03
```



2. Example 2: PK and immediate response PD model using the libraries of PK and PD Models (ODE)

- 100 subjects with a dose of 100
- Allowed sampling times for PK response: 0.5, 2, 30, 49, 180
- Allowed sampling times for PD response: 0.5, 2, 14, 110, 150
- Number of sampling times to be optimized: 3

2.1. Input File (P-FIM)

```
##########################################################################
##                    INPUT FILE FOR PFIM 4.0                           ##
##########################################################################


#Name of the project
#--------------------
project<-"EXAMPLE 2"
#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"
#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"OPT"
################## MODEL OPTION ############################

#Model form: Differential equations (DE) or analytical form (AF)
#---------------------------------------------------------------

modelform<-"DE"
#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5, 2, 30))
protB<-list(c(14, 110,150))
```

```
############ONLY FOR OPTIMISATION ################################

#Identical sampling times for each response
# (only if you do not have sampling times==NULL)
#-------------------------------------------------------------------------------
identical.times<-F

######## OPTIMISATION ALGORITHM OPTION ###############

#Character string for choice of the optimisation algorithm:
#      "FW" for the Fedorov-Wynn algorithm
#      "SIMP" for the Simplex algorithm
#-----------------------------------------

algo.option<-"FW"
############################
#FEDOROV-WYNN SPECIFICATION #
############################


#Number of sampling windows
#-------------------------
nwindA<-1
nwindB<-1


#List of vector of the allowed sampling times for each sampling window
#---------------------------------------------------------------------

sampwinA<-list(c(0.5, 2, 30, 49, 180))
sampwinB<-list(c(0.5, 2, 14, 110, 150 ))


#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#---------------------------------------------------------------------
fixed.timesA<-c()
fixed.timesB<-c()


#List of vector of allowed number of points to be taken from each sampling window
#--------------------------------------------------------------------------------

nsampA<-list(c(3))
nsampB<-list(c(3))

#Maximum total number of sampling times per subject
#-------------------------------------------------

nmaxptsA<-3
nmaxptsB<-3

#Minimum total number of sampling times per subject
#-------------------------------------------------

nminptsA<-3
nminptsB<-3
############# END OF OPTIMISATION ALGORITHM OPTION ###############
```

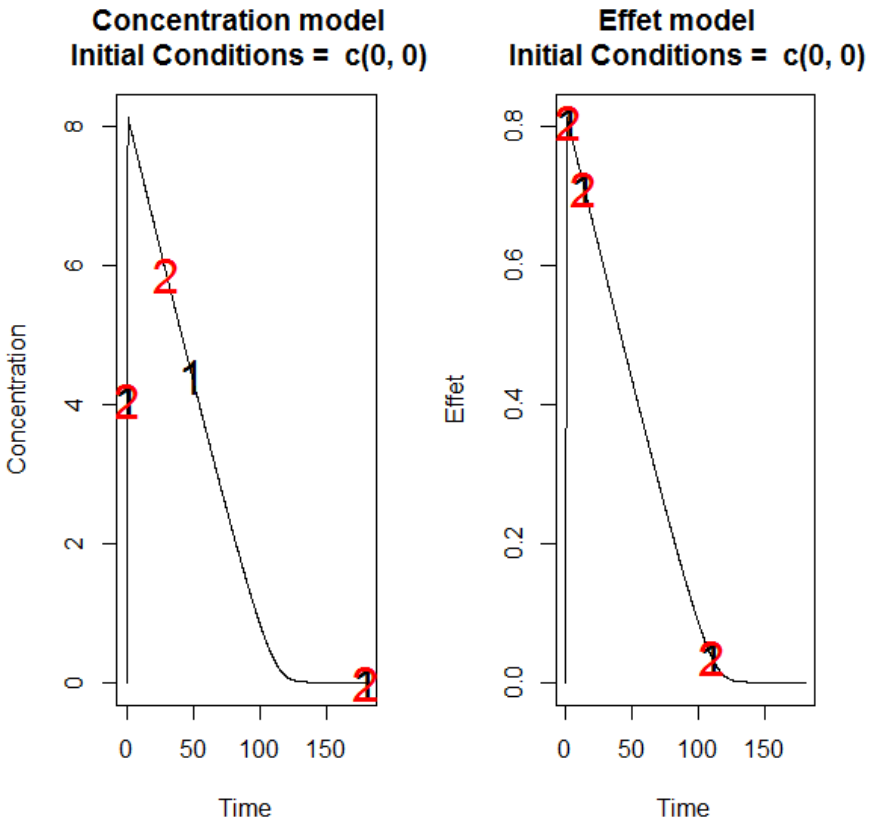
2.2. Output File

