

PopED Manual

Release version 2.06

Introduction

PopED (Population Experimental Design) is a software tool for computing optimal experimental designs. The software has been developed with an emphasis on drug trials based on population models (non-linear mixed effects models).

The purpose of this manual is **NOT** to teach Optimal Design but rather to give an introduction and help to the PopED Graphical User Interface GUI and PopED script version. PopED GUI is a Windows based program written in the language C# .NET 2.0 that will wrap around the script version of PopED (written in Matlab) that performs the calculations needed to get an optimal design. The purpose of the GUI is to get an easy way to build up an experiment and to optimize the design variables in that experiment. There are also tools available for interpretation of the outcome of the optimal design and ways to validate models and simulate models prior to the optimal design. All these tools are accessible via the script version of PopED but then the user needs knowledge about the Matlab programming language and how to set up an experiment in the Matlab environment, therefore the GUI was developed to minimize the skills needed by the user in terms of programming.

The PopED GUI provides model templates and examples that will help the user to set up their own experiments. Some knowledge in the Matlab language might be useful but the model templates should give a good introduction to defining PopED models in Matlab.

In Addition to this manual, the [Matlab manual](#) and literature in the fields of Population pharmacokinetic and pharmacodynamic (PK-PD) modeling and Optimal Design is suggested.

PopED is a open source program developed by the division of Pharmacokinetics and drug therapy, department of Pharmaceutical Bioscience, Faculty of Pharmacy at Uppsala University.

The PopED Development Team

Installation

PopED is developed for a Microsoft Windows environment. PopED is mainly tested on a Windows XP Professional (Service Pack 2) platform.

Requirements

PopED needs the following packages/programs to work perfectly:

- 1) Microsoft .NET 2.0, use Windows Update or download and install the package from www.microsoft.com. Don't use the SDK for .NET 2.0, (the size is unnecessarily big) instead use the redistributable package.
- 2) To run optimization within the Graphical User Interface (GUI), Matlab needs to be installed. The Statistics toolbox and The Symbolic Toolbox is used in some functions. If Matlab is not installed the PopED GUI could be used as a help to build up PopED runs. PopED is developed with Matlab version 2007a 7.4 with a registered COM Server from the same version.

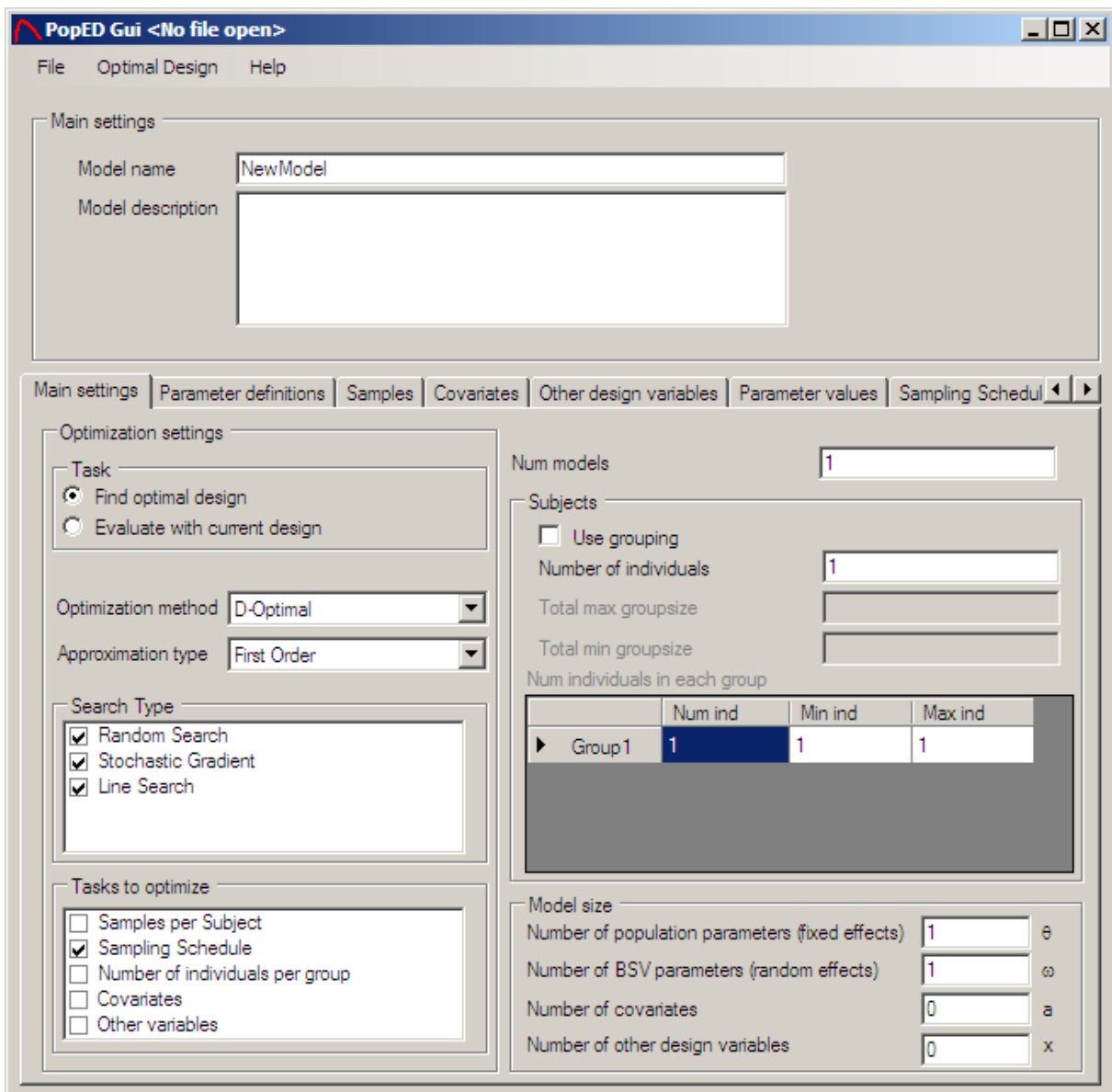
Installation step by step

- 1) Fulfill the requirements above.
- 2) Run the setup file (setup.exe) and then walk through the setup wizard.
- 3) Open PopED GUI from the Start Menu and Open File/Settings. Set the paths to the different directories.
- 4) If the PopED program is **NOT** installed in the directory *C:\Program Files\PopED*, change the path in the *poped2_0.m* file and the *convert_xml.m* file in the *installation dir\program\xml* directory to your local path.
- 5) Setup is now completed.

Running PopED

Start PopED GUI from the start menu or run the script version (without graphics) of PopED by starting Matlab. In the script version; add the path to the PopED script version (e.g. *C:\Program Files\PopED\program*) to the working directory of Matlab. This can be done by using the *addpath* command or by changing the directory to PopED and then type *poped2_0()*. A third way is to use the Matlab *Set Path* command under the File menu in the Matlab GUI.

PopED GUI Main Window



If the PopED GUI version is started the main window will appear. From this window the user can define new PopED GUI settings files, run optimization (if a Matlab COM server is available) and use the diagnostic tools that are available within the GUI.

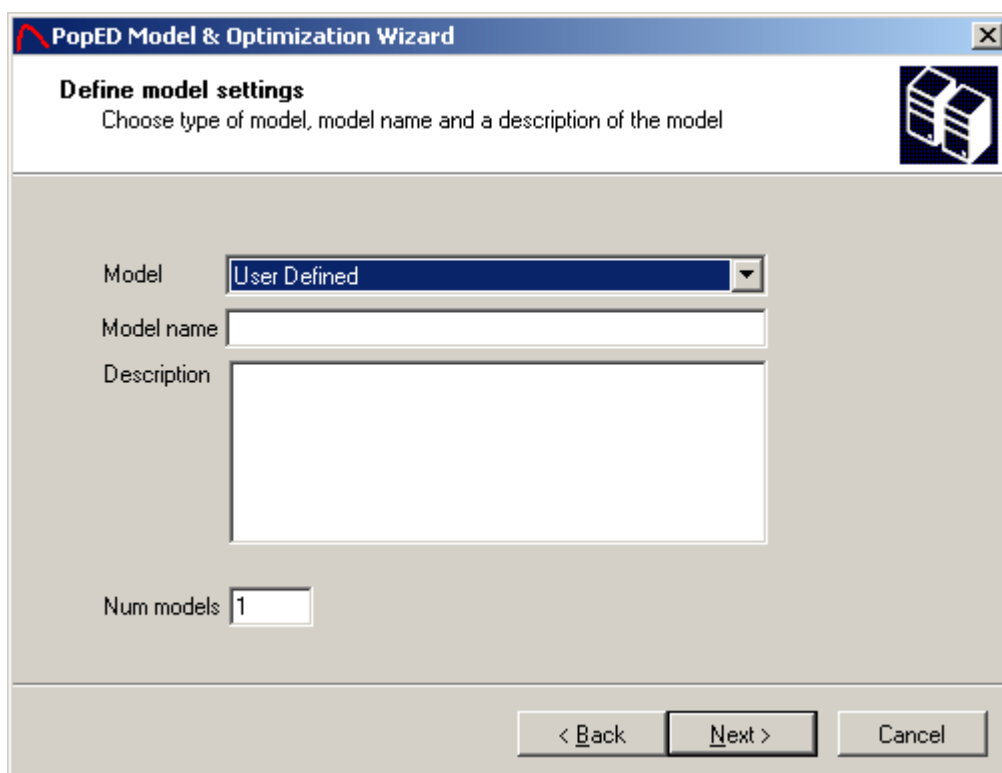
Creating a new Model with the GUI

There is several ways to create a new model in the PopED GUI.

- 1) Under the File Menu choose Wizard and New.
 - Define a user specified model.
 - Use the predefined model templates that are available.
- 2) Under the File Menu choose New (Ctrl+N).

This manual will walk through the creation of a model in the same way as the Wizard does it in PopED.

Define the model settings



The screenshot shows the 'PopED Model & Optimization Wizard' dialog box. The title bar includes the text 'PopED Model & Optimization Wizard' and a close button. The main window has a title 'Define model settings' and a subtitle 'Choose type of model, model name and a description of the model'. There is a small icon of a 3D box in the top right corner. The dialog contains the following fields:

- 'Model': A dropdown menu with 'User Defined' selected.
- 'Model name': An empty text input field.
- 'Description': A large empty text area.
- 'Num models': A text input field containing the number '1'.

At the bottom, there are three buttons: '< Back', 'Next >', and 'Cancel'.

Choose a predefined model or choose to create a User Defined model as above. The Model name can be any string (containing spaces). The description can be any string containing white spaces. To define a new line in the description use the Soft Return, e.g. Ctrl+Return. Num models are the number of sub-models (responses) that are going to be used in the optimal design. E.g. Optimizing on the parameters for both a PK and a PD model will be 2 sub-models, concurrent optimizing on n different drug models will be n sub-models etc.

Optimization Settings

Choose the optimization method:

- D-Optimal Design – Optimization by maximizing the determinant of the Fisher Information Matrix. A prior model is assumed to be known (the population mean, the Inter Individual Variability and the Residual Variability). Fast but sensitive to model misspecification.
- ED-Optimal Design – Optimization by maximizing the expectation value of the determinant of the Fisher Information Matrix. A prior model is assumed to be known but an uncertainty of the model parameters could be taken into account. E.g. assuming a normal distribution around all population mean parameters. Slow but can deal with model misspecification.
- No optimization – Calculate the Fisher Information Matrix (FIM) and the Criterion function/Objective Function Value (OFV) of the FIM e.g. the determinant of the FIM. The FIM is calculated with the given initial design.

Choose the approximation type

- First Order – The model is linearized around the first derivative evaluated at the typical values ($b=0$). The residual error model is also linearized around the typical values.
- First Order Conditional – The model is linearized around the first derivative evaluated at the individual mixed effects equal to an individual sample. The

number of samples could be specified in the search settings. The default is to use 1000 samples per Fisher Information Matrix calculation. The residual variability is linearized around the typical values.

- First Order Conditional Interaction - The model is linearized around the first derivative evaluated at the individual mixed effects equal to an individual sample. The number of samples could be specified in the search settings. The default is to use 1000 samples per Fisher Information Matrix calculation. The residual variability is linearized around the individual samples.

Note that if a conditional approximation method is used the calculation of the Fisher Information Matrix can give different results if the individual samples is not the same. It is also notable that the individual samples during an optimization (several calculation of the FIM) will be the same. I.e. the individual samples are **not** re-sampled between each calculation of the FIM.

In most cases the first order approximation linearized around the typical values (the default option) will yield a very similar design compared to the other approximation methods and it is much faster to calculate.

Choose the different design parameters to optimize over:

- Samples per Subject – Number of samples/measurements per design group or individual.
- Sampling Schedule – Optimize when to take the samples.
- Number of individuals per group – Optimizing over the group size.
- Covariates – Optimize for the optimal covariate value in the design. Could be any design dependent variable, e.g. Dose, Infusion length, Weight, Age, Study length etc.
- Other Variables – Optimize over other design variables. In this version of PopED, there is no difference between a covariate and ‘Other design variables’.

The sample times, the covariates and the other design variables are all assumed to be continuous, while the Samples per Subject and Number of Individuals per group are discrete variables. A group in Optimal Design is a number of individuals that will get the same design, e.g. the same Sampling Schedule.

Search Types available are:

- Random Search (RS) – Does a random search over the whole search space initially but will collapse to an Adaptive Narrowed Random Search as soon as the Random Search finds a good Objective Function Value (OFV). The Adaptive Random Search will search randomly close to the previous best OFV found by the Random Search. The Random Search is global but it will be local with the Adaptive Random Search. Random Search converges towards an

optimal OFV when the number of iterations goes towards infinity. The default number of iterations in the Random Search is 300.

