SPK USER MANUAL

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SPK Help

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Before You Start

This Help document is meant as a guide throughout the operation of the Model Design Agent (MDA). The MDA is an interface to the server-based SPK (System for Population Kinetics) computational engine for mixed effects models, and it allows the user to define, fit and simulate mixed effects nonlinear models, and view results. The MDA also produces a NONMEM(R)-compatible control file.

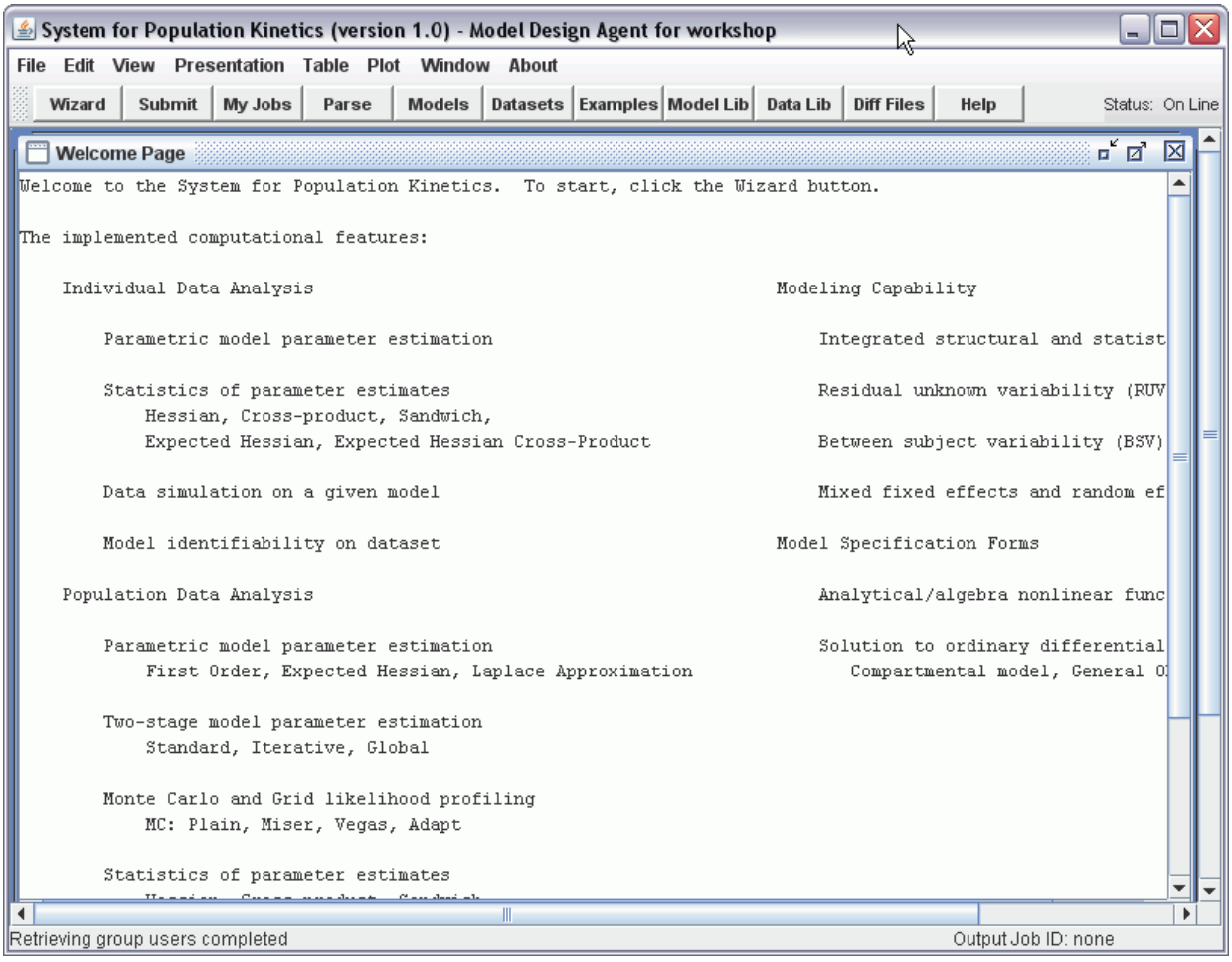
The following assumes that you have an account on MySPK and have downloaded the MDA on your computer. If you have not done so, please visit http://spk.rfpk.washington.edu/info/ and click on the **MySPK** link. There you will also find instructions for installing the Java Runtime Environment necessary for running the MDA.

A printed version of the documentation is available by accessing the **User Manual** link on the MySPK webpage.
Bug reports are encouraged and very welcome. They should be filed through the SPK Bug Report page, http://bugzilla.rfpk.washington.edu/. The SPK Software Development Team uses the Bugzilla system. If you have problems filing a bug report, please use the contact information on the website. If you are a first time user, you may find it helpful to look at the **Getting Started** link on the MySPK webpage.

The development of the software described in this User Manual was partially supported by NIH/NIBIB grant P41 EB001975, "Resource Facility for Population Kinetics". If you use this software in a publication, please acknowledge this funding source using the wording above and please send a publication reprint or a PubMed citation to: RFPK Principal Investigator, Box 355061, University of Washington, Seattle, WA 98195-5061.

Introduction

This is the first screen you will see once you have logged into MySPK and have downloaded the Model Design Agent (MDA)



If you see "Status: On Line" on the upper right corner of the MDA, you are connected to the Internet and you can use the MDA to view old jobs or submit new jobs to the SPK server. Buttons on the top have the following functions:

- **Wizard**: Starts an interactive tool that helps the user to interactively create a model file. The model file is compatible with a NONMEM(R) control file, and is saved as a SPK input file in XML. The tool can also take an existing model file or SPK input file, and helps the user

to modify it. If you are just getting started, this is the first button to click.