```
PFIM 4.0

Option: 1


Project: EXAMPLE 2

Date: Sun Mar 23 19:53:50 2014



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

Differential Equations form of the model:

function(t,y,p){
V<-p[1]
Vm<-p[2]
km<-p[3]
Alin<-p[4]
pk<-y[1:1]
pd<-y[2:2]
conc<-y[1]
if(t<=1){
dpk1<-(100/(1*V))+(-Vm)*pk[1]/(km+pk[1])}
else{
dpk1<-(-Vm)*pk[1]/(km+pk[1])}
dpd1<-0
pdIm<-Alin*conc
return(list(c(dpk1,dpd1),c(pk[1],pdIm)))
}


Initial Conditions at time 0 :

0 0

Error tolerance for solving differential equations system: RtolEQ = 1e-08 , AtolEQ
= 1e-08 , Hmax =  Inf

Initial design:


Sample times for response: A
        Protocol subjects condinit
1 c=(0.5, 2, 30)      100  c(0, 0)


Sample times for response: B
          Protocol subjects condinit
1 c=(14, 110, 150)      100  c(0, 0)


Total number of samples: 600

Associated criterion value: 1098.507

Identical sampling times for each response: FALSE
```

```
 Random effect model: Trand =  2

Variance error model response A : ( 0 + 0.2 *f)^2
Variance error model response B : ( 0.1 + 0 *f)^2



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.5 2 30 49 180
    Nb of sampling points to be taken in this window, n[ 1 ]= 3
Maximum total number of points in one elementary protocol : 3
Minimum total number of points in one elementary protocol : 3


Sampling windows for the response: B
Window 1 : t= 0.5 2 14 110 150
    Nb of sampling points to be taken in this window, n[ 1 ]= 3
Maximum total number of points in one elementary protocol : 3
Minimum total number of points in one elementary protocol : 3



Now evaluating the Fisher Information Matrix for the 100 protocols generated


BEST ONE GROUP PROTOCOL:

Sample times for response: A
            times freq Subjects condinit
1 c(0.5, 49, 180)    1      100  c(0, 0)
Sample times for response: B
          times freq Subjects condinit
1 c(2, 14, 110)    1      100  c(0, 0)


Associated criterion: 2549.118



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



Optimised design:
Sample times for response: A
            times      freq Subjects condinit
1 c(0.5, 49, 180) 0.8449125 84.49125  c(0, 0)
2 c(0.5, 30, 180) 0.1550875 15.50875  c(0, 0)


Sample times for response: B
          times      freq Subjects condinit
1 c(2, 14, 110) 0.8449125 84.49125  c(0, 0)
2 c(2, 14, 110) 0.1550875 15.50875  c(0, 0)
```

```
Associated optimised criterion: 2549.662



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

             [,1]        [,2]        [,3]          [,4]         [,5]
 [1,]   2.6759559    10.42278   -56.61471    -0.7251327 0.000000e+00
 [2,]  10.4227805 50031.09185  7276.78572   657.1611100 0.000000e+00
 [3,] -56.6147102  7276.78572 18134.47440 -6628.5770930 0.000000e+00
 [4,]  -0.7251327   657.16111 -6628.57709 38614.6748550 0.000000e+00
 [5,]   0.0000000     0.00000     0.00000     0.0000000 7.931719e+02
 [6,]   0.0000000     0.00000     0.00000     0.0000000 5.505482e-01
 [7,]   0.0000000     0.00000     0.00000     0.0000000 3.962926e-03
 [8,]   0.0000000     0.00000     0.00000     0.0000000 2.159984e+00
 [9,]   0.0000000     0.00000     0.00000     0.0000000 9.940642e+00
             [,6]         [,7]         [,8]         [,9]
 [1,]   0.0000000 0.000000e+00    0.0000000     0.000000
 [2,]   0.0000000 0.000000e+00    0.0000000     0.000000
 [3,]   0.0000000 0.000000e+00    0.0000000     0.000000
 [4,]   0.0000000 0.000000e+00    0.0000000     0.000000
 [5,]   0.5505482 3.962926e-03    2.1599843     9.940642
 [6,] 566.1136216 1.470446e-01   80.1122193   369.810105
 [7,]   0.1470446 7.455466e+02    0.5814468   131.816702
 [8,]  80.1122193 5.814468e-01 7762.5613244  1446.770561
 [9,] 369.8101053 1.318167e+02 1446.7705613 23734.044514




