



## PFIM Interface 4.0

### PFIM Group

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# User guide

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## 1. Introduction

Model based optimal design approaches are increasingly performed in population pharmacokinetic/pharmacodynamics (PKPD) [1], which consist in determining a balance between the number of subjects and the number of samples per subject, as well as the allocation of times and doses, according to experimental conditions. A good choice of design is crucial for an efficient estimation of model parameters, especially when the studies are conducted in patients where only a few samples can be taken per subject. These approaches rely on the Fisher information matrix (FIM) for nonlinear mixed effect models (NLMEM), available in several software tools [2] and are a good alternative to clinical trial simulation. They require a *priori* knowledge of the model and its parameters, which can usually be obtained from previous experiments.

PFIM ([www.pfim.biostat.fr](http://www.pfim.biostat.fr)), developed in our group since 2001 [3,4], is the first tool for design evaluation and optimisation that has been developed in R. Two versions are available: a R script version and a graphical user interface version. PFIM Interface 4.0 is an extension of the graphical user version PFIM Interface 3.1 and includes several new features based on the R script program of PFIM 4.0 [5].

In this new version, for population designs, optimisation can be performed with fixed parameters or fixed sampling times. The Fisher information matrix obtained after evaluation or optimisation can be saved in a file. Additional features for Bayesian designs are now available. The Bayesian Fisher information matrix has been implemented. Design for maximum a *posteriori* estimation of individual parameters can be evaluated or optimised and the predicted shrinkage is also reported [6]. A new way has been added to specify user-defined models through an R function. It is now possible to visualise the graphs of the model and the sensitivity functions without performing evaluation or optimisation.

This documentation describes the methodology implemented in PFIM Interface 4.0 in Section 2. Section 3 describes how to specify models, either by using the PKPD library or the user-defined model option. Sections 4 and 5 explain how to install and use PFIM Interface 4.0. Section 6 present in detail an evaluation and an optimisation output of PFIM Interface 4.0. Lastly, Section 7 shows a list of available examples when downloading PFIM Interface 4.0.

## 2. Methodology

### 2.1 Design

The elementary design  $\xi_i$  of individual  $i$  ( $i = 1, \dots, N$ ) is defined by the number  $n_i$  of samples and their allocation in time  $(t_{i1}, \dots, t_{ini})$ .

For  $N$  individuals, the population design is composed of the  $N$  elementary designs such as  $\mathcal{E} = \{\xi_1, \dots, \xi_N\}$ . Usually, population designs are composed of a limited number  $Q$  of groups of individuals with identical design  $\xi_q$  within each group, performed in a number  $N_q$  of individuals. The population design can thus be written as  $\mathcal{E} = \{[\xi_1, N_1]; \dots; [\xi_Q, N_Q]\}$ .

Individual and Bayesian designs include only one elementary design.

### 2.2 Nonlinear mixed effects models

A nonlinear mixed effects model, or a population model, is defined as follows. The vector of observations  $Y_i$  for the individual  $i$  ( $i = 1, \dots, N$ ) is defined as

$$Y_i = f(\theta_i, \xi_i) + \varepsilon_i,$$

where the function  $f$  defines the nonlinear structural model,  $\theta_i$  is the vector of the  $p$ -individual parameters for individual  $i$ ,  $\xi_i$  is the elementary design of individual  $i$  and  $\varepsilon_i$  is the vector of residual error.

The vector of individual parameters  $\theta_i$  depends on  $\mu$ , the  $p$ -vector of the fixed effects parameters and on  $b_i$ , the  $p$ -vector of the random effects for individual  $i$ . The relation between  $\theta_i$  and  $(\mu, b_i)$  can be additive for a normal distribution of parameters, that is

$$\theta_i = \mu + b_i,$$

or exponential for a lognormal distribution of parameters so that

$$\theta_i = \mu \times \exp(b_i).$$

It is assumed that  $b_i \sim N(0, \Omega)$  with  $\Omega$  defined as a  $p \times p$  diagonal variance-covariance matrix, for which, each diagonal element  $\omega_j$ ,  $j = 1, \dots, p$ , represents the inter-individual variability of the  $j^{\text{th}}$  component of the vector  $b_i$ .

It is also supposed that  $\varepsilon_i \sim N(0, \Sigma_i)$ , where  $\Sigma_i$  is a  $n_i \times n_i$ -diagonal matrix such that

$$\Sigma_i(\mu, b_i, \sigma_{inter}, \sigma_{slope}, \xi_i) = \text{diag}(\sigma_{inter} + \sigma_{slope} \times f(\theta_i, \xi_i))^2.$$

The terms  $\sigma_{inter}$  and  $\sigma_{slope}$  are the additive and proportional parts of the error model, respectively. Conditionnally on the value of  $b_i$ , it is assumed that the  $\varepsilon_i$  errors are independently distributed.

In the case of  $K$  multiple responses, the vector of observations  $Y_i$  can then be composed of  $K$  vectors for the different responses:

$$Y_i = [y_{i1}^T, y_{i2}^T, \dots, y_{iK}^T]^T,$$



where  $y_{ik}$ ,  $k=1, \dots, K$ , is the vector of  $n_{ik}$  observations for the  $k^{th}$  response. Each of these responses is associated with a known function  $f_k$ , which can be grouped in a vector of multiple response model  $F$ , such as

$$F(\theta_i, \xi_i) = [f_1(\theta_i, \xi_{i1})^T, f_2(\theta_i, \xi_{i2})^T, \dots, f_K(\theta_i, \xi_{iK})^T]^T,$$

where  $\xi_i$  is composed of  $K$  sub-designs such that  $\xi_i = (\xi_{i1}, \xi_{i2}, \dots, \xi_{iK})$ . The sub-design  $\xi_{ik}$  is then defined by  $(t_{ik1}, t_{ik2}, \dots, t_{ikn_{ik}})$ , with  $n_{ik}$  sampling times for the observations of the  $k^{th}$  response, so that  $n_i = \sum_{k=1}^K n_{ik}$ . Each response can have its error model and  $\varepsilon_i$  is then the vector composed of the  $K$  vectors of residual errors  $\varepsilon_{ik}$ ,  $k=1, \dots, K$ , associated with the  $K$  responses.

## 2.3 Fisher information matrix

### 2.3.1 Population Fisher information matrix

The population Fisher information matrix  $M_F(\Psi, \xi)$  for multiple response models, for an individual with an elementary design  $\xi$ , with the vector of population parameters  $\Psi$ , is given as:

$$M_F(\Psi, \xi) \equiv \frac{1}{2} \begin{pmatrix} A(E, V) & C(E, V) \\ C^T(E, V) & B(E, V) \end{pmatrix}$$

with  $E$  and  $V$  the approximated marginal expectation and the variance of the observations of the individual. The vector of population parameter  $\Psi$  is defined by  $\Psi^T = (\mu^T, \lambda^T)$  with  $\mu$  the  $p$ -vector of the fixed effects and  $\lambda$  the vector of the variance terms.  $M_F$  is given as a block matrix (more details are given in [7-9]) with:

$$(A(E, V))_{ml} = 2 \frac{\partial E^T}{\partial \mu_m} V^{-1} \frac{\partial E}{\partial \mu_l} + \text{tr} \left( \frac{\partial V}{\partial \mu_l} V^{-1} \frac{\partial V}{\partial \mu_m} V^{-1} \right) \text{ with } m \text{ and } l = 1, \dots, p$$

$$(B(E, V))_{ml} = \text{tr} \left( \frac{\partial V}{\partial \lambda_m} V^{-1} \frac{\partial V}{\partial \lambda_l} V^{-1} \right) \text{ with } m \text{ and } l = 1, \dots, \text{dim}(\lambda)$$

$$(C(E, V))_{ml} = \text{tr} \left( \frac{\partial V}{\partial \lambda_l} V^{-1} \frac{\partial V}{\partial \mu_m} V^{-1} \right) \text{ with } l = 1, \dots, \text{dim}(\lambda) \text{ and } m = 1, \dots, p$$

If the dependence of  $V$  in  $\mu$  is neglected so that  $\frac{\partial V}{\partial \mu} = 0$ , the population

Fisher information matrix is a block diagonal matrix that is to say the block  $C$  of the matrix is supposed to be 0. Also, the block  $A$  is simplified and expressed as:

$$(A(E, V))_{ml} = 2 \frac{\partial E^T}{\partial \mu_m} V^{-1} \frac{\partial E}{\partial \mu_l} \text{ with } m \text{ and } l = 1, \dots, p$$

Since PFIM Interface 3.1, the user can choose to compute either a full or a block diagonal matrix for population designs. However, based on publications showing the better performance of the block diagonal expression compared to the full one with linearisation [2], the default option in PFIM is the block diagonal information matrix.

### Prediction of standard errors

According to the inequality of Cramer-Rao, the inverse of  $M_F$  is the lower bound of the variance-covariance matrix of any unbiased estimate of the parameters. From the square roots of the diagonal elements of the inverse of  $M_F$ , the predicted standard errors (SE) for estimated parameters can be calculated.

#### 2.3.2 Bayesian Fisher information matrix

**New feature:** The new version 4.0 of PFIM Interface enables design evaluation and optimisation for maximum a posteriori estimation of individual parameters based on the Bayesian Fisher information matrix [6].

We are interested in the precision estimation of individual parameters for a subject  $i$ , associated to the vector of observation  $y$  (index  $i$  being omitted). These individual parameters can be estimated by maximum a posteriori (MAP). As  $\mu$  is known, estimating  $\theta$  is similar to estimating  $\eta$ . More precisely, the MAP estimate of  $\eta$  is given by

$$\hat{\eta} = \operatorname{argmax} (p(\eta | y)) = \operatorname{argmax} \left( \frac{p(y | \eta) p(\eta)}{p(y)} \right) = \operatorname{argmax} (\log (p(y | \eta)) + \log (p(\eta)))$$

where  $p$  is the probability density. The Bayesian Fisher information matrix, taking into account the a priori distribution of the random effects, is expressed as

$$\begin{aligned} M_{BF}(\xi) &= -E_{\eta} \left( \frac{\partial^2 \log(p(\eta | y))}{\partial \eta \partial \eta^T} \right) = -E_{\eta} \left( E_{y | \eta} \left( \frac{\partial^2 \log(p(y | \eta))}{\partial \eta \partial \eta^T} \right) \right) - E_{\eta} \left( \frac{\partial^2 \log(p(\eta))}{\partial \eta \partial \eta^T} \right) \\ &= E_{\eta} (M_{IF}(\mathcal{G}(\mu, \eta), \xi)) - \Omega^{-1} \end{aligned}$$

where  $M_{IF}(\theta, \xi) = -E_y \left( \frac{\partial^2 \log(p(y | \theta))}{\partial \theta \partial \theta^T} \right)$ , expression of the individual Fisher

information matrix in classical nonlinear regression models. The expectation  $E_{\eta} (M_{IF}(\mathcal{G}(\mu, \eta), \xi))$  can be obtained by first order approximation of the model around the expectation of random effects (i.e., 0).

The shrinkage (Sh) is quantified from the ratio of the estimation variance predicted by  $M_{BF}^{-1}$  and the a priori variance, and can be calculated as the diagonal elements of the matrix  $I - W(\xi) = M_{BF}(\xi)^{-1} \Omega^{-1}$  (see [6] for more details).



When a parameter has an a priori variance equal to 0, it will be considered as fixed to the mean value and no predicted shrinkage will be computed.

## **2.4 Design evaluation**

Population, individual and Bayesian design evaluation is based on the computation of the population, individual and Bayesian Fisher information matrix, respectively. During this process, the expected standard errors on the population or individual parameters with the design are evaluated. The user can choose to fix one or several parameters in the model that will not be computed in the Fisher information matrix.

Eigenvalues and conditional number are given by default. When considering design for Bayesian estimation of individual parameters, the shrinkages are also reported.

The computed Fisher information matrix can be saved in a file if requested.

## **2.5 Design optimisation**

PFIM Interface 4.0 allows to optimise exact or a statistical designs. In the case of an exact optimisation, the group structure of the design is fixed: the number of elementary designs, the number of samples per elementary design and the number of subjects per elementary design are given and the design variables to optimise are only the sampling times. In the case of statistical optimisation, the sampling times (number and allocation) and the proportions of subjects in each elementary design are optimised.

PFIM Interface 4.0 optimises population design using the D-optimal criterion, *i.e.* maximising the determinant of the population Fisher information matrix, or, similarly, minimising its inverse.

The Fedorov-Wynn algorithm and the Simplex algorithm are available to design optimisation. Compared to the Simplex algorithm, the Fedorov-Wynn algorithm better affords high design variables optimisation. Moreover, it considers only pre-specified sampling times, avoiding, clinically unfeasible sampling times. The drawback is the huge number of elementary designs to be created (with corresponding huge number of Fisher information matrices to compute) when the set of allowed sampling times is very large.

### **2.5.1 Simplex algorithm**

The Simplex algorithm optimises statistical or exact designs in constrained intervals, given a total number of samples.

An initial population design needs to be supplied to start the optimisation. The maximum number of elementary designs and the number of sampling times per elementary design are fixed, the sampling times and the proportions of subjects in each elementary design are then optimised. From this initial design, initial vertices for the simplex algorithm are derived, reducing successively each component by 20% (a default value which can be changed) from the original component.

PFIM Interface 4.0 uses the Splus function "fun.amoeba" from Daniel Heitjan (revised 12/94), which is a translation from the Numerical Recipes for Nelder and Mead Simplex function [10].

### **2.5.2 Fedorov-Wynn algorithm**

The Fedorov-Wynn algorithm is specifically dedicated to design optimisation problems and has the property to converge towards the D-optimal design [11-

13]. It optimises statistical designs for a given total number of samples. The sampling times are chosen among a given finite set of times. Minimum and maximum numbers of samples per subject are specified. To start the algorithm, an initial population design is then required. The Fedorov-Wynn algorithm is programmed in a C code and is linked to PFIM Interface 4.0 through a dynamic library, called libFED.dll and libFED64.dll for R 32-bit and 64-bit respectively. Moreover, PFIM Interface uses the function `combn` in the R package "combinat".

**New feature:** The best one group protocol, which maximises the determinant of the elementary Fisher information matrix of all elementary protocols chosen among the predefined set of samples, is given by default when running Fedorov-Wynn algorithm (before calling the dynamic library). This is the optimal protocol for individual design and Bayesian design. Moreover, in PFIM Interface 4.0, optimisation with Fedorov-Wynn algorithm can be performed assuming that some sampling times are fixed.

### 3. Models

Models in PFIM Interface 4.0 can be specified either through their analytical form or as a solution of system of differential equations. PFIM Interface provides libraries of models (see Section 3.1), and users may also define their own model analytically or using a system of differential equations (see Section 3.2).

The PFIM Interface 4.0 library implements R expressions or differential equation systems for PKPD models. The PK model library includes one, two and three compartment models with linear elimination and with Michaelis-Menten elimination. The PD model library supports immediate response models (alone or linked to a pharmacokinetic model) and the turnover response models (linked to pharmacokinetic model). These libraries have been derived from the PKPD library developed by Bertrand and Mentré for the MONOLIX software, and all analytical expressions are in that document [14]. A documentation of PKPD models for PFIM Interface is available when downloading PFIM Interface 4.0. Presently, there is no model with lag time in the library.

**New feature:** In the previous versions of PFIM Interface, a user-defined model given in analytical form needed to be specified through an R expression. An alternative way to write the model is now available, through an R function with a specific format (see section 3.2.3).

#### 3.1 Library of models

##### 3.1.1 Library of pharmacokinetic models

Two types of PK models can be used in PFIM Interface 4.0, PK models with a first order linear elimination or PK models with a Michaelis-Menten elimination. The PK models with a linear elimination are written using an analytical form through an R expression whereas the PK models with a Michaelis-Menten elimination are written using a differential equation system.

The following sections show the list of models for each type of PK model in separate tables. These tables display all the information in order to use the model function chosen. The model is described by:

- a **name**
- the type of **input**
- the type of **elimination**
- the **number of compartments**
- the parameters used (**parameterisation**)
- the type of **administration** (**sd** : single dose, **md**: multiple dose, **ss**: steady state) depending on administration type, additional variables may be required. They are specified in the arguments (**N**: number of doses, **tau**: interval between two doses, **TInf**: duration of the infusion, **dose**: dose)

For models with infusion, the user has to specify the duration of infusion (TInf) in the needed variables. The rate of infusion is computed automatically in the function model by the expression: dose/TInf. The dose has to be specified in the tab design (see section 5.4).

For example, if one uses after a multiple dose administration, the first order oral absorption with one compartment model (**orall\_1cpt\_kaVCl\_md**) from the library which has three parameters (**ka**, **Cl** and **V**) and two needed

variables (**N**, **tau**), the number of doses (**N**) and the interval between two doses (**tau**) have to be specified.

#### **Pharmacokinetic models with a linear elimination**

The library of PK models with linear elimination is composed of one, two and three compartment models for the three types of input (bolus, infusion and first order oral absorption) and the three types of administration (single dose, multiple dose, steady state).

The list of these PK models is given in Table 1.

Table 1. Pharmacokinetic models with first order linear elimination included in the library of models

Name	Input	Cpt	Elimination	Parameterisation	Administration	Arguments
<b>bolus_1cpt_Vk</b>	IV-bolus	1	1st order	V, k	sd	-
					md	N, tau
					ss	tau
<b>bolus_1cpt_VC1</b>	IV-bolus	1	1st order	V, Cl	sd	-
					md	N, tau
					ss	tau
<b>infusion_1cpt_Vk</b>	IV-infusion	1	1st order	V, k	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
<b>infusion_1cpt_VC1</b>	IV-infusion	1	1st order	V, Cl	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
<b>oral1_1cpt_kaVk</b>	1st order	1	1st order	ka, V, k	sd	-
					md	N, tau
					ss	tau
<b>oral1_1cpt_kaVC1</b>	1st order	1	1st order	ka, V, Cl	sd	-
					md	N, tau
					ss	tau
<b>bolus_2cpt_Vkk12k21</b>	IV-bolus	2	1st order	V, k, k12, k21	sd	-
					md	N, tau
					ss	tau
<b>bolus_2cpt_C1V1QV2</b>	IV-bolus	2	1st order	Cl, V1, Q, V2	sd	-
					md	N, tau
					ss	tau
<b>infusion_2cpt_Vkk12k21</b>	IV-infusion	2	1st order	V, k, k12, k21	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau

<b>infusion_2cpt_C1V1QV2</b>	IV-infusion	2	1st order	Cl, V1, Q, V2	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
<b>oral1_2cpt_kaVkk12k21</b>	1st order	2	1st order	ka, V, k, k12, k21	sd	-
					md	N, tau
					ss	tau
<b>oral1_2cpt_kaC1V1QV2</b>	1st order	2	1st order	ka, Cl, V1, Q, V2	sd	-
					md	N, tau
					ss	tau
<b>bolus_3cpt_Vkk12k21k13k31</b>	IV-bolus	3	1st order	V, k, k12, k21, k13, k31	sd	-
					md	N, tau
					ss	tau
<b>bolus_3cpt_C1V1Q1V2Q2V3</b>	IV-bolus	3	1st order	Cl, V1, Q1, V2, Q2, V3	sd	-
					md	N, tau
					ss	tau
<b>infusion_3cpt_Vkk12k21k13k31</b>	IV-infusion	3	1st order	V, k, k12, k21, k13, k31	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
<b>infusion_3cpt_C1V1Q1V2Q2V3</b>	IV-infusion	3	1st order	Cl, V1, Q1, V2, Q2, V3	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
<b>oral1_3cpt_kaVkk12k21k13k31</b>	1st order	3	1st order	ka, V, k, k12, k21, k13, k31	sd	-
					md	N, tau
					ss	tau
<b>oral1_3cpt_kaC1V1Q1V2Q2V3</b>	1st order	3	1st order	ka, Cl, V1, Q1, V2, Q2, V3	sd	-
					md	N, tau
					ss	tau



## Pharmacokinetic models with a Michaelis-Menten elimination

One, two and three compartment models are implemented for the three types of input. For bolus input, only single dose models are implemented. For infusion and first order absorption input, single dose and multiple dose are implemented. There is no steady-state form for PK models with Michaelis-Menten elimination (in this case the user can use a multiple dose model with enough doses to reach SS). The list of these PK models is given in Table 2.



For models with a bolus input, the dose has to be specified in the tab of the ODE variables (see section 5.3) as the initial condition of the differential equation system. For models with infusion or first order absorption input, dose has to be specified as an argument and NOT IN THE INITIAL CONDITION OF THE MODEL IN THE ODE VARIABLE TAB.



As the dose is an argument, it is not possible to specify different doses per group for models with infusion or first order absorption input. All groups of the design considered have the same dose. Otherwise, the user should use the user defined model option.

Table 2. Pharmacokinetic models with Michaelis-Menten elimination included in the library of models

Name	Input	Cpt	Elimination	Parameterisation	Administration	Arguments
<b>bolus_1cpt_VVmkm</b>	IV-bolus	1	Michaelis-Menten	V, Vm, km	sd	-
<b>infusion_1cpt_VVmkm</b>	IV-infusion	1	Michaelis-Menten	V, Vm, km	sd md	doseMM, TInf doseMM, TInf, tau
<b>oral1_1cpt_kaVVmkm</b>	1st order	1	Michaelis-Menten	ka, V, Vm, km	sd md	doseMM doseMM, tau
<b>bolus_2cpt_Vk12k21Vmkm</b>	IV-bolus	2	Michaelis-Menten	V, k12, k21, Vm, km	sd	-
<b>bolus_2cpt_V1QV2Vmkm</b>	IV-bolus	2	Michaelis-Menten	V1, Q, V2, Vm, km	sd	-
<b>infusion_2cpt_Vk12k21Vmkm</b>	IV-infusion	2	Michaelis-Menten	V, k12, k21, Vm, km	sd md	doseMM, TInf doseMM, TInf, tau
<b>infusion_2cpt_V1QV2Vmkm</b>	IV-infusion	2	Michaelis-Menten	V1, Q, V2, Vm, km	sd md	doseMM, TInf doseMM, TInf, tau
<b>oral1_2cpt_kaVk12k21Vmkm</b>	1st order	2	Michaelis-Menten	ka, V, k12, k21, Vm, km	sd md	doseMM doseMM, tau
<b>oral1_2cpt_kaV1QV2Vmkm</b>	1st order	2	Michaelis-Menten	ka, V1, Q, V2, Vm, km	sd md	doseMM doseMM, tau
<b>bolus_3cpt_Vk12k21k31k13Vmkm</b>	IV-bolus	3	Michaelis-Menten	V, k12, k21, k13, k31, Vm, km	sd	-
<b>bolus_3cpt_V1Q1V2Q2V3Vmkm</b>	IV-bolus	3	Michaelis-Menten	V1, Q1, V2, Q2, V3, Vm, km	sd	-
<b>infusion_3cpt_Vk12k21k13k31Vmkm</b>	IV-infusion	3	Michaelis-Menten	V, k12, k21, k13, k31, Vm, km	sd md	doseMM, TInf doseMM, TInf, tau
<b>infusion_3cpt_V1Q1V2Q2V3Vmkm</b>	IV-infusion	3	Michaelis-Menten	V1, Q1, V2, Q2, V3, Vm, km	sd md	doseMM, TInf doseMM, TInf, tau
<b>oral1_3cpt_kak12k21k13k31Vmkm</b>	1st order	3	Michaelis-Menten	ka, k12, k21, k13, k31, Vm, km	sd md	doseMM doseMM, tau
<b>oral1_3cpt_kaV1Q1V2Q2V3Vmkm</b>	1st order	3	Michaelis-Menten	ka, V1, Q1, V2, Q2, V3, Vm, km	sd md	doseMM doseMM, tau

### 3.1.2 Library of pharmacodynamic models

The library of PD models supports immediate response models (either as a function of observed concentrations, or linked to a pharmacokinetic model) and turnover response models (linked to pharmacokinetic models). The following tables present these models, giving the following elements for each drug model:

- the **name** of the model function in the library
- the parameters used (**parameterisation**)

#### Immediate response pharmacodynamic models alone

Linear, quadratic, logarithmic, Emax, sigmoid Emax, I<sub>max</sub>, sigmoid I<sub>max</sub> models with null or constant baseline are available. The list of these models is given in Table 3.