- Stochastic Gradient (SG) – Does a stochastic walk in the direction of the best OFV. In D-Optimal design and ED-optimal design with a discrete user defined distribution there is no stochastic value for the derivative of the OFV and therefore the SG will collapse to a steepest descent algorithm. The SG is a local search method. The SG will converge to a local optimum when the number of iterations reaches infinity. The default number of iterations in SG is 150.
- Line Search (LS) – Line search does a grid search in one dimension, i.e. over one parameter at a time. Line Search will only work when optimizing over continuous variables like sample times, covariates and/or other design variables. Line Search is a pure global search method but it will not alone converge toward a global optimum even though the number of grid points reaches infinity. This is because the LS could restrict the search space by the order of the design parameter that is used in the LS. The default number of grid points is 50.

All the search types should be used to obtain the best result. The optimization is assumed to have converged if the LS don't change the optimization results of the previous SG (or RS if no SG is selected). If the Line Search is not selected the method will search with a predefined number of search iterations, i.e. one search iteration run the RS, SG or both. See Calculation Settings for more information. The default number of Search Iterations when LS is not selected is 10.

Population Parameters

PopED Model & Optimization Wizard

Choose number of Population Parameters
Select the number of population parameters for your model.

Number of population parameters (fixed effects)	<input type="text" value="1"/>	θ
Number of BSV parameters (random effects)	<input type="text" value="1"/>	ω
Number of covariates	<input type="text" value="0"/>	a
Number of other design variables	<input type="text" value="0"/>	x

< Back Next > Cancel

Choose the number of population mean parameters, also called typical values or fixed effects. The number of population mean parameters (bpop) should be the number of typical value parameters for all sub-models. In NONMEM these population parameters are called THETA.

Random effects are the parameters that define the variability between individuals (IIV, BSV). In NONMEM these parameters are called OMEGA. The number of random effects should be the number of random effects for all sub-models.

The numbers of covariates are the number of covariate parameters to have in the model, e.g. Dose, Age, Weight etc. In this version the covariates couldn't have a distribution so they are only continuous variables. The number of covariates should be the number of covariates for all sub-models.

The numbers of other design variables are primarily available for coming version. In this version they are treated exactly as covariates. The number of other design variables should be the number of other design variables for all sub-models.

Number of Subjects

PopED Model & Optimization Wizard

Choose Number of Subjects
Select number of subjects in the study and if individuals are grouped etc.

Use grouping

Number of groups:

Total max groupsize:

Total min groupsize:

Num individuals in each group

Group	Num individuals	Min num ind	Max num ind
Group1	15	10	20
▶ Group2	5	1	25

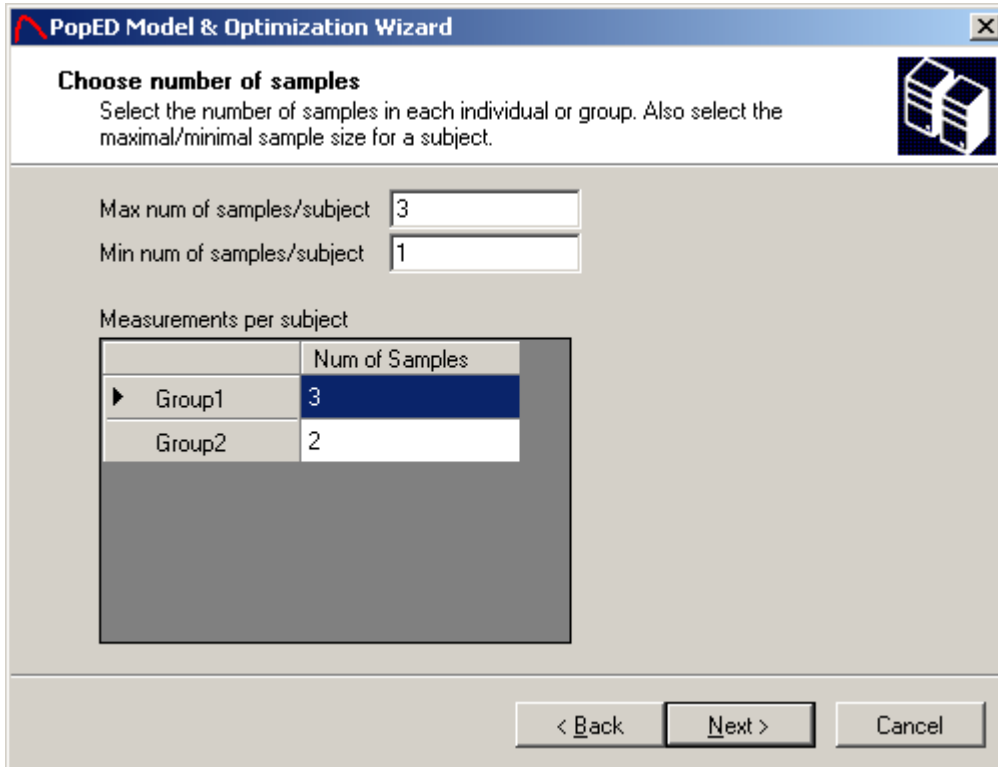
< Back Next > Cancel

If use grouping are selected there is a possibility to optimize over the number of individuals in each group. In this case it's important to choose the minimal number of individuals in the group and also the maximal number of individuals in the group. If *Use grouping* is not checked, the numbers of individuals in each group are fixed to 1. If *Use grouping* is checked the number of individuals in the group will affect the optimal design even though the optimization procedure only optimize over e.g. the sample times. A group in optimal design is a number of individuals that will have the same design. The *total max groupsize*, i.e. the maximal sum of individuals in all groups and the minimal sum of individuals in all groups must be entered. The sum of initial number of individuals in all groups must be at least equal to the *total min groupsize*. The sum initial number of individuals must also be less (or equal) to the *total max groupsize*.

Example: Optimization of the sampling schedule within a study with at the most, 25 individuals split into 2 groups with initially 15 individuals in group 1 and 5 individuals in group 2. These optimized sampling times will yield one schedule for the 15 individuals and a 2nd sampling schedule for the 5 individuals.

If optimizing on *number of individuals per group*; the optimization procedure will check all possible combinations of individuals divided into the two groups with the restrictions above.

Number of Samples

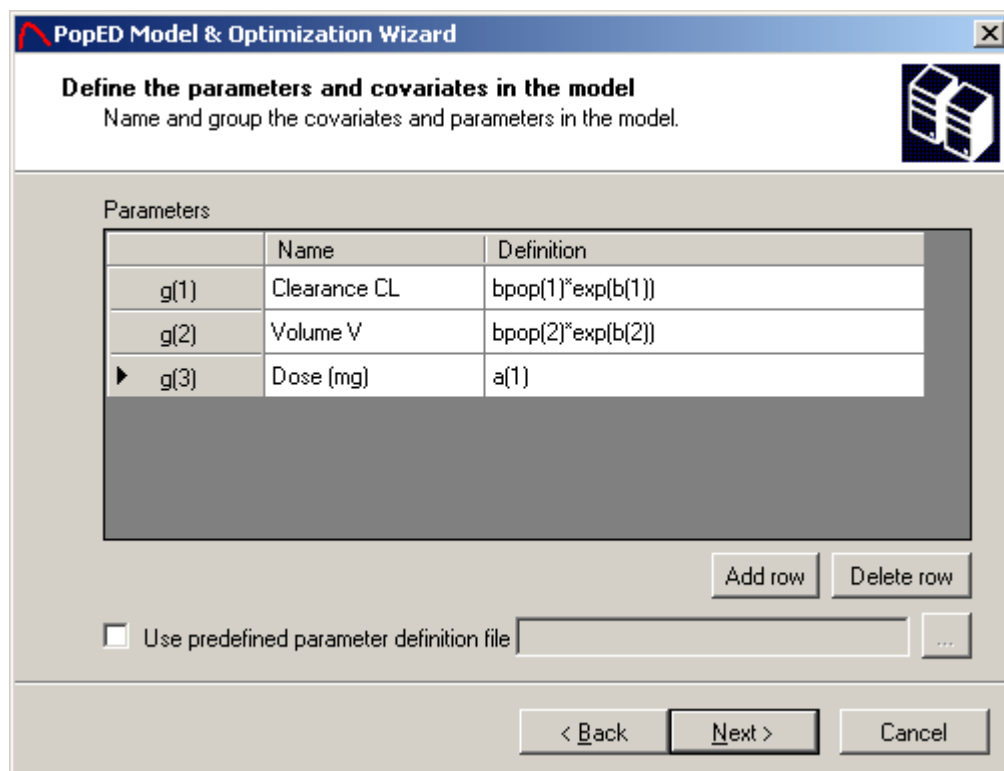


The screenshot shows a dialog box titled "PopED Model & Optimization Wizard" with a close button (X) in the top right corner. The main heading is "Choose number of samples". Below the heading is a descriptive text: "Select the number of samples in each individual or group. Also select the maximal/minimal sample size for a subject." To the right of this text is a small icon of a server rack. Below the text are two input fields: "Max num of samples/subject" with the value "3" and "Min num of samples/subject" with the value "1". Underneath these fields is the label "Measurements per subject" followed by a table. The table has two columns: the first column lists groups, and the second column is labeled "Num of Samples". The first row is "Group1" with a value of "3", and the second row is "Group2" with a value of "2". At the bottom of the dialog box are three buttons: "< Back", "Next >", and "Cancel".

	Num of Samples
▶ Group1	3
Group2	2

The number of sample/measurements per subject (group or one individual) could be different for each subject. The minimum number of samples per subject should at least be one. The minimum and maximum numbers of samples per subject are only important when optimizing over the number of samples per subject, except that the maximum number of samples per subject should always be larger or equal to the number of samples in each group.

Parameter Definitions



The parameters are defined and stored in a vector called **g**. The definition of a parameter could be of any type, e.g. normal, exponential etc. The typical values (fixed effects) are a vector called **bpop** and the inter-individual variability is a vector called **b**. In NONMEM the b's are called ETA. The different covariates and other design variables that should be used in the sub-models should also be defined here. The covariates is a vector called **a** and the other design variables is a vector called **x**. It's perfectly fine to make transformations to cover other IIV distributions than the normal distribution, e.g. the Box-Cox transformation. The number of parameters are unlimited but the number of bpop, b, a and x is limited to the numbers specified in population parameters window. The definition is written in the Matlab language and could therefore use any Matlab function.

It is possible to define a predefined parameter definition file instead of defining the **g** vector in the GUI. This is done by producing a Matlab function file (*.m) with the following syntax:

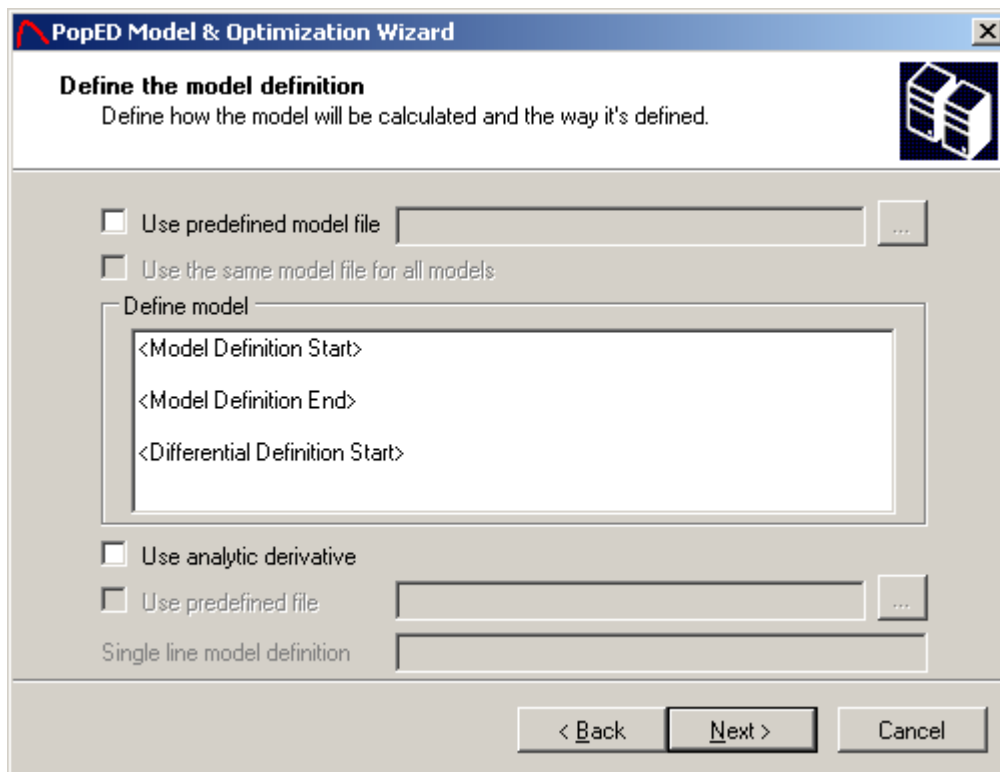
```
function pop_params = fg(x,a,bpop,b,bocc)

% -- Parameter definition file --
% -- { Clearance CL, Volume V, Dose (mg) }

pop_params=[ bpop(1)*exp(b(1)); bpop(2)*exp(b(2)); a(1)];

end
```

Define model



Every sub-model (response) will have a window similar to the one above except that the checkbox *Use the same model file for all models* only will be available at the first sub-model. If this option is checked no more sub-model definitions are needed even though there is more than one sub-model. In the PopED main window only one tab page for all models will be available.

The sub-models could be defined with a predefined model file or directly in the window by adding Matlab code and tags between the model definition start tag and the model definition end tag. If a differential equation is needed for the current sub-model the code could be added within the differential equation start tag and the differential equation end tag.