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

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

       Beta    StdError      RSE
V    12.200 0.637550069 5.225820 %
Vm    0.082 0.004646813 5.666846 %
km    0.370 0.008266279 2.234130 %
Alin  0.100 0.005290312 5.290312 %



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

     omega²   StdError      RSE
V      0.25 0.03550730 14.20292 %
Vm     0.25 0.04226093 16.90437 %
Alin   0.25 0.03664206 14.65682 %
```

```
----------------------- Standard deviation of residual error ---------------------

           Sigma    StdError      RSE
sig.slopeA   0.2 0.011419528 5.709764 %
sig.interB   0.1 0.006562738 6.562738 %


******************************* DETERMINANT *********************************

4.553482e+30

******************************* CRITERION ***********************************

2549.662




****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     14719.494342            2.46017
max     51662.449933        14719.49434
max/min     3.509798         5983.12052


****************** CORRELATION MATRIX ******************

             [,1]        [,2]       [,3]        [,4]          [,5]
 [1,]  1.00000000 -0.10289582  0.2826168  0.07960564  0.000000e+00
 [2,] -0.10289582  1.00000000 -0.2708936 -0.08784124  0.000000e+00
 [3,]  0.28261681 -0.27089364  1.0000000  0.27291243  0.000000e+00
 [4,]  0.07960564 -0.08784124  0.2729124  1.00000000  0.000000e+00
 [5,]  0.00000000  0.00000000  0.0000000  0.00000000  1.000000e+00
 [6,]  0.00000000  0.00000000  0.0000000  0.00000000 -5.760357e-04
 [7,]  0.00000000  0.00000000  0.0000000  0.00000000  6.305945e-05
 [8,]  0.00000000  0.00000000  0.0000000  0.00000000 -6.134416e-04
 [9,]  0.00000000  0.00000000  0.0000000  0.00000000 -2.145170e-03
               [,6]          [,7]          [,8]        [,9]
 [1,]  0.0000000000  0.000000e+00  0.0000000000  0.00000000
 [2,]  0.0000000000  0.000000e+00  0.0000000000  0.00000000
 [3,]  0.0000000000  0.000000e+00  0.0000000000  0.00000000
 [4,]  0.0000000000  0.000000e+00  0.0000000000  0.00000000
 [5,] -0.0005760357  6.305945e-05 -0.0006134416 -0.00214517
 [6,]  1.0000000000  2.866158e-03 -0.0277520479 -0.09748089
 [7,]  0.0028661579  1.000000e+00  0.0030368822 -0.03161925
 [8,] -0.0277520479  3.036882e-03  1.0000000000 -0.10337783
 [9,] -0.0974808856 -3.161925e-02 -0.1033778325  1.00000000



Time difference of 4.783273 secs
sys.self
     0.2
```



3. Example 3: PK model with inter-occasion variability

- 40 subjects with a dose of 30
- Allowed sampling times: 0.5,1,1.5,2,4,6,8
- Number of sampling times to be optimized: 4

3.1. Input File (P-FIM)

```
##############################################################################
##                          INPUT FILE FOR PFIM 4.0                         ##
##############################################################################


#Name of the project
#--------------------
project<-"EXAMPLE 3"

#FIM: Population  (P) or Individual (I) or Bayesian (B) Fisher information matrix
#-------------------------------------
FIM<-"P"


#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"OPT"

################## MODEL OPTION ############################

#Model form: Differential equations (DE) or analytical form (AF)
#-------------------------------------------------------------
```

```
modelform<-"AF"

###### ANALYTICAL MODEL OPTION ############################
############################################################

#Identical dose in each elementary design (Yes=T, No=F)
#-----------------------------------------------------------
dose.identical<-T

# If 'Yes', enter the value of the dose,
# else, enter the vector of the dose values for each elementary design
#-------------------------------------------------------------------
dose<-c(30)

#Vector of the times intervals of each expression
#-----------------------------------------------------------
boundA<-list(c(0,Inf))

#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-----------------------------------------------------------
NUM<-F

###### END ANALYTICAL MODEL OPTION ########################

#Name of the fixed effects parameters
#-------------------------------------
parameters<-c("ka","V","Cl")

#Fixed effects parameters values
#--------------------------------
beta<-c(1,3.5,2)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#---------------------------------
beta.fixed<-c(F,F,F)

#Number of occasions
#-------------------------------------------------------------------------
n_occ<-2