- **Submit**: Submits a job to the SPK server. Before clicking on this button, an SPK input file should be opened and displayed in the editor window. This button, when activated, brings up the **Job Submission Dialog**. In this dialog there are three tabbed panes for "Model", Dataset" and "Job", respectively. The "Model' and the "Dataset" panes allow the user to specify the names and descriptors of the model and the dataset used in the job. If one of the likelihood numerical integration methods is being used, these panes are ignored (since the parent job's model and dataset must be used in this case, and the system will do it automatically). The "Job" pane displays the analysis method for the job and allows the user to enter a short job abstract. Again, if a likelihood evaluation method (the radio button text is ended with "integration on likelihood") is selected, the job must have a parent and the parent job's input file must be loaded from the server before clicking the "Submit Job" button.
- **My Jobs**: Displays the user's job list in the SPK server. If a job is selected, the job information dialog box is displayed showing the model and dataset used by the job. The model, the dataset or the SPK job input/output can be returned and displayed in the MDA editor window, or the user may choose to automatically start the SPK input file preparation tool or the SPK output processing tool. The user can also find the job's history, the job's parent job and the job's identification number in the dialog.
- **Parse**: Processes the SPK output file shown in the editor window, parses the SPK output file in XML and allows the user to save data and tables that was returned from the server.
- **Models**: Displays the user's model list in the SPK server, gets and displays user selected model version in the editor window.
- **Datasets**: Displays the user's dataset list in the SPK server, gets and displays user selected dataset version in the editor window.
- **Examples**: Displays an example job list in the SPK server. If a job is selected, a dialog box is displayed showing the model and dataset used by the job. The model, the dataset or the SPK job input/output can be displayed in the MDA editor window, or the user may choose to start the SPK input file preparation tool or the SPK output

processing tool. The user can also find the job's history and the job's parent job in the dialog.

- **Model Lib**: Displays a list of the models available in the model library in the SPK server, retrieves and displays user selected model version in the editor window.
- **Data Lib**: Displays dataset list of the dataset library in the SPK server, gets and displays user selected dataset version in the editor window.
- **Diff Files**: Compares two text files. Any of the files may be either on the SPK server as model or data archives or on the user's computer.
- **Help**: Displays this document.

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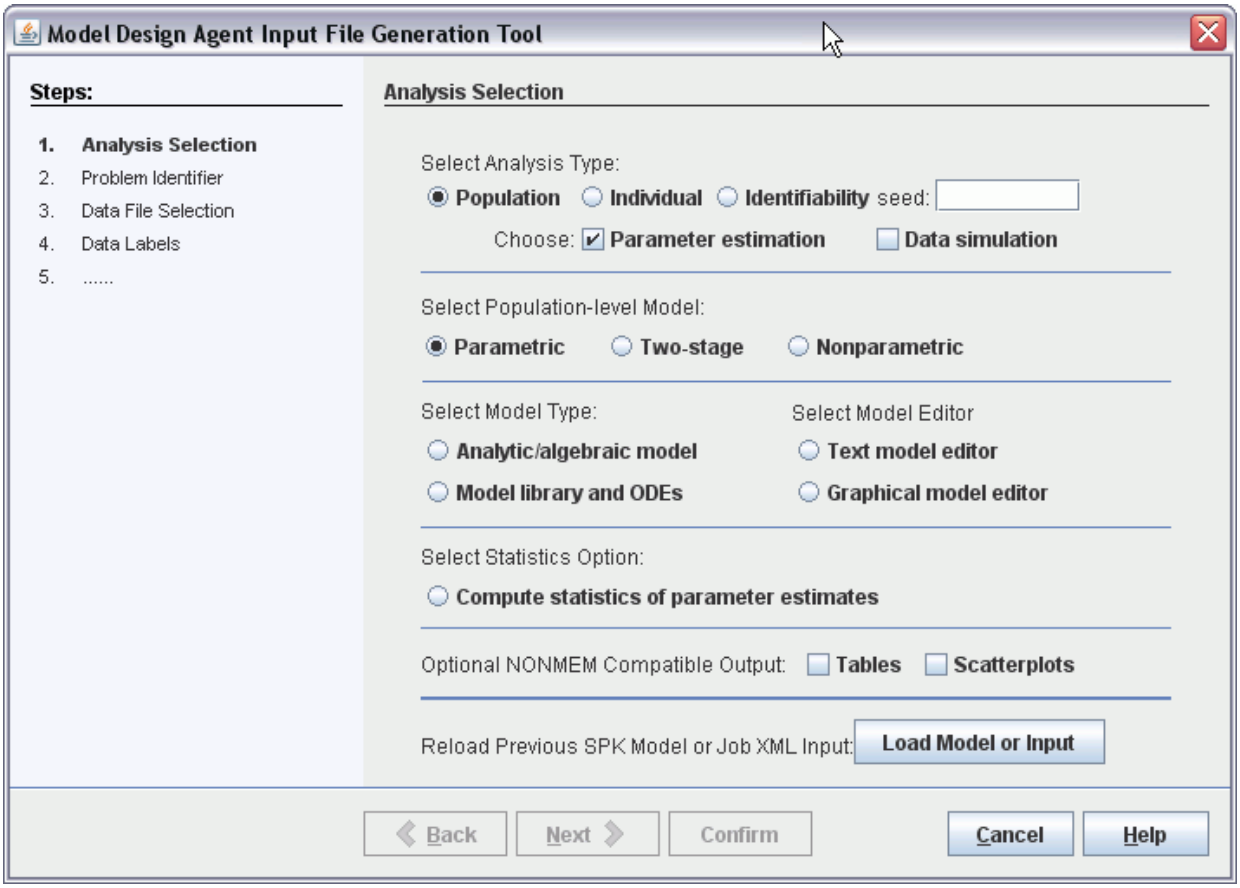
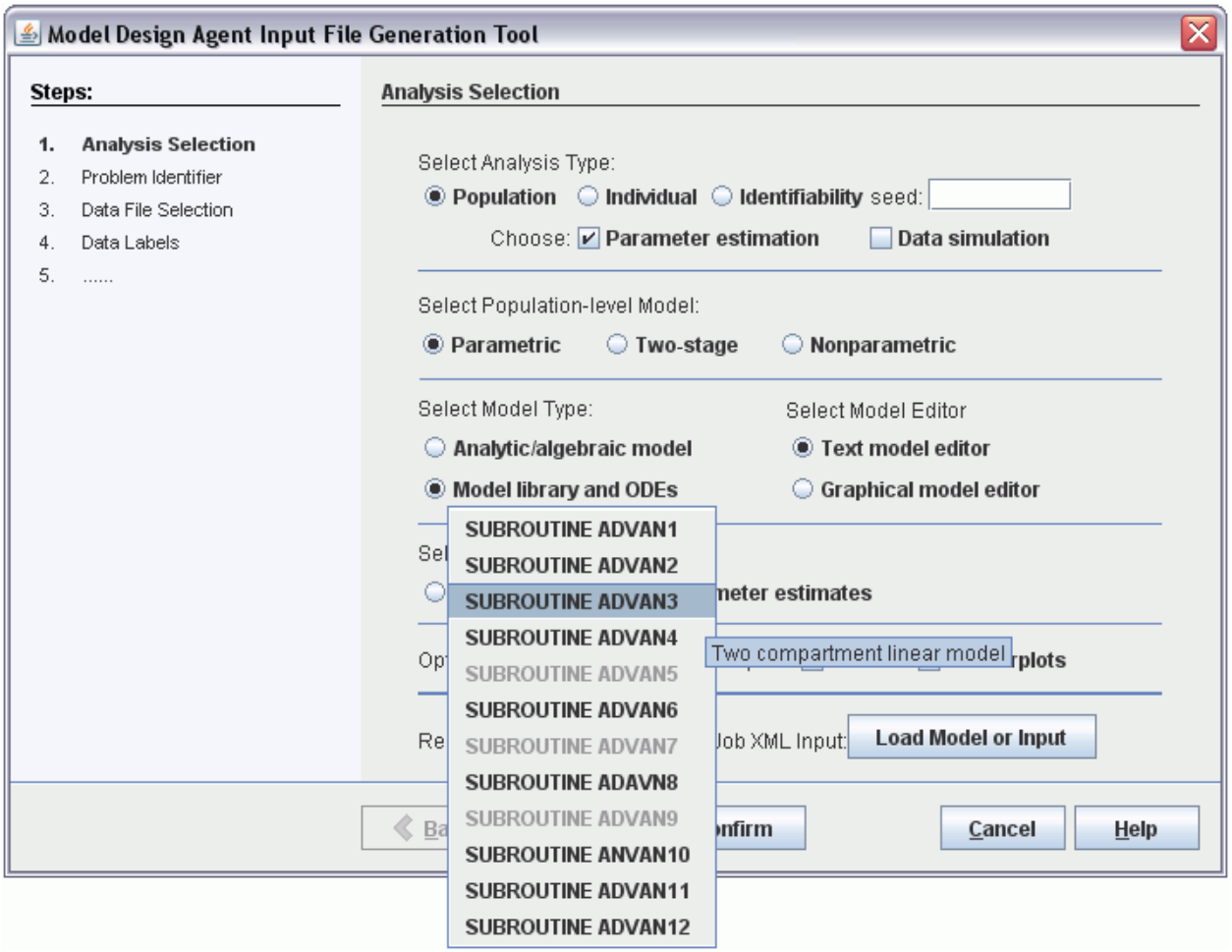
Prepare Input: Analysis Selection