Analytic derivative could be calculated by checking the *Use analytic derivative* option. To calculate the analytic derivative a single line model definition is needed or a predefined analytic derivative file could be specified. Analytic derivative therefore only works for "simple" models and is very slow to use compared to the numerical derivatives that are used by default. The single line model definition should be written in Matlab code and use the variables mentioned below. Analytic derivatives only work for continuous variable optimization in this version. The predefined analytic derivative file is not fully functional in this version of PopED. Furthermore, there is a restriction that the additive and proportional residual variability must be fixed. The user defined error model could not be used. The Matlab Symbolic Toolbox must be installed to calculate the analytic derivatives.

Predefined model files

The model file could be specified for one sub-model or for all sub-models at the same time (by checking the *Use the same model file for all models* checkbox). If a file is specified only for this sub-model the Matlab function file (*.m) should have this syntax:

```
function [y,numericalSettings]=modell(t,g,numericalSettings)

% g = {CL, V, E0, Emax, EC50, Dose}
%PK-model
y=g(6)/g(2)*exp(-g(1)/g(2)*t);

end
```

Input should be a scalar value time t and the parameter definition vector g. As output y is set to a scalar value. All sub-models could be defined either by a model file like above or within the GUI independent of the other sub-models.

If a file is specified for all sub-models (even if it's only one sub-model) the file is again a Matlab function file (*.m) with this syntax:

```
function
[y,numericalSettings]=model_example(model_switch,xt,g,numericalSettings)

%-- Model: One comp IV bolus with direct Emax effect
%-- {CL,V,E0,EMax,EC50,Dose}

y=xt;
for i=1:length(model_switch)
    t=xt(i);
    if (model_switch(i)==1)
        %g = {CL,V,E0,Emax,EC50,Dose}
        %PK-model
        y(i)=((g(6)/g(2))*(exp(-g(1)/g(2)*t)));
    end
    if (model_switch(i)==2)
        %g = {CL,V,E0,Emax,EC50,Dose}
        %PD-model
        pkmodel=(g(6)/g(2))*(exp(-g(1)/g(2)*t));
        y(i) = g(3)+pkmodel*g(4)/(g(5)+pkmodel);
    end
end
end

end
```

The input to this function should be a vector model_switch that define which sub-model a specific time point i belongs to. The length of the model_switch vector is the same as the length of the xt vector containing all the time points for a design subject. The input g is the parameter definition vector g for the current subject. The last input is the numericalSettings structure that contains information about the differential equation solver and differential equation solver options. See advanced settings.

Models defined in PopED GUI

A model could be defined for every sub-model in the PopED GUI. The models are written in an extended version of Matlab code. The models should be defined within the <Model Definition Start> tag and the <Model Definition End> tag. Differential equations for a sub-model can be specified within the <Differential Definition Start> tag and the <Differential Definition End> tag. Three different tags/reserved word are available for the model specification except the regular Matlab code:

- **<vector>** - Specifies that the definition of this sub-model will be vector wise, i.e. the time vector is called *xt* and the output vector for all the time points *xt* is called *y*. If the vector tag is not present the time will be a scalar value called *t* and the output will be called *y(i)*. The vector tag can only be used in one sub-model; with several sub-models, use *t* and *y(i)* as the time and the output.
- **<diff>** - Specifies a call to the differential equation solver, typically used like this: *amount = <diff>*; The amount will be a vector of the amount for every time point *xt* if the vector tag is used. Otherwise amount will be the amount at time *t*. If <diff> is specified; a differential equation must be written in the differential definition part of the sub-model. User defined input parameters to the differential equation are stored in the vector *params* that could be of any length. These values are then accessible in the differential equation. If the differential equation contains several compartments, amount will be a matrix with the amount for all compartments and time points. If e.g. compartment two contains the dependent variable/the output it's accessible by typing *amount(:,2)*. This will be a vector if the vector tag is used, otherwise a scalar. For more information about the differential equation solver, see Advanced Settings.
- **<init>** - Specifies a vector of the initial values for the compartments in the differential equation, typically used like this: *<init> = [init1 init2]*; where *init1* and *init2* are the values at compartment one and two at time zero. If the *init* tag is specified a differential equation definition should be specified.

Example of a GUI defined model:

```
<Model Definition Start>
%Define that operations should be vector wise
<vector>

%g = {ka,ke,V,Dose}
%Store the values needed in the differential equation
params(1) = g(1); %ka
params(2) = g(2); %ke

%The initialization vector for the two compartments (absorption and
central)
<init> = [g(4) 0];

%Call the differential equation
amount = <diff>;
y = amount(:,2)./g(3); %Make the DV a concentration
```

<Model Definition End>

<Differential Definition Start>

```
%params(1) = ka
%params(2) = ke
dA(1,:) = -params(1)*A(1);
dA(2,:) = params(1)*A(1) - params(2)*A(2);
```

<Differential Definition End>

See the model templates and the distributed examples for more information about how to code the model files.

Population parameter values

	Value	Fixed
Bpop1	0.5	<input type="checkbox"/>
Bpop2	0.2	<input type="checkbox"/>
Bpop3	1	<input type="checkbox"/>
Bpop4	1	<input type="checkbox"/>
Bpop5	1	<input type="checkbox"/>
d1	0.01	<input type="checkbox"/>
d2	0.01	<input type="checkbox"/>

User defined distribution file ...

Use correlation between random effects

< Back Next > Cancel

Enter the model population mean values (bpop, THETA in NONMEM) and the variance of the IIV normal distribution (d). The d variables are stored as variances, hence a variance 0.01 correspond to 10% inter individual variability for an exponential b (ETA in NONMEM), i.e. $\exp(b)$. The d is interpreted in the same way as the OMEGA in NONMEM.

If there is correlation between the IIV parameters, this could be addressed by clicking the *Use correlation between random effects* checkbox. This will enable a correlation matrix for the random effects. The matrix will be enabled after clicking on the next button.

If ED-optimal design is going to be used the typical values (bpop) and the IIV variance parameters could have a distribution.

	Distribution	Mean	Variance	Fixed
Bpop1	Normal	242	585.64	<input type="checkbox"/>
Bpop2	Normal	24	5.76	<input type="checkbox"/>
Bpop3	Normal	3	0.09	<input type="checkbox"/>
d1	Normal	0.01	1E-06	<input type="checkbox"/>
d2	Normal	0.01	1E-06	<input type="checkbox"/>
d3	Normal	0.01	1E-06	<input type="checkbox"/>

All parameter distributions selected as Point distributions will yield the same result as the D-optimal design. The other available distributions are normal, log-normal, zero-truncated normal and uniformed. There is also possible to define a user specified distribution (stochastic and non-stochastic). To use a user defined distribution; enter the filename pointing to the distribution function. See the examples for more details. In the picture above the variances of the distributions are entered as 10 % but in variance terms. In the uniform distribution the variance is the length of the uniform distribution, **not** the usual definition $(\frac{length^2}{12})$.

The zero-truncated normal distribution is left- or right truncated at zero depending on the sign of the mean. I.e. if a negative mean is used the distribution is right truncated at zero and if a positive mean is used the distribution is left truncated at zero.

If a parameter is in the model, but is of no interest for estimation, the parameter could be fixed by checking the checkbox corresponding to the variable that is going to be fixed. This means that the variable would not be represented in the Fisher Information Matrix (FIM) and therefore the FIM wouldn't give any expected parameter uncertainty (SE (%)) of that parameter.

Correlation between random effects

PopED Model & Optimization Wizard

Set the correlation between random effects
Enter the correlation between the d parameters in covariance terms.

Between subject variability covariance matrix (d-matrix)

	d1	d2	d3	d4	d5
d1	0.01	0	0	0	0
d2	0	0.01	0	0	0
d3	0	0	0.01	0	0
d4	0	0	0	0.01	0
d5	0	0	0	0	0.01

< Back Next > Cancel

Enter the correlation between all random effects expected the diagonal elements, i.e. the actual random effect variance defined in the previous wizard window. The correlation should be entered in covariance terms. A zero means that the random effects are uncorrelated.

Initial values for covariates

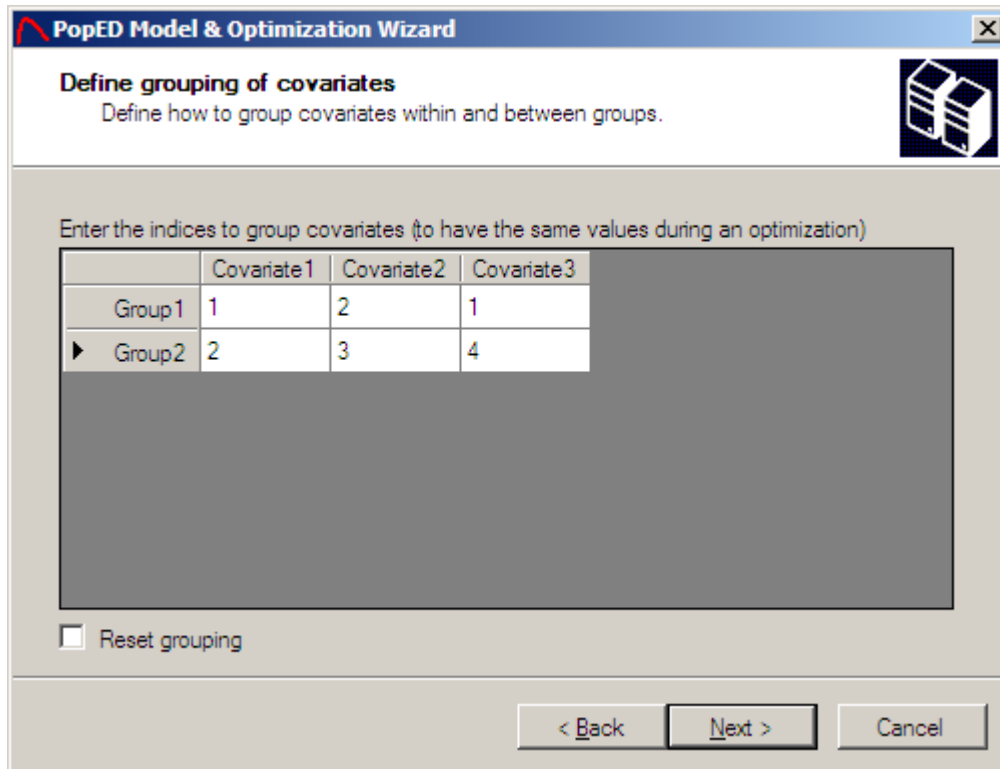
The screenshot shows a dialog box titled "PopED Model & Optimization Wizard" with a close button in the top right corner. The main heading is "Enter initial values for covariates" with a sub-instruction: "Enter the initial values and the maximal and minimal value for each covariate and for each group/individual." There is a small icon of a server rack to the right of the instruction. Below this is a checkbox labeled "Use the same initial values for all groups/individuals." which is currently unchecked. Underneath is a section titled "Covariates" containing a table with the heading "Initial, min and max values". The table has five columns: "Min a1", "Init a1", "Max a1", and "Description a1". The first column is partially obscured by a grey arrow icon. The table contains two rows: "Group1" and "Group2". At the bottom of the dialog are three buttons: "< Back", "Next >", and "Cancel".

	Min a1	Init a1	Max a1	Description a1
Group1	10	100	500	Dose
Group2	10	80	500	Dose

The initial values for the covariates should be entered for all covariates and all subjects (groups/individuals). A minimum value for the covariate and a maximal value for the covariate should be entered as well. The minimum and maximal value is used when optimizing over a covariate. A description for the covariate could be entered as a string. If there are several groups it could be convenient to enter initial, min and max values for all groups at the same time. This is done by checking the *Use the same initial values for all groups/individuals* checkbox. The numbers of covariates are determined by the number specified in the population parameters windows.

A covariate can be fixed even if the optimization method optimizes over the covariate values. To fix a covariate value set the min and max value to the initial value.

Grouping of covariates



There is a possibility to group covariates between subjects and within a subject. If covariates are said to be grouped it is similar as they will have the same value during an optimization. In the example above Covariate 1 in group 1 will have the same value as the third covariate in group 1. Also covariate 2 in group 1 will have the same value as the covariate 1 in group 2.

Covariates grouped together should have the same initial, max and min value. The grouping should be defined in an increasing order like the example above. Remove the grouping by clicking *Reset grouping*. Pointing with the mouse on a certain covariate will show the grouping for that covariate.

Initial Values for Other Design Variables

PopED Model & Optimization Wizard

Enter initial values for other design variables
Enter the initial values, the maximal and minimal value for each other design variable and for each group/individual.

Use the same initial values for all groups/individuals.