#Random effect model (1) = additive  (2) = exponential
#-----------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#---------------------------------------------------
omega<-diag(c(0.09,0.09,0.09))

#Diagonal Matrix of variance for inter-occasion random effects:
#---------------------------------------------------
gamma<-diag(c(0.0225,0.0225,0.0225))

#Standard deviation of residual error (sig.inter+sig.slope*f)^2:
#-----------------------------------------------------------------
sig.interA<-0.1
sig.slopeA<-0
```

```
#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5,2,4,8))

#Vector of initial proportions or numbers of subjects for each elementary design
#-------------------------------------------------------------
subjects<-c(40)

#Subjects input: (1) for number of subjects (2) for proportions of subjects
#-----------------------------------------------------------------------------
subjects.input<-1

#If 'proportions of subjects' give the total number of samples
#-------------------------------------------------------------
#Ntot<-40
```

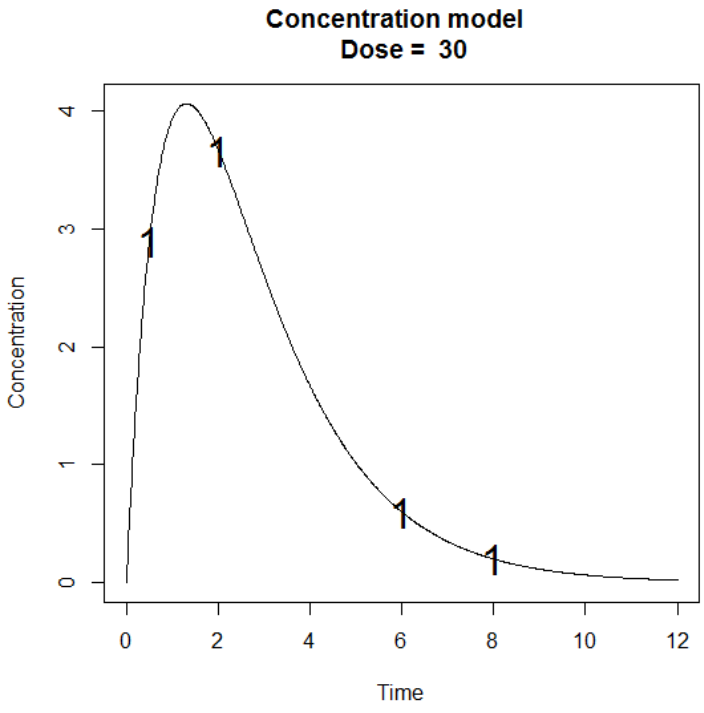
3.2. Output File

```
PFIM 4.0

Option: 1


Project: EXAMPLE 3

Date: Wed Jan 29 10:30:16 2014



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

Analytical function model:

dose/V * ka/(ka - (Cl/V)) * (exp(-(Cl/V) * t) - exp(-ka * t))



Initial design:


Sample times for response: A
          Protocol subjects doses
1 c=(0.5, 2, 4, 8)       40    30


Total number of samples: 160

Associated criterion value: 1826.068

Identical sampling times for each response: FALSE

Number of occasions: 2

Random effect model: Trand =  2

Variance error model response A : ( 0.1 + 0 *f)^2

 Optimization step:
```

```
Sampling windows for the response: A
Window 1 : t= 0.5 1 1.5 2 4 6 8
    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



Now evaluating the Fisher Information Matrix for the 35 protocols generated


BEST ONE GROUP PROTOCOL:

Sample times for response: A
            times freq Subjects doses
1 c(0.5, 2, 6, 8)    1       40    30


Associated criterion: 1913.953


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


Optimised design:
Sample times for response: A
            times freq Subjects doses
1 c(0.5, 2, 6, 8)    1       40    30