Congratulations! You have just started the creation of a new model in the MDA. This is the screen you are seeing:



There are several data processing options in the MDA:

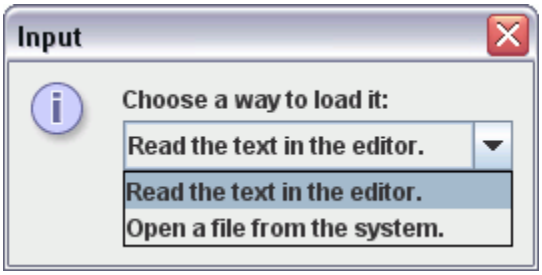
- The first option has to do with specifying whether you would like to analyze your data using **Population Analysis** (more than one subject), **Individual Analysis** (just one subject) or **Identifiability** (checking wether the model parameters can be uniquely identified by the given data). Briefly, individual analysis is applicable to an individual data set, while pooled (population) data should be analyzed using either a population analysis method or a two-stage method.
- The next step is to select the data analysis possibilities. One is **Parameter Estimation**, while the other is **Data Simulation**. At this stage the user can select both simultaneously or just one of them, depending on the intent. The parameter estimation features will quantify model parameters from available data; the simulation feature will create synthetic data from a model and its parameter values. Selecting both will first simulate data and then estimate parameters from the synthetic data.
- If a population analysis is selected, one of the analysis type radio buttons below must also be selected. The options are: **Parametric**, to use a likelihood approximation method such as the First Order, conditional on parametric population distributions such as Gaussian or log-normal; **Two-Stage**, to estimate the population parameters by sample averaging across individuals (recommended for rich data only); and lastly, **Nonparametric**, to estimate population probability distribution without assuming anything about their shape.
- The next option is the model type. You will have to specify whether you will be creating an **Analytic/Algebraic Model**, or whether you will be using the **Model Library and ODEs**. The Model Library includes the standard differential equation ADVAN and TRANS modeling frameworks used by NONMEM(R); the available ADVANs are visible in a drop-down menu, and their parameterizations are visible by pointing the mouse to the library model name. if you have selected **Model Library and ODEs**, you will also have the option to use a **Text Model Editor** (a textual wizard to write model equations and/or differential equations) and a **Graphical Model Editor** (where the model is built on the screen using point-and-click capabilities). This selection should be made at this time.



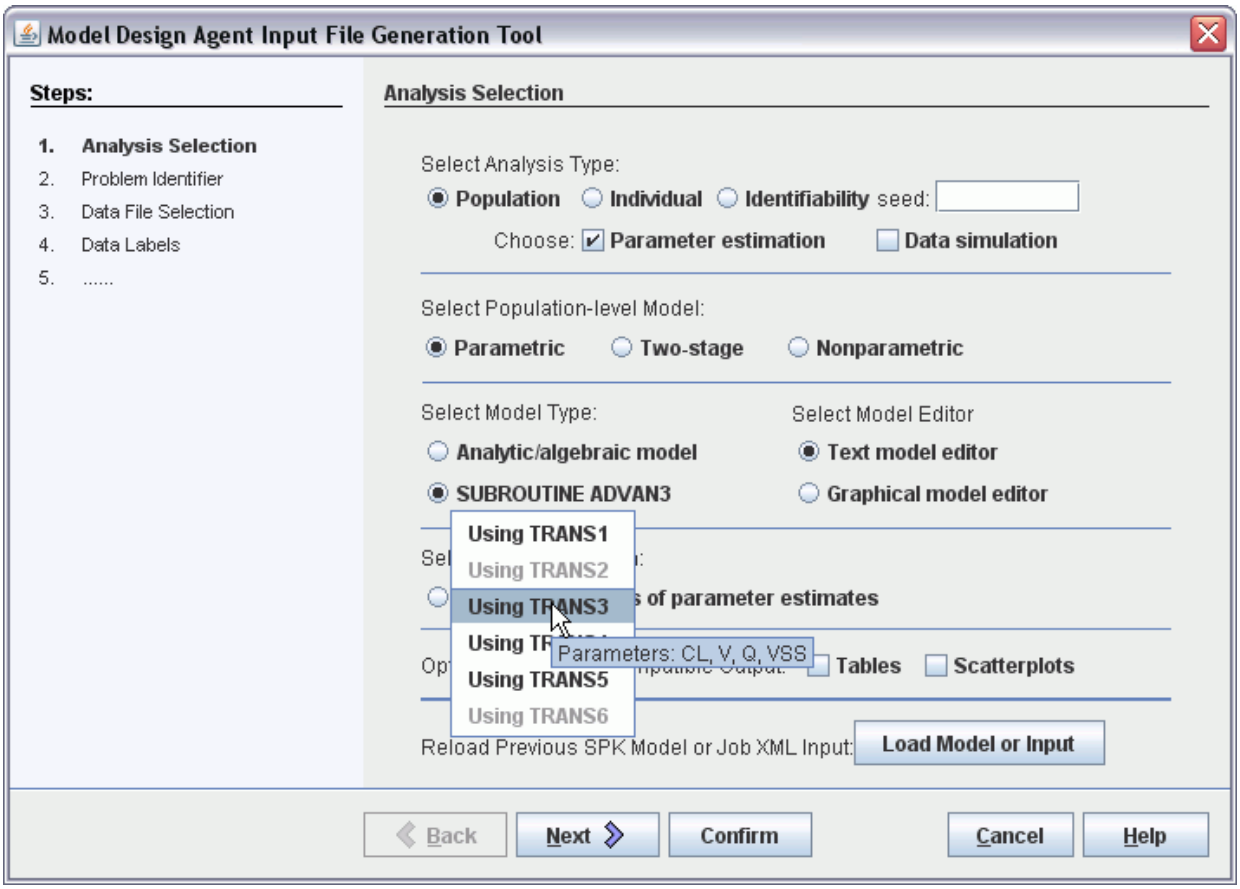
- Lastly, you will have to specify whether you desire statistics of the estimates by clicking next to **Compute Statistics of Parameter Estimates**. The calculation of statistical output requires computational resources, so it may lengthen the time it takes for your model to solve.
- Tables and plots are *automatically generated* by the MDA. However, if a NONMEM(R) compatible control file is desired, and depending on the desired output format, one or both of **Tables** or **Scatterplots** must be checked to obtain tabular and graphical output respectively. In other words, custom scatterplots and tables can always be created after the SPK model run is completed, so these buttons are only supplied for creating a NONMEM(R)-compatible input file.