These models are written in closed form and can be used in the case of a model with one response (PD evaluation or optimisation).

For these models, the design variables are the concentrations or the doses instead of the sampling times.

For example, if one uses a linear drug action model with a constant baseline (**immed\_lin\_const**) from the library, the model uses two parameters (**Alin, S0**).

#### Pharmacodynamic models linked to pharmacokinetic model

In this section, we consider models with two responses, with one response for the PK and the other one for the PD. We thus optimise sampling times for both responses using a PK/PD model. Using the libraries of models, we have four cases to compose the PK/PD model depending on the form for each submodel: either with an analytical form (AF) or a differential equation system (ODE).

Therefore, there are four cases of PK/PD models in PFIM library:

1. PK model with linear elimination (AF) and immediate response PD model (AF)
2. PK model with linear elimination (AF) and turnover response PD model (ODE)
3. PK model with Michaelis-Menten elimination (ODE) and immediate response PD model (AF)
4. PK model with Michaelis-Menten elimination and turnover response PD model (ODE)

Table 3. Immediate response pharmacodynamic models included in the PD library for PD alone and for PK/PD model

Drug action models	Baseline			
	Null baseline		Constant baseline	
	Name	Parameterisation	Name	Parameterisation
Linear	<b>immed_lin_null</b>	Alin	<b>immed_lin_const</b>	Alin, S0
Quadratic	<b>immed_quad_null</b>	Alin, Aquad	<b>immed_quad_const</b>	Alin, Aquad, S0
Logarithmic	<b>immed_log_null</b>	Alog	<b>immed_log_const</b>	Alog, S0
E <sub>max</sub>	<b>immed_E<sub>max</sub>_null</b>	E <sub>max</sub> , C50	<b>immed_E<sub>max</sub>_const</b>	E <sub>max</sub> , C50, S0
Sigmoid E <sub>max</sub>	<b>immed_gammaE<sub>max</sub>_null</b>	E <sub>max</sub> , C50, gamma	<b>immed_gammaE<sub>max</sub>_const</b>	E <sub>max</sub> , C50, gamma, S0
I <sub>max</sub>	<b>immed_I<sub>max</sub>_null</b>	I <sub>max</sub> , C50	<b>immed_I<sub>max</sub>_const</b>	I <sub>max</sub> , C50, S0
Sigmoid I <sub>max</sub>	<b>immed_gammaI<sub>max</sub>_null</b>	I <sub>max</sub> , C50, gamma	<b>immed_gammaI<sub>max</sub>_const</b>	I <sub>max</sub> , C50, gamma, S0

To use PFIM Interface for design evaluation and optimisation for a PK/PD model, the two models must be in the same format.

In the first case, immediate response pharmacodynamic models are written with an analytical form and thus they can be associated to pharmacokinetic models with first order linear elimination (Table 1) which are also written with analytical forms. In this case, the user has to complete the tab using analytical form options.

However, for the three other cases, the PK response and the PD response are written either with different forms or both with a differential equation system (Case 4). That is why, PFIM Interface 4.0 calls a specific function in order to create a system of differential equations describing the corresponding PK/PD model.

For these cases, the user has thus to complete the tab of the ODE variables (section 5.3.3).

The list of the immediate response PD models is thus given in Table 3 plus those of Table 4. The list of the turnover response PD models is given in Table 5.

For the second case where a PK model with linear elimination is associated to a turnover PD response model, the PK model is written with a differential equations system. Consequently, only some PK models from the Table 1 are implemented:

- for bolus input, only single dose models;
- for infusion input, single dose and multiple dose
- for first order absorption input, single dose and multiple dose\\



For models with a bolus input, the dose has to be specified in the tab of the ODE variables (section 5.3.3) as the initial condition of the differential equation system. For models with infusion or first order absorption input, dose has to be specified as an argument. Consequently, it is not possible to specify different doses per group for models with infusion or first order absorption input. All groups of the design considered have the same dose. Otherwise, the user should use the user defined model option.

Table 4. Immediate response pharmacodynamic models linked to a pharmacokinetic model included in the library\*

Drug action models	Baseline/disease models					
	Linear progression		Exponential increase		Exponential decrease	
	Name	Param.	Name	Param.	Name	Param.
Linear	<b>immed_lin_lin</b>	Alin, S0, kprog	<b>immed_lin_exp</b>	Alin, S0, kprog	<b>immed_lin_dexp</b>	Alin, S0, kprog
Quadratic	<b>immed_quad_lin</b>	Alin, Aquad, S0, kprog	<b>immed_quad_exp</b>	Alin, Aquad, S0, kprog	<b>immed_quad_dexp</b>	Alin, Aquad, S0, kprog
Logarithmic	<b>immed_log_lin</b>	Alog, S0, kprog	<b>immed_log_exp</b>	Alog, S0, kprog	<b>immed_log_dexp</b>	Alog, S0, kprog
E <sub>max</sub>	<b>immed_E<sub>max</sub>_lin</b>	E <sub>max</sub> , C50, S0, kprog	<b>immed_E<sub>max</sub>_exp</b>	E <sub>max</sub> , C50, S0, kprog	<b>immed_E<sub>max</sub>_dexp</b>	E <sub>max</sub> , C50, S0, kprog
Sigmoid E <sub>max</sub>	<b>immed_gammaE<sub>max</sub>_lin</b>	E <sub>max</sub> , C50, gamma, S0, kprog	<b>immed_gammaE<sub>max</sub>_exp</b>	E <sub>max</sub> , C50, gamma, S0, kprog	<b>immed_gammaE<sub>max</sub>_dexp</b>	E <sub>max</sub> , C50, gamma, S0, kprog
I <sub>max</sub>	<b>immed_I<sub>max</sub>_lin</b>	I <sub>max</sub> , C50, S0, kprog	<b>immed_I<sub>max</sub>_exp</b>	I <sub>max</sub> , C50, S0, kprog	<b>immed_I<sub>max</sub>_dexp</b>	I <sub>max</sub> , C50, S0, kprog
Sigmoid I <sub>max</sub>	<b>immed_gammaI<sub>max</sub>_lin</b>	I <sub>max</sub> , C50, gamma, S0, kprog	<b>immed_gammaI<sub>max</sub>_exp</b>	I <sub>max</sub> , C50, gamma, S0, kprog	<b>immed_gammaI<sub>max</sub>_dexp</b>	I <sub>max</sub> , C50, gamma, S0, kprog

\* In addition to those in Table 3.

Table 5. Turnover response pharmacodynamic models linked to a pharmacokinetic model included in the library

Types of response	Models with impact on the			
	Input		Output	
	Name	Parameterisation	Name	Parameterisation
<b>E<sub>max</sub></b>	turn_input_Emax	Rin, kout, Emax, C50	turn_output_Emax	Rin, kout, Emax, C50
<b>Sigmoid E<sub>max</sub></b>	turn_input_gammaEmax	Rin, kout, Emax, C50, gamma	turn_output_gammaEmax	Rin, kout, Emax, C50, gamma
<b>I<sub>max</sub></b>	turn_input_Imax	Rin, kout, Imax, C50	turn_output_Imax	Rin, kout, Imax, C50
<b>Sigmoid I<sub>max</sub></b>	turn_input_gammaImax	Rin, kout, Imax, C50, gamma	turn_output_gammaImax	Rin, kout, Imax, C50, gamma
<b>Full I<sub>max</sub><sup>a</sup></b>	turn_input_Imaxfull	Rin, kout, C50	turn_output_Imaxfull	Rin, kout, C50
<b>Sigmoid full I<sub>max</sub><sup>a</sup></b>	turn_input_gammaImaxfull	Rin, kout, C50, gamma	turn_output_gammaImaxfull	Rin, kout, C50, gamma

<sup>a</sup> Full I<sub>max</sub> means I<sub>max</sub> is fixed equal to 1

### 3.2 User-defined models

Users can also define their own model, analytically (as an R expression or an R function) or using a system of differential equations. A file has to be created according to each model form (see Section 5.3.2).

#### 3.2.1 Analytical form defined through an R expression

##### Description

The model file must start with the three following red lines, without any space between each line; moreover they have to start with the key symbol "\$" to be understood by PFIM.

```
#$Model definition  
#$ka, V, Cl  
#$  
formA <-expression()  
form<-c(formA)  
tf<-list(Inf)
```

The first line cannot be changed. The second line indicates the names of the parameters of the model to be estimated. The third line specified the argument(s) when a function is specified on the fourth line.

The user must start to specify the model from the fourth line. Here only "\$" is written on the third line (no additional argument to be specified since the model equation is given directly using the R function "expression" on the fourth line.

In case of analytical form, the model for each response should be written assigned in an object called 'formi' where i is the letter of the alphabet A,B,C,... The "formi" for all the responses are then grouped in a vector called "form":

```
form<-c(formA, formB, formC, ...)
```

If the model for a response is defined over intervals by different expressions, each response should be written as a vector of expressions. Each expression can be defined in an object 'formI', where I = 1, 2, 3,... For example, if the user wants to give three expressions for the first response, he can write as follows:

```
formA<-c(form1, form2, form3)
```

formA can be a model of the PFIM libraries or defined by the user.

User also needs to define an object "tf" which indicates the time until when to use the model for the expression form1. "tf" has to be a list of objects corresponding to "tf" for each response. The length of "tf" must be equal to the number of responses. In case of one response model, using one expression defined from 0 to Infinity:

```
tf<-c(Inf)
```



### Example 1: Single response model at steady-state in analytical form using an R expression

```
##$Model definition
##$k,V
##$
formA <-expression(1/(V)/(1-exp(-k*24))*(exp(-k*t)))
form<-c(formA)
tf<-list(Inf)
```

The analytical expression in this example describes a one compartment model after IV bolus at steady-state, with a dose interval equal to 24h (bolus\_lcpt\_Vk). In this case, if the dose is not equal to 1, the user has to specify the variable "dose" in the expression and the value of the dose in the design tab (see section 5.4). However, if the user defines his model, he can also specified the value of the dose in the analytical expression by replacing 1 by 500 for instance for a dose equal to 500. In this case, the user has to put in the design tab the dose equal to 1. If the dose is defined by the user in the analytical expression of the model, the options of design with multiple groups with different doses can no longer be used. The "tf" object indicates the time until when to use the specified expression for the model (here, time Infinity).

### Example 2: PK model with a linear elimination and immediate response PD model in analytical form using an R expression

```
##$Model definition
##$ka,V,C1,Imax,C50,S0
##$
formA<-expression(dose/V*ka(ka-(C1/V))*(exp(-(C1/V)*t)-exp(-ka * t)))
formB<-paste("-Imax*",formA,"/(C50+",formA,")+S0")
formB<-parse(text=formB)
tf<-list(Inf,Inf)
form<-c(formA,formB)
```

These analytical expressions describe a PK/PD model. The PK model is a one compartment model with a first order absorption and elimination (**formA**) and the PD model (**formB**) is an immediate response model with a constant baseline. In this case, the user has to specify the dose in the design tab (see section 5.4).

Note that to write formB, we use the R function *paste* which converts its arguments to character strings and concatenate them. The R function *parse* is used in order to obtain an expression of the model.

The "tf" object indicates the time until when to use the model for the PK (here, time Infinity) and until when to use the PD model (here, time Infinity). Here, "tf" is thus a list of two elements.

"form" is the vector of the models for all responses, and the second object is "tf".

**Example 3: PK model after multiple dose administration using an analytical form, based on functions from the library of models**

It is also possible to use the functions of the library of models to create new models. This is illustrated in the following example.

```
##$Model definition
##$ka,V,k
##$
form1<-oral_1cpt_kaVk() [[1]]
form2<-oral_1cpt_kaVk_md(N=5,tau=12) [[1]]
formA<-c(form1,form2)
tf<-list(c(12,Inf))
form<-formA
```

In this illustration, the user creates a model combining two analytical expressions for a one compartment oral absorption: the first expression corresponds to the model after the first administration (form1) and the second expression corresponds to the model after the fifth administration (form2). Use of predefined functions of the library of models implies the use of "[[1]]" at the end of the call of the function to select the part of the function corresponding to the expression of the model.

The "tf" object indicates the time until when to use the model for the first administration (here, time 12) and until when to use the model for the fifth administration (here, time Infinity). Then, the user defines two objects: the first object is "form", the vector of the models, and the second one is "tf".

This case is useful for evaluation and optimisation of a design including sampling times after the first and the fifth administration. If the user defines the model by using the library of model, he has to specify the dose in the design tab (see section 5.4).

**Example 4: PK model with a linear elimination and immediate response PD model in analytical form, based on functions from the library of models**

This example illustrates how to write a PK/PD model using functions implemented the PKPD library.

```
##$Model definition
##$ka,V,Cl,Imax,C50,S0
##$
formA<-orall_1cpt_kaVCl() [[1]]
formB<-immed_Imax_const(formA) [[1]]
tf<-list(Inf,Inf)
form<-c(formA,formB)
```

### 3.2.2 Analytical form defined through an R function

#### Description

The R function for a PFIM Infertace 4.0 model should take the following form:

```
#$Model definition
#$ ka,k,V
#$
form<-function(t,p,X) {
. . .
}
```

The four lines in red have to be written, without any space between each line; moreover the three first lines have to start with the key symbol "\$" to be understood by PFIM. The first line cannot be changed. The second line indicates the names of the parameters of the model to be estimated. The third line specified the additional argument(s) of the function. Here there is no additional argument except t, y and p which are default arguments. Therefore only "\$" is written on the third line. Last, the fourth line indicates the name of the function (form) which **must remain unchanged**. The 3 arguments of the function are:

- a vector of times t
- a vector of parameters p
- a scalar X which represents **the dose**

The function returns a vector of predictions of each time point in t, computed using the dose X and the parameters p.

#### Example 5: PK model after single dose administration using an analytical form with user-defined R function

```
#$Model definition
#$ ka,k,V
#$
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)
}
```

In this example, the user creates a function of a one response model describing a one compartment oral absorption.

**Example 6: PK model after multiple dose administration using an analytical form with user-defined R function**

```
##$Model definition
##$ ka,V, Cl
##$
form<-function(t,p,X){
ka<-p[1]
V<-p[2]
Cl<-p[3]

N<-5
tau<-12

y<-0
for (n in 1:N)
{
indic<-t>=(n-1)*tau
yn<-indic*(X/V*ka/(ka-Cl/V)*(exp(-Cl/V*(t - (n - 1) * tau))-exp(-ka*(t -
(n - 1) * tau))))
y<-y+yn
}
return(y)
}
```

In this illustration, the user creates a function of one response model describing a one compartment oral absorption after five administration doses with a between dose interval equal to twelve hours. The number of doses and the between dose interval are defined within the function.

### 3.2.3 Models defined through a differential equation system

#### Description

Model defined as a solution of a differential equation system must be called "formED". It can be given by the users who need to write an R function in a format suitable for the solver package deSolve, using the following form:

```
##$Model definition ODE
##$ka,km,Vm,V
##$
formED<-function(t,y,p)
{
...
}
```

The four lines in red have to be written, without any space between each line; moreover, the three first lines have to start with the key symbols "\$". The first line of this Block, '\$Model definition ODE' cannot be changed. The second line indicates the names of the parameters of the model to be estimated. The third line specified the additional argument(s) of the function. Here there is no additional argument, except t, y and p which are default arguments. Therefore only "\$" is written on the third line. Last, the fourth line indicates the name of the function (formED) which **must remain unchanged**. The 3 arguments of the function are:

- a vector of time t
- the current estimate of the variables in the ode system y
- a vector of parameters p

Within the function, the user has to define the name of the parameters in vector p and the differential equation system.

The function returns a list with 2 elements:

- the first element is a vector giving the values of the derivatives for each equation in the differential equation system, computed for each time point in t using the parameters p
- the second element is a vector of predictions computed for each time point in t using the parameters p; in PFIM, this vector contains the response(s) we are observing

The initial values of the system have to be specified in the ODE tab presented in the section 5.3.3.

The implementation of differential equations system requires the use of the lsoda function included in the library "deSolve" (R. Thomas Petzoldt) and of the fdHess function included in the library "nlme" developed by Jose Pinheiro and Douglas Bates.

The lsoda function uses a function of the same name written in Fortran by Linda R. Petzold and Alan C. Hindmarsh. This function solves system of differential equations using the Adams method, a predictor - corrector method for non-stiff systems; it uses the Backward Differentiation Formula (BDF) for stiff systems. The fdHess is used for numerical derivation. It evaluates an approximate gradient of a scalar function using finite differences.

**Example 7: Single response PK model using a differential equation system created by the user**

```

#$Model definition ODE
#$ka,km,Vm,V
#$
formED<-function(t,y,p)
  {
    ka<-p[1]
    km<-p[2]
    Vm<-p[3]
    V<-p[4]

    yd1<--ka*y[1]
    yd2<-+ka*y[1]- V * (Vm * y[2]/(V * km + y[2]))

    list(c(yd1,yd2),c(y[[2]]/V))
  }

```

This example describes a one compartment model first order absorption and Michaelis-Menten elimination.

The first four lines in the body of the function assign model parameters from the vector p. The next two lines describe the derivatives of the system (yd1 and yd2). More specifically, each derivative represent the drug concentration in the specific compartment at the instant t, and its elements can be either positive or negative. The notation ydX denotes the

derivative of the variable in compartment X while the notation  $y[X]$  denotes the quantity in the same compartment (see documentation for the deSolve package for details). The last line defines the elements returned by the function:

- the first item is mandatory for the deSolve package, and should always consist of a vector with the derivatives of the system (here, the two elements  $yd1$  and  $yd2$ )
- the second item defines the response, here the concentration in the second (central) compartment which is defined by the quantity in this compartment ( $y[2]$ ) divided by the volume of distribution  $V$ . Several responses can be given.

**Example 8: Multiple response PK model using a differential equation system created by the user**

```

#$Model definition ODE
#$ka,cl,V,Clm,R
#$
formED<-function(t,y,p)
{
  ka<-p[1]
  cl<-p[2]
  V<-p[3]
  clm<-p[4]
  R<-p[5]
  yd1<--ka*y[1]
  yd2<-ka*y[1]-cl/V*y[2]-R*y[2]
  yd3<-R*y[2]-clm*y[3]

  list(c(yd1,yd2,yd3),c(y[2]/V,y[3]))
}

```

This example describes a two response model using a differential equation system. In this case, the second argument of the list is composed of two objects corresponding to: the first measure of interest is the concentration in the compartment 2 scaled by the volume and the second measure of interest is the concentration in the compartment 3, respectively.

**Example 9: PK model after multiple dose administration using a differential equation system created by the user**

```
#$Model definition ODE
#$ka,V, Cl
#$
formED<-function(t,y,p)
{
  ka<-p[1]
  V<-p[2]
  Cl <-p[3]

  tau<-12
  input_orall<-function(ka,V,dose,n,tau,t){
    if(n==0){return(dose*ka/V*exp(-ka*t))}
    else{return(dose*ka/V*exp(-ka*(t-
n*tau))+input_orall(ka,V,dose,n-1,tau,t))}
  }
  n<-t/%tau
  input<-input_orall(ka,V,dose,n,tau,t)

  dy<--Cl/V*y[1]+input

  list(c(dy),c(y[1]))
}
```

In this illustration, the user creates a function of one response model describing a one compartment oral absorption after multiple dose administration with a between dose interval between two doses equal to twelve hours. The number of doses and the between dose interval are defined within the function.

## 4. Installation

The R 2.6 or higher and available in Windows operating system (32bits or 64bits) needs to be installed. Depending on the use of PFIM Interface 4.0, additional packages available in the R library are needed:

to use a differential equation system to describe the model: "deSolve" and "nlme" packages

to use the Federov-Wynn algorithm: "combinat" package.

An additional package "numDeriv" is needed for the computation of the full Fisher information matrix and for numerical derivatives of models written as standard R functions

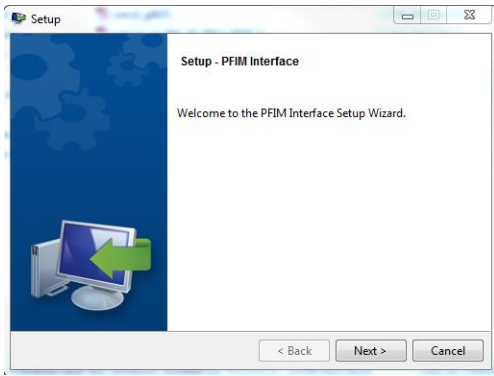
The easiest way to install packages is directly from the web. To install the packages deSolve, nlme, combinat and numDeriv, start R and choose the Packages item from the menu. Choose Install package(s) from CRAN to install from the web (you will see a list of all available packages pop up -- choose deSolve, nlme, combinat and numDeriv).

### 4.1 Windows installation

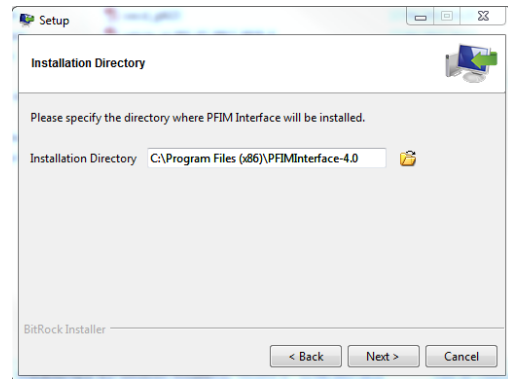
To install the **Windows version** of PFIM Interface 4.0, download the application '<http://www.pfim.biostat.fr/download/PFIMInterface-4.0-windows-installer.exe>' available on the webpage [www.pfim.biostat.fr](http://www.pfim.biostat.fr). Then simply double click on this application and click on the button to execute the program.

To complete the installation of PFIM interface 4.0, follow the different steps detailed below.