Associated optimised criterion: 1913.953



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

            [,1]       [,2]      [,3]         [,4]         [,5]         [,6]
 [1,] 342.070959 -11.909950  2.294299    0.0000000    0.0000000    0.0000000
 [2,] -11.909950  29.371134  0.624963    0.0000000    0.0000000    0.0000000
 [3,]   2.294299   0.624963 98.030214    0.0000000    0.0000000    0.0000000
 [4,]   0.000000   0.000000  0.000000 1462.6567613   21.7203074    0.2631903
 [5,]   0.000000   0.000000  0.000000   21.7203074 1618.1679873    0.2392295
 [6,]   0.000000   0.000000  0.000000    0.2631903    0.2392295 1921.9845543
 [7,]   0.000000   0.000000  0.000000  731.3283806   10.8601537    0.1315952
 [8,]   0.000000   0.000000  0.000000   10.8601537  809.0839937    0.1196147
 [9,]   0.000000   0.000000  0.000000    0.1315952    0.1196147  960.9922772
[10,]   0.000000   0.000000  0.000000  414.3130643  276.7056180   28.1724200
              [,7]          [,8]         [,9]       [,10]
 [1,] 0.000000e+00 0.000000e+00 0.000000e+00     0.00000
 [2,] 0.000000e+00 0.000000e+00 0.000000e+00     0.00000
 [3,] 0.000000e+00 0.000000e+00 0.000000e+00     0.00000
 [4,] 7.313284e+02 1.086015e+01 1.315952e-01   414.31306
 [5,] 1.086015e+01 8.090840e+02 1.196147e-01   276.70562
 [6,] 1.315952e-01 1.196147e-01 9.609923e+02    28.17242
 [7,] 1.252260e+04 4.388584e+03 3.991645e+01  2608.00290
```

```
 [8,] 4.388584e+03 1.961824e+04 6.185025e+01  1889.93103
 [9,] 3.991645e+01 6.185025e+01 3.560094e+04   926.11512
[10,] 2.608003e+03 1.889931e+03 9.261151e+02 20551.58326



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

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

   Beta   StdError      RSE
ka  1.0 0.05445931 5.445931 %
V   3.5 0.18585115 5.310033 %
Cl  2.0 0.10101646 5.050823 %


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

   omega²   StdError      RSE
ka   0.09 0.02660961 29.56624 %
V    0.09 0.02516549 27.96165 %
Cl   0.09 0.02296550 25.51722 %


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

   gamma²    StdError      RSE
ka 0.0225 0.009552479 42.45546 %
V  0.0225 0.007539081 33.50703 %
Cl 0.0225 0.005339183 23.72970 %


------------------------ Standard deviation of residual error ---------------------

           Sigma    StdError      RSE
sig.interA   0.1 0.007098313 7.098313 %


****************************** DETERMINANT *******************************

6.596486e+32

****************************** CRITERION *********************************

1913.953

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min     18402.235009           28.91084
max     35690.090280        18402.23501
max/min     1.939443          636.51680


****************** CORRELATION MATRIX ******************

             [,1]        [,2]        [,3]          [,4]          [,5]
 [1,]  1.00000000  0.11898386 -0.01401299  0.0000000000  0.0000000000
```

```
 [2,]  0.11898386  1.00000000 -0.01323044  0.0000000000  0.0000000000
 [3,] -0.01401299 -0.01323044  1.00000000  0.0000000000  0.0000000000
 [4,]  0.00000000  0.00000000  0.00000000  1.0000000000 -0.0192963816
 [5,]  0.00000000  0.00000000  0.00000000 -0.0192963816  1.0000000000
 [6,]  0.00000000  0.00000000  0.00000000 -0.0001505132 -0.0001422569
 [7,]  0.00000000  0.00000000  0.00000000 -0.1695130986  0.0478699472
 [8,]  0.00000000  0.00000000  0.00000000  0.0533692914 -0.1475617586
 [9,]  0.00000000  0.00000000  0.00000000  0.0019716819  0.0016536078
[10,]  0.00000000  0.00000000  0.00000000 -0.0509821501 -0.0400931222
               [,6]          [,7]          [,8]         [,9]         [,10]
 [1,]  0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
 [2,]  0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
 [3,]  0.0000000000  0.0000000000  0.0000000000  0.000000000  0.0000000000
 [4,] -0.0001505132 -0.1695130986  0.0533692914  0.001971682 -0.0509821501
 [5,] -0.0001422569  0.0478699472 -0.1475617586  0.001653608 -0.0400931222
 [6,]  1.0000000000  0.0002223017  0.0002468429 -0.116089527 -0.0005440808
 [7,]  0.0002223017  1.0000000000 -0.2776209058  0.003259840 -0.1332452332
 [8,]  0.0002468429 -0.2776209058  1.0000000000 -0.000289734 -0.0472408862
 [9,] -0.1160895270  0.0032598400 -0.0002897340  1.000000000 -0.0341367622
[10,] -0.0005440808 -0.1332452332 -0.0472408862 -0.034136762  1.0000000000