The button labeled "**Load Model or Input**" allows you to reload a model you created with the MDA or a full SPK input file (which contains both model and data specifications). The model can be loaded from the MDA

Editor Window or from a file stored on your local file system. If you select this option, you will see a window that prompts you for a choice.



For example, the situation where we want to perform population analysis using the predefined ADVAN3 (two-compartment model with input in the first compartment) module and we are also requesting statistics on the estimates and both tabular and graphical outputs compatible with NONMEM(R) is shown in the screen shot below. Note that you will have to select a parameterization (TRANS) for ADVAN3



After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the

MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

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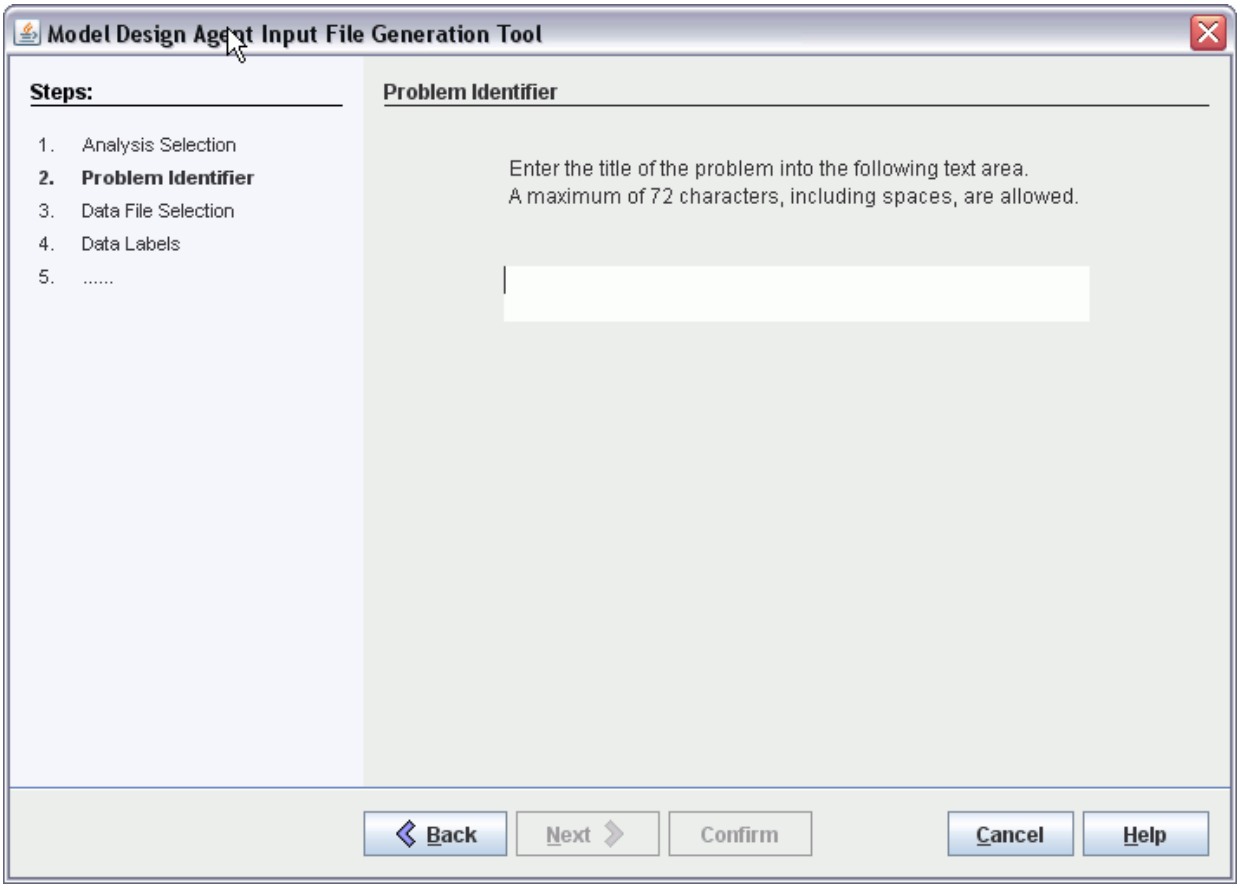
Prepare Input: Problem Identifier

This area of the MDA allows you to define an identifier for the problem you are building. This is the screen you should see:



The identifier is up to 72 characters long and any alphanumeric character can be used. Special characters are also supported.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