Other Design Variables

Initial, min and max values

	Min x1	Init x1	Max x1	Description x1	Min x2	I
Group1	1	2	3	x1	2	3
▶ Group2	1	2	3	x1	2	3

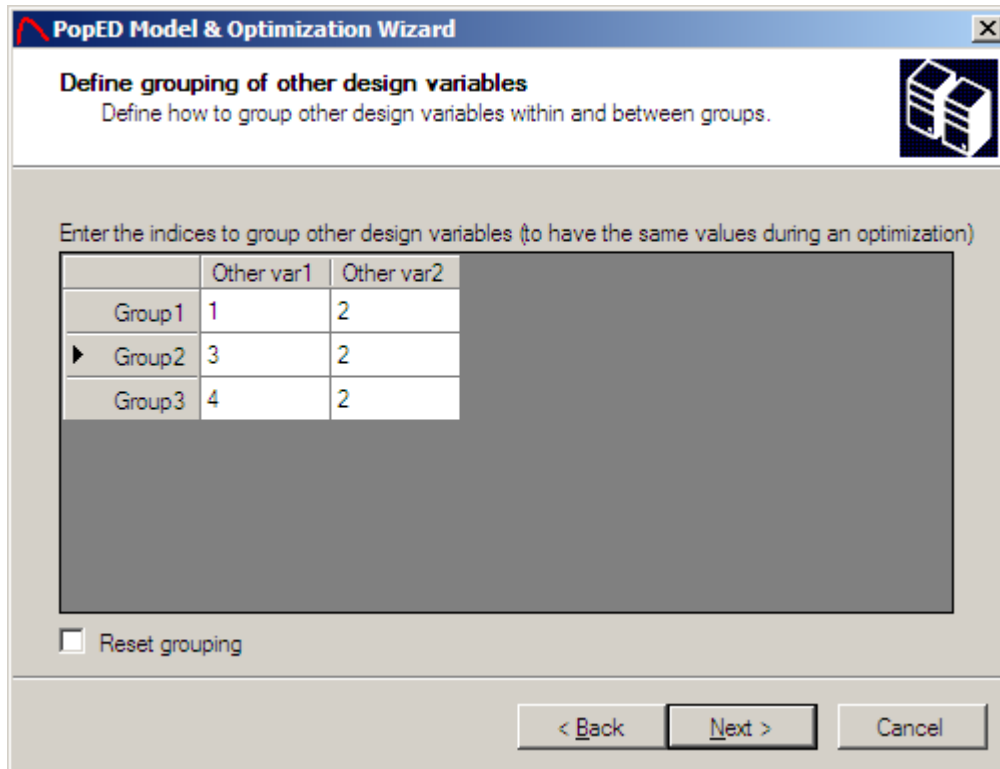
< Back Next > Cancel

The initial values for the other design variables should be entered for all design variables and all subjects (groups/individuals). A minimum value for the design variable and a maximal value for the design variable should be entered as well. The minimum and maximal value is used when optimizing over a design variable. A description for the variable could be entered as a string. If there are several groups it could be convenient to enter initial, min and max values for all groups at the same time. This is done by checking the *Use the same initial values for all groups/individuals* checkbox. The numbers of design variables are determined by the number specified in the population parameters windows.

A design variable can be fixed even if the optimization method optimizes over the design variables values. To fix a design variable value set the min and max value to the initial value.

There is a possibility to group other design variables between subjects and within a subject (see example 1 and below).

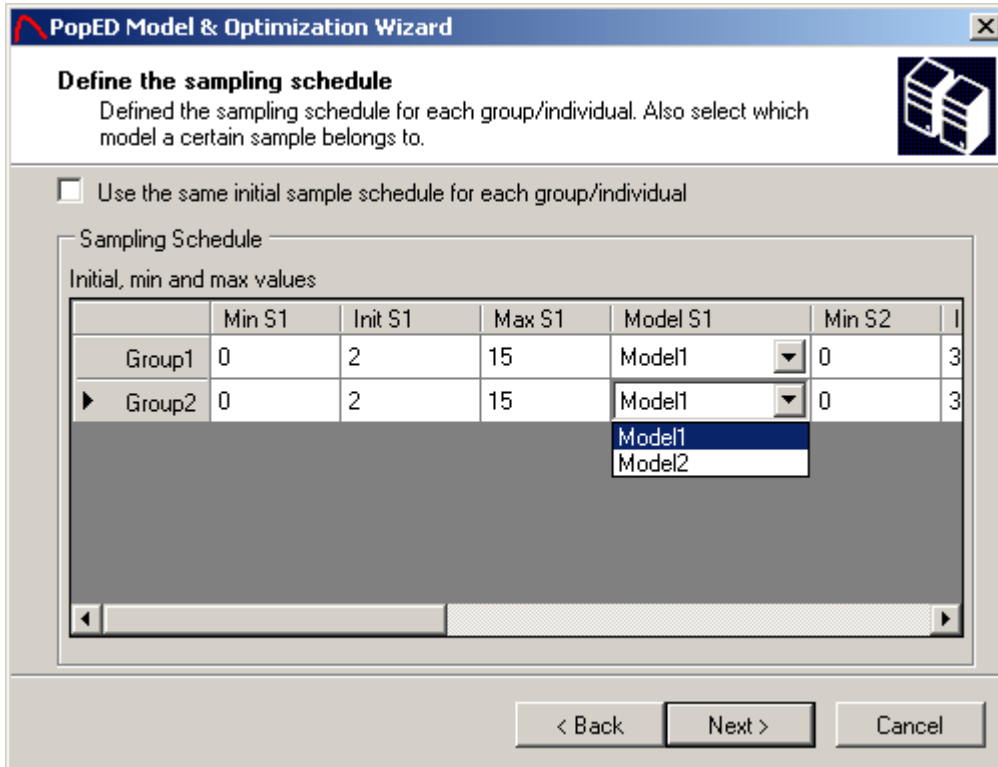
Grouping of Other Design Variables



There is a possibility to group other design variables between subjects and within a subject. If the other design variables are said to be grouped it is similar as they will have the same value during an optimization. In the example above the other design variable 2 is the same for all three groups.

Other design variables grouped together should have the same initial, max and min value. The grouping should be defined in an increasing order like the example above. Remove the grouping by clicking *Reset grouping*. Pointing with the mouse on a certain design variable will show the grouping for that design variable.

Initial Sampling Schedule



PopED Model & Optimization Wizard

Define the sampling schedule
Defined the sampling schedule for each group/individual. Also select which model a certain sample belongs to.

Use the same initial sample schedule for each group/individual

Sampling Schedule

Initial, min and max values

	Min S1	Init S1	Max S1	Model S1	Min S2	I
Group1	0	2	15	Model1	0	3
▶ Group2	0	2	15	Model1	0	3

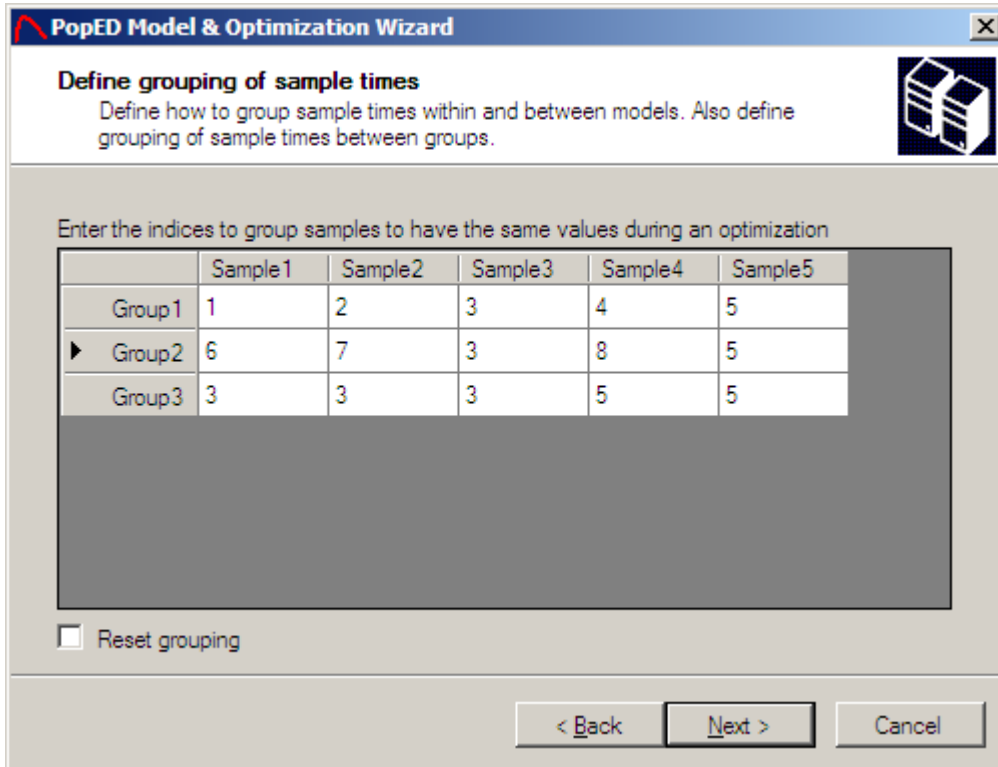
< Back Next > Cancel

The sampling schedule is defined for all subjects (groups/individuals) and the sample belongs to a sub-model. For all samples; a minimum and maximal sampling time could be specified. This is important when optimizing over the sampling schedule but will not affect the design if the optimization is not performed over the sampling schedule. Number of samples per group will be specified in the number of samples window. If a subject has fewer samples than another subject the subject with fewer samples should define as many samples as the subject with more samples. These samples will not be taken into account when optimizing but are entered to make a consistent matrix of sample times versus subjects. If there are several groups it could be convenient to enter initial, min and max values for all groups at the same time. This is done by checking the *Use the same initial values for all groups/individuals* checkbox.

A sampling time can be fixed even if the optimization method optimizes over the sampling schedule. To fix a sample time set the min and max sample time to the initial sample time.

There is a possibility to group sampling time between subjects and within a subject, e.g. between models (see example 1 and below).

Grouping of samples



PopED Model & Optimization Wizard

Define grouping of sample times
Define how to group sample times within and between models. Also define grouping of sample times between groups.

Enter the indices to group samples to have the same values during an optimization

	Sample1	Sample2	Sample3	Sample4	Sample5
Group1	1	2	3	4	5
▶ Group2	6	7	3	8	5
Group3	3	3	3	5	5

Reset grouping

< Back Next > Cancel

There is a possibility to group samples between subjects and within a subject. If the samples are said to be grouped it is similar as they will have the same value during an optimization. In the example above the sample 3 should be the same in all groups. Further the sample 1 and sample 2 in group 3 should be the same as the sample 3 in group 1. Finally sample 5 in all groups and sample 4 in group 3 should be the same as sample 5 in group 1.

Samples grouped together should have the same initial, max and min value. The grouping should be defined in an increasing order like the example above. Remove the grouping by clicking *Reset grouping*. Pointing with the mouse on a certain sample will show the grouping for that sample. It is also possible to group samples that belong to different models.

Define the Residual Variability

PopED Model & Optimization Wizard

Define the error model
Enter a proportional and/or additive error for all your submodels or choose an error model file.

	Additive	Fixed	Proportional	Fixed
Model1	0.1	<input type="checkbox"/>	0	<input type="checkbox"/>
▶ Model2	0	<input type="checkbox"/>	0	<input type="checkbox"/>

Use predefined error model file ...

< Back Next > Cancel

The residual variability model could be defined either by an additive part and/or a proportional part or by a predefined error model file. When there is only an additive and/or a proportional part in the error model the error definitions in the PopED GUI works perfectly fine. If more complex error models is going to be used a predefined error model file should be used.

The error values are entered as variances of the residual normal distribution. In NONMEM these variances/variables are called SIGMA.

If a residual error parameter exists in the model, but is of no interest for estimation, the parameter could be fixed by checking the checkbox corresponding to the variable that is going to be fixed. This means that the variable would not be a row in the Fisher Information Matrix (FIM) and therefore the FIM wouldn't give any expected parameter uncertainty (SE (%)) of that residual parameter.

In the case with no error model file specified; one additive error and one proportional error could be defined for each sub-model.

If the *Use predefined error model file* is checked a new window where the residual error variances could be entered will be available when pressing the next button.

Enter user defined residual variances
Enter number of user defined random errors and the values for them. Also specify if the random errors should be fixed or not.

Number of random measurement error:

	Value	Fixed	Description
Sigma1	0.1	<input type="checkbox"/>	
Sigma2	0.4	<input type="checkbox"/>	
Sigma3	0.2	<input type="checkbox"/>	
Sigma4	34.5	<input type="checkbox"/>	
▶ Sigma5	99.7	<input checked="" type="checkbox"/>	
Sigma6	0.26	<input type="checkbox"/>	

< Back Next > Cancel

The error model file should be written in Matlab code and have the following syntax:

```
function [y,numericalSettings] =
feqs(model_switch,xt,g,epsi,numericalSettings)

%Error model for model 1 and model 2

%A pointer to the model function
global ff_pointer

[y,numericalSettings]=ff_pointer(model_switch,xt,g,numericalSettings);
for i=1:size(xt,1)
    if (model_switch(i)==1) %The error model for model 1
        y(i) = y(i).*(1+epsi(:,1).*(epsi(:,3).^(epsi(:,4)))));
    end
    if (model_switch(i)==2) %The error model for model 2
        y(i) = epsi(:,2) + y(i).*(1+epsi(:,5).*exp(epsi(:,6)));
    end
end
end
end
```

Input should be a vector with the model switches, the sample time's xt , the parameter definition vector g and the vector with the individual residual error $epsi$. The last input parameter is a Matlab structure and contains information about the differential equation solver. See Advanced Settings for more information. $epsi$ is called EPS in NONMEM.

There is also possible to enter a description for the residual error variance parameter. The description could be any string.

Output and input directories

PopED Model & Optimization Wizard

Add output and input directories
Add the full path to the output file that will contain information about the design during optimization.

Input function name:

Result function name:

Output file: ...

Log file: ...

Analytic derivative output: ...

< Back Next > Cancel

Enter the name of the Matlab input function and the Matlab result function structure created by Matlab before running PopED. The name should be a valid Matlab function name. The input function will be overwritten each time a new run is started (from the GUI) but the result function will create a new function_output_x where x is the next available number in the running directory.

Also enter the full path to the output file containing information about the current design during optimization. Random Search and Stochastic Gradient will append RS_SG_i.txt to the output path, where i is the search iteration number. If Line Search is used a file with the appendix LS_i.txt, where i is the search iteration, will appear in the output file directory. There must be an output path and file specified to save the optimization settings. The log file is not used in this version of PopED. The Analytic derivative output will store the analytic derivatives for each sub-model in a *.txt file specified by the *Analytic derivative output* path.

Optimization and calculation settings

PopED Model & Optimization Wizard

Optimization and calculation settings
Add some optimization and calculation settings and enter more advanced options.