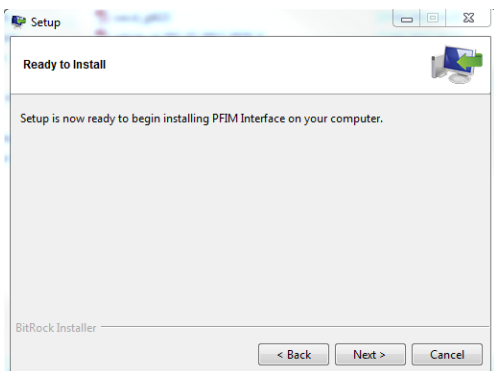




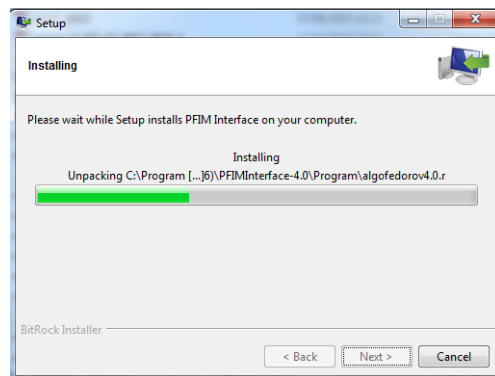
**Figure 1: Click the button "Next" to continue the procedure**



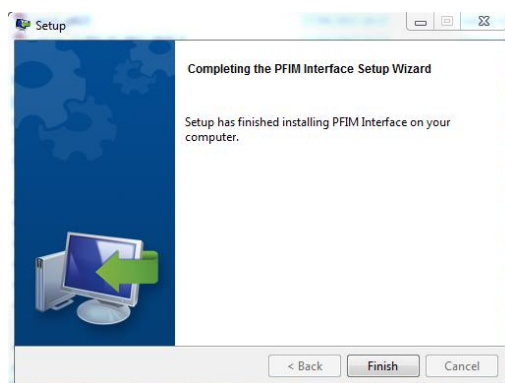
**Figure 2: Indicate the path to install the directory files and click the button next**



**Figure 3: Click the button « Next » To begin the installation**



**Figure 4: The setup is proceeding**



**Figure 5: To complete the installation click on the button "Finish". Installation is successful**

## 5. Use

### 5.1 Main user Interface

Figure 6 shows the screen that appears when the user starts the program PFIM Interface 4.0.

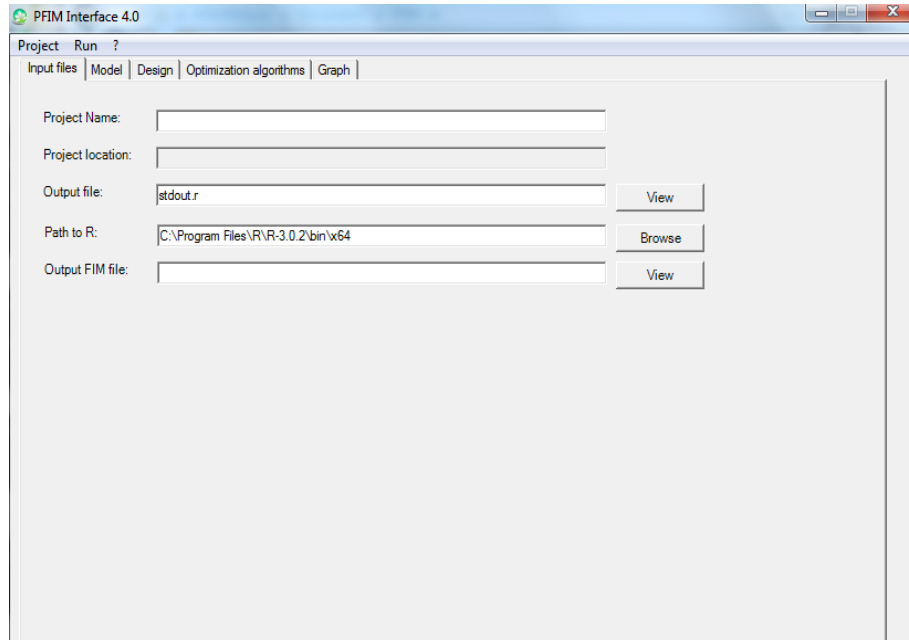


Figure 6: PFIM Interface 4.0: initial screen.

The user can either create a new project directory (File/New project) or load an existing one (File/ Open project) as it is shown in Figure 7.

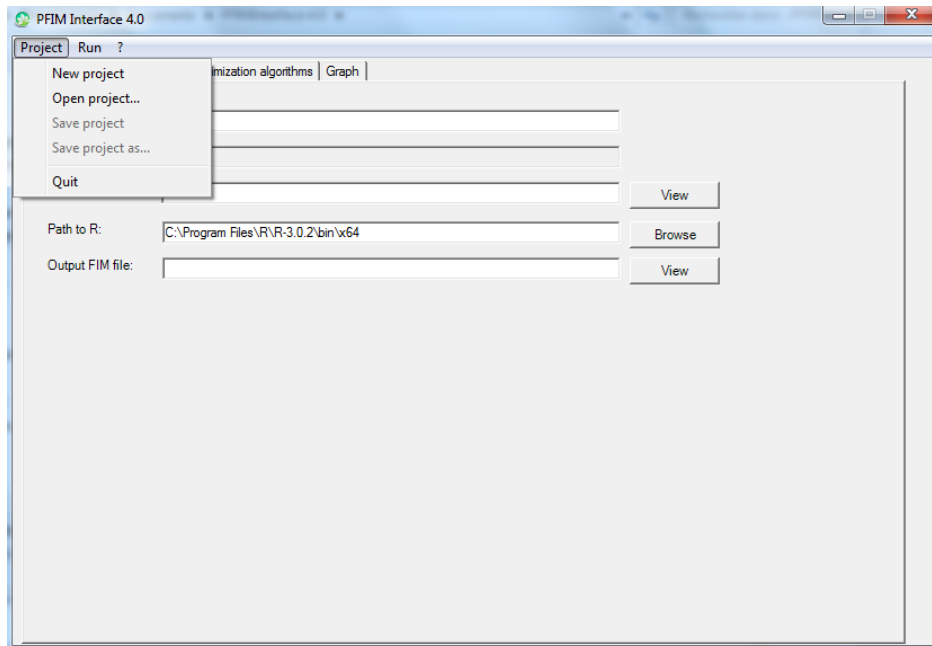
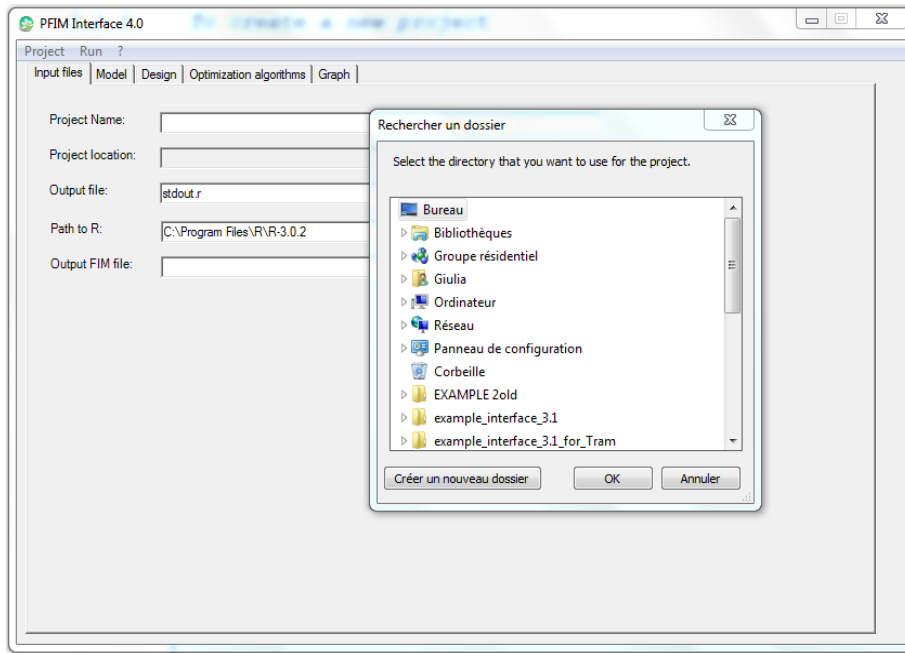


Figure 7: Load or create a new project.

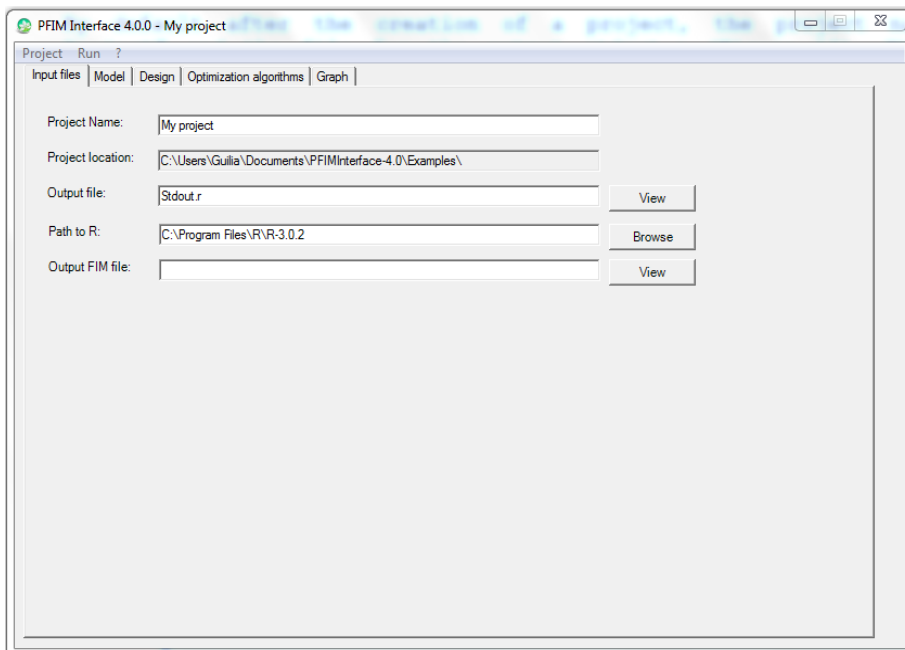
#### 5.1.1 Creation of a new project

In order to create a new project, the path of the directory for the "New project" must be specified as shown in Figure 8.



**Figure 8: Choose directory for the new project**

By default, the names of the new project and of the output file (Figure 9) are "My Project" and Stdout.r, respectively, but these names can be modified.



**Figure 9: Default tab after the creation of a project.**

### 5.1.2 Loading existing project

In order to load an existing project, it is either possible to use the Menu of PFIM Interface 4.0 as shown in Figure 10, or by clicking on the stdin.pfim file stored in the directory of the project selected.

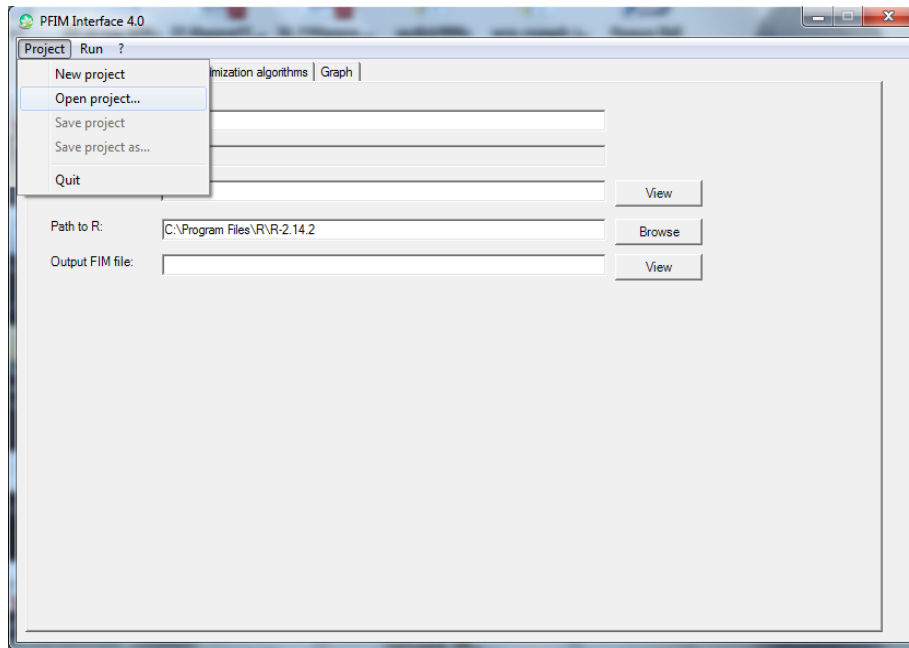


Figure 10 Loading existing project tab

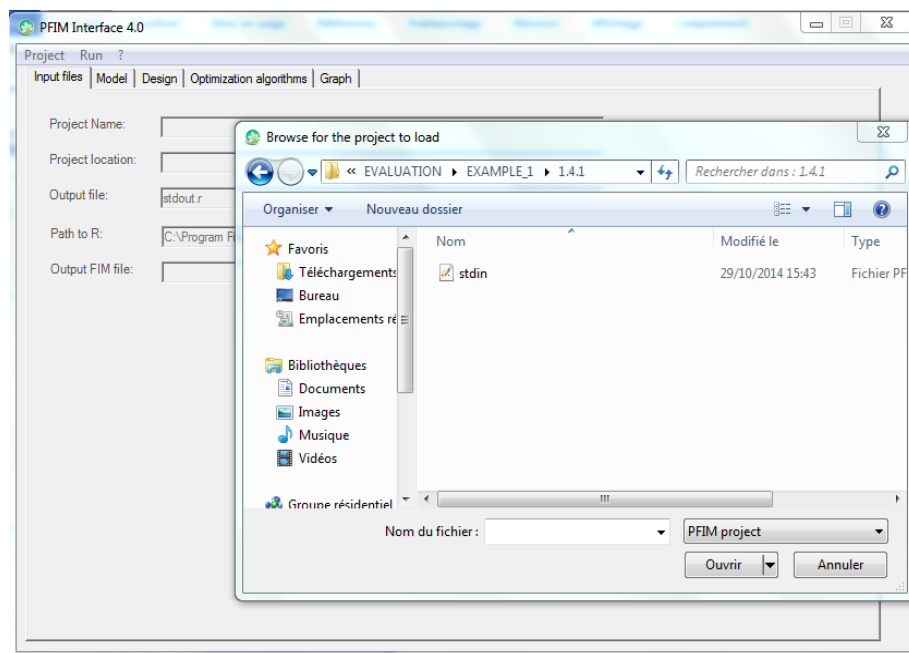


Figure 11 Browsing project to be loaded tab

## 5.2 Input tab

The user should enter a name for the project and specify the name for the output file where the results will be stored. The Project location is created automatically once selected the folder where the new project can be stored. The user can choose the R version to be used by specifying the path in the "Path to R" section. It is also possible to require the saving of

the Fisher Information Matrix in a text file by specifying the name of the text file ("filename.txt") in the "Output FIM file" section.

### 5.3 Model tab

This tab is for model specification. A model can be either selected from the PFIM library or it can be written in a user defined form, using either analytical form or a system of differential equations (ODE). Below some figures showing how specify a model in the PFIM Interface 4.0. In the "Models" section of this documentation, model writings and examples are reported in more details.

#### 5.3.1 Model from the library

After having opened a project or created a new project in PFIM Interface 4.0 it is possible to select the preferred model from the library of models using the scroll bar in the model tab (Figure 12) and choose the regimen (Single dose, Multiple doses, Steady State). For the first example we selected a PK one compartment first order absorption model, with parameters  $k_a$ ,  $V$ ,  $k$ , and a single dose regimen.

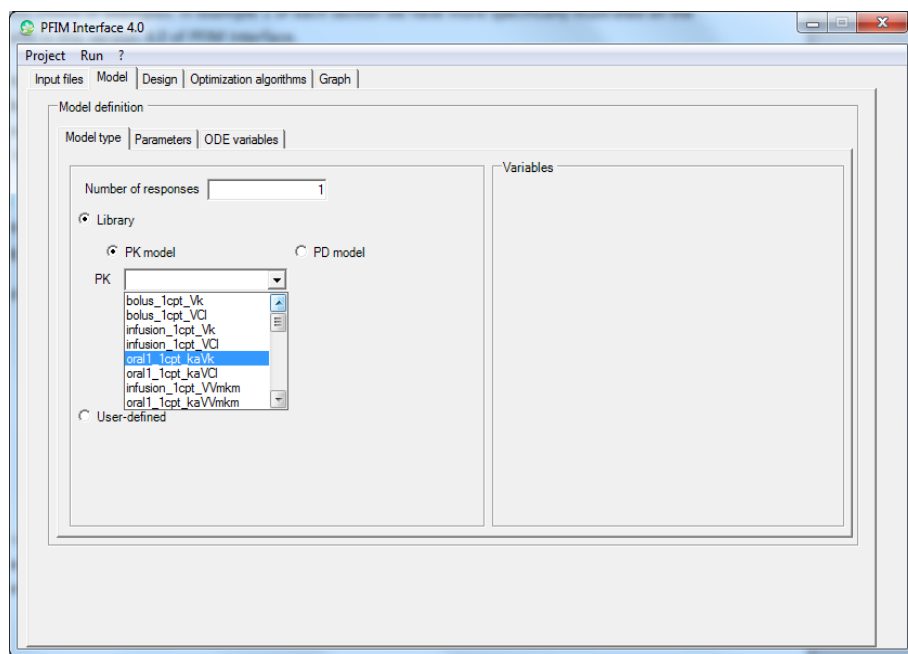
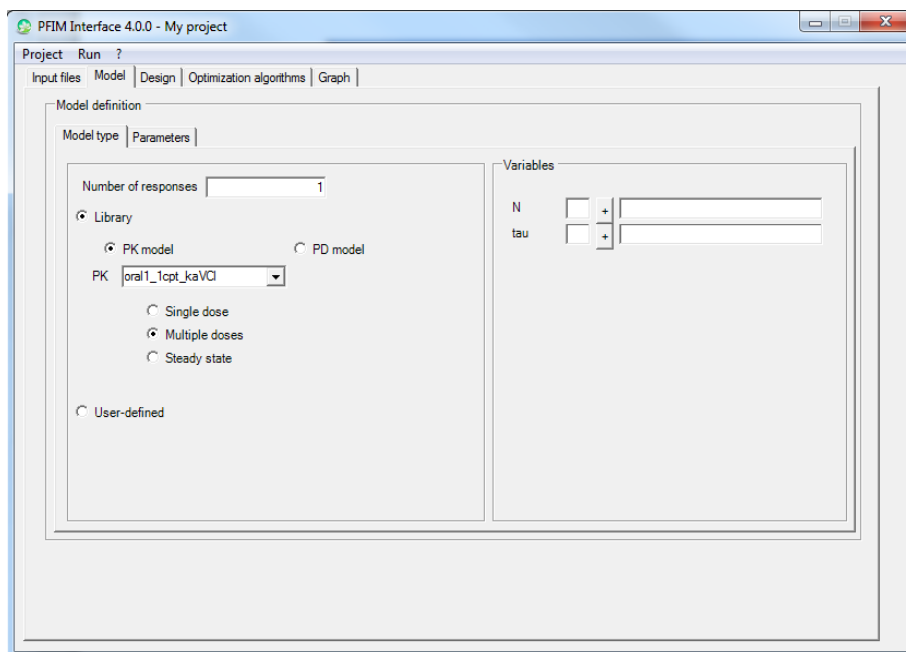
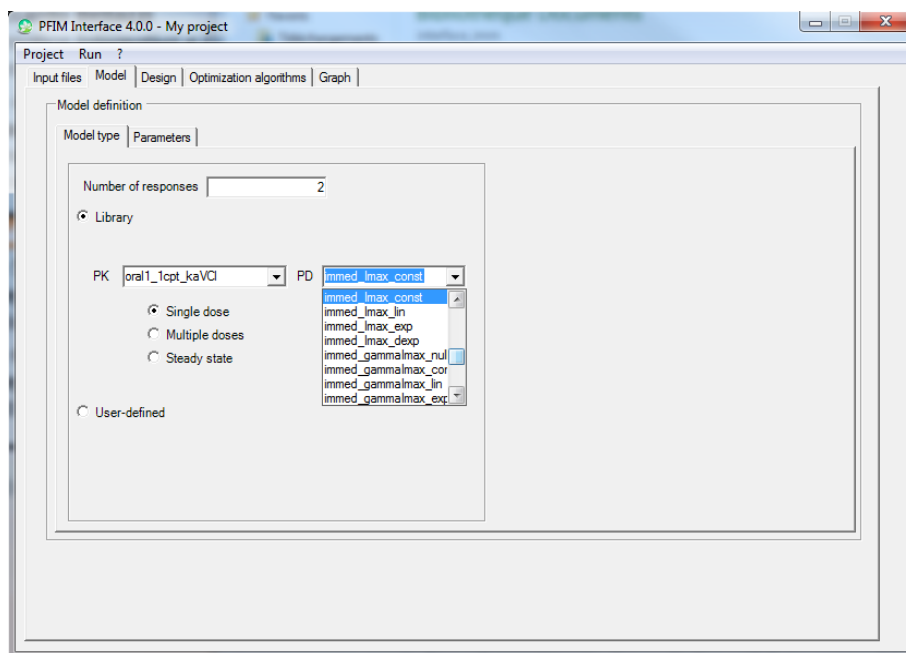


Figure 12: Model-selection from the model library



**Figure 13: Specification of multiple doses administration type and specification of the needed variables N and tau**

It is also possible to define a PKPD model through the model library as shown is Figure 14. Please mind to specify the two responses in the number of responses section.



**Figure 14: PKPD model selection from the model library. The PK is a one compartment first order oral absorption model, with function in the library parameterized in  $k_a$ ,  $V$  and  $k$ . The PD is an  $I_{max}$  model with constant baseline parameterized in  $I_{max}$ ,  $C_{50}$  and  $S_0$ .**

### 5.3.2 User-defined model

The user can create either an analytical model or an ODE system (Figure 15). If a user defined model has already been specified in this project, it can also be edited and modified. See "Models" section for details on how to write its own model.

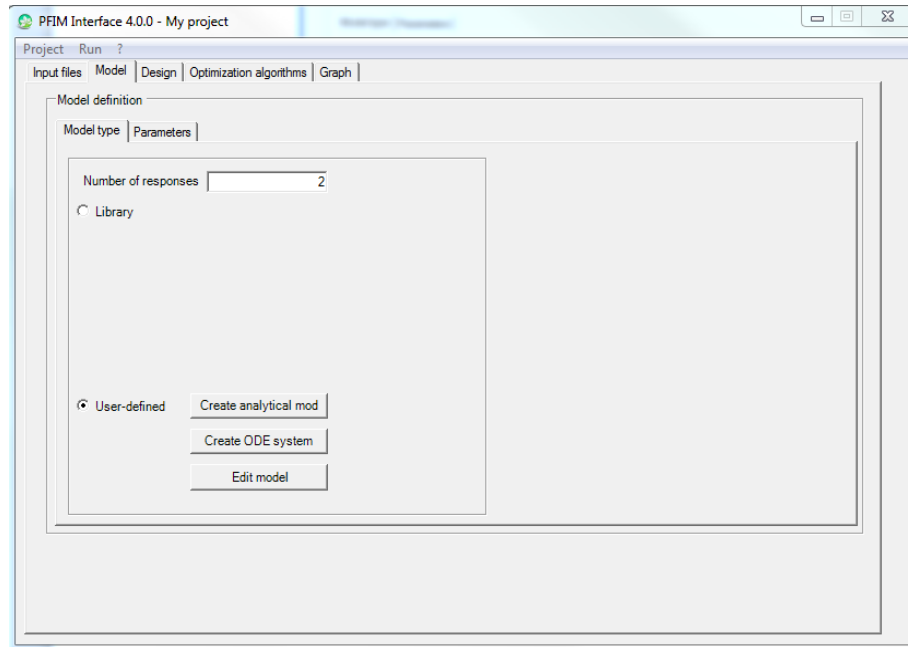


Figure 15: Definition of the model by the user here for a model with two responses

### 5.3.3 Parameters of the model

Once the model is specified, one can click on the "Parameters" section (Figure 16), where values of the mean and the variance of the population parameters have to be defined.