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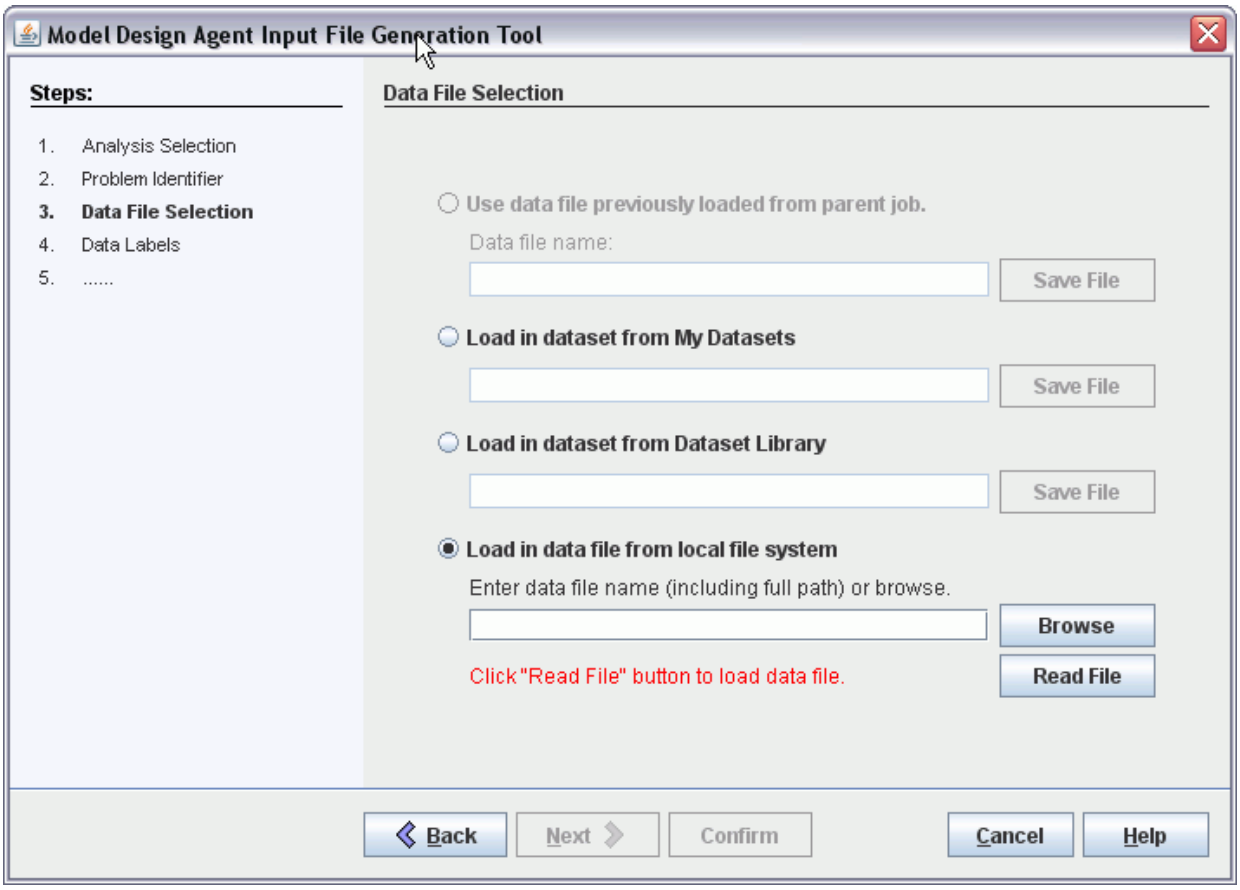
Prepare Input: Data File Selection

This area of the MDA is where data are selected for association with the model file. Data should be in tab, space or comma delimited column format with identifiers or other labels preceded by the character "C". There is no limit to the number of columns that can be in a single data file.

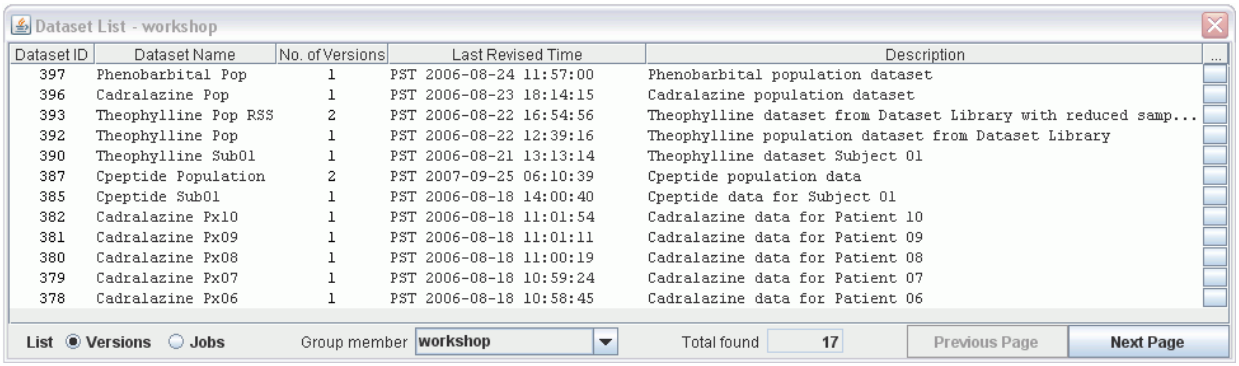
There are four options available. If you have previously loaded an entire SPK input file (model and data), then the MDA has that data file in memory and can access it. You also have the option to load a new data file here. This is the screen shot you should be seeing:



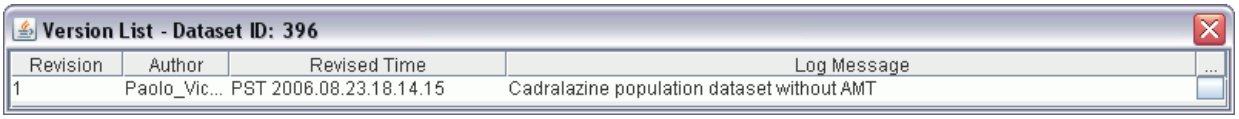
The dataset could be loaded from your database account, under My Datasets, it could be loaded from the Dataset Library or it could be loaded from the local file system. In this instance, if you select to browse, a dialog window will open and allow you to browse your local file system. The window may open in a different location on your hard disk. Select your data file name and click "Open". No special suffixes are necessary for the data file. Once your data file has been selected, you will need to

click the "Read File" button to proceed. The MDA will parse your data file and display a message with the number of columns it would find in your data file, for example: "There are 3 columns in your data file".