Settings

Interpret as zero: 1E-05

FIM calculation type: Default

Number of search iterations: 10

Seed: Random

Use graphical output during optimization

Advanced

< Back Next > Cancel

When working with numerical problems numerical issues can arise when numbers are exactly zero, therefore PopED needs to define a small number that will be interpret as zero. The Fisher Information Matrix (FIM) calculation type is by default the full FIM calculation but can be changed to a reduced FIM. In the reduced case it is assumed that the derivatives of the variance of the model with respect to the typical values (bpop) are zero. This is a quite ruff approximation but has been shown to give similar design as the full FIM because of the fact that in most models the variance is explained by the inter-individual variability and the residual variability. It's recommended to use the full FIM by default but the reduced FIM can decrease the run time if necessary. The number of search iterations is used when Line Search is not in the search algorithm. See optimization Settings. The seed could be set to a number or bet set to *Random*. A Random seed shouldn't affect the optimization result but could clearly affect the simulation function. See simulate from model. The checkbox *Use graphical output during optimization* will show the current design. In this version it will only show the continuous variables, i.e. the sampling times, the covariates and the other design variables.

Advanced settings for the search algorithms and convergence criterions for ED-optimal design could be entered by clicking the advanced button.

Advanced Settings

Different steplengths and search parameters

Random search

Iterations	300
Discrete iterations	50
Iterations until adaptive narrowing	50
Locality factor for sample time	4
Locality factor for covariates	4
Locality factor for other criteria	4

Stochastic Gradient parameters

Maximum iterations	150
Discrete iterations	0
Convergence criteria	1E-08
First step factor for sample times	0.001
First step factor for covariates	0.001
First step factor for other criteria	0.001

Differential equation settings

Relative tolerance	1E-05
Absolute tolerance	1E-05
Solver	Default (ode45)

Store differential equation results in memory

Stepsizes

Stepsize for dModel/dTem	0.0001
Stepsize for dTem/dRandom effect	0.0001
Stepsize for dModel mean/dFixed effect	0.0001
Stepsize for dModel variance/dFixed effect	0.0001
Stepsize for linearizing random error	0.0001
Stepsize for calculating FIM	0.0001

Numerical derivative method: Complex & Central difference

Line search parameters

Number of grid points	50
-----------------------	----

ED-optimal design settings

ED sample size	45
Num iter to calc diff between LS and SG	30
Stop criteria diff between LS and SG	10 %

Conditional samples

Number of conditional samples	1000
Sampling technique	Random Sampling

Ok Cancel

A lot of different search settings and step sizes could be entered. Below follows an explanation of the different options.

Random Search Settings

Iterations are the number of random search iterations when optimizing over a continuous variable. The number of discrete iterations is the number of Random Search (RS) iterations to use when optimizing over discrete variables (e.g. Number of samples/Subject, Number of individuals in group). The RS algorithm used is adaptive and therefore it will narrow the search when the number of iterations increases. The adaptive narrowing is started when the Random Search doesn't find a better Objective Function Value (OFV) within the number of iterations entered in *Iterations until adaptive narrowing*. The locality factor for RS will control the localness of the RS algorithm before the adaptive narrowing. If for example a sampling time is in the range of [5-15] hours a locality factor for the sample time of 4 will let the initial RS cover a range of $(15-5)/4 = 2.5$ hours from the initial sample time. A larger locality factor will produce a better optimization, but then the number of iterations must also be increased.

Stochastic Gradient Settings

Maximum iterations are the maximal number of Stochastic Gradient (SG) search iterations when optimizing over a continuous variable. The number of discrete iterations is the number of SG iterations to use when optimizing over discrete variables. The convergence criteria for the SG in ED-optimal design will stop the search when the difference between previous optimal variable value and the variable value after taking a gradient step is less or equal to convergence criteria. In D-optimal design the convergence criteria represent the difference between the current OFV and the OFV of the previous iteration. If the difference is less or equal to the stop criteria the SG search will stop. It's by default set to 1E-08. Stochastic Gradient performs steps in the experiment design variables domain that are guided in direction by the gradient. The magnitude of these steps requires them to be scaled according to iterations history. The first iteration requires a user-defined step, expressed relative to the size of the defined range of the parameters. The required values are the relative values (≤ 1) specifying the size of the first step of the SG algorithm. Increasing the first step factor increases convergence speed, but at the same time increases the probability that the first step moves away from an optimal OFV found by the RS, thus increasing the probability of ending in a local optimum.

Line Search Settings

The number of grid point could be specified in the line-search. That is the number of point each defined range (e.g. a sample time), will be split in. If optimizing over a time point with a range of 5-15 hours and the number of grid points is 50 the OFV will be calculated in 50 points from 5 -15 hours with a step length ≈ 0.2 . The best OFV will give the sample time to proceed with. The LS could not be used when optimizing over discrete variables. If LS is used in the optimization the optimization will converge if the LS don't change the OFV from the previous SG or RS.

Step sizes

The step sizes are used to define the accuracy when approximating the derivative of different functions numerically. All derivatives used to calculate the Fisher Information Matrix (FIM) are approximated with a central difference approach with a truncation error of $O(h^2)$ where h is the step size. A forward difference approximation is used in the SG algorithm to calculate the derivative of FIM with respect to a continuous variable, e.g. the sample time. This method will have a truncation error of $O(h)$.

ED-Optimal design settings

If the optimization method used is ED-optimal design some ED-optimal settings must be defined. ED sample size is the number of samples that will be drawn from the parameter distribution to calculate the expectation value. One Fisher Information Matrix is calculated for each ED - sample, therefore the execution time will increase linearly with the number of samples. If a user defined distribution is used that are not stochastic this number should be set to the number of parameters in the user defined distribution and the stop criteria below could be set to a very small number e.g. 0.01%. The number of iterations to calculate the difference between SG and LS is

the number of calculations of expectation values that will be used to compare the LS and SG. For example an ED sample size of 45 and the number of iterations to calculate difference between SG and LS set to 30 will yield $45 \cdot 30 = 1350$ calculations of the FIM. When using a user defined distribution that is not stochastic the number of iterations should be one. This is only to have an automated way to look if the search has converged. The ED search converges if the LS don't find a better OFV within the previous SG value multiplied with the percentage value.

Differential equation settings

For the differential equation solver the relative tolerance (RelTol) and the absolute tolerance (AbsTol) must be set. The solvers will then have an error precision of $e_i = \max(\text{relTol} \cdot |y_i|, \text{absTol})$. The solver method is by default the *ode45* solver but could be changed to a stiff solver (*ode15s*) if the differential equation is stiff. The RelTol, AbsTol and differential equation method could be changed "on the fly" during an optimization. *Store differential equation results in memory* enables the user to store the solutions of the differential equation solver in the memory. This could increase speed a lot when optimizing over number of samples or sampling times. The option should **not** be used when optimizing on continuous covariates or other design variables.

Numerical derivative method

There are different methods to calculate numerical derivatives. In PopED two different approaches (except analytic derivatives) are available:

- Complex & Central difference – PopED uses complex differentiation when possible, otherwise central difference is used. The complex approach is very robust and accurate for small step lengths and will sometimes be twice as fast as the central difference approach. The precision for the first order complex difference is $O(h^2)$ where h is the step length.
- Central difference – PopED could use the central difference approach. This could be valid when the function couldn't handle complex numbers or when the complex approach is slow due to complex numbers. The precision for the first order central difference is $O(h^2)$ where h is the step length.

Number of conditional samples

If the approximation type is first order conditional or first order conditional with interaction the number of individuals samples could be specified here. A large number of samples will yield a more robust design against different individuals in a coming study but will take more time to compute.

Sampling technique

The sampling technique is used to generate simulations and to generate sample for ED-optimal design. The normal technique uses standard random numbers (see Matlab manual) while the Latin Hypercube Sampling is more evenly distributed within the sampling region. This could have advantages in ED-optimal design in terms of faster convergence and robustness.

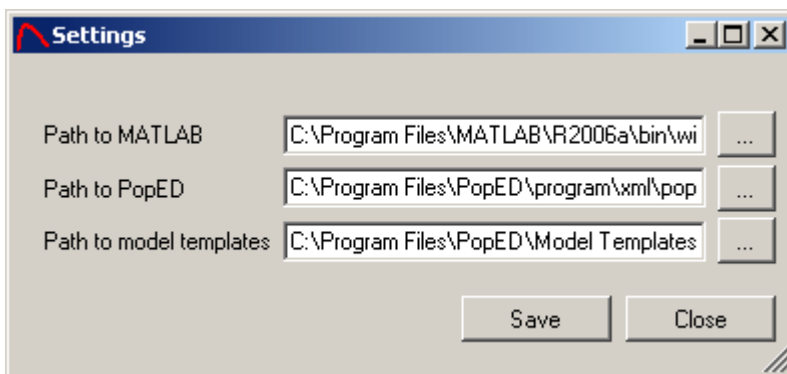
Save the PopED settings

The settings can be saved by using the save function (Ctrl+S) or Save as under the file menu or by walking thru the wizard. If a settings file is saved in the model template directory the model templates will be updated with the new model template. A warning will occur to prevent adding unnecessary files to the model templates directory.

Open a PopED settings file

A PopED Settings file (*.xml) can be open by using Open under the file menu.

PopED GUI Directories Settings



A path to the Matlab executable, usually <Matlab dir>\bin\win32\matlab.exe must be entered to run PopED within the GUI. A path to the PopED script must also be entered to allow for execution of PopED runs within the GUI. This should be <PopED dir>\programs\poped2_0.m. A path could also be set to the model templates directory. All the path settings will be stored in the Windows Registry when pressing save.

Diagnostics before the optimization

Some diagnostics can be used to see that the model works correctly prior to the optimization procedure. The model typical values could be plot and simulation could be performed to validate the model.

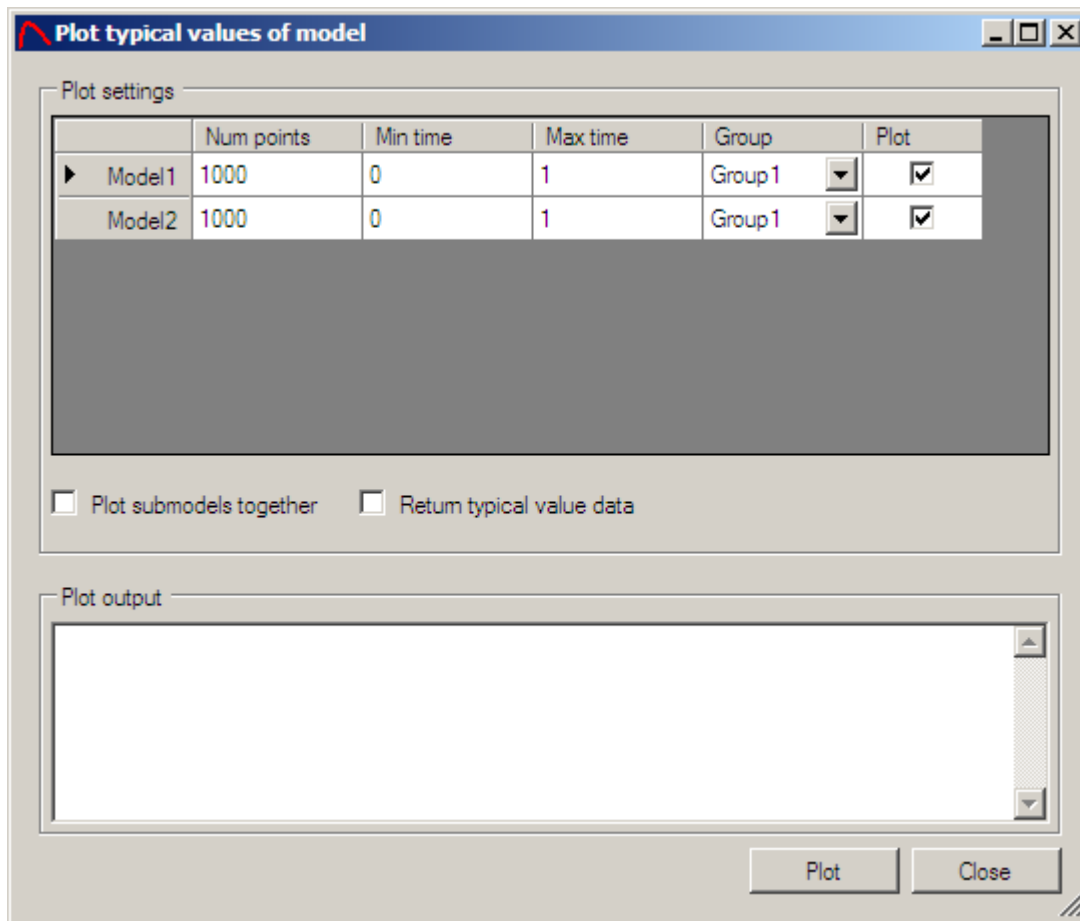
Convert PopED Settings to script version

The *poped2_0* function in Matlab can take the *.xml PopED GUI settings as an input or it could take a Matlab function representing the settings. A Matlab function containing the settings information is created when the function *poped2_0* is called or can be created by a call to the function *convert_xml.m* that will take a *.xml filename as input. The Matlab function containing the settings is often one of the inputs to the diagnostic functions.

Run PopED script commands from the GUI

A number of script commands in PopED can be run from the GUI. The GUI will convert the current settings file to a Matlab function (see above) and call the script command via the Matlab COM Server. This is all done in the GUI code but the Matlab COM Server needs to work properly to run PopED script from the GUI. Otherwise the PopED script version must be used (i.e. run optimization and plots from Matlab command line).

Plot Typical Values



PopED GUI has a function that could plot the typical values for all sub-models. The function is available if a PopED setting is saved and open and it's accessible from the Optimal Design menu.

For each sub-model the number of points that will be used to calculate the dependent variable must be entered. For example if the number of time points are 1000 and the time interval are 0-1 the dependent variable (DV) will be calculate every 0.001 time unit. It is also possible to plot the typical value from a certain group (the covariate values can affect the plot, e.g. different doses in different groups). A checkbox indicates whether this sub-model should be plotted or not. If *Plot sub-models together* is checked all the sub-models will be plotted in the same window/figure. The plot output will be the DV for all the sub-models that are plotted and figure windows will show all the sub-models. In the figure window; the data, titles, axis settings etc. could be modified and saved. If the *Return typical value data* is checked the output from the plot (the typical values) will be presented in the Plot output.