If the between-subject variance of a parameter is assumed to be zero, this should be specified under the variance column of the related parameter. PFIM would then remove the corresponding row and column in the Fisher information matrix. In the parameter tab it is also possible to indicate whether some parameter should be kept fixed in the evaluation or optimisation of FIM. In that case, the variance of the correspondent fixed parameter will be automatically set to 0.

In the same tab it is possible to choose between either additive or exponential model for the between-subject variance.

Values of the standard deviation of the residual error should be specified. The residual error is additive with a general model for variance:  $\text{var}(\varepsilon) = (\sigma_{\text{inter}} + \sigma_{\text{slope}} * f)^2$ , where  $f$  is the structural model. This variance error model includes the constant variance model ( $\sigma_{\text{slope}} = 0$ ) or the constant coefficient of variation model ( $\sigma_{\text{inter}} = 0$ ) as special cases. The parameters  $\sigma_{\text{inter}}$  and  $\sigma_{\text{slope}}$  are included in the population parameters to be estimated.

Regarding a multiple response model, the user has to complete the different values for the standard deviation of the residual error for all responses one by one using the list box (Figure 17).

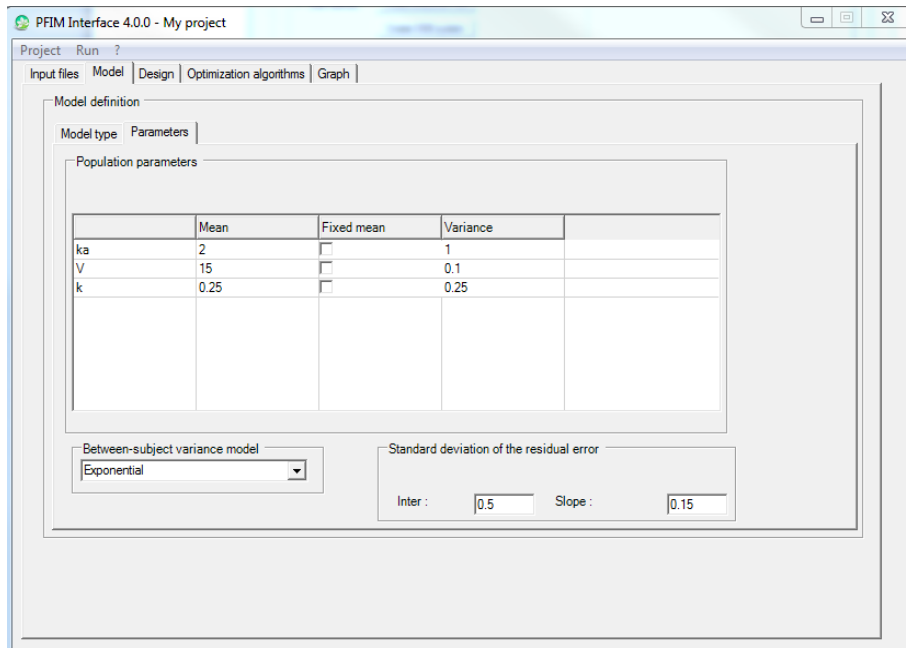


Figure 16: Parameters section tab for a single response model

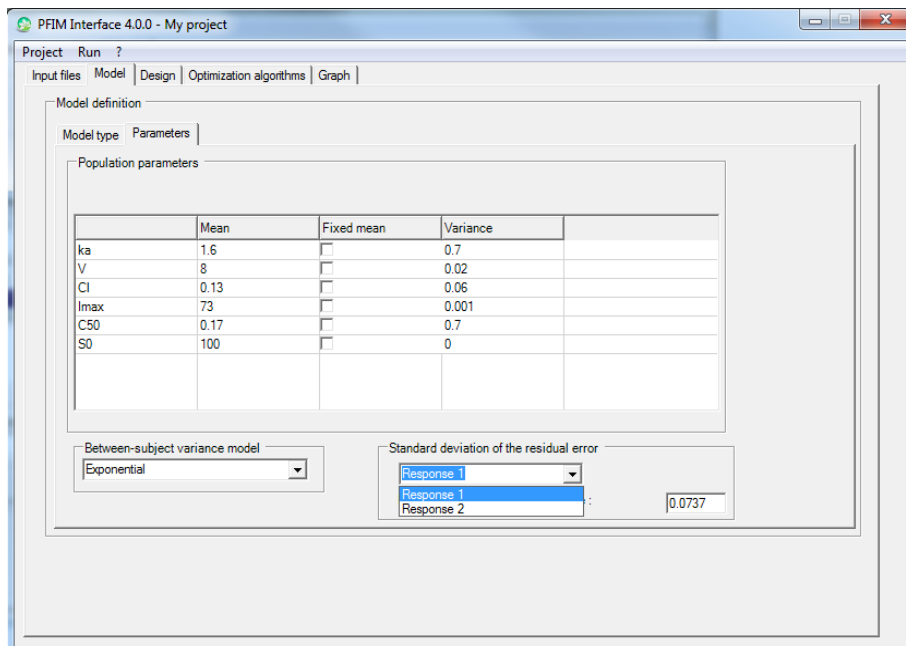


Figure 17: Parameters section tab for a multiple response model with the list box to choose the parameters of the residual error for each response

In case of an ODE system, the ODE variables section has to be filled as in Figure 18.



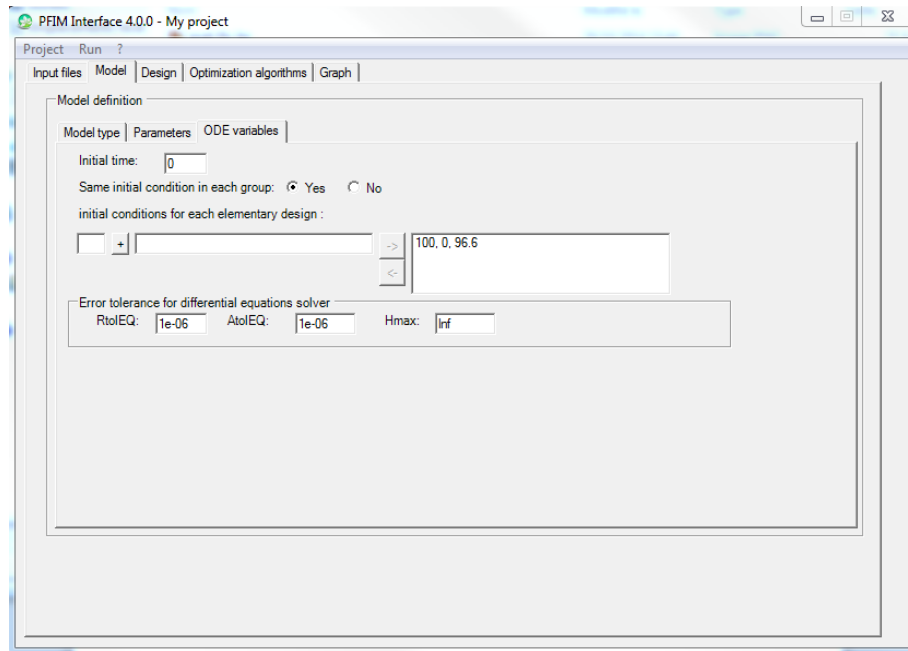


Figure 18: Tab of the ODE variables

In this case, the time for the initialisation of the system must be given (usually 0) and the initial values in each compartment at this time have to be given as a vector in the "initial conditions for each elementary design". The size of this vector has to be equal to the number of equations of the system. **For the models coming from the libraries, the number of equations of the system is equal to the number of compartments of the model.** Several vectors can be specified in case of different groups of subjects with different initial conditions.

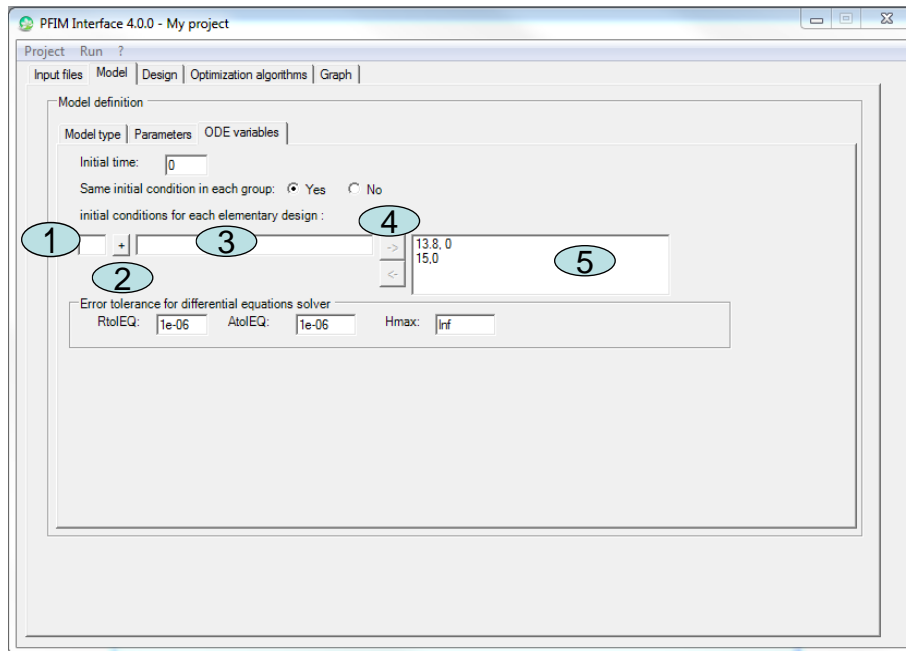
To use this tab, an example is presented below illustrated in Figure 19 using a system with two equations.

If there are two elementary design with different initial conditions defined as (13.8; 0) and (15; 0) respectively for the first and the second elementary design. The size of the vectors for the initial conditions is equal to 2 due to the two equation system.

To input the initial condition for the first elementary design, the user has to follow the next instructions with the illustration on Figure 19.

- Put the value 13.8 in the white box **1**.
- To validate the value click on the button **2**, the value is in the box **3**.
- Repeat these two previous steps for the value 0.
- Click on the button **4**, the first elementary design is specified and validated in the box **5**.

In order to validate the initial conditions for the second elementary design defined here 15 and 0, the user has to repeat the previous steps. The screen showed on Figure 19 should be obtained. The first line and the second line in the box **5** correspond respectively to the initial conditions for the first and the second elementary design.



**Figure 19: Tab of the ODE variables: illustration to enter the initial conditions**

Finally, parameters of "Error tolerance for the differential equation solver" are set by default but can be changed by the user. Those parameters are the following:

- RtolEQ: relative error tolerance, either a scalar or an array as long as 'y'. See details in help for lsoda function. Default value is 1e-06.
- AtolEQ: absolute error tolerance, either a scalar or an array as long as 'y'. See details in help for lsoda function\*. Default value is 1e-06
- Hmax: an optional maximum value of the integration stepsize. A maximum value may be necessary for non-autonomous models (with external inputs), otherwise the simulation possibly ignores short external events. Default value is Inf.

\*Copied from help for lsoda:

"The input parameters 'rtol', and 'atol' determine the error control performed by the solver. The solver will control the vector \*e\* of estimated local errors in \*y\*, according to an inequality of the form  $\max\text{-norm of } ( *e*/*ewt* ) \leq 1$ , where \*ewt\* is a vector of positive error weights. The values of 'rtol' and 'atol' should all be non-negative. The form of \*ewt\* is:

$$*RtolEQ* * abs(*y*) + *AtolEQ*$$

where multiplication of two vectors is element-by-element. If the request for precision exceeds the capabilities of the machine, the Fortran subroutine lsoda will return an error code; under some circumstances, the R function 'lsoda' will attempt a reasonable reduction of precision in order to get an answer. It will write a warning if it does so."

#### 5.4 Design tab

In this tab, the user specifies the characteristics of the population design to be evaluated or optimised.

In the Fisher Information Matrix section, the type of Fisher information matrix to be evaluated or optimised can be selected. Three possible Fisher information matrices are implemented in PFIM Interface 4.0.: Population

(also available in previous versions of PFIM Interface), Individual and Bayesian.

In the Dose regimen section, the user specifies if the dose is the same or not for all the involved groups in the population design. If the dose is the same, its value should be specified; if not, the values for each group can be defined (Figure 20).

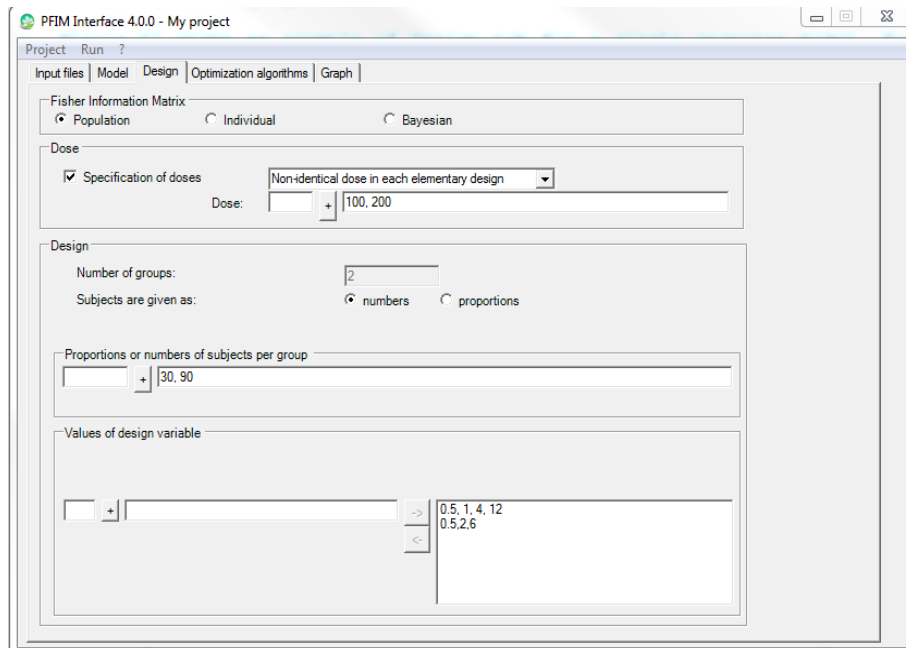
**NB: if the model used is a user-defined model in which the dose was defined, the default value of a dose of 1 should be kept here.**

**NB2: for models of the library after infusion, total dose should be given and the rate of infusion will be computed using the needed variable TInf.**

In the initial population design section, the user enters, for each group, the corresponding elementary designs. The value for the number of groups in the population design is then computed automatically.

The user specifies also if the subjects in each elementary design are given as numbers or as proportions and enter the values.

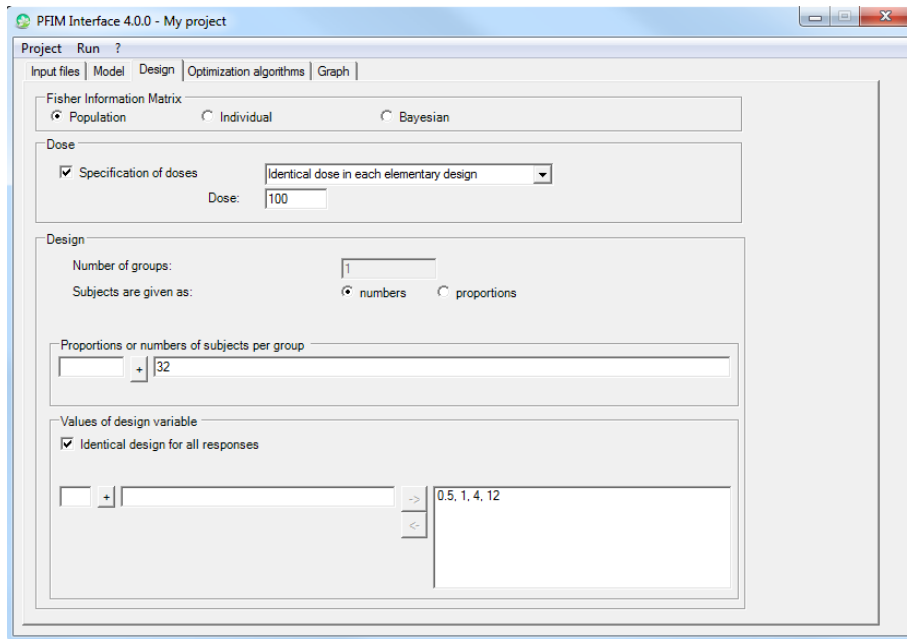
Figure 20 shows an example of Design tab for a single response model, for which the population design is composed of 2 groups of 30 and 90 subjects respectively, both with dose of 100 and 200, respectively, with the sampling times (0.5, 1, 4, 12) and (0.5, 2, 6) respectively.



**Figure 20: Design tab example for a single response model**

Figure 21 provides with an example of Design tab for a two response model with the same sampling times for both responses. Indeed the button "identical design for all responses" is selected.

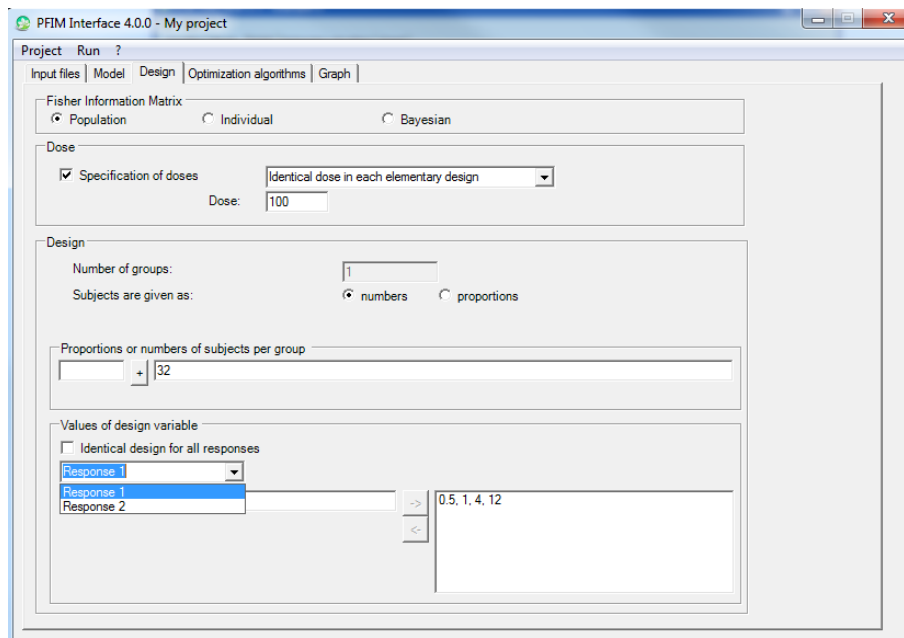
The population design is composed of one group of 32 subjects with a dose of 100 and with the same sampling times for both responses (0.5, 1, 4, 12).



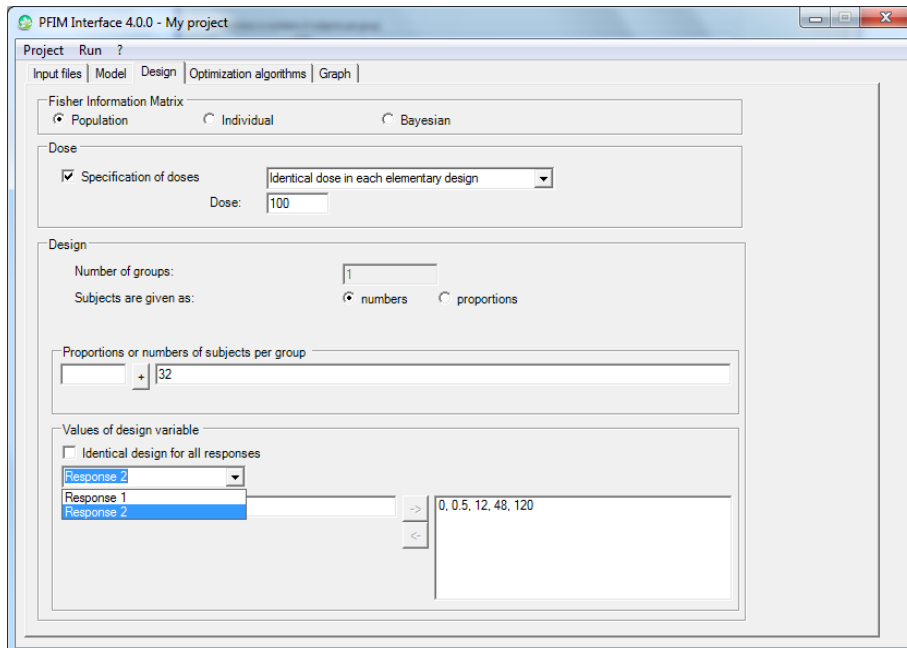
**Figure 21: Design tab example for a two response model with the same sampling times for both responses**

Figure 22 and Figure 23 give an example of Design tab for a two response model with different sampling times for each response. The button "identical design for all responses" has to be unselected.

The population is composed of one group of 32 subjects with a dose of 100 and with the sampling times for the first response (0.5, 1, 4, 12) (Figure 22) and for the second response: (0, 0.5, 12, 48, 120) (Figure 23).



**Figure 22: Design tab example for a two response model with different sampling times for each response: choice of the design for the first response**

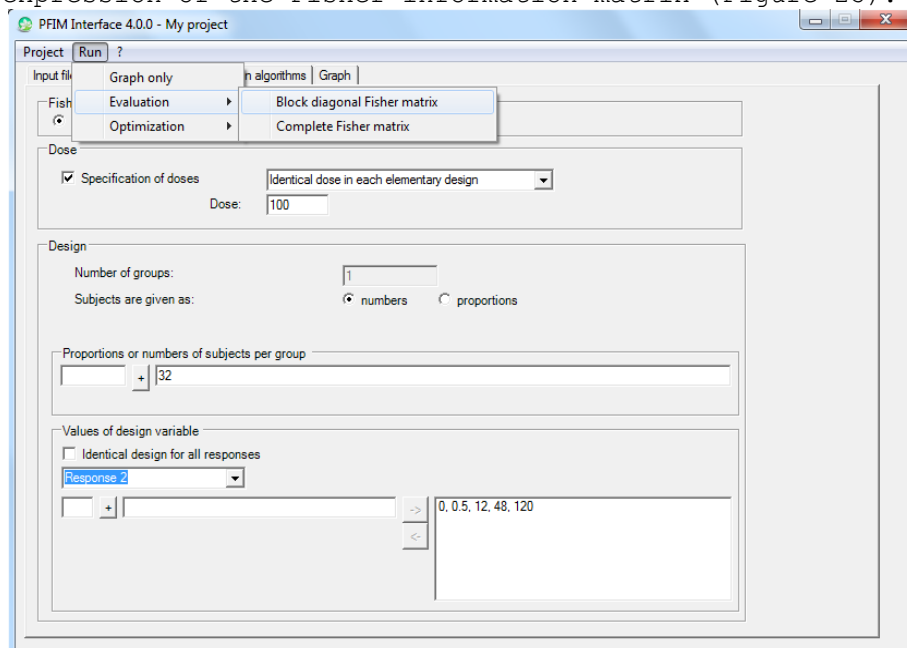


**Figure 23: Design tab example for a two response model with different sampling times for each response: choice of the design for the second response**

In all these examples (Figure 20 - Figure 23) the requested Fisher information matrix to be evaluated or optimized is the Population one.