Time difference of 1.110063 secs
sys.self
    0.05
```



4. Example 4: PK model with inter-occasion variability and covariate effects (Equivalence test)

- 40 subjects with a dose of 30
- Allowed sampling times: 0.5, 2, 4, 6, 8

- Number of sampling times to be optimized: 3

4.1. Input File (P-FIM)

```
#########################################################################
##                          INPUT FILE FOR PFIM 4.0                    ##
#########################################################################


#Name of the project
#--------------------
project<-"EXAMPLE 4"

#Name of the file containing the PK or PD model
#-----------------------------------------
file.model<-"model.r"

#Name of the output file for the results and for the Fisher information matrix
#--------------------------------------
output<-"Stdout.r";
outputFIM<-"";

#FIM: Population (P) or Individual (I) or Bayesian (B) Fisher information matrix
#--------------------------------------
FIM<-"P"

#RUN:  Evaluation (EVAL) or Optimisation (OPT)
#-----------------------------------------------------
run<-"OPT"

#To display only  graphs of models and/or sensitivity functions before evaluating
the Fisher Information matrix
graph.only<-F

#Block diagonal Fisher information matrix (option<-1) or complete Fisher
information matrix (option<-2)
#-----------------------------------------------------------
option<-1

#Number of responses
#-------------------------------------------------------------------
nr<-1

################### MODEL OPTION ############################

#Model form: Differential equations (DE) or analytical form (AF)
#-------------------------------------------------------------

modelform<-"AF"

###### ANALYTICAL MODEL OPTION ############################
#########################################################

#Identical dose in each elementary design (Yes=T, No=F)
#-----------------------------------------------------------
dose.identical<-T

# If 'Yes', enter the value of the dose,
# else, enter the vector of the dose values for each elementary design
#-----------------------------------------------------------------
```

```
dose<-c(30)

#Vector of the times intervals of each expression
#-------------------------------------------------------
boundA<-list(c(0,Inf))

#Numerical derivatives  (Yes=T, No=F)
#If 'Yes', specify the model function "form" in the model file
#If 'No', specify the object "form" which is a vector of expressions in the model
file
#-------------------------------------------------------
NUM<-T

###### END ANALYTICAL MODEL OPTION ########################



#Name of the fixed effects parameters
#-----------------------------------
parameters<-c("ka","V","Cl")

#Fixed effects parameters values
#------------------------------
beta<-c(1,3.5,2)

#Some parameters may not be estimated (not estimated = T, estimated = F)
#---------------------------------
beta.fixed<-c(F,F,F)

#Number of occasions
#-------------------------------------------------------------------------
n_occ<-2

#Random effect model (1) = additive  (2) = exponential
#-----------------------------------------------------------------
Trand<-2;

#Diagonal Matrix of variance for inter-subject random effects:
#-------------------------------------------------
omega<-diag(c(0.09,0.09,0.09))

#Diagonal Matrix of variance for inter-occasion random effects:
#-------------------------------------------------
gamma<-diag(c(0.0225,0.0225,0.0225))

#List of the vectors of sampling times for each elementary design
#You can specify that a group has no sampling time by writing NULL
#(ONLY if you have several response)
#-----------------------------------------------------------------
protA<-list(c(0.5,2,4))
############################
#FEDOROV-WYNN SPECIFICATION #
############################


#Number of sampling windows
#--------------------------
nwindA<-1
#nwindB<-1
```

```
#List of vector of the allowed sampling times for each sampling window
#-------------------------------------------------------------------

sampwinA<-list(c(0.5,2,4,6,8))
#sampwinB<-list(c(0, 0.5, 1, 2, 6, 9, 12, 24, 36, 48, 72, 96, 120))


#Fixed times (times which will be in all evaluated protocols, corresponding to
fixed constraints)
#-------------------------------------------------------------------
fixed.timesA<-c()
#fixed.timesB<-c()


#List of vector of allowed number of points to be taken from each sampling window
#-------------------------------------------------------------------------------

nsampA<-list(c(3))
#nsampB<-list(c(3))