The script version of plotting the typical values is:

```
model_values = plot_model(bPlotModel,model_num_points,model_minxt,model,
                          maxxxt,groups_to_plot,popedInput,bShowGraph,bPlotInSame)
```

bPlotModel is a vector with the length of number sub-models indicating if this sub-model should be plotted or not. 1 equals plot, 0 equals not plot.

model_num_points is the number of time points used to plot the sub-model. This is a vector of the length of the number of sub-models.

model_minxt is a vector with the minimal time point to plot for all sub-models. The length is equal to the number of sub-models.

model_maxxt is a vector with the maximal time point to plot for all sub-models. The length is equal to the number of sub-models.

groups_to_plot is a vector with the group number to plot the sub-model with.

popedInput is the PopED settings function created from the xml file (see above). The function is often accessible by typing *function_input()*.

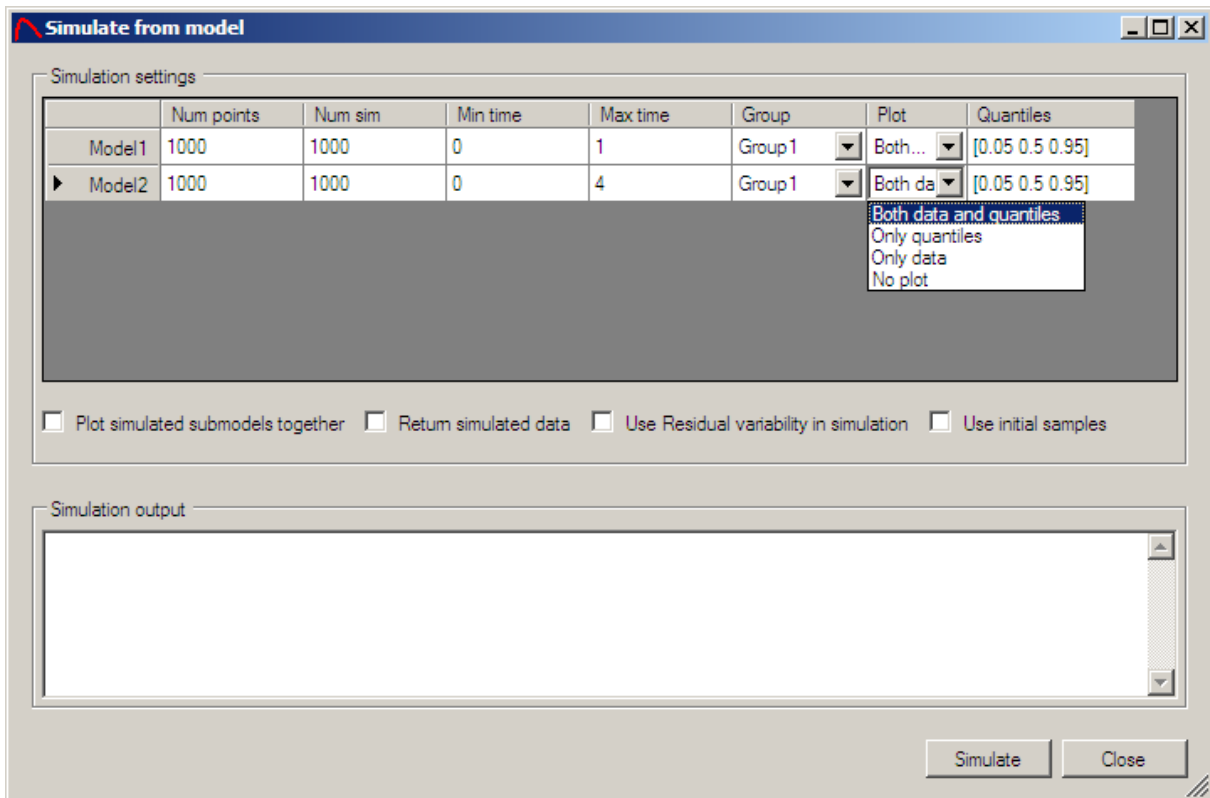
bShowGraph indicates whether a figure will be created or not. If it's set to false or 0 the *model_values* will be calculated and returned but no figure will be shown. This option could be useful to get the typical values within a script.

bPlotInSame is set to true or 1 if all sub-models should be plotted in the same figure. Otherwise it is set to false or 0.

Example: This will produce the same plot as above:

```
plot_model([1 1],[1000 1000],[0 0],[1 1],[1 1],function_input(),1,0)
```

Simulation of Model



PopED GUI has a function that can simulate data and plot the result for all sub-models. The function is available if a PopED setting is saved and open and it's accessible from the Optimal Design menu.

For each sub-model the number of points that will be used to calculate the dependent variable (DV) is specified, furthermore the num of simulations (number of individual curves to simulate) are specified. All simulations are simulated within a minimum and a maximum time and the group used to simulate can also be specified (the covariates in a group could affect the simulation, e.g. the dose). There is also a plot option that allows for different plots to be created. For each sub-model the plot options are:

- Both data and quantiles – Plot the data from all simulated individual curves and the quantiles specified in the quantiles column.
- Only quantiles – Plot only the quantiles specified in the quantiles column.
- Only data – Plot only the simulated individual curves.
- No plot – Don't plot this sub-model.

In the quantiles column all quantiles that should be plotted from this sub-model could be specified. The quantiles should be specified within brackets ([]) and it should be a value between 0-1. E.g. [0.01 0.5 0.99] will plot the 1 and 99 percentile and the mean value of the model given the simulated data. The figure windows produced by the plot could be used to change the plot properties and axis-settings etc. The output returned by the plot is the simulated data but only for the last sub-model that don't have the Plot option – No plot. The data is presented only when the *Return simulated data* is checked. All the sub-models could be plotted in the same window by checking the *Plot simulated submodels together*. The simulation can be done with or without the residual variability by clicking *Use Residual variability in simulation*. If *Use initial samples* is checked the function will only simulate from the current design (the initial samples) and the *Number points* column is ignored. The sample method used in the simulation could be either Latin Hypercube Sampling or normal sampling, see advanced settings.

The script version of the simulate function is:

```
sim_dat = plot_simulation(bUseResiduals,model_num_simulations,
                        model_num_points,model_minxt,model_maxxt,
                        groups_to_plot,popedInput,sim_quantiles,bShowVector,
                        bPlotInSame,bUseInitialDesign)
```

bUseResiduals is set to true (1) or false (0) if the residuals should be used in the simulation.

model_num_simulations is vector with the length of number of sub-models indicating the number of individuals that should be simulated for this sub-model.

model_num_points is the number of time points used to plot the sub-model. This is a vector of the length of the number of sub-models.

model_minxt is a vector with the minimal time point to plot for all sub-models. The length is equal to the number of sub-models.

model_maxxt is a vector with the maximal time point to plot for all sub-models. The length is equal to the number of sub-models.

groups_to_plot is a vector with the group number to plot the sub-model with.

popedInput is the PopED settings function created from the xml file (see above). The function is often accessible by typing *function_input()*.

sim_quantiles is a Matlab cell structure with the length of number of sub-models. The cell structure contains a vector for all sub-models with the quantiles that should be plotted for a sub-model.

bShowVector is vector with the length of the number of sub-models. The show vector will contain information how each sub-model should be plotted and if it should be plotted. The option for the show vector is 0 – Plot data and quantiles, 1 – Plot only quantiles, 2 – Plot only data, 3 – Don't plot this sub-model.

bPlotInSame is set to true or 1 if all sub-models should be plotted in the same figure. Otherwise it is set to false or 0.

bUseInitialDesign is set to true or 1 if the initial design should be used in the simulation. Otherwise it is set to false or 0

Example: This will produce the same simulation plot as above:

```
plot_simulation(0,[1000 1000],[1000 1000],[0 0],[1 1],[1 1],
               function_input(),{[0.05 0.5 0.95] [0.05 0.5 0.95]},[0 0],0,0)
```

Optimize with PopED

Optimization from the GUI can be performed under the Optimal Design menu, Run optimization. To run the optimization from the script version type `poped2_0('file_to_optimize.xml')` or call the function with a transformed input function (see Convert PopED settings to script version).

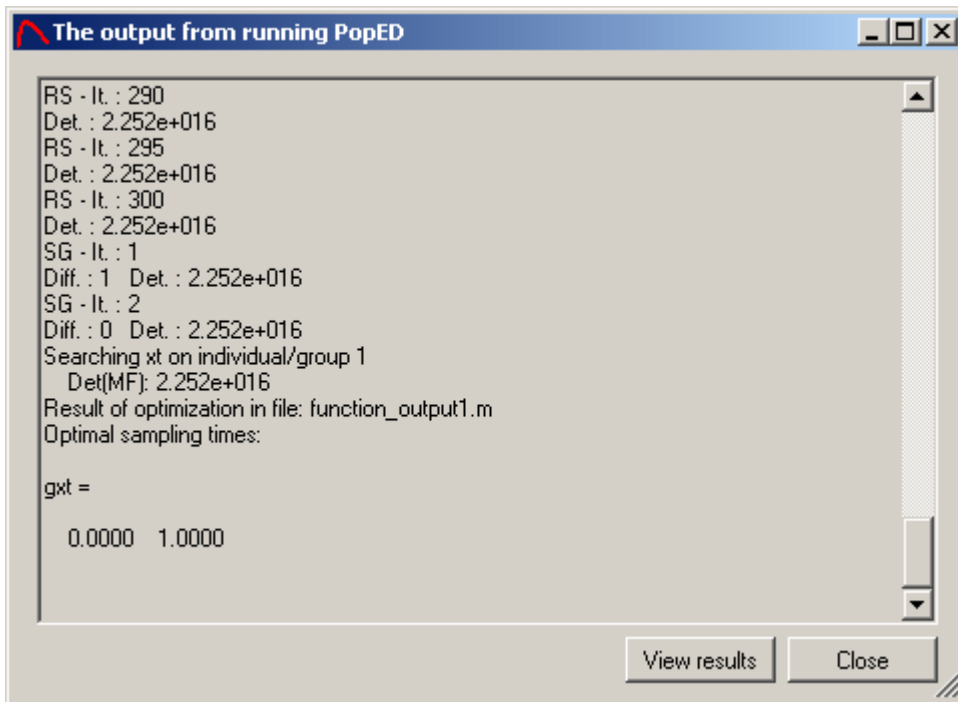
Example:

```
poped2_0('MyFile.xml')
poped2_0(function_input())
```

During the optimization, Matlab figure windows will show the optimization current status, i.e. the OFV and the continuous variable values in the optimization. If optimizing over discrete variables no figure windows will be shown in this version. Furthermore no figure windows will be shown if the *Use graphical output during optimization* option is unset (see Optimization and calculation settings).

During the optimization, output to the Matlab command window is outputted in the script version of PopED and the output from the different search algorithms are stored in the output file specified in the PopED settings file (*.xml or the input function *function_input.m* (see Output and input directories)). Stochastic Gradient and Random Search will store their result in the output file with an extension `_RS_SG_i.txt`, where *i* is the search iteration number. Line Search will have an extension `_LS_i.txt` where *i* is the search iteration number.

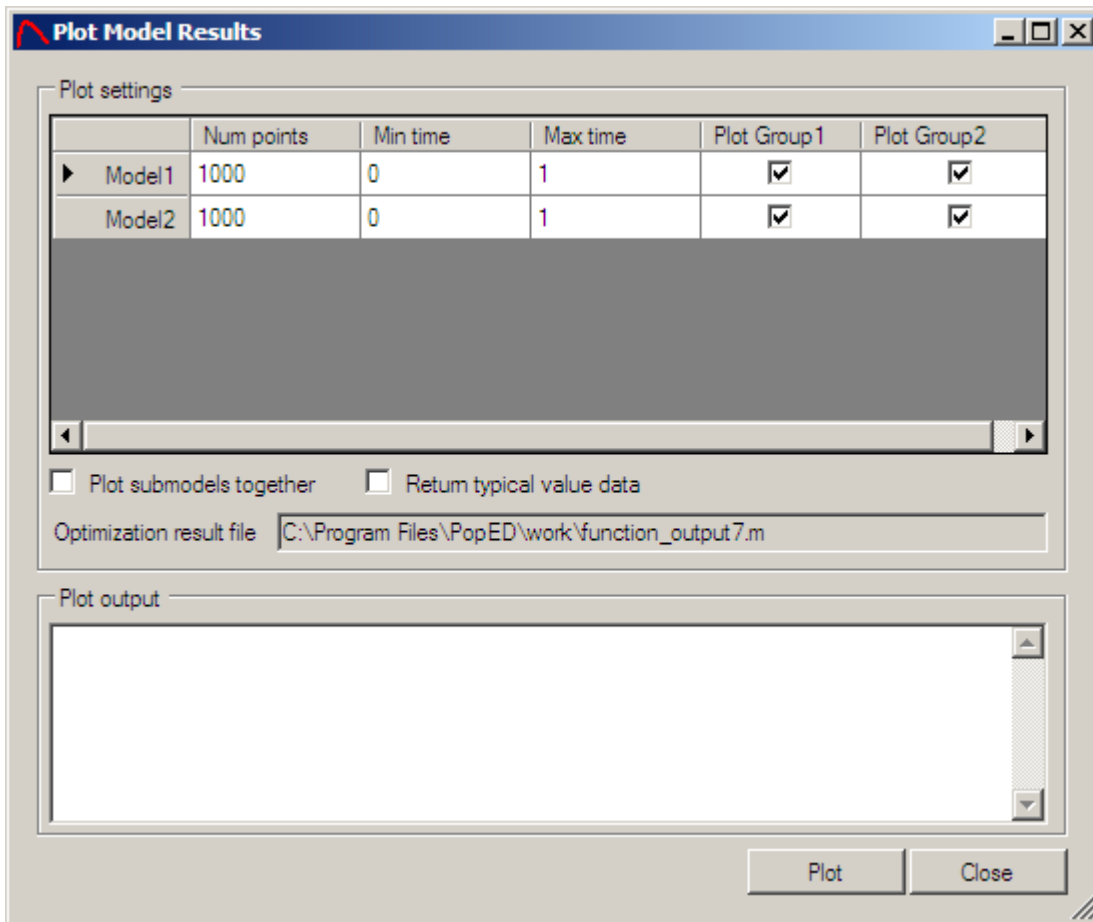
When the optimization are done or if an error occurs, output from the Matlab command window will be shown in an optimization output window for the GUI version and in the Matlab command window in the script version. A Matlab function file with the results from the optimization is also written, the output function is called: *function_outputi.m* (see Output and input directories) where *i* is the lowest number to create a non-existent filename in the current directory.