### 5.5 Design evaluation step tab

At this step, evaluation of the population design entered in the "Design tab" can be performed by clicking on the 'Run' button on the windows toolbar, following with a click on the 'Evaluation' (see Figure 24). See Section 6 for the output. Evaluation can be performed either using the expression of the block diagonal Fisher information matrix (Figure 24) or the full expression of the Fisher information matrix (Figure 25).



**Figure 24: How to perform evaluation with the "run" button using the block diagonal expression of the Fisher information matrix**

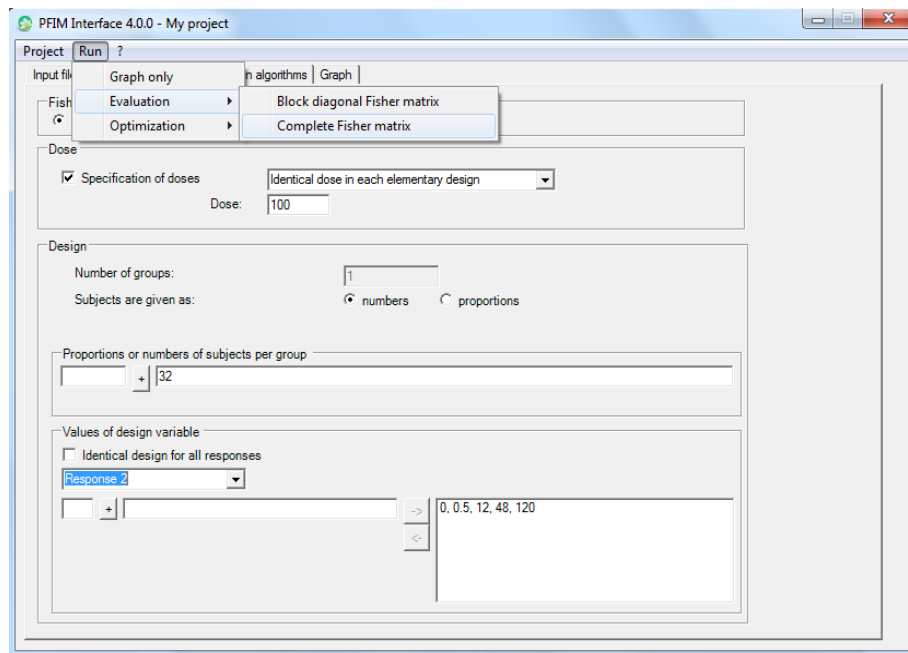


Figure 25: How to perform evaluation with the "run" button using the full expression of the Fisher information matrix

## 5.6 Optimisation algorithms tab

This tab must be filled in to optimise a design. The optimisation can be performed with either the Simplex or the Fedorov-Wynn algorithm. Corresponding section of the chosen algorithm must be filled in. In the case of multiple response models, the selection of the button "**identical design for all responses**" on the Design tab allows to optimise the design with the same sampling times for all responses.

### 5.6.1 Simplex algorithm

The first option to be chosen is whether optimising or not the proportions or number of subjects. Then, a value for the minimum delay between two sampling times can be entered. By default, this delay is set to 0. It is then possible to specify whether the iteration step should be printed or not in the R command window.

If different optimal sampling times for each response are required, the allowed intervals of sampling times for the optimisation must be provided for each response (Figure 26).

Parameters for the Simplex algorithm are set by default but they can be changed by the user. These are:

- the parameter for the initial simplex building gives the percentage of change from the initial design to create the initial vertices of the Simplex algorithm. Default is 20%
- the maximum iteration number of the Simplex algorithm which is set by default to 5000
- the relative convergence criterion of the Simplex algorithm set by default to  $1e-6$ .

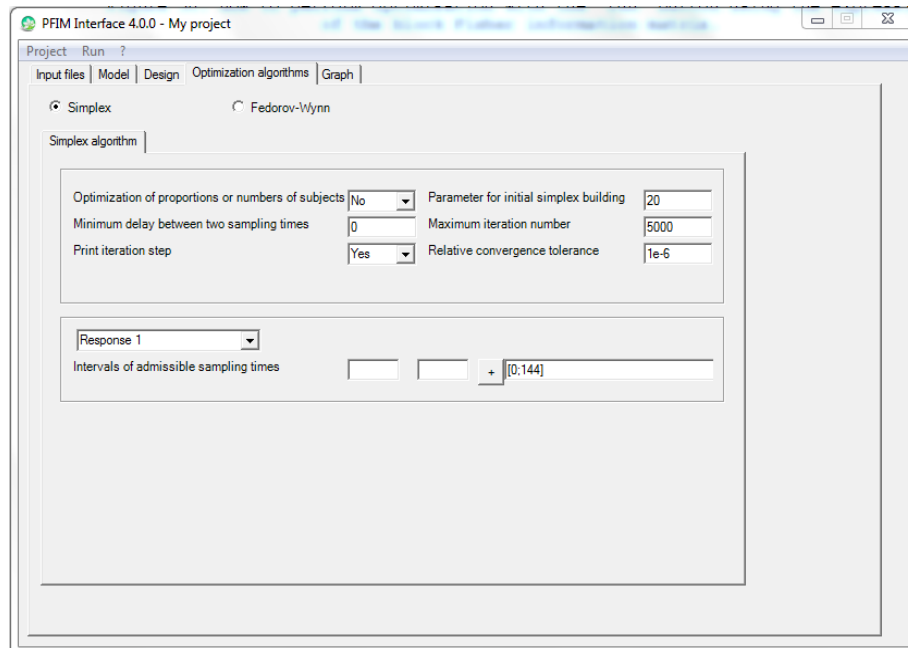


Figure 26: Optimisation algorithms tab for the Simplex algorithm

### 5.6.2 Fedorov-Wynn algorithm

Allowed sampling times can be specified in the Fedorov-Wynn algorithm corresponding tab. Several set of allowed sampling times may be provided, each set being called the sampling interval.

Then, the user must specify the number of sampling times to be taken from each sampling interval. More flexibility can be given by specifying for each sampling interval several numbers: the Fedorov-Wynn algorithm will then select the best ones.

The number of sampling intervals and the total number of samples per subject are then computed automatically.

The Federov-Wynn algorithm always optimises the number of groups and the proportions of subjects per group.

**Please note that the initial population design given in the "Design" tab must correspond to the constraint specified in this Fedorov-Wynn algorithm: the sampling times must be included in the sampling interval and the number of sampling times from each interval must be concordant with the allowed numbers.**

An example of the Fedorov-Wynn section is given in Figure 27 for a single response model. In this example, two sampling intervals are specified with the allowed sampling times (0.5, 1, 2, 3, 4, 6, 8, 10, 12) and (48.5, 49, 50, 51, 52, 56, 58, 60) respectively. The user allowed optimization of a design with either two or three sampling times in each interval. The minimal total number of allowed sampling times per subject is then 4 and the maximum 6.

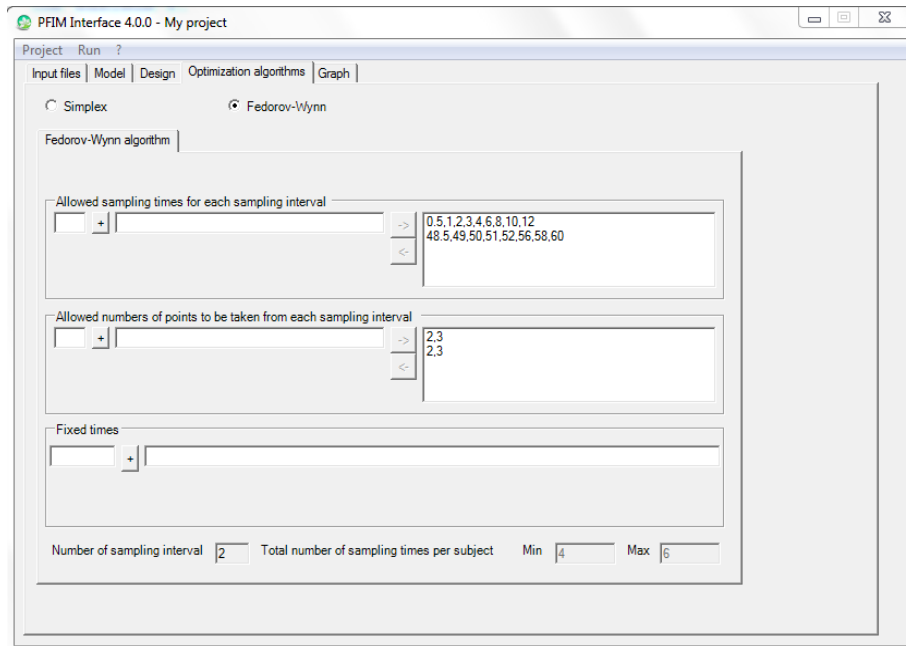


Figure 27: Example of the Optimisation algorithms tab for the Fedorov-Wynn algorithm for a single response model

An example of the Fedorov-Wynn section is given in Figure 28 and Figure 29 for a two response model. In this example, one sampling interval is specified with the allowed sampling times (0, 0.5, 1, 6, 12, 24, 48, 72, 96, 120, 144) for the first response (see Figure 28) and for the second response (0, 24, 36, 48, 72, 96, 120, 144) (see Figure 29). The user allowed optimization of a design with five sampling times in this interval for each response. The minimal total number of allowed sampling times per subject is then 4 and the maximum 4.

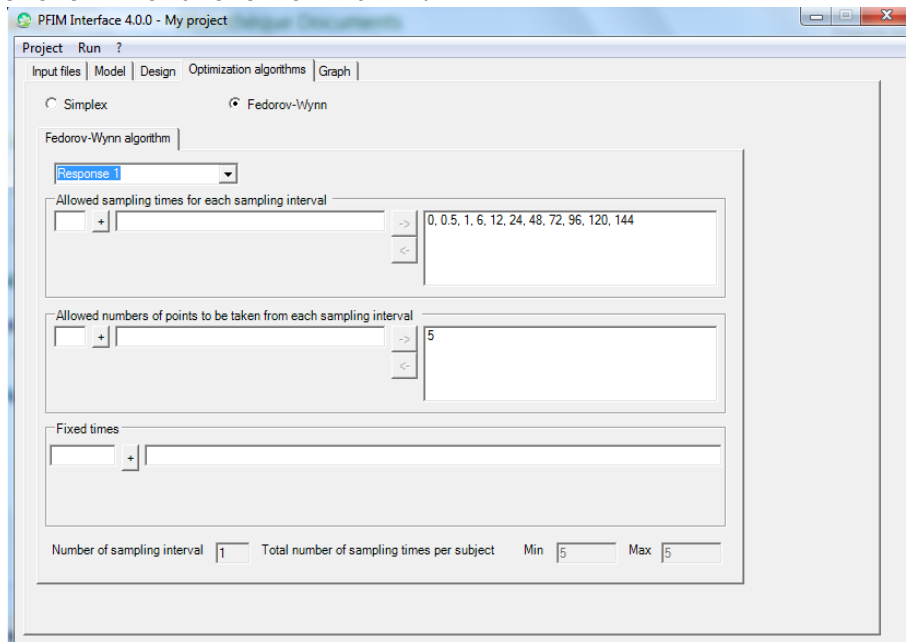


Figure 28: Example of the Optimisation algorithms tab for the Fedorov-Wynn algorithm for a two response model: choice for the first response



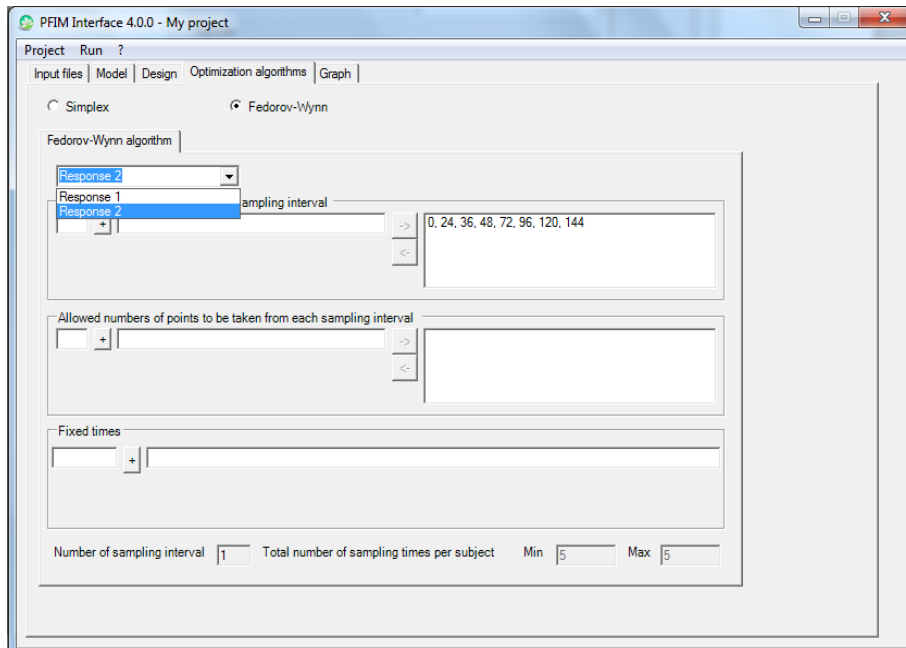


Figure 29: Example of the Optimisation algorithms tab for the Fedorov-Wynn algorithm for a two response model: choice for the second response

### 5.7 Design optimisation step tab

At this step, optimisation can be performed by clicking on the 'Run' button on the windows toolbar and then choosing 'Optimization'.

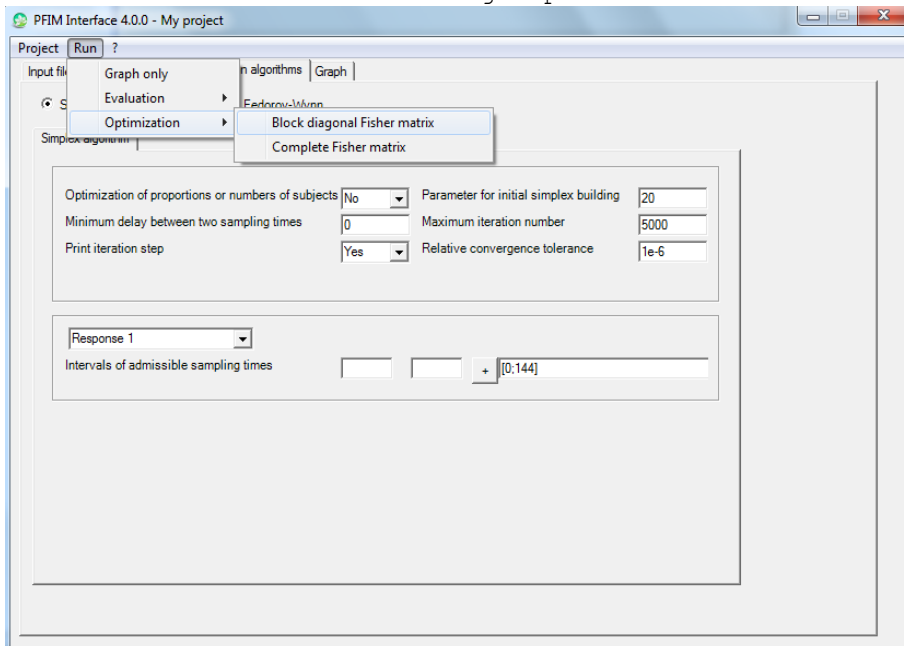
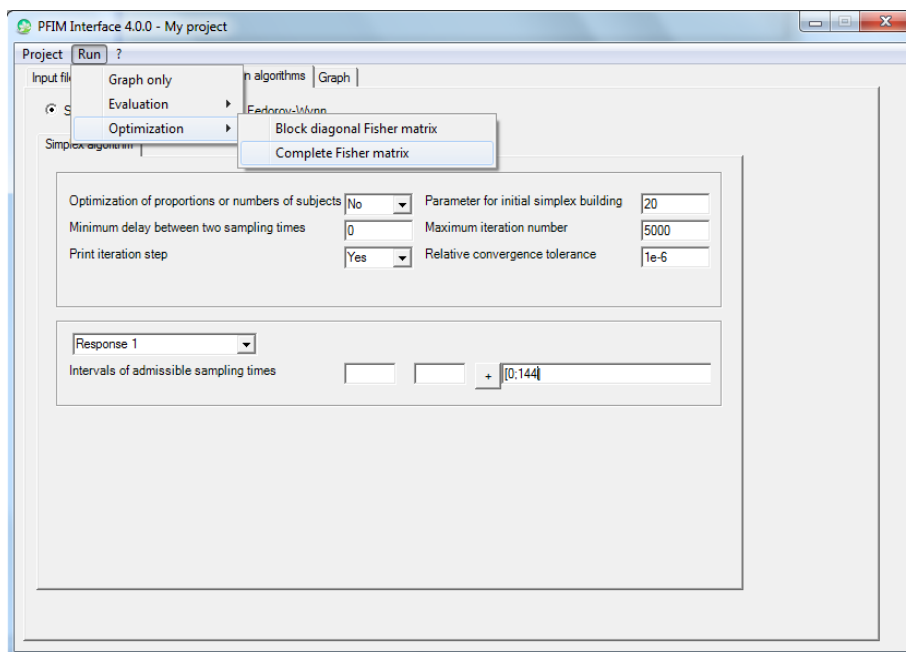


Figure 30: How to perform optimisation with the 'run' button using the expression of the block Fisher information matrix



**Figure 31: How to perform optimisation with the 'run' button using the expression of the complete Fisher information matrix**

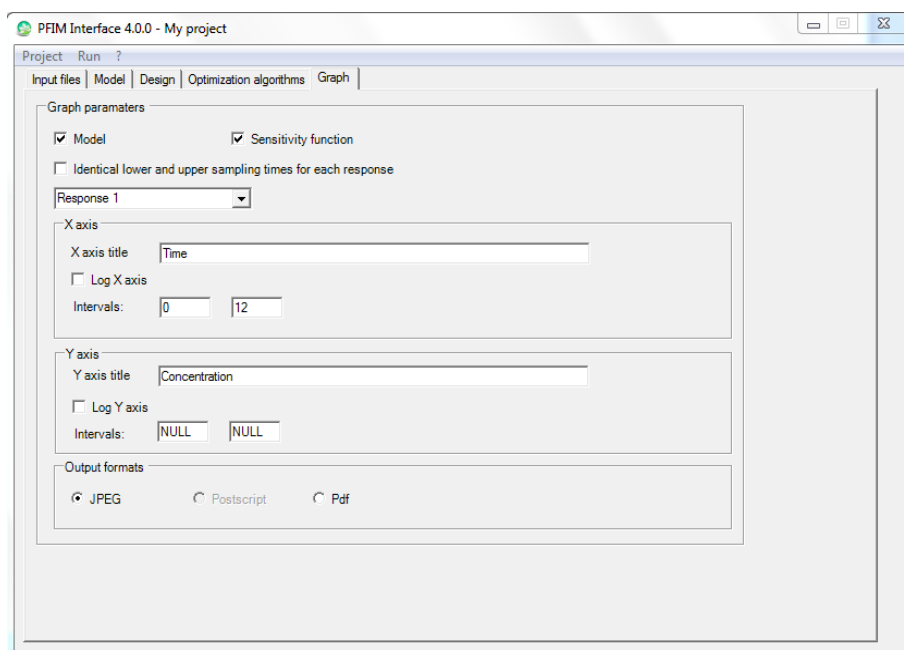
## 5.8 Graph tab

Graph of either the model or sensitivity function or both can be requested by selecting corresponding button(s) (Figure 32). Intervals for the times (X axis) have to be specified. Intervals for the Y axis are set by defaults to the range of the concentrations but can be changed.

It is possible to plot a graph with a log scale for X and/or Y axis by selecting respectively the 'Log X axis' button and/or the 'Log Y axis' button.

Format of the graph can be either jpeg or pdf.

Regarding multiple response models, the user can choose to have a graph for each response with different scales and different labels. To do that, the user has to unselect the button entitled "Identical lower and upper sampling times for each response".



**Figure 32: Graph tab**

Please note that graphs of the model or sensitivity function may also be obtained before performing any design evaluation or optimisation by clicking the 'Run' button on the windows toolbar and then choosing "Graph only" (Figure 33)

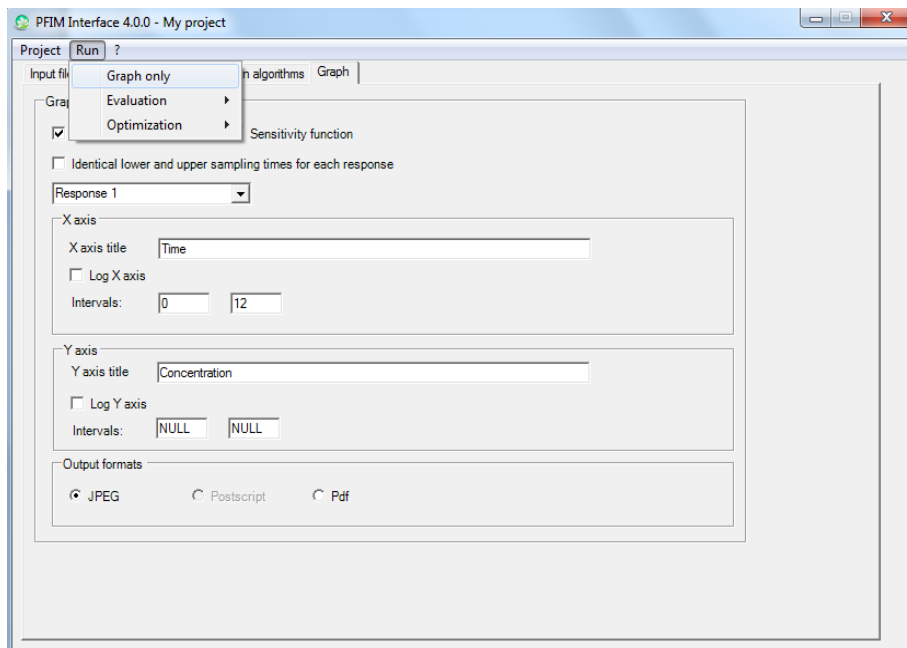


Figure 33: Run graph only

## 6. Results

PFIM Interface 4.0 opens an R command window to run the evaluation or the optimisation (Figure 34). At the end, an output file (named by default Stdout.r or with the name specified in the input files tab) is created in the directory of the project. It can be viewed by clicking on the button "View output file" in the output R command window.