#Maximum total number of sampling times per subject
#-------------------------------------------------

nmaxptsA<-3
#nmaxptsB<-3

#Minimum total number of sampling times per subject
#-------------------------------------------------

nminptsA<-3
#nminptsB<-3
############## END OF OPTIMISATION ALGORITHM OPTION ###############
```

4.2. Output File

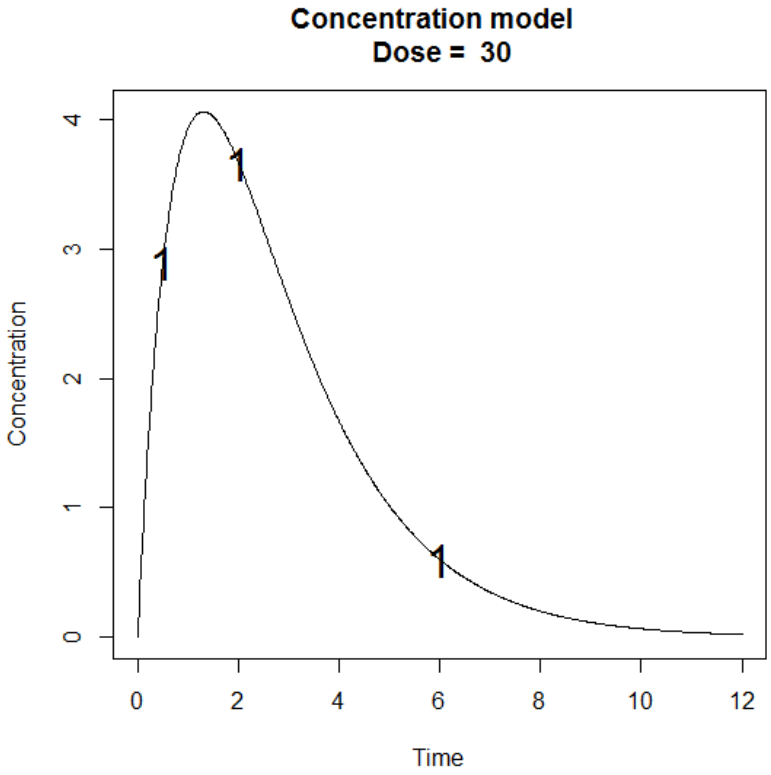
```
PFIM 4.0

Option: 1


Project: EXAMPLE 4

Date: Wed Jan 29 10:52:55 2014


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

Analytical function model:

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


Initial design:
```

```
Sample times for response: A
       Protocol subjects doses
1 c=(0.5, 2, 4)       40    30


Total number of samples: 120

Associated criterion value: 1115.614

Identical sampling times for each response: FALSE

Number of occasions: 2

Random effect model: Trand =  2

Variance error model response A : ( 0.1 + 0 *f)^2


Covariate model :

      NB: Covariates are additive on log parameters

      Covariates not changing with occasion

      Covariate 1 : Sex ( V )
    Categories References Proportions
(1)          M          *         0.5
(2)          F                    0.5



      Covariates changing with occasion

      Covariate  1 : Treat ( Cl )
    Categories References
(1)          A          *
(2)          B


    Sequences Proportions
(1)       A B         0.5
(2)       B A         0.5



Optimization step:

Sampling windows for the response: A
Window 1 : t= 0.5 2 4 6 8
    Nb of sampling points to be taken in this window, n[ 1 ]= 3
Maximum total number of points in one elementary protocol : 3
Minimum total number of points in one elementary protocol : 3




Now evaluating the Fisher Information Matrix for the 10 protocols generated
```

```
BEST ONE GROUP PROTOCOL:

Sample times for response: A
         times freq Subjects doses
1 c(0.5, 2, 6)    1       40    30


Associated criterion: 1189.867


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


Optimised design:
Sample times for response: A
         times freq Subjects doses
1 c(0.5, 2, 6)    1       40    30




Associated optimised criterion: 1189.867



Computation of the Population Fisher information matrix: option =  1

****************** FISHER INFORMATION MATRIX *****************

                                          s2
   329.525019 -14.8691158  3.6912288 -22.229595   3.834115    0.0000000
   -14.869116  28.6258030  0.9910258  51.227048   1.140631    0.0000000
     3.691229   0.9910258 97.7403300   1.572171  97.536153    0.0000000
s2 -22.229595  51.2270485  1.5721714 179.294670   1.950838    0.0000000
     3.834115   1.1406306 97.5361532   1.950838 921.108493    0.0000000
     0.000000   0.0000000  0.0000000   0.000000   0.000000 1357.8361093
     0.000000   0.0000000  0.0000000   0.000000   0.000000   34.5732189
     0.000000   0.0000000  0.0000000   0.000000   0.000000    0.6847072
     0.000000   0.0000000  0.0000000   0.000000   0.000000  693.0899074
     0.000000   0.0000000  0.0000000   0.000000   0.000000   34.3142049
     0.000000   0.0000000  0.0000000   0.000000   0.000000   24.8299228
     0.000000   0.0000000  0.0000000   0.000000   0.000000  471.2181021