The continuous optimized variables are outputted as text and the result function filename is also visible. If the optimization didn't terminate due to an error the View results button will be visible.

Plot model results

The optimized result for continuous optimization could be viewed with the plot model result function available in the GUI from the Optimal Design menu. To be able to run the function from the GUI an output function corresponding to the optimization of the open PopED GUI Settings file (*.xml) must be specified.



The function works similar to the plot model function and plots the typical values for the different sub-models. The main difference is that the optimal sample times are marked in the plot with red rings. Like in the model plot function the number of time points to calculate the model with is specified in the num point's column. The time interval to plot over is also specified besides which group in each sub-model to plot. If the *Plot submodel together* checkbox are checked the entire plot will appear in the same figure window. If the *Return typical value data* is checked the typical value are presented in the Plot output.

The script version of plot model result function is:

```
[model_values opt_value opt_time opt_group opt_model] =
plot_model_results(bPlotModel,model_num_points,model_minxt,model_maxxt,pope
dInput,bShowGraph,bPlotInSame,bPlotGroups,popedOutput)
```

bPlotModel is a vector with the length of number sub-models indicating if this sub-model should be plotted or not. 1 equals plot, 0 equals not plot.

model_num_points is the number of time points used to plot the sub-model. This is a vector of the length of the number of sub-models.

model_minxt is a vector with the minimal time point to plot for all sub-models. The length is equal to the number of sub-models.

model_maxxt is a vector with the maximal time point to plot for all sub-models. The length is equal to the number of sub-models.

popedInput is the PopED settings function created from the xml file (see above). The function is often accessible by typing *function_input()*.

bShowGraph indicates whether a figure will be created or not. If set to false or 0 the *model_values* will be calculated and returned but no figure will be shown. This option could be useful to get the typical values within a script.

bPlotInSame is set to true or 1 if all sub-models should be plotted in the same figure. Otherwise it is set to false or 0.

bPlotGroups is matrix with the length of number of groups multiplied with the number of sub-models. E.g. the matrix contains a 1 in the first row and 2nd column if the 2 group should be plotted in the first sub-model.

popedOutput should be a PopED output function e.g. *function_output1*.

model_values is a output matrix containing the data from all plotted sub-models. The *model_values* does not necessarily contain the optimal sampling points. See below.

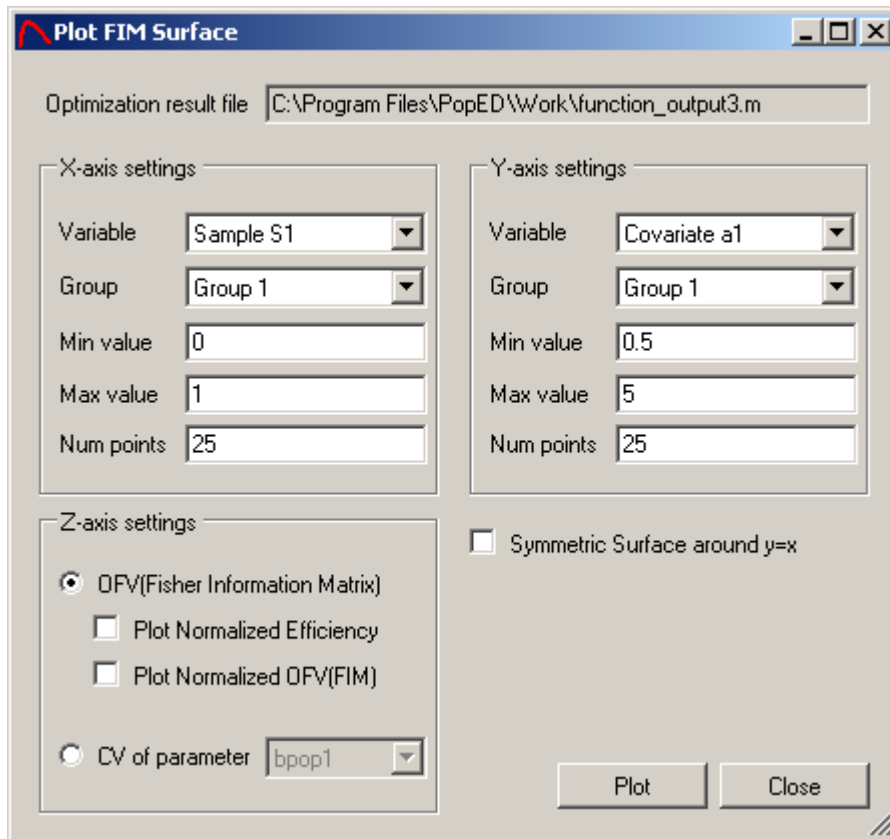
opt_value, *opt_time*, *opt_group* and *opt_model* are output vectors. *opt_value* contains the dependent variable value, *opt_time* the time point that the *opt_value* is calculated at, *opt_group* in which group the DV are calculated and *opt_model* has information about which sub-model the sample belong to.

Example:

```
plot_model_results([ 1 1],[ 1000 1000],[ 0 0],
[1 1],function_input(),1,0,[1 1 1; 1 1 1],function_output1())
```

Plot Fisher Information Matrix Surface

The surface of the OFV can be plotted against two of the design variables. This plot is available in the GUI from the Optimal Design menu. To get access to this plot a valid output function file needs to be specified.



The x and y axis settings are similar and all the variables in the current design are available in the Variable combo box. Choose a group for that design variable and a min/max value of the axis. Num of points to split the axis in and to calculate the OFV should also be specified. The surface will calculate the OFV number of points in the x-axis multiplied by the number of points in the y-axis, i.e. $25 \times 25 = 625$ in the example above. The surfaces that can be plotted are the OFV or the normalized OFV, i.e. scaled to the power of one divided by the number of unfixed parameters in the model ($FIM^{(1/p)}$). The third alternative is to plot the normalized efficiency, i.e. the value of OFV divided by the optimal OFV scaled with the number of parameters in the FIM. One other option is to plot the SE (%) of an unfixed parameter in the model. The CV will be presented as a percentage value in the plot. If the surface is known to be symmetric, e.g. plotting sample1 and sample2 within the same group the *Symmetric Surface around y=x* can be checked, this will half the run-time.

This diagnostic must be considered very carefully even though it could be a powerful tool to visualize the surface of the FIM. In most cases the dimensionality of the FIM is greater than 3 and to look only of 2 of these dimensions and draw conclusions could be misleading. There is also possible to change the min and max values to higher or lower values than the bounds used in the optimization. In this case e.g. the efficiency calculations might be false because the optimal OFV might be in the wider region. Also be very careful to use variables that are not optimized for in the surface, e.g. only optimization on sampling schedule but plotting a sample versus the dose. Again the optimal OFV might be wrong. This option is still available because sequential optimization might have been performed before the last optimization.

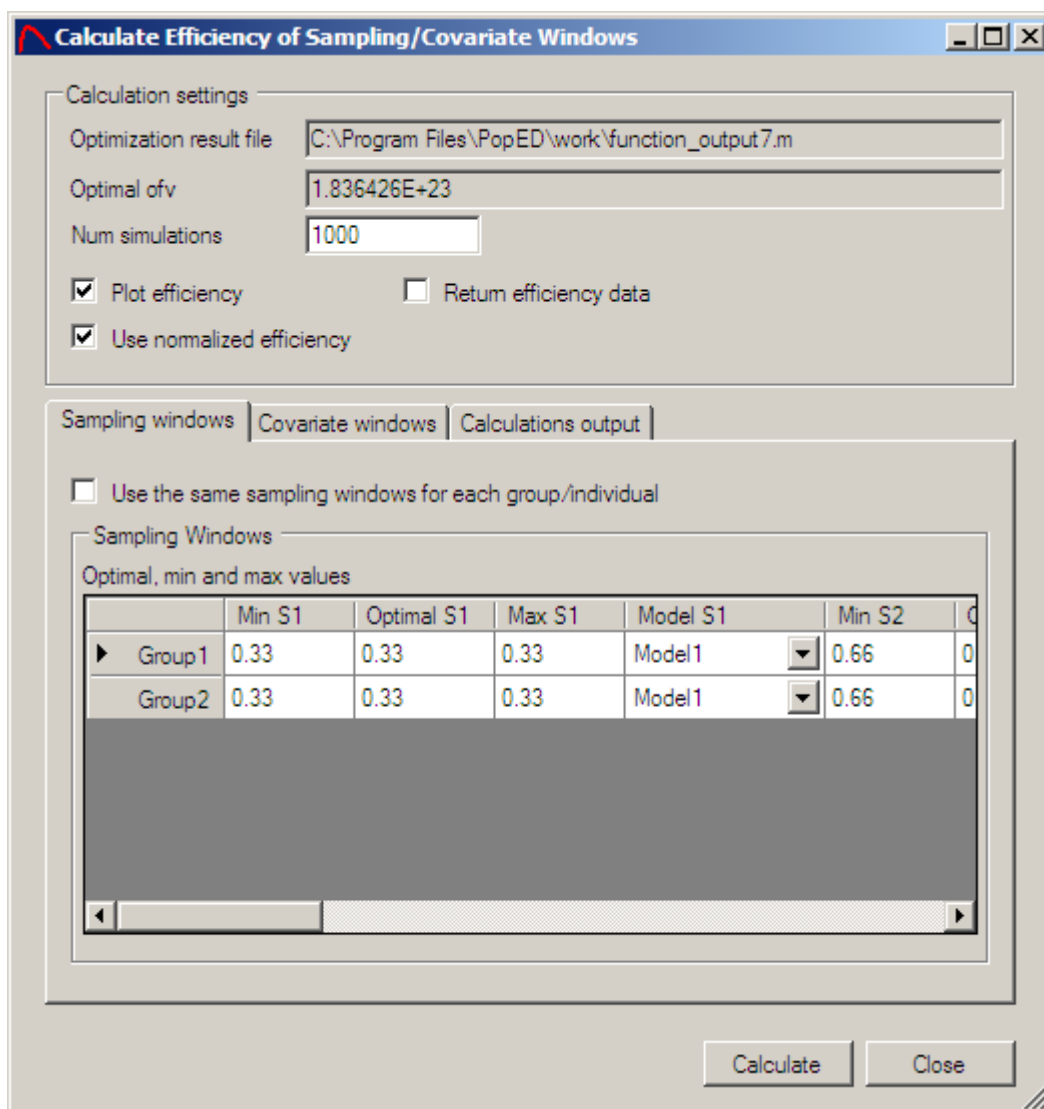
If the plot is not visible the render method might be wrong, this could be the case when the OFV is very large. Change the render from OpenGL to z-buffer in the Matlab figure properties. Another possibility is that the FIM calculation is nearly singular or singular. Try to change the max and min value to be close to the optimal design or use the script version of the surface plot to catch warning messages.

The script version of the FIM surface plot is available from the Matlab command window and the function is named:

```
plot3d_fim
```

The script function has a lot of options and will not be described here but there is a describing help text in the function. Type `plot3d_fim` in the Matlab command window and help text will be printed.

Calculate Design Windows



Often the optimal sampling times, optimal covariates values or optimal other design variables values are not feasible in practice. Therefore borders around each optimal

value could be calculated that will produce a feasible design instead of an optimal design, this is called sampling windows or covariate windows. This option is available in the GUI from the Optimal Design menu and it's also available as a script function.

Depending if covariate and/or other design variables are in the design, tab pages for covariates windows and other design variable windows will be enabled. Sampling windows is always available because samples need to be taken in an informative design. In the sampling windows the optimal sampling time is written and the window is defined by changing the min and max values. The optimal value and the model could not be changed. The sampling window couldn't be outside of the borders defined before the optimization.

The tool will calculate the efficiency of a sample within a window by randomly (uniformly) take sample times from the window and calculate the OFV and compare the value to the optimal OFV. This could be done by using the normalized OFV (scaled to the number of parameters) or the un-scaled efficiency. The number of simulations indicates how many samples that will be drawn from the windows. There is also a possibility to plot the efficiency in a Matlab figure window by checking the *Plot efficiency* check box.

The windows function will return the efficiency in a vector and it's visible in the calculation output tab after the calculations if the *Return efficiency data* is checked.

The script version of the sampling windows calculation function is:

```
[eff min_eff mean_eff max_eff] =
efficiency_in_windows(iNumSimulations,optdetfim,xt_windows,a_windows,x_windows,
bNormalizedEfficiency,bPlot,popedInput)
```

iNumSimulations is a scalar that specifies how many samples that will be picked from the sampling windows.

optdetfim is a scalar with the optimal OFV from the optimization.

xt_windows is a matrix with the sampling windows for all groups. For each row in the matrix the min and max value of the window for each sample should be entered.

a_windows is a matrix with the covariate windows for all groups. For each row in the matrix the min and max value of the window for each covariate should be entered.

x_windows is a matrix with the other design variable windows for all groups. For each row in the matrix the min and max value of the window for each other design variable should be entered.

bNormalizedEfficiency if the efficiency should be scaled to the number of unfixed parameters in the model or not. 1 if normalized, 0 otherwise.