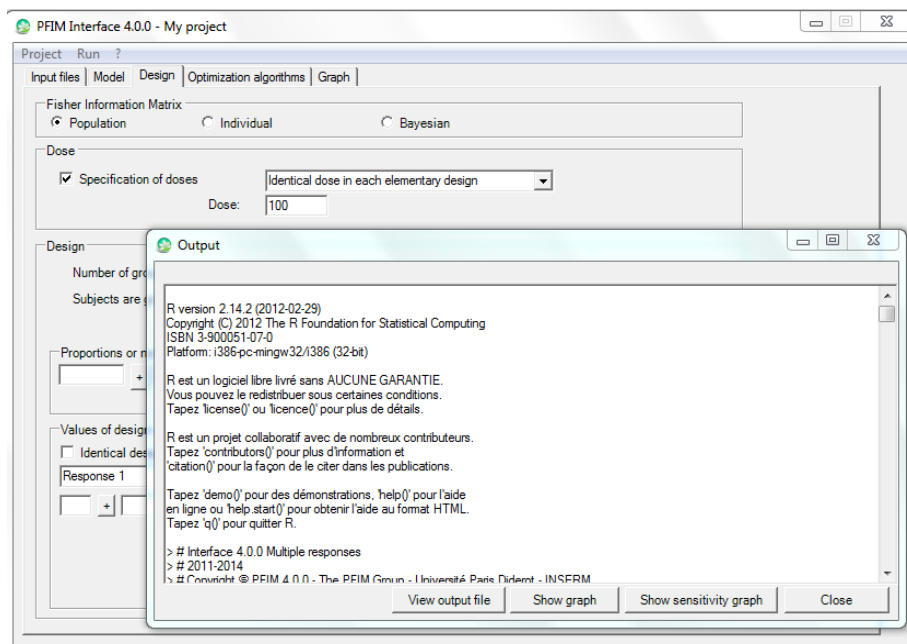
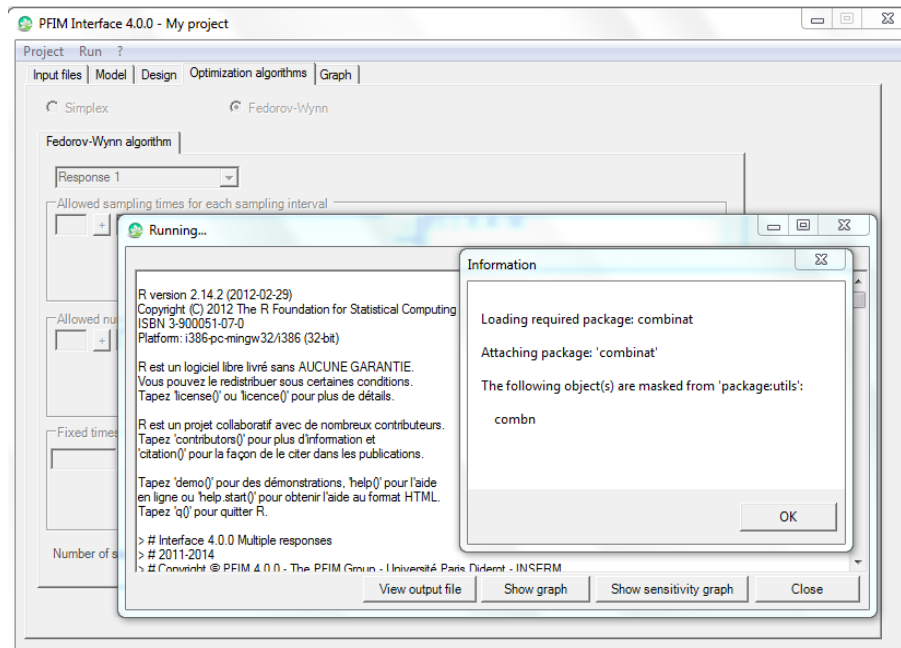


Figure 34: Tab of the results with buttons to see the output file and the graph

Regarding optimisation step with the Fedorov-Wynn algorithm, in addition to the R command windows PFIM Interface 4.0 opens a warning window (Figure 35)

but as it does not prevent the PFIM Interface to run it can just be ignored. It will be removed for the next version of PFIM.



**Figure 35: Tab of the results with buttons to see the output file and the graph and a warning window**

If any graph was requested, a file called 'Rplots' is also created in the project directory and can be viewed by clicking on the "Show graph" or "Show sensitivity graph" button in the same output R command window. The results are also written in the output file named by default stdout.r. According design evaluation or design optimisation, the following sections are going to describe the different elements of the output file.

## 6.1 Evaluation output file and objects

### 6.1.1 Single response model

Figure 36 represents the output file from the design evaluation as in the Example 1 - described in the "Examples" section.

The user can read on Figure 36:

- ① The name of the function used: PFIM Interface 4.0.
- ② The name of the project and the date.
- ③ A summary of the input: model, variance error model, residual between-subject variance model, initial population design, initial numbers or proportions of subjects and doses, initial conditions values, errors tolerances for the solver of differential equations system if used and the expression of the Fisher information matrix used (block or full).
- ④ The population Fisher information matrix, a dim\*dim symmetric matrix where dim is the total number of population parameters to be estimated.
- ⑤ The value of each population parameter with the expected standard error on each parameter and the corresponding coefficient of variation.

6 The value of the determinant of the Fisher information matrix and the value of the criterion (determinant^(1/dim)) where dim is the total number of population parameters.

The eigenvalues of the Fisher information matrix and the correlation matrix.

PFIM Interface 4.0

Project: Example 1.1\_ExpressionMod\_1.2.1

Date: Tue May 12 08:16:29 2015

\*\*\*\*\* INPUT SUMMARY \*\*\*\*\*

Analytical function models :

dose/V \* ka/(ka - k) \* (exp(-k \* t) - exp(-ka \* t))

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]	[,7]
[1,]	38.467601	82.86694	-3.770151	0.000000	0.000000	0.000000	0.000000
[2,]	82.866939	8310.88576	77.977971	0.000000	0.000000	0.000000	0.000000
[3,]	-3.770151	77.97797	4.938229	0.000000	0.000000	0.000000	0.000000
[4,]	0.000000	0.000000	0.000000	59.190253	4.291831	31.98158	28.15946
[5,]	0.000000	0.000000	0.000000	4.291831	674.519747	213.76982	193.67427
[6,]	0.000000	0.000000	0.000000	31.981582	213.769824	3086.36693	295.74230
[7,]	0.000000	0.000000	0.000000	28.159462	193.674273	295.74230	1208.60606
[8,]	0.000000	0.000000	0.000000	85.786235	226.638153	1167.39328	1544.00257

[,8]

[1,]	0.000000
[2,]	0.000000
[3,]	0.000000
[4,]	85.78624
[5,]	226.63815
[6,]	1167.39328
[7,]	1544.00257
[8,]	4118.40001

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

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

	Beta	StdError	RSE
ka	2.00	0.17480765	8.740383 %
k	0.25	0.01239415	4.957658 %
V	15.00	0.52291110	3.486074 %

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

	omega2	StdError	RSE
ka	1.00	0.13203572	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 %

1

2

3

4

5

```

***** DETERMINANT *****
2.930397e+20
***** CRITERION *****
361.7144
***** EIGENVALUES OF THE FISHER INFORMATION MATRIX *****

      FixedEffects VarianceComponents
min      2490.782416      3.598669
max      8312.446928      702.614507
max/min   3.337283      195.242884
***** CORRELATION MATRIX *****

      [,1]      [,2]      [,3]      [,4]      [,5]      [,6]
[1,] 1.0000000 -0.2836926  0.3614018  0.0000000000  0.0000000000  0.0000000000
[2,] -0.2836926  1.0000000 -0.4466787  0.0000000000  0.0000000000  0.0000000000
[3,]  0.3614018 -0.4466787  1.0000000  0.0000000000  0.0000000000  0.0000000000
[4,]  0.0000000  0.0000000  0.0000000  1.0000000000  0.0008945383 -0.01707708
[5,]  0.0000000  0.0000000  0.0000000  0.0008945383  1.0000000000 -0.13147266
[6,]  0.0000000  0.0000000  0.0000000 -0.0170770841 -0.1314726648  1.0000000000
[7,]  0.0000000  0.0000000  0.0000000  0.0186040109 -0.1824110325  0.12863647
[8,]  0.0000000  0.0000000  0.0000000 -0.1283097535  0.0574454432 -0.31004589

      [,7]      [,8]
[1,] 0.00000000  0.00000000
[2,] 0.00000000  0.00000000
[3,] 0.00000000  0.00000000
[4,] 0.01860401 -0.12830975
[5,] -0.18241103  0.05744544
[6,]  0.12863647 -0.31004589
[7,]  1.00000000 -0.68199073
[8,] -0.68199073  1.00000000

```

6

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Figure 36: Example of design evaluation output file for a single response model

Moreover, several R objects are returned in the R command window:

```

dose
prot: design evaluated for each response
subjects: number of subjects for each group
mfisher: the population Fisher information matrix
determinant: the determinant of the population Fisher information matrix
crit: the value of the criterion
p: the vector
se: the vector of the expected standard errors for each parameter
cv: the corresponding coefficient of variation, expressed in percent.
EigenValues: the eigenvalues of the Fisher information matrix
corr.matrix: the correlation matrix

```

### 6.1.2 Multiple response model

Figure 37 represents the output file from the design evaluation as in the Example 2 described in the "Examples" section.

The user can read on the Figure 37:

- ① The name of the function used: PFIM Interface 4.0.
- ② The name of the project and the date.
- ③ A summary of the input: model(s), sampling times in the elementary designs for each model(s), doses or initial conditions and subjects corresponding to those designs, residual variance error model for each model(s), residual between-subject variance model, initial population design, errors tolerances for the solver of differential equations system if used and the expression of the Fisher information used (block or full).

The figure shows a two responses model (differential equations form) with a group described by 5 sampling times for both first and second responses for 100 subjects. The dose is equal to 100.

④ The population Fisher information matrix, a dim\*dim symmetric matrix where dim is the total number of population parameters to be estimated.

⑤ The value of each population parameter with the expected standard error on each parameter and the corresponding coefficient of variation.

⑥ The value of the determinant of the Fisher information matrix and the value of the criterion (determinant^(1/dim)) where dim is the total number of population parameters.

⑦ The eigenvalues of the Fisher information matrix and the correlation matrix.

PFIM Interface 4.0

Project: Example 2

Date: Tue May 12 08:24:26 2015

①

} ②

\*\*\*\*\* 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  
 FIM saved in FIM.txt

} ③

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

	[,1]	[,2]	[,3]	[,4]	[,5]
[1,]	2.6770341	9.444202	-57.39048	-0.7254162	0.000000e+00
[2,]	9.4442023	50919.213161	7982.73905	657.4076389	0.000000e+00
[3,]	-57.3904833	7982.739050	33057.82792	-6714.1078293	0.000000e+00
[4,]	-0.7254162	657.407639	-6714.10783	38772.8151987	0.000000e+00
[5,]	0.0000000	0.000000	0.00000	0.0000000	7.938111e+02
[6,]	0.0000000	0.000000	0.00000	0.0000000	4.463216e-01
[7,]	0.0000000	0.000000	0.00000	0.0000000	3.916193e-03
[8,]	0.0000000	0.000000	0.00000	0.0000000	2.546794e+00
[9,]	0.0000000	0.000000	0.00000	0.0000000	8.097541e+00

	[,6]	[,7]	[,8]	[,9]
[1,]	0.0000000	0.000000e+00	0.000000e+00	0.000000
[2,]	0.0000000	0.000000e+00	0.000000e+00	0.000000
[3,]	0.0000000	0.000000e+00	0.000000e+00	0.000000
[4,]	0.0000000	0.000000e+00	0.000000e+00	0.000000
[5,]	0.4463216	3.916193e-03	2.546794e+00	8.097541
[6,]	586.1230244	1.453005e-01	9.449987e+01	301.234913
[7,]	0.1453005	7.516656e+02	8.332548e-01	116.540931
[8,]	94.4998735	8.332548e-01	1.725786e+04	1714.876645
[9,]	301.2349133	1.165409e+02	1.714877e+03	64572.948196

4

\*\*\*\*\* 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 %

5

----- 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

6



\*\*\*\*\* 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]
[1,]	1.00000000	-0.06785010	0.2062542	0.04352023	0.000000e+00
[2,]	-0.06785010	1.00000000	-0.2101514	-0.05600795	0.000000e+00
[3,]	0.20625422	-0.21015142	1.00000000	0.19876898	0.000000e+00
[4,]	0.04352023	-0.05600795	0.1987690	1.00000000	0.000000e+00
[5,]	0.00000000	0.00000000	0.00000000	0.00000000	1.000000e+00
[6,]	0.00000000	0.00000000	0.00000000	0.00000000	-5.826757e-04
[7,]	0.00000000	0.00000000	0.00000000	0.00000000	1.311462e-05
[8,]	0.00000000	0.00000000	0.00000000	0.00000000	-6.146867e-04
[9,]	0.00000000	0.00000000	0.00000000	0.00000000	-1.068259e-03

	[,6]	[,7]	[,8]	[,9]
[1,]	0.0000000000	0.000000e+00	0.0000000000	0.0000000000
[2,]	0.0000000000	0.000000e+00	0.0000000000	0.0000000000
[3,]	0.0000000000	0.000000e+00	0.0000000000	0.0000000000
[4,]	0.0000000000	0.000000e+00	0.0000000000	0.0000000000
[5,]	-0.0005826757	1.311462e-05	-0.0006146867	-0.001068259
[6,]	1.0000000000	5.840399e-04	-0.0272653545	-0.047524772
[7,]	0.0005840399	1.000000e+00	0.0006127203	-0.016746938
[8,]	-0.0272653545	6.127203e-04	1.0000000000	-0.050000216
[9,]	-0.0475247719	-1.674694e-02	-0.0500002164	1.0000000000

7

Figure 37: Example of design evaluation output file for a two response model

Moreover, the PFIM() function returns the following R objects:

- dose**
- prot:** design evaluated for each response
- subjects:** number of subjects for each group
- mfisher:** the population Fisher information matrix
- determinant:** the determinant of the population Fisher information matrix
- crit:** the value of the criterion
- p:** the vector
- se:** the vector of the expected standard errors for each parameter
- cv:** the corresponding coefficient of variation, expressed in percent.
- EigenValues:** the eigenvalues of the Fisher information matrix
- corr.matrix:** the correlation matrix

## 6.2 Optimisation output file and objects

Figure 38 represents the output file corresponding to the optimal Bayesian design described in the Examples section in the paragraph 1.3.

The user can read on the Figure 38:

- ① The name of the function used: PFIM Interface 4.0
- ② The name of the project and the date.
- ③<sub>a</sub> A summary of the input: structural model, between-subject and error variance model, initial design, initial numbers or proportions of subjects and doses, total number of allowed samples, criterion associated to the initial design.
- ③<sub>b</sub> Sampling times specifications (according to the algorithm used) within which the optimal samples will be chosen and error tolerances for the solver of differential equations system if used.
- ④ The optimised design and the associated criterion.  
For the simplex algorithm, the number of iterations performed and the number of function evaluations, the status of the convergence (false or achieved) are reported  
For the Fedorov-Wynn algorithm for optimal population design, the optimal group structure with the proportion of subjects and the equivalence in number are then reported. The best one group protocol is also always reported with associated criterion.  
When optimising a Bayesian or an individual design, the resulted design correspond to the best one group protocol.
- ⑤ The population or individual or Bayesian Fisher information matrix, a  $\text{dim} \times \text{dim}$  symmetric matrix where  $\text{dim}$  is the total number of population parameters to be estimated, the number of individual parameters + the number of the error model parameters or only the number of individual parameters respectively. The name of the file where is possibly saved the Fisher information matrix is given.
- ⑥ The value of each parameter with the expected standard error (StdError) and relative standard error (RSE). In case of Bayesian design, the associated shrinkages values are also reported.
- ⑦ The value of the determinant of the Fisher information matrix and the value of the criterion ( $\text{determinant}^{(1/\text{dim})}$ ) where  $\text{dim}$  is defined in ⑤
- ⑧ The eigenvalues of the Fisher information matrix and the correlation matrix.

PFIM Interface 4.0

Project: Example Optimisation

Date: Thu Jul 31 09:22:17 2014

1

2

\*\*\*\*\* 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

3a

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

3b

BEST ONE GROUP PROTOCOL:

Sample times for response: A  
times freq Subjects doses  
1 c(0.33, 1.5, 5, 8) 1 1 100

4

Associated criterion: 3.8066

```

Computation of the Bayesian Fisher information matrix

FIM saved in FIM.txt

***** 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

```

5

6

7

8

Figure 38: Example of design optimisation output file

Moreover, the PFIM() function returns the following R objects:

- mfisher:** the population or individual or Bayesian Fisher information matrix corresponding to the optimised protocole
- determinant:** the determinant of the Fisher information matrix
- crit:** the value of the criterion
- se:** the vector of the expected standard errors for each parameter
- cv:** the corresponding coefficient of variation, expressed in percent (relative standard error)
- sh:** the shrinkage values for each parameter in case of Bayesian design
- EigenValues:** the eigenvalues of the Fisher information matrix
- corr.matrix:** the correlation matrix

## 7. Examples

This section 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 Interface 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 Interface.

Furthermore, examples available from the previous version of PFIM Interface, version 3.1, were also implemented in PFIM Interface 4.0. All the input, model and output codes used for these examples are available when PFIM is downloaded, in the directory "Examples" stored in Documents in the directory "PFIM Interface 4.0". They are detailed below.

### Evaluation

#### 1. Example 1: PK Model

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

Random effects are exponentially modelled.

	Mean	Fixed mean	Variance
$k_a$	2	<input type="checkbox"/>	1
$k$	0.25	<input type="checkbox"/>	0.25
$V$	15	<input type="checkbox"/>	0.1
$\sigma_{inter}$		0.5	
$\sigma_{slope}$		0.15	

Please note: as we don't fix here any parameter, the "Fixed mean" column is kept as default that is without any of the squares checked

#### 1.1 Model Files

Four possible and exchangeable ways for defining the model are available in PFIM. These are described in section 3 of this documentation. Below are reported the figures of the 4 possible models (Figure 39-42).

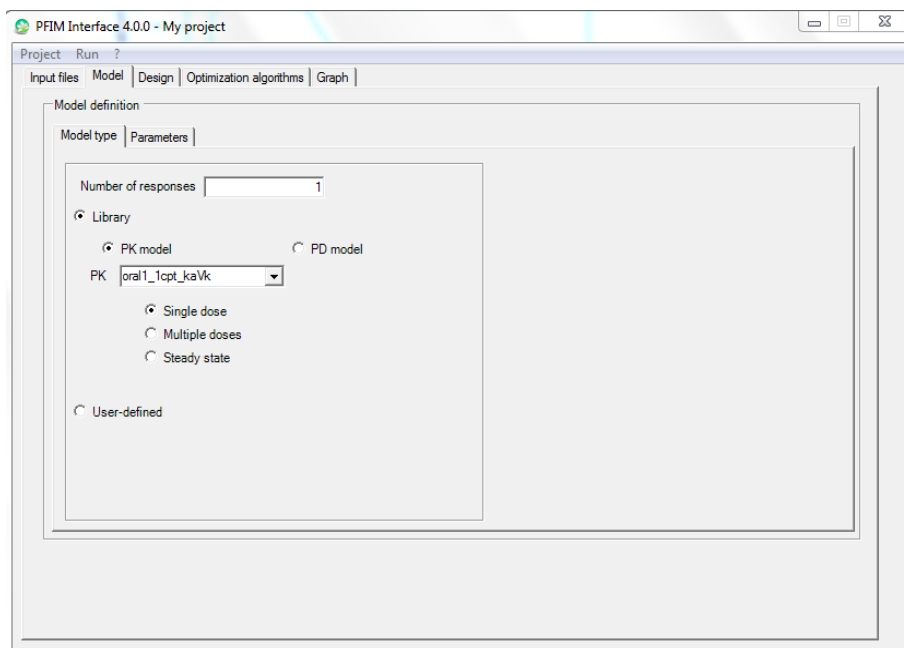


Figure 39 : Model defined from the library

```

model - Bloc-notes
Fichier Edition Format Affichage ?
#$Model definition
#$ka,k,V
#$
formA <-expression(dose/V*ka/(ka-k)*(exp(-k*t)-exp(-ka*t)))
form<-c(formA)
tf<-list(Inf)

```

Figure 40 : User defined model through analytical expression

```

model - Bloc-notes
Fichier Edition Format Affichage ?
#$Model definition
#$ ka,k,V
#$
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)
}

```

Figure 41 : User defined model through analytical function

```

model - Bloc-notes
Fichier Edition Format Affichage ?
#$Model definition ODE
#$ka,k,V
#$
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))
}

```

Figure 42 : User defined model through differential equations

### Graphs pre-evaluation

Graphs of the simulated model and sensitivity function with respect to parameters were obtained by running "Graph only" (see the "Use" section paragraph 6.8 "Graph tab").