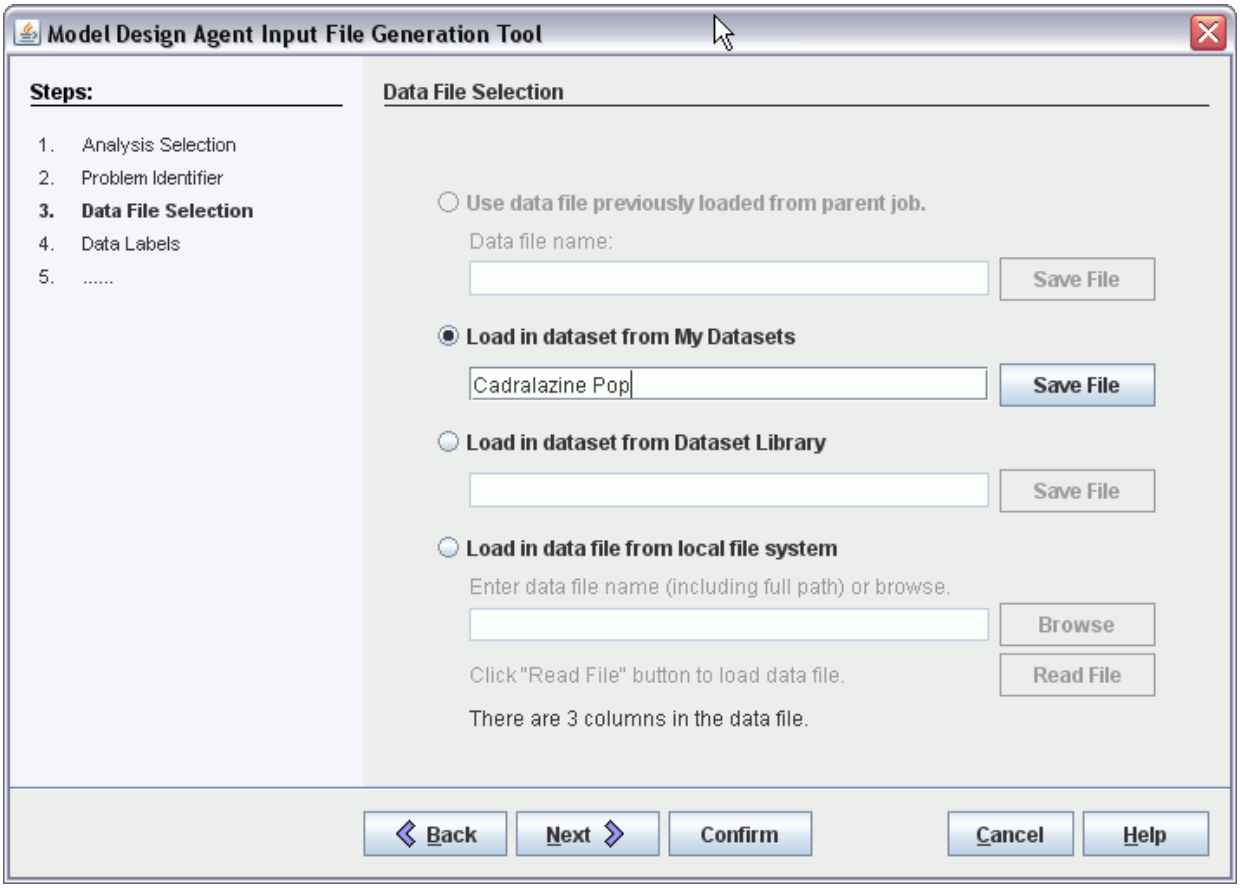
If you instead choose to select a dataset from your own datasets, a database browsing window will become available:



Clicking once on the dataset name will load the data into memory. In this particular instance, if we select the cadralazine dataset from Wakefield et al., 1996, you will be prompted for selecting a particular version:



After you select it, the dataset name will appear in the Data File Selection Window, and you may click Next to proceed, as shown below:



Selection of a dataset from the Dataset Library is done similarly.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

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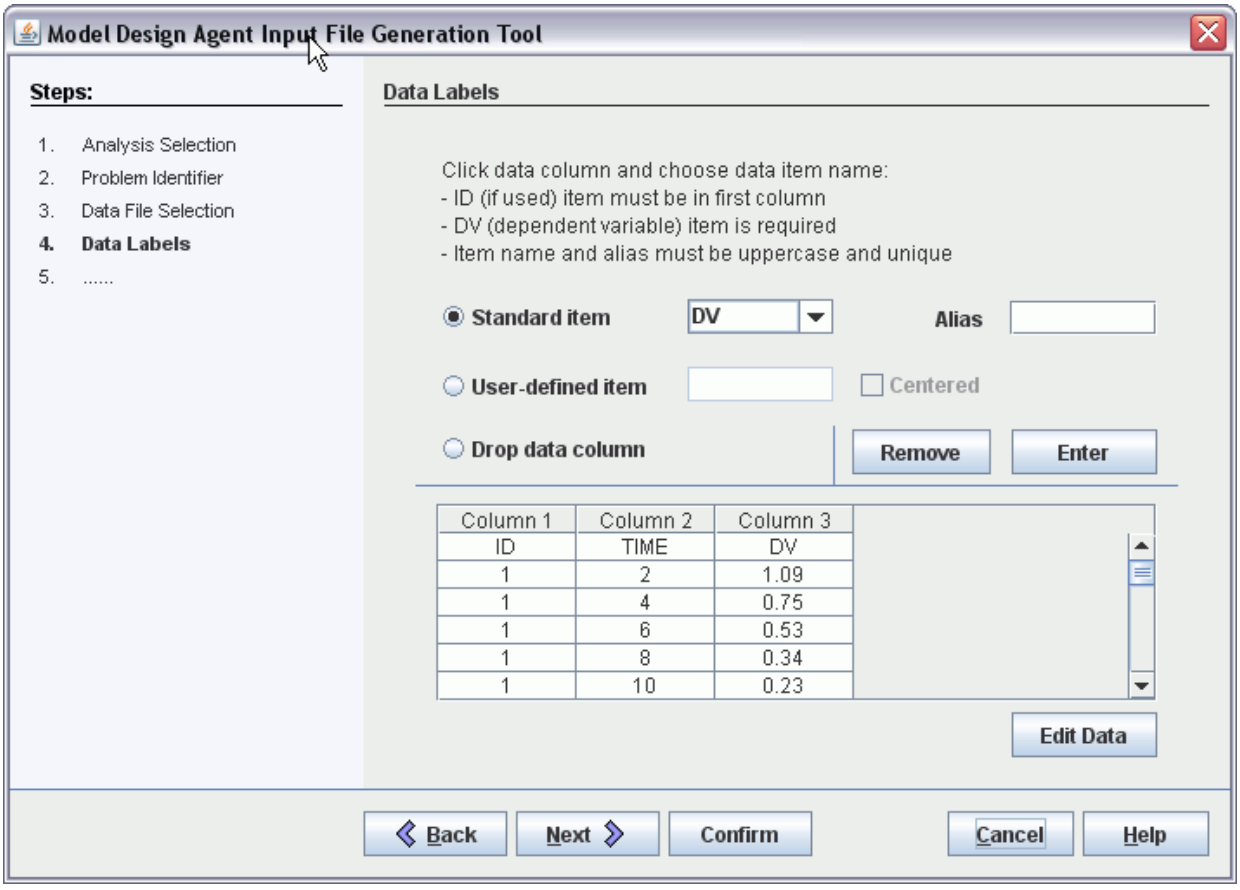
Prepare Input: Data Labels