      0.0000000    0.0000000 0.000000e+00 0.000000e+00     0.00000    0.00000
      0.0000000    0.0000000 0.000000e+00 0.000000e+00     0.00000    0.00000
      0.0000000    0.0000000 0.000000e+00 0.000000e+00     0.00000    0.00000
s2    0.0000000    0.0000000 0.000000e+00 0.000000e+00     0.00000    0.00000
      0.0000000    0.0000000 0.000000e+00 0.000000e+00     0.00000    0.00000
     34.5732189    0.6847072 6.930899e+02 3.431420e+01    24.82992  471.21810
   1537.8685241    0.6068128 2.694200e+01 7.729341e+02    26.16533  318.44875
      0.6068128 1910.6360130 3.082288e-01 9.221043e-01   954.18480   37.92596
     26.9419991    0.3082288 1.123026e+04 5.252065e+03   167.39074 2376.07691
    772.9340538    0.9221043 5.252065e+03 1.996723e+04   197.52750 2192.63445
     26.1653310  954.1848020 1.673907e+02 1.975275e+02 35807.24708 1526.11630
    318.4487533   37.9259602 2.376077e+03 2.192634e+03  1526.11630 5510.31204

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

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

                     Beta   StdError       RSE
ka              1.00000000 0.05577975  5.577975 %
V               3.50000000 0.26955025  7.701436 %
Cl              2.00000000 0.10700134  5.350067 %
beta_V_Sex_2    0.18232156 0.10686697 58.614553 %
beta_Cl_Treat_B 0.09531018 0.03484141 36.555810 %


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

   omega²   StdError      RSE
ka   0.09 0.02788743 30.98604 %
V    0.09 0.02590788 28.78653 %
Cl   0.09 0.02303141 25.59046 %


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

   gamma²    StdError      RSE
ka 0.0225 0.010554907 46.91070 %
V  0.0225 0.007702135 34.23171 %
Cl 0.0225 0.005353992 23.79552 %


------------------------ Standard deviation of residual error ---------------------

           Sigma   StdError      RSE
sig.interA   0.1 0.01451322 14.51322 %


****************************** DETERMINANT ********************************

8.053415e+36

****************************** CRITERION **********************************

1189.867

****************** EIGENVALUES OF THE FISHER INFORMATION MATRIX ******************

        FixedEffects VarianceComponents
min       1883.79090           12.66685
max      35923.72080         1883.79090
max/min     19.06991          148.71823


****************** CORRELATION MATRIX ******************

                                                        s2
    1.0000000000  0.1263435890 -0.022352927 -0.026138657 -0.0004354741
    0.1263435890  1.0000000000 -0.016440418 -0.712334240 -0.0004483848
   -0.0223529273 -0.0164404185  1.000000000  0.002774252 -0.3249099148
s2 -0.0261386565 -0.7123342396  0.002774252  1.000000000 -0.0003998150
   -0.0004354741 -0.0004483848 -0.324909915 -0.000399815  1.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
```

```
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000
    0.0000000000  0.0000000000  0.000000000  0.000000000  0.0000000000

    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
s2  0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    0.0000000000  0.0000000000  0.0000000000  0.0000000000  0.0000000000
    1.0000000000 -0.0194471821 -0.0002298133 -0.1511036995  0.0781512752
   -0.0194471821  1.0000000000 -0.0000652991  0.0711693764 -0.1362821286
   -0.0002298133 -0.0000652991  1.0000000000  0.0005569804  0.0003365315
   -0.1511036995  0.0711693764  0.0005569804  1.0000000000 -0.3212630803
    0.0781512752 -0.1362821286  0.0003365315 -0.3212630803  1.0000000000
    0.0125884017  0.0078633772 -0.1147072179  0.0201752344  0.0078965258
   -0.1327148141 -0.0943115113  0.0005960777 -0.2303374371 -0.1100174414

    0.000000000  0.0000000000
    0.000000000  0.0000000000
    0.000000000  0.0000000000
s2  0.000000000  0.0000000000
    0.000000000  0.0000000000
    0.012588402 -0.1327148141
    0.007863377 -0.0943115113
   -0.114707218  0.0005960777
    0.020175234 -0.2303374371
    0.007896526 -0.1100174414
    1.000000000 -0.1117917937
   -0.111791794  1.0000000000



Time difference of 0.5230298 secs
sys.self     0.06
```


Concentration model
Dose = 30
Concentration
Time
0
1
2
3
4
0
2
4
6
8
10
12
1
1
1