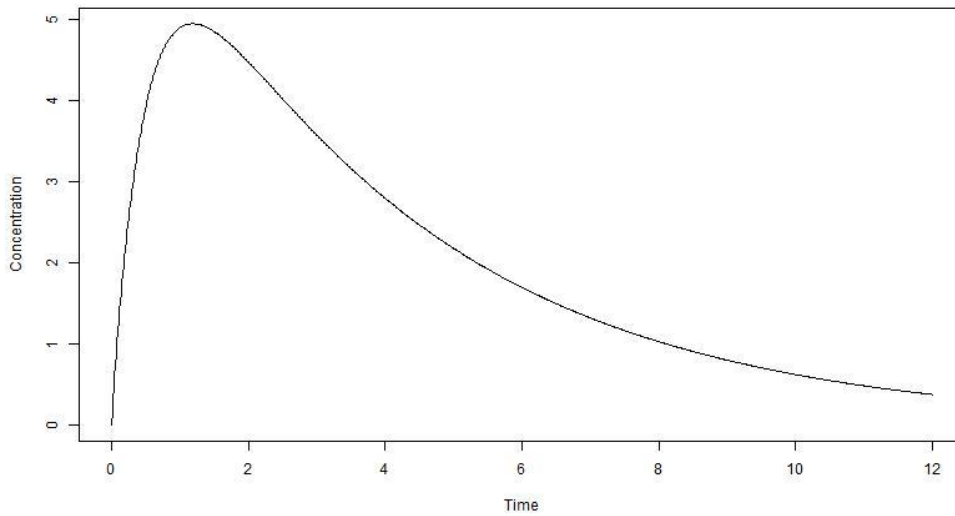


Figure 43 : Simulated model

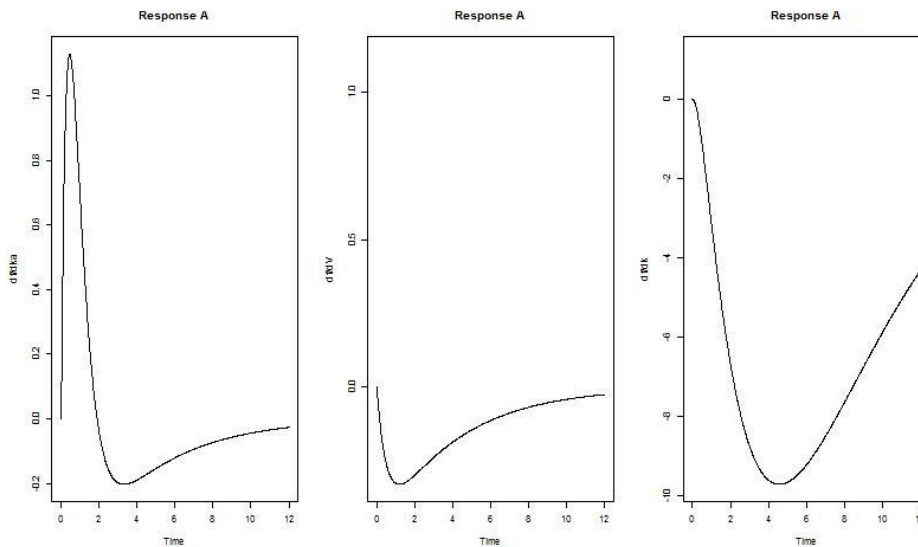


Figure 44 : Sensitivity function with respect to parameters

### Population Fisher Information Matrix (P-FIM)

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

#### 1.1.1.1 One group with Elementary Design $\xi_1$

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 files (stdin.R, model.r and Stdout.r) for each possible model form (see paragraph 1.1 of this section of Examples). We therefore repeated the example four times, using four input files. Those PFIM files are stored in the directory of Examples, under EVALUATION and EXAMPLE\_1 in 4 different folders that are called:

"Exemple 1.1.\_ModLibrary\_1.2.1; 1.1\_ExpressionMod\_1.2.1; 1.1\_ModeOde\_1.2.1; 1.1\_UserDefMod\_1.2.1.

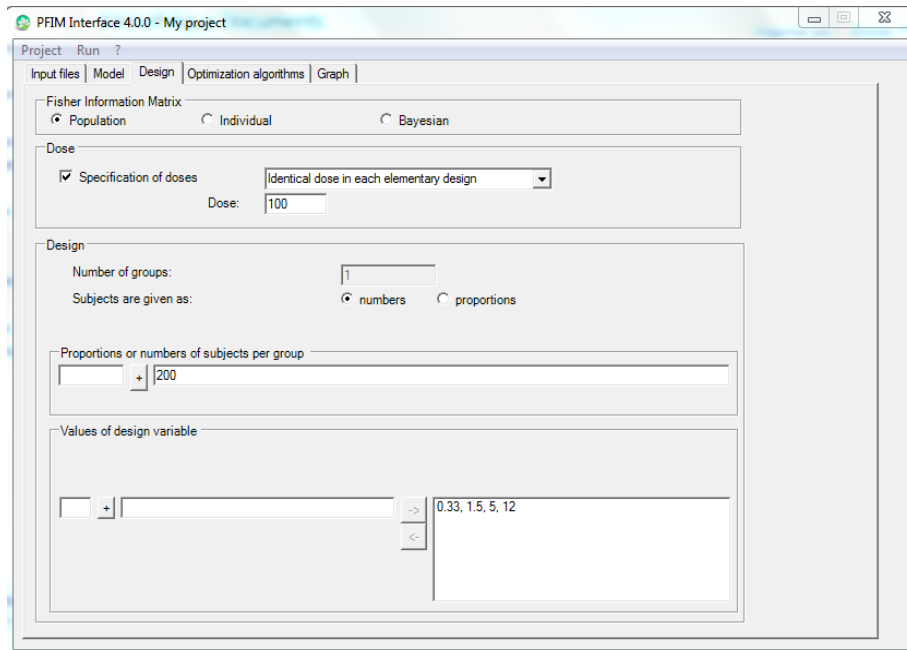


Figure 45 : Design tab for examples of section 1.1.1

### 1.1.2 One group with Elementary Design $\xi_2$

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

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

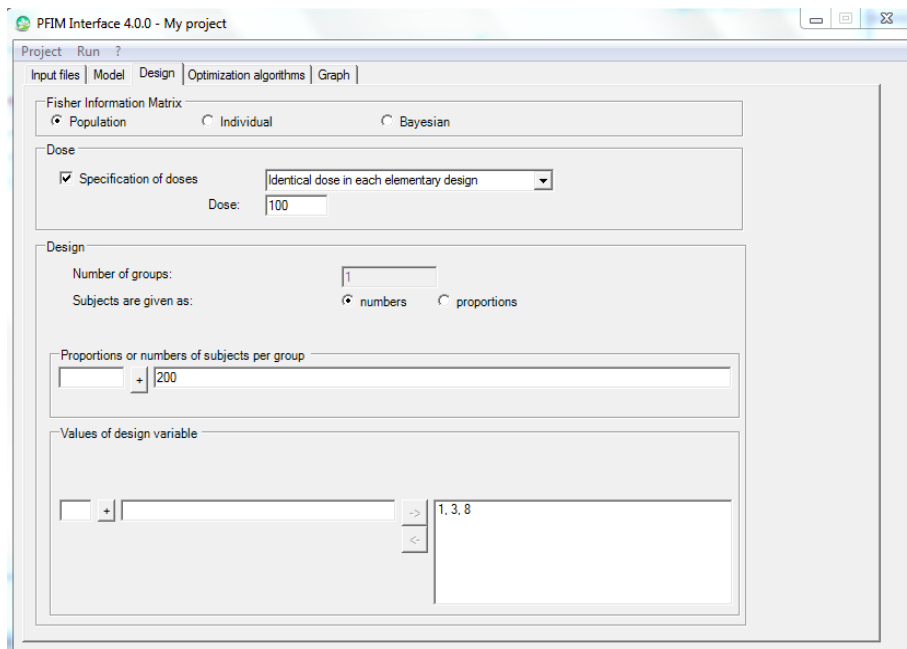


Figure 46: Design tab for example 1.1.2

### 1.1.3 Two Groups Design

Two group population design of 400 subjects: 200 with elementary designs  $\xi_1$  and 200 with elementary design  $\xi_2$ .



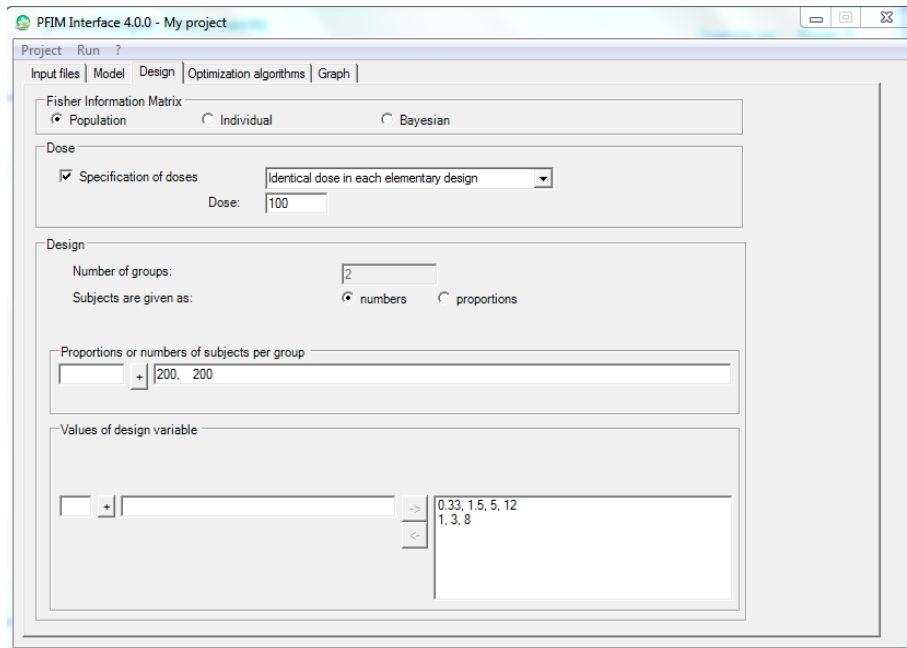


Figure 47: Design tab for example 1.1.3

## 1.2 Individual Fisher Information Matrix (I-FIM)

Evaluation of the Individual Fisher Information Matrix for the elementary design  $\xi_1$  and then  $\xi_2$ .

### 1.2.1 Elementary Design $\xi_1$

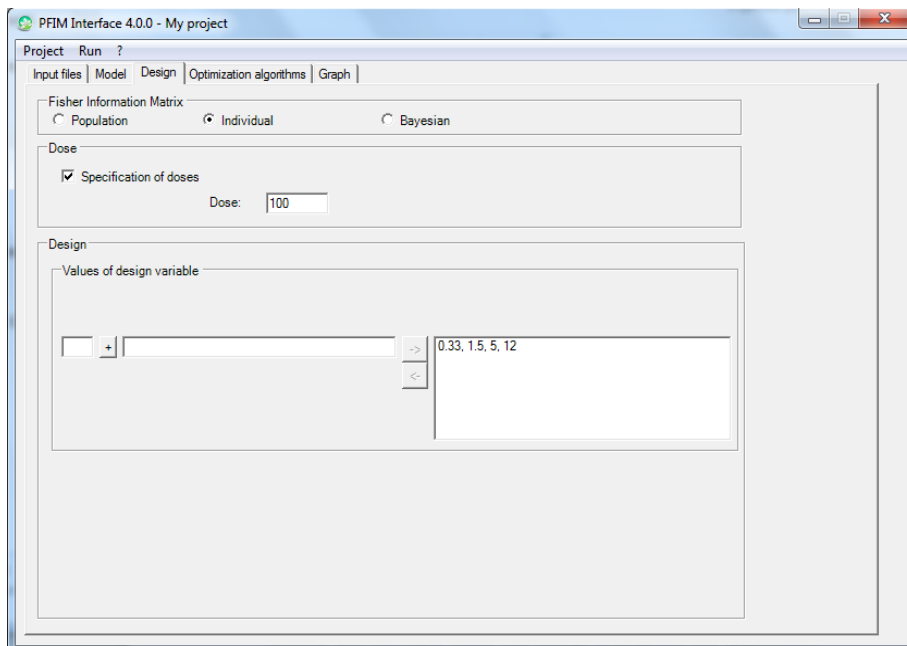


Figure 48 : Design tab for example 1.2.1

### 1.2.2 Elementary Design $\xi_2$

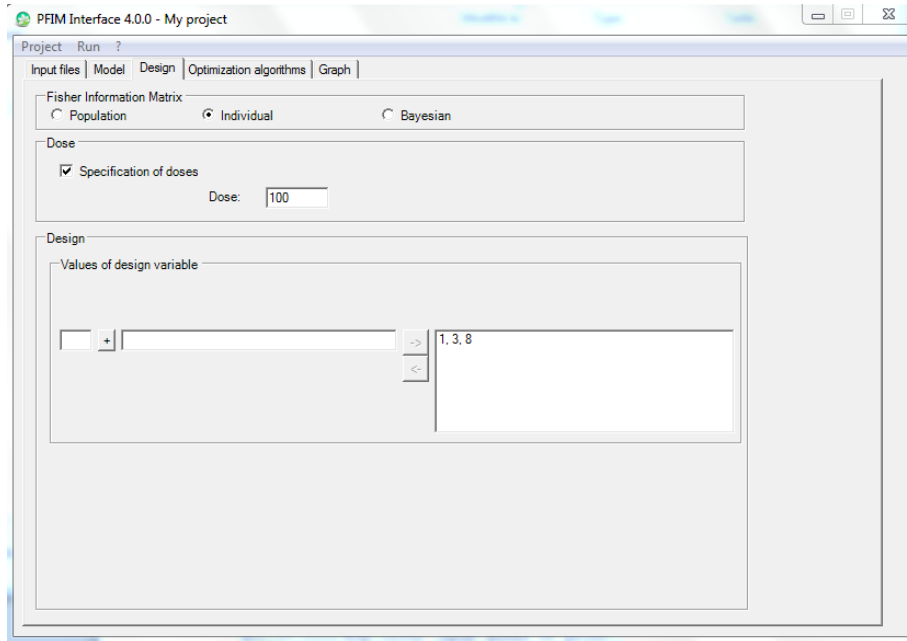


Figure 49: Design tab for example 1.2.2

### 1.3 Bayesian Fisher Information Matrix (B-FIM)

Evaluation of the Bayesian Fisher Information Matrix for the elementary design  $\xi_1$  and then  $\xi_2$ .

#### 1.3.1 Elementary Design $\xi_1$

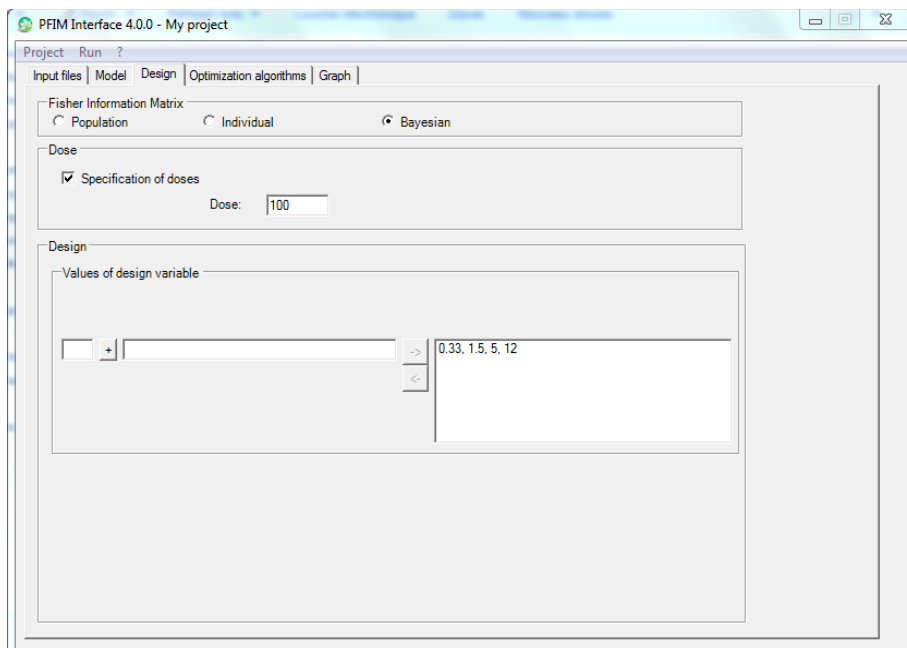


Figure 50: Design tab for example 1.3.1

### 1.3.2 Elementary Design $\xi_2$

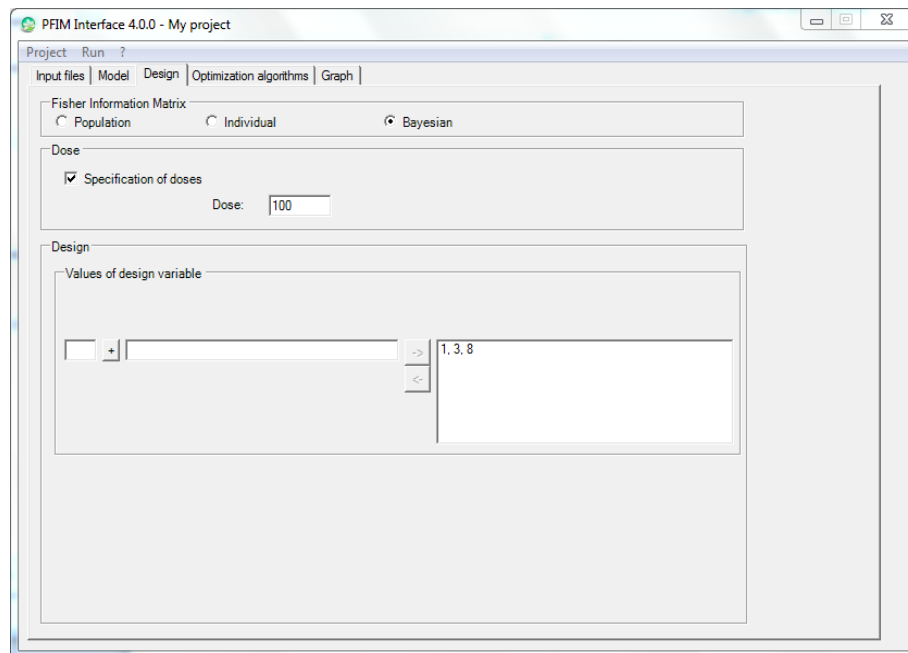


Figure 51: Design tab for example 1.3.2

#### Comment on results

Comparing examples in 1.2 and 1.3 it is noticeable that the evaluation of B-FIM leads to smaller RSE particularly for the parameter  $k_a$ , 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  $\xi_1$  than with  $\xi_2$ , as the variability on  $k_a$  is kept lower and the criterion is slightly higher. For B-FIM, shrinkage values are provided and they show that with  $\xi_1$  more information is obtained than with  $\xi_2$ .

### 1.4 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  $\xi_1$  assuming that the parameter  $k_a$  is fixed (and has no variability). Those examples are stored in the directory of EXAMPLE→EVALUATION→EXAMPLE1, and the names of their folder are: 1.4.1, 1.4.2, 1.4.3 for P-FIM, I-FIM or B-FIM evaluation, respectively.

#### Comment on results

Comparing the output of example 1.4.1 with the one in section 1.1.1, we can see that the standard errors are slightly reduced in this example.

As for example 1.4.1, fixing  $k_a$  resulted in slight improvements of the Relative Standard Errors in 1.4.2 with respect to the results in section 1.2.1

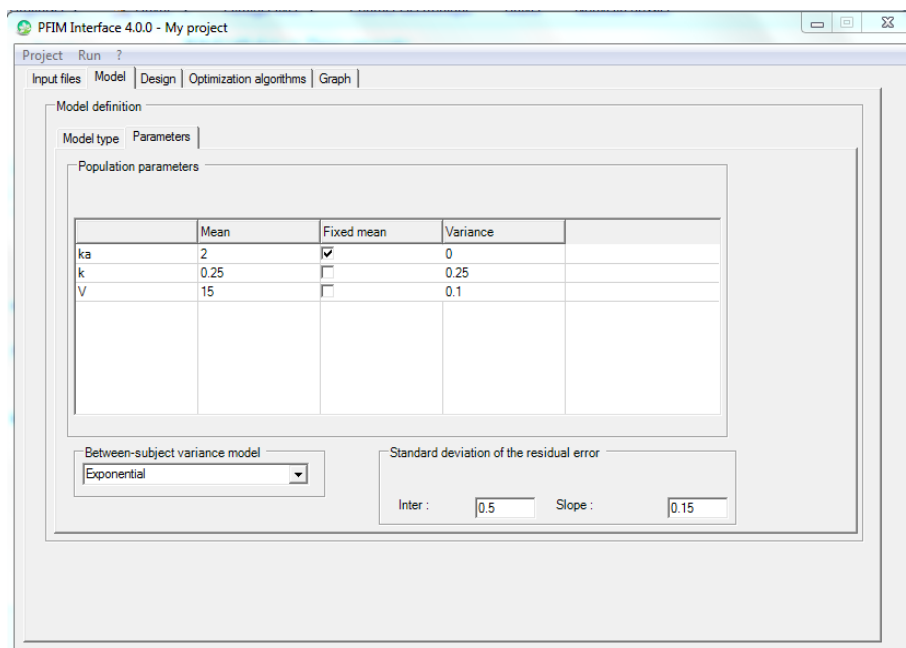


Figure 52: Parameters tab when fixing parameter  $k_a$

## 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

The aim is to evaluate, in a population approach, the following one group designs:

- sampling times for PK response: 0.5, 2, 30, 49, 180
- sampling times for PD response: 0.5, 2, 14, 110, 150

for a PKPD model, where the PK is one compartment infusion input with Michaelis-Menten elimination after a single dose administration with parameters  $V$ ,  $V_m$  and  $k_m$  and the PD is an immediate response model with a linear drug action and without baseline, where the parameter is  $A_{lin}$ .

		<b>Mean</b>	Fixed mean	Variance
	V	12.2	<input type="checkbox"/>	0.25
	$V_m$	0.082	<input type="checkbox"/>	0.25
	$k_m$	0.37	<input type="checkbox"/>	0
	$A_{lin}$	0.1	<input type="checkbox"/>	0.25
Resp A	$\sigma_{inter}$	0		
	$\sigma_{slope}$	0.2		
Resp B	$\sigma_{inter}$	0.1		
	$\sigma_{slope}$	0		

## Optimisation

### 1. Example 1: PK Model

We illustrate optimisation algorithms with the same examples used in the Evaluation section and with an additional example (Example 3) that shows a case of repeated dose regimen. As for Evaluation, Example 1 is more detailed with all the new features. For Example 2 and 3 optimisation was

performed only with Federow-Wynn (FW) algorithm. For Example 1 and 2 we therefore show only the parts concerning optimisation.

### 1.1 Population Fisher Information Matrix (P-FIM)

The aim is to optimise 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:  $(0, 12)$

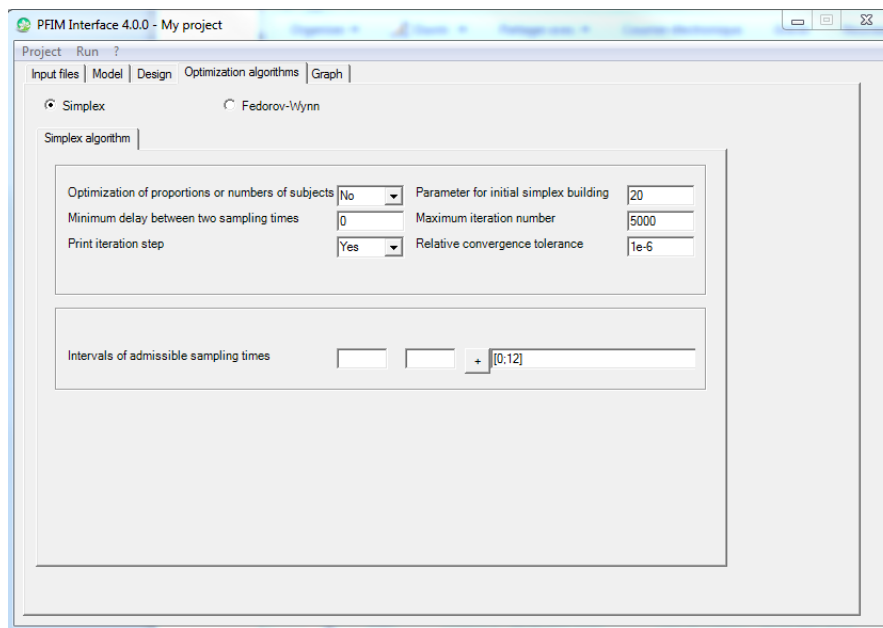


Figure 53: Simplex algorithm specifications

#### Comment on results

The criterion associated with the initial times ( $\xi_1$ ) 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

Optimal times were found for three groups of approximately 71, 123 and 6 subjects, respectively. These are:  $(0.33, 1, 1.5, 8)$ ;  $(0.33, 1.5, 8, 12)$  and  $(0.33, 1.5, 3, 12)$  for the first, second and third group, respectively. 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 parameters

The aim is to optimise 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. Corresponding examples are stored in the directory of PFIM interface 4.0 (Examples  $\rightarrow$  OPTIMISATION  $\rightarrow$  EXAMPLE\_1) in the folder 1.1.3.1 and 1.1.3.2 for the examples optimisation with Simplex or with FW algorithm, respectively.