This is the section of the MDA where data labels are defined. This is the screen you should see:

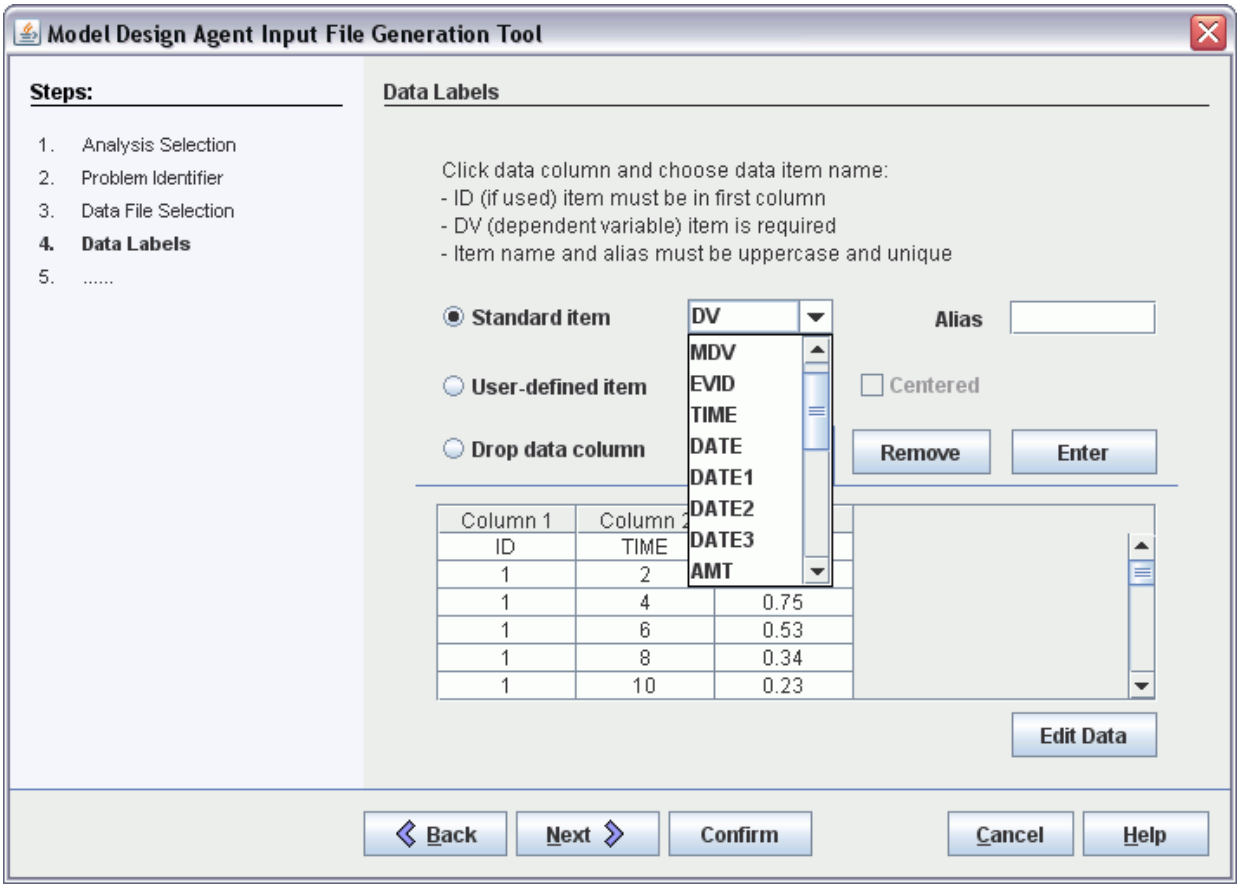


A data label is an identifier for the corresponding data column. The particular dataset shown above has three columns. Data labels have been chosen with NONMEM(R) compatibility in mind, so there are a few reserved data labels that are identical to NONMEM convention. They are referred to as "Standard Items", and they are:

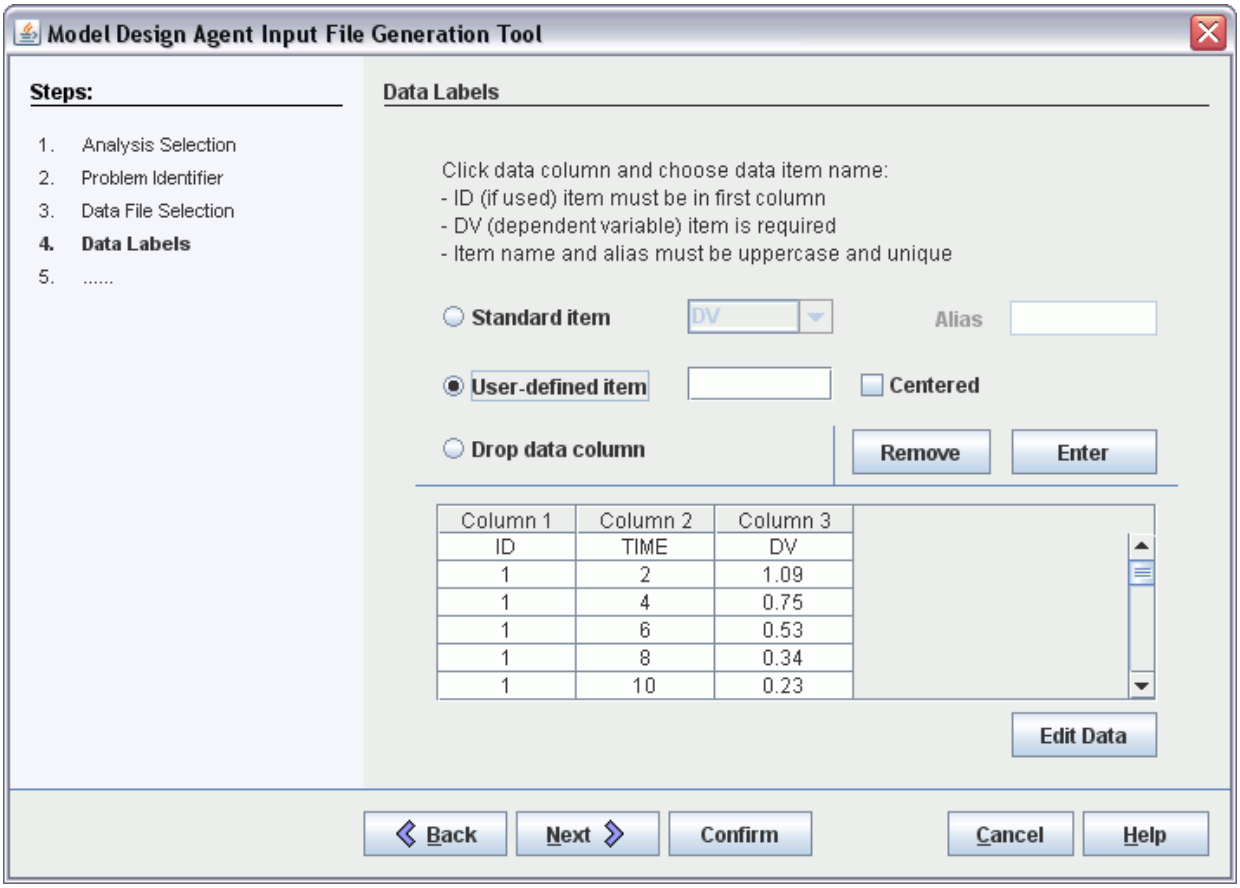
- ID: The patient ID is required to be in the first column, if the data are for multiple individuals.
- DV: The data value, i.e. the column that contains the data. There is only one column of data. This item is required for analysis.
- MDV: A flag that determines whether a data valule is missing or not. MDV should be handled in your model, i.e. a different provision should be executed depending on the values that MDV assumes.
- EVID: This is the EVent IDentifier, which may for example be used to mark a certain event as a measurement, or an input, etc.
- TIME: Time is by default the independent variable. If you have a different independent variable, it should still be called TIME or it should be reassigned.

- DATE DATE1 DATE2 DATE3: This option allows you to express time in date format, where DATE1, DATE2 and DATE3 are day, month and calendar year.
- AMT: This is the amount administered in the dose. If the variable RATE (see below) is defined, duration of the infusion is given by AMT divided by RATE. If RATE is not given, then the dose is assumed to be an instantaneous bolus of amount AMT.
- RATE: This is the rate of infusion administration, defined as amount over time. The amount injected is given by AMT (see above).
- CMT: This is the compartment number of a compartment model.
- SS, ADDL, II, ABS, LAG, UPPER, LOWER, L1, L2, PCMT, CALL, CONT are currently disabled and their functionality will be added to the system at a later date.

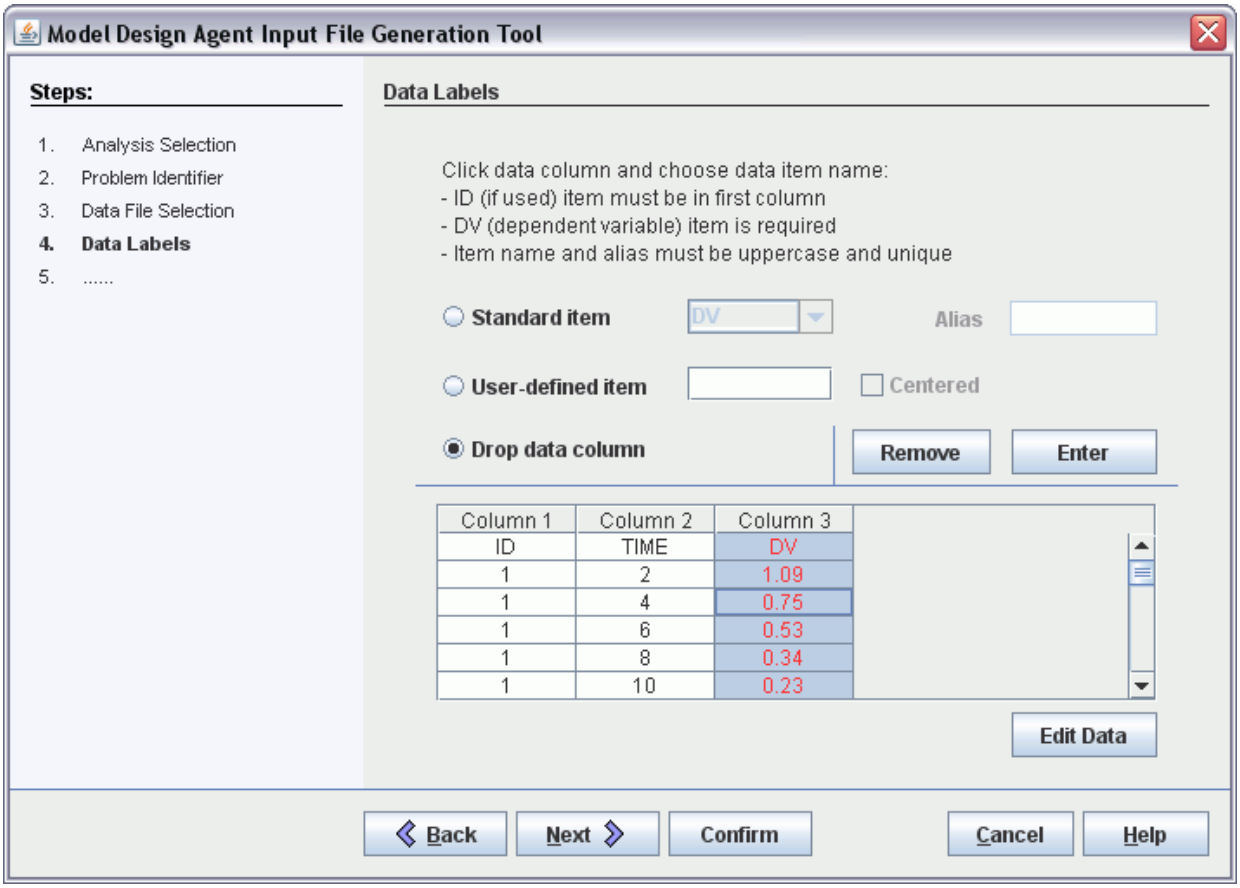
Standard data items can be selected by using a pull-down menu:



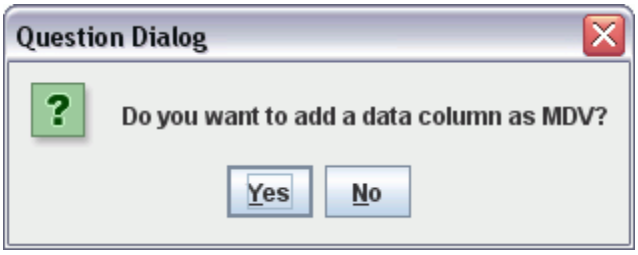
By