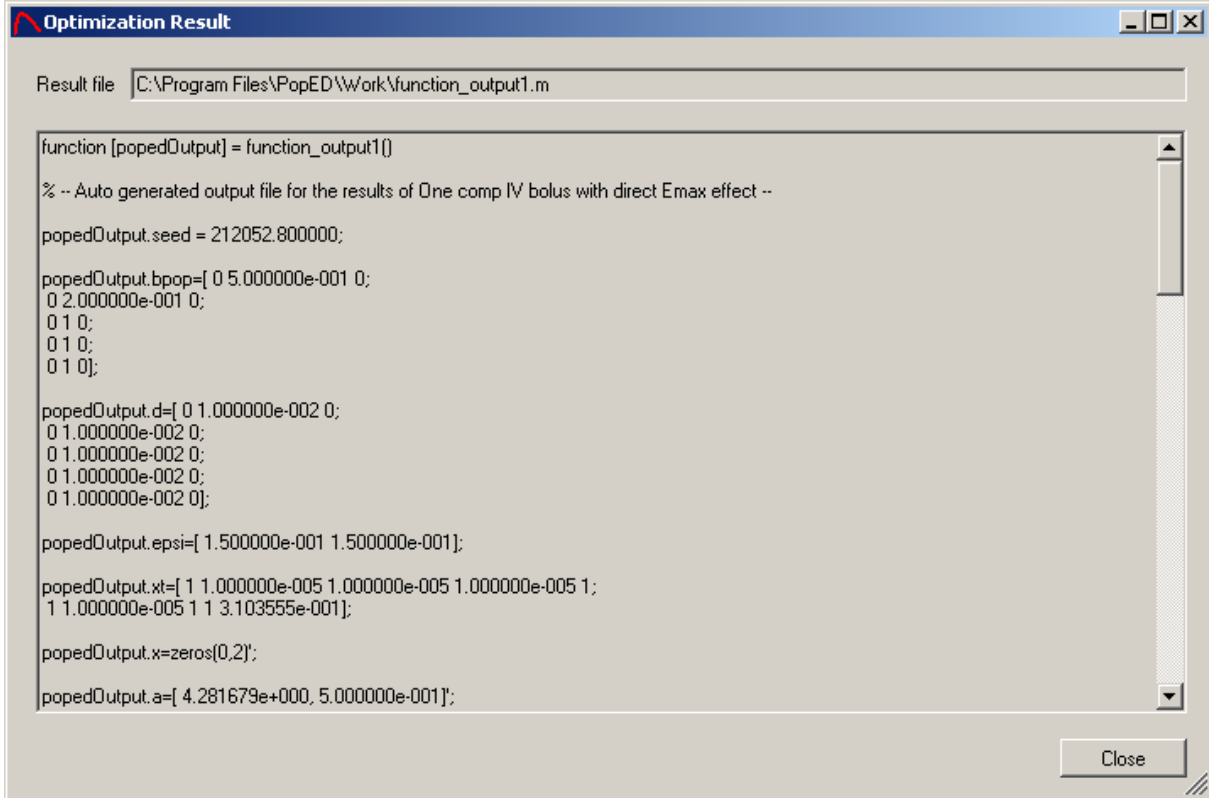
bPlot if the efficiency should be plotted, true or false.

popedInput is the PopED settings function created from the xml file (see above). The function is often accessible by typing *function_input()*.

Example:

```
efficiency_in_windows(1000,1.154813e020,[0 1.2 0 0.5 1 2],[50
150],[ ],0,1,function_input())
```

View Optimization Output



```
function [popedOutput] = function_output1()

% -- Auto generated output file for the results of One comp IV bolus with direct Emax effect --

popedOutput.seed = 212052.800000;

popedOutput.bpop=[ 0 5.000000e-001 0;
0 2.000000e-001 0;
0 1 0;
0 1 0;
0 1 0];

popedOutput.d=[ 0 1.000000e-002 0;
0 1.000000e-002 0;
0 1.000000e-002 0;
0 1.000000e-002 0];

popedOutput.epsi=[ 1.500000e-001 1.500000e-001];

popedOutput.xt=[ 1 1.000000e-005 1.000000e-005 1.000000e-005 1;
1 1.000000e-005 1 1 3.103555e-001];

popedOutput.x=zeros(0,2)';

popedOutput.a=[ 4.281679e+000, 5.000000e-001];
```

The optimization result is a Matlab function file that contains a lot of information about the optimization result. The variables in the output function file are.

- seed – The seed number used in the optimization.
- bpop – The typical values, the distributions and variability.
- d – The IIV distribution, the distributions and variability.
- sigma – The Residual variability.
- xt – The final sampling times.
- x – The final other design variables.
- a – The final covariates.
- gni – Number of samples per subject.
- groupsize – Group size for each group.

- `modelswitch` – The vector defining which samples that belong to which sub-model.
- `iFIMCalculationType` – The full or reduced FIM.
- `ApproximationMethod` – FO, FOCE or FOCEI.
- `FOCENumInd` – The number of individual samples if a conditional approximation method was used.
- `fmf` – The Fisher Information Matrix.
- `imf` – The inverse of Fisher Information Matrix.
- `ofvmf` – The objective function value.
- `d_switch` – If optimized using D or ED-optimal design.
- `ofv_calc_type` – The criterion used to calculate the OFV. E.g. $\det(\text{FIM}) = 1$ and $\ln(\det(\text{FIM})) = 4$.
- `param_var` – A vector with the unfixed parameter variances, the vector start with the `bpop`, then the unfixed `d` and last is the unfixed `epsi`.
- `param_cv` – A vector with the unfixed parameter CV in fractions, the vector start with the `bpop`, then the unfixed `d` and last is the unfixed `epsi`.
- `notfixed_bpop` – A vector with a 1 if a `bpop` is not fixed and a 0 if the `bpop` is fixed.
- `notfixed_d` – A vector with a 1 if a `d` is not fixed and a 0 if the `d` is fixed.
- `notfixed_sigma` – A vector with a 1 if a `sigma` is not fixed and a 0 if the `sigma` is fixed.

The function output could also be called within a script by typing `function_output(i)` where `i` is the function output number.

Update initial design from output

The initial design (sample times, covariates, other design variables, number of samples per group and the number of individuals per group) could be updated after an optimization. This is done by clicking *Update initial design from output* under the Optimal Design menu. The output file must be consistent with the xml file (i.e. similar number of groups, sample points etc.)

Model Templates

A number of model templates are distributed with the PopED program to illustrate how different models can be implemented. The model templates can be accessed by the Wizard; new option, under the File menu in the GUI. The model templates directory could be extended by own user defined templates by saving a PopED GUI settings file (*.xml) in the template directory. A recommendation is to write user defined templates as general as possible and not to add specific design of models that are already in the template directory. The templates available in the PopED version 2.06 are:

- One compartment IV Bolus dose. Parameterized by CL and V.
- One compartment zero order infusion. Parameterized by k_e and V.
- One compartment 1st order absorption. Parameterized by k_a , k_e , F and CL.
- One compartment IV Bolus dose with Michaelis Menten elimination. Parameterized by V_{max} , K_m and V. Explicit solution.
- One compartment IV Bolus dose with Michaelis Menten elimination. Parameterized by V_{max} , K_m and V. Differential equation.
- One compartment with transit compartment absorption. Parameterized by k_a , CL, V, MTT and n.
- One compartment IV bolus with a direct E_{max} effect. Parameterized by CL, V, E_0 , E_{max} and EC_{50} .
- One compartment 1st order absorption with repeated dosing. Parameterized by k_a , k_e , V and τ .
- Two compartment IV Bolus dose. Parameterized by V, k_{12} , k_{21} and k_e .
- Two compartment zero order infusion. Parameterized by V, k_{12} , k_{21} and k_e .
- Two compartment 1st order absorption. Parameterized by k_a , k_{12} , k_{21} , V, F and k_e .
- Three compartment IV Bolus Dose, Parameterized by V, k_{12} , k_{21} , k_{13} , k_{31} and k_e .
- Three compartment zero order infusion. Parameterized by V, k_{12} , k_{21} , k_{13} , k_{31} and k_e .
- Three compartment 1st order absorption. Parameterized by k_a , k_{12} , k_{21} , k_{13} , k_{31} , V, F and k_e .

- Biological rhythm (3 cos rhythms). Each rhythm parameterized by Peak time, Amplitude and the period.

Most of the model templates are analytical solutions of the different compartment models; therefore it could be good to use the templates because the analytic solutions are much faster than the differential equations. Feel free to distribute and share user written templates with other users of PopED.

Examples

The examples are available in the *<PopED Install dir>\PopED Examples* and will cover more of the script specific options of the PopED program. The examples can be run from the GUI (except example 2) and most of the design options can be changed and viewed by the GUI version of PopED. The examples are not always optimized for speed, instead they are written to be easy to understand and to follow.

To run an example, open the PopED GUI settings file (*.xml) for the example and change the path to the model file. The model file for each example will be in the same directory as the PopED GUI settings file. For example 2, after changing the model file path, open the Matlab version of PopED (see Running PopED) and type *run* in the Matlab command prompt.

Example 1, Multiple Drug optimization and grouping of sample times

In this example optimization will be done in three drugs concurrently. PopED will find an optimal design for parameter estimation of the three drugs at the same time. The drug models are written with analytic solutions but an identical differential equation example is also available by setting the flag `bUseAnalytic` to false in the model file. All drugs have different profiles; one is a one-compartment drug with a zero order infusion, the second drug is a one-compartment drug with an IV bolus dose and finally the third drug is a one-compartment drug with 1st order absorption. The design contains four different groups with 10 individuals in each group, all with four sample times. The sampling schedule is coded as 12 different sample times per group but the sample times are grouped in 3, i.e. to cover the measurements of the three drugs at the same time. There is also grouping of the sample times between groups, i.e. the first sample of the first and third group are grouped together meaning that they will be taken at the same time. There is also a grouping of the last sample time between the second and the 4th group. Use the model validation tools from the PopED GUI (plot model and simulate) to look at the different drug profiles.

The grouping forces some of the sample times to be the same within and between groups. The grouping assumes that the residual variability of simultaneous samples of the three drugs is independent. This is probably not a correct assumption but the residual variability correlation in the samples only depends on the difference in the analysis method of the samples.

Before running the experiment, transform the PopED GUI settings xml file to a Matlab function (see Convert PopED Settings to script version).

Example 2, User defined distributions on model parameters

In this example a user defined distribution (UDD) is assumed on the typical value parameter for clearance. For a parameter like CL a normal distribution for the typical value or a normal/transformed IIV distribution probably would be better but this example is only an illustration how a user defined distribution can be implemented. The user defined distribution can be discrete or stochastic and in this example a discrete distribution of 25 values for CL is used. In ED-optimal design the expectation value can be approximated by a Laplace integral approximation but this is not used for the user defined distributions. For a user defined distribution that is not stochastic, the ED-sample size variable should be set to the length of the distribution and the stop criteria for ED-optimal design should be small (see ED-optimal design settings). A user defined distribution function should have this syntax:

```
function ret = user_distribution(ret,t,sample_number)
%A user defined distribution function.
%The value from the user defined distribution (UDD) should be returned in
%ret.
%Input:
%t is a vector that contains all the distributions of the
%parameters in the model. t(i) == 3 is a user defined distribution,
```

```

% 0 is point distribution, 1 a normal and 2 a uniform distribution. Ret is
%also an input variable with the values for the other distributions, if
%t(i)~=3 the value ret(i) should not be change, but the user distribution
%value can depend on the other parameters current values. The sample number
%is the ED-sample number; this shouldn't be larger than the distribution
length for a discrete distribution.
typCL = [1 2 4 3 3.2];
IIVCL = [0.01 0.02 0.012 0.011 0.022];
j=1;
for i=1:length(t)
    if (t(i)==3) %This is an user defined distribution parameter
        if (j==1) %If it's the first parameter with a UDD
            ret(i) = typCL(mod(sample_number-1,length(typCL))+1);
        else
            ret(i) = IIVCL(mod(sample_number-1,length(IIVCL))+1);
        end
        j=j+1;
    end
end
end
end

```

In the example the distribution is defined by a global definition outside the distribution function, i.e. in the run.m file. This is to illustrate that if a large discrete distribution is used it might be computationally run-time efficient to declare the distribution outside the distribution function. Look in the run.m file and the user_distribution.m file to see how the UDD is defined. The model is a one-compartment model with an IV bolus dose. The path to the UDD might need to be changed in the run.m file.

Before running the experiment, transform the PopED GUI settings xml file to a Matlab function (see Convert PopED Settings to script version).

Example 3, Analytic Fisher Information Matrix of PK-PD model

In this example, analytic derivatives are used/calculated instead of numerical approximations of the FIM. There are two sub-models; a one-compartment IV bolus dose and a direct e-max effect model. Run the example from the GUI. If the run produced an error, it might be that the analytical derivative file has not been flushed to the operating file system before the execution of the FIM. Retry the run or run it from the Matlab command line in the example directory by typing:

```
poped2_0('analytic_derivative.xml')
```

Abbreviations and Variables

FIM – Fisher Information Matrix ~ Inverse of the expected Covariance-Variance matrix of the unknown parameter.

Criterion Function – The function that is optimized in the optimization procedure.

OFV – Objective Function Value – See criterion function.

RS – Random Search – A random search algorithm.

SG – Stochastic Gradient – A stochastic gradient search algorithm.

LS – Line Search – A line search algorithm.

GUI – Graphical User Interface – A graphical tool that communicates with the user.

bpop – Population mean variable.

b – Inter Individual variable.

d - Inter individual distribution variance.

a – Covariate variable.

x – Other design variable.

g – Parameter definition vector.

epsi – Residual variance.

sigma – Residual distribution variance.

IIV – Inter individual Variability – The variability between individuals.

BSV – Between Subject Variability See IIV.

NONMEM – NON linear Mixed Effects Modeling.

UDD – User Defined Distributions.