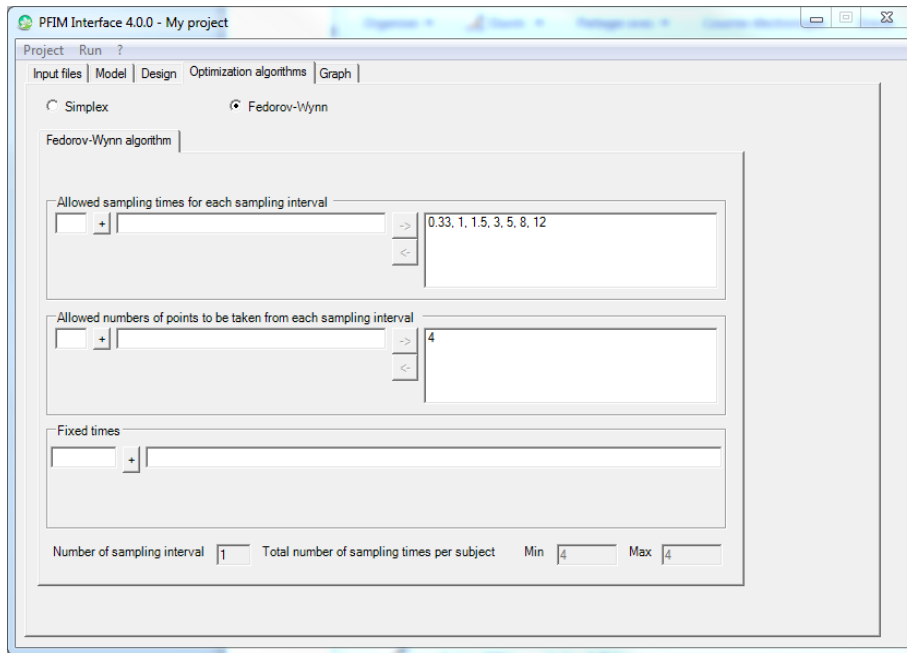


Figure 54: Fedorov-Wynn algorithm specifications

#### 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. (In PFIM Interface 4.0 it is possible to fix times only with the Fedorov-Wynn algorithm).

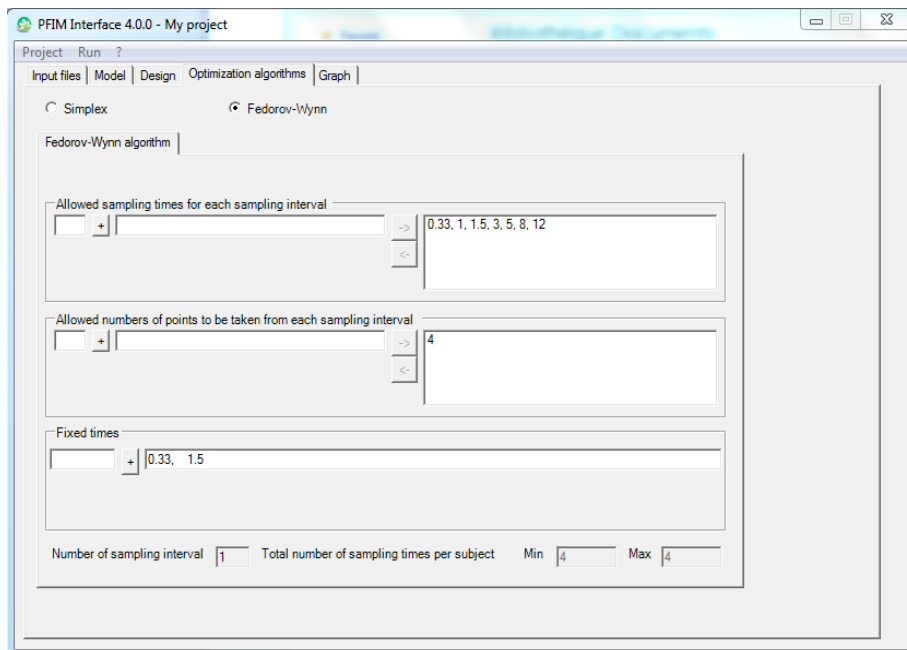


Figure 55: Fedorov-Wynn algorithm specifications: fixed sampling times

#### 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).

Essentially this example is the combination of examples 1.1.3.2 and 1.4.1.

### **1.2 Individual Fisher Information Matrix (I-FIM)**

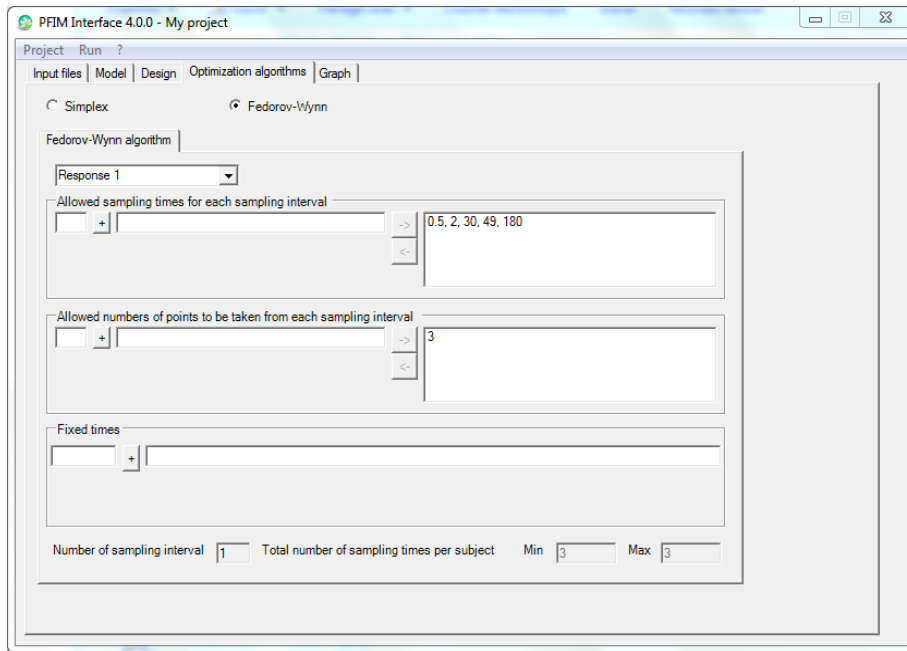
Optimize the design in 1.1 this time for the Individual Fisher Information Matrix (I-FIM). Use same constraints in 1.1.1 and 1.1.2. The optimisations performed for P-FIM are repeated in case of I-FIM. Examples 1.2.1 and 1.2.2 show the optimisation of I-FIM with the Simplex algorithm and Fedorov-Wynn algorithm, respectively; in Example 1.2.3 the optimisation is performed with the Fedorov-Wynn algorithm, fixing parameter  $k_a$  and two sampling times (0.33, 1.5).

### **1.3 Bayesian Fisher Information Matrix (B-FIM)**

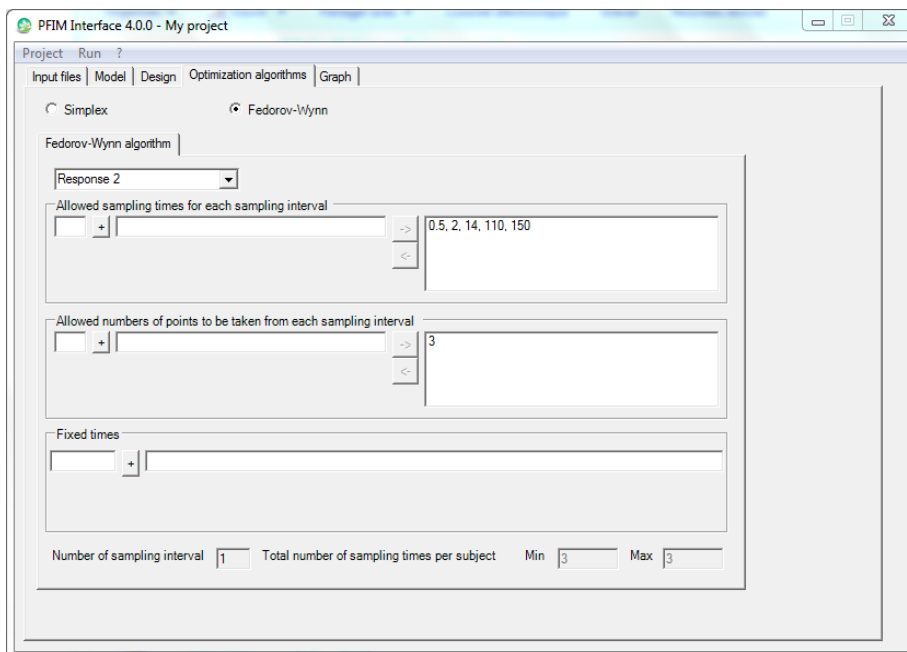
Optimize the design in 1.1 this time for the Bayesian Fisher Information Matrix (I-FIM). Use same constraints in 1.1.1 and 1.1.2. The optimisations performed for P-FIM are repeated in case of B-FIM. Examples 1.3.1 and 1.3.2 show the optimisation of B-FIM with the Simplex algorithm and Fedorov-Wynn algorithm, respectively; in Example 1.3.3 the optimisation is performed with the Fedorov-Wynn algorithm, fixing parameter  $k_a$  and two sampling times (0.33, 1.5).

## **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



**Figure 56: Fedorov-Wynn algorithm specifications for the first response**



**Figure 57: Fedorov-Wynn algorithm specifications for the second response**



### 3. Example 3: Repeated doses

This example deals with the optimisation of a design using the Fedorov-Wynn algorithm and with a model defined by the user using the functions of the library of models.

Repeated doses of 100 with oral absorption every 12 hours are considered. The model is a one compartment model first order absorption, parameterized with rate constant of absorption ( $k_a$ ), volume ( $V$ ) and clearance ( $Cl$ ). The mean and the variance of those parameters are given in the table below. The random effects are exponentially modelled and the variance error model is proportional.

	<b>Mean</b>	Fixed mean	Variance
$k_a$	0.7	<input type="checkbox"/>	0.25
$Cl$	0.5	<input type="checkbox"/>	0.25
$V$	5	<input type="checkbox"/>	0.25
$\sigma_{inter}$		0	
$\sigma_{slope}$		0.2	

The purpose is to optimise a design with 90 subjects, with sampling times after the first and the fifth doses, using the Fedorov-Wynn algorithm. After the first dose, 2 or 3 samples per subject are allowed in the following set (0.5, 1, 2, 3, 4, 6, 8, 10, 12). After the fifth dose, 2 or 3 samples per subject are also allowed in the following set: (48.5, 49, 50, 51, 52, 56, 58, 60).

The initial population design used to run the Fedorov-Wynn algorithm is composed of four sampling times: (0.5, 12, 50, 60) to be performed in 90 subjects.

## 4. Examples from PFIM Interface 3.1

### 4.1 Single response model

#### 4.1.1 Evaluation

##### 4.1.1.1 Example A

This example deals with the evaluation of a population design using the library of model.

The purpose is to evaluate a design using a one compartment model after a single bolus administration. The parameters and their values are given in the table. The random effects are modelled exponentially. The variance error model is a combined error model.

The design to be evaluated is composed of two groups: one group of 30 subjects with a dose of 100 and sampling times at (0.5, 2, 3, 10) and one group of 90 subjects with a dose of 200 and sampling times at (1, 4, 12).

	<b>Mean</b>	Fixed mean	Variance
V	10	<input type="checkbox"/>	0.25
k	0.2	<input type="checkbox"/>	0.25
$\sigma_{inter}$	0.5		
$\sigma_{slope}$	0.15		

##### 4.1.1.2 Example B

This example deals with the evaluation of a design using a differential equation system. The model is a one compartment model first order absorption and Michaelis-Menten elimination. The parameters and their values are given in the table below.

The design to be evaluated is 0.5, 2, 16, 23.5 with a dose of 13.8 performed in 30 subjects.

The variance error model is proportional and the modelling of the random effects is exponential.

	<b>Mean</b>	Fixed mean	Variance
ka	2.72	<input type="checkbox"/>	0.25
V	12.2	<input type="checkbox"/>	0.25
Vm	1.004	<input type="checkbox"/>	0.25
km	0.37	<input type="checkbox"/>	0.25
$\sigma_{slope}$	0.2		

#### 4.1.2 Optimisation



Be careful, remember that, with the Fedorov-Wynn algorithm, the sampling times of the initial population design should be included in the allowed sampling times, so as the number of allowed samples per group.

#### 4.1.2.1 Example C

This example deals with the optimisation of a design using the Fedorov-Wynn algorithm and with a model defined by the user using the functions of the library of models.

Repeated doses of 100 with oral absorption every 12 hours are considered. The model is a one compartment model first order absorption, parameterized with rate constant of absorption ( $k_a$ ), volume ( $V$ ) and clearance ( $Cl$ ). The mean and the variance of those parameters are given in the table below. The random effects are exponentially modelled and the variance error model is proportional.

	<b>Mean</b>	Fixed mean	Variance
$k_a$	0.7	<input type="checkbox"/>	0.25
$Cl$	0.5	<input type="checkbox"/>	0.25
$V$	5	<input type="checkbox"/>	0.25
$\sigma_{slope}$	0.2		

The purpose is to optimise a design with 90 subjects, with sampling times after the first and the fifth doses, using the Fedorov-Wynn algorithm. After the first dose, 2 or 3 samples per subject are allowed in the following set (0.5, 1, 2, 3, 4, 6, 8, 10, 12). After the fifth dose, 2 or 3 samples per subject are also allowed in the following set: (48.5, 49, 50, 51, 52, 56, 58, 60).

The initial population design used to run the Fedorov-Wynn algorithm is composed of four sampling times: (0.5, 12, 50, 60) to be performed in 90 subjects.

#### 4.1.2.2 Example D

This example deals with the optimisation of a design using the Fedorov-Wynn algorithm. The model is described by a two compartment model after infusion administration, parameterized in volume ( $V$ ), rate constant of elimination ( $k$ ), and inter-compartmental parameters  $k_{12}$  and  $k_{21}$ . The total dose is equal to 550 and the duration of infusion is 0.0625. The random effects are modelled exponentially. The variance error model is proportional.

The mean, the variance of the parameters and the parameters of the variance error model are given in the tab bellow.

	<b>Mean</b>	Fixed mean	Variance
$V$	3.08	<input type="checkbox"/>	0.1
$k$	0.0808	<input type="checkbox"/>	0.2
$k_{12}$	0.175	<input type="checkbox"/>	0.3
$k_{21}$	0.116	<input type="checkbox"/>	0.1
$\sigma_{slope}$	0.25		

A set of eleven allowed sampling times is given: (0.0625, 1, 2, 3, 4, 6, 7, 10, 14, 18, 21).

90 subjects can be involved with either 3 or 4 samples per subject.

An initial design is proposed, with 4 samples per subject, the same into the 90 subjects: (0.0625, 7, 14, 21).

#### 4.1.2.3 Example E

This example deals with the optimisation of a design using the Simplex algorithm and with a model defined by the user using the functions of the library of models.

Ten repeated doses of 2.5 with oral absorption every 24 hours are considered. The model is a two compartment model first order absorption, parameterized with rate constant of absorption ( $k_a$ ), volume for the first compartment ( $V_1$ ), clearance ( $Cl$ ), volume ( $V_2$ ) and the intercompartmental clearance ( $Q$ ). The between subject variance model is exponentially and the variance model is additive.

Values of the parameters are given in the tab bellow:

	<b>Mean</b>	Fixed mean	Variance
$k_a$	1.5	<input type="checkbox"/>	0.502
$Cl$	0.345	<input type="checkbox"/>	0.059
$V_1$	8	<input type="checkbox"/>	0.018
$Q$	0.145	<input type="checkbox"/>	0
$V_2$	18	<input type="checkbox"/>	1.9
$\sigma_{inter}$	0.08		

The aim is to optimise a design with 250 subjects, with sampling times between the first dose and the tenth doses and also five days after the last one, using the Simplex algorithm. Thus, the admissible sampling times are between 0 and 360 hours.

The initial population design used to run the Simplex algorithm is composed of 6 sampling times: (1, 24, 96, 180, 250, 300) to be performed into 250 subjects.

## 4.2 Multiple response model

### 4.2.1 Evaluation

#### 4.2.1.1 Example F

This example deals with the evaluation of a joint modelling of a drug concentration and its effect (two responses): a one compartment model with a first order absorption and elimination for the drug concentration is used and an immediate response model with a constant baseline for the effect. The model is described using the libraries of models. The between subject variance model is exponentially and the variance model is combined for the first response and additive for the second response.

Values of the parameters are given in the tab bellow:

	<b>Mean</b>	Fixed mean	Variance
$k_a$	1.6	<input type="checkbox"/>	0.70
$V$	8	<input type="checkbox"/>	0.02
$Cl$	0.13	<input type="checkbox"/>	0.06
$Imax$	0.73	<input type="checkbox"/>	0.001
$C_{50}$	0.17	<input type="checkbox"/>	0.7
$S_0$	100	<input type="checkbox"/>	0
$\sigma_{inter}$ (first response)	0.6		
$\sigma_{slope}$	0.07		
$\sigma_{inter}$ (second response)	8		

The aim is to evaluate a design with one group with sampling times at 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120 hours for the first response and 0, 24, 36, 48, 72, 96, 120, 144 hours for the second response with 32 subjects. The total dose is equal to 100.

#### 4.2.1.2 Example G

This example deals with the evaluation of a design for a joint model for a drug and its metabolite. The first response is described by a one compartmental model with first order absorption and the second response is described by a one compartment with a first order metabolic rate constant. Because of structural identifiability problem in absence of urinary data, we fix the volume of distribution ( $V_m$ ) of the metabolite equal to 1, and thus estimate  $Cl_m$  and  $k_m$ . The model is described using a differential equation system. The length of vector in the "initial conditions for each elementary design" is equal to 3. The first element of this vector is the dose equal to 300 in this example. The between subject variance model is exponentially and the variance model is combined for the first response and proportional for the second response.

Values of the parameters are given in the tab bellow:

	<b>Mean</b>	Fixed mean	Variance
ka	2.86	<input type="checkbox"/>	0.7
V	300	<input type="checkbox"/>	0.02
Cl	160	<input type="checkbox"/>	0.06
$Cl_m$	0.16	<input type="checkbox"/>	0.17
$k_m$	0.03	<input type="checkbox"/>	0
$\sigma_{inter}$ (first response)		0.003	
$\sigma_{slope}$		0.28	
$\sigma_{inter}$ (second response)		0.13	

The design to be evaluated is composed of 1 group of 80 subjects with sampling times at (1, 3, 6, 12) for the first response and sampling times at (1, 6, 11, 12) for the second response.

#### 4.2.1.3 Example H

This example deals with the evaluation of a design study for a PK/PD model (two responses). The PK model is a one compartmental model with first order absorption and elimination. The drug effect (PD model) is described by a turnover model with inhibition of the input.

This PK/PD model is described using the libraries of models. In this example, we are in the case where we have a PK model with linear elimination (written using an analytical form) and a turnover response PD model (written using a differential equation system). Thus, the user has to complete the tab of the ODE variables because PFIM Interface 3.1 calls a specific function in order to create a system of differential equation system describing the corresponding PK/PD model. The between subject variance model is exponentially. The variance model is combined for the PK model and additive for the second response.

Values of the parameters are given in the tab bellow:

	<b>Mean</b>	Fixed mean	Variance
ka	1.6	<input type="checkbox"/>	0.70
V	8	<input type="checkbox"/>	0.02
Cl	0.13	<input type="checkbox"/>	0.06
Rin	5.4	<input type="checkbox"/>	0.2
kout	0.06	<input type="checkbox"/>	0.02
Imax	1	<input type="checkbox"/>	0
C50	1.2	<input type="checkbox"/>	0.01
<hr/>			
$\sigma_{inter}$ (first response)		0.6	
$\sigma_{slope}$		0.07	
$\sigma_{inter}$ (second response)		8	

The design to be evaluated is composed of one group of 32 subjects with sampling times at 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120 for the PK model and 0, 24, 36, 48, 72, 96, 120, 144 for the PD model. The dose is equal to 100.

#### 4.2.2 Optimisation

##### 4.2.2.1 Example I

This example deals with the optimisation of a design using the Simplex algorithm for a joint modelling of a drug concentration and its effect: a one compartment model with a first order absorption and elimination for the drug concentration is used and an immediate response model with a constant baseline for the effect. The model is described using analytical forms with the 'user defined model' option.

This model has been used for design evaluation in the Example F using the library of models.

Values of the parameters are given in the tab bellow:

	<b>Mean</b>	Fixed mean	Variance
ka	1.6	<input type="checkbox"/>	0.70
V	8	<input type="checkbox"/>	0.02
Cl	0.13	<input type="checkbox"/>	0.06
Imax	0.73	<input type="checkbox"/>	0.001
C50	0.17	<input type="checkbox"/>	0.7
S0	100	<input type="checkbox"/>	0
<hr/>			
$\sigma_{inter}$ (first response)		0.6	
$\sigma_{slope}$		0.07	
$\sigma_{inter}$ (second response)		8	

The aim is to optimise a design with one group of 32 subjects with 5 sampling times between 10 min and 120 hours for the drug concentration measurements and 5 sampling times between 0 and 144 hours for the effect measurements.

#### 4.2.2.2 Example J

This example deals with the optimisation of a design using the Fedorov-Wynn algorithm for a joint model for a drug and its metabolite (two responses). The first response is described by a one compartmental model with first order absorption and the second response is described by a one compartment with a first order metabolic rate constant. The model is described using a differential equation system. The between subject variance model is exponentially and the variance model is combined for the first response and proportional for the second response.

This model has been used for design evaluation in the Example G.

Values of the parameters are given in the tab below:

	<b>Mean</b>	Fixed mean	Variance
ka	2.8	<input type="checkbox"/>	0.70
V	300	<input type="checkbox"/>	0.02
Cl	160	<input type="checkbox"/>	0.06
Clm	0.16	<input type="checkbox"/>	0.001
R	0.03	<input type="checkbox"/>	0.7
<hr/>			
$\sigma_{\text{inter}}$ (first response)		0.03	
$\sigma_{\text{slope}}$		0.28	
$\sigma_{\text{slope}}$ (second response)		0.13	

The aim is to optimise a design (same sampling times for both responses) with 4 sampling times for a total number of samples equal to 400 using the following allowed sampling times: 0.0625, 1, 3, 6, 11, 12, 14 and 15hours.



Be careful, remember that, with the Fedorov-Wynn algorithm, the sampling times of the initial population design should be included in the allowed sampling times, so as the number of allowed samples per group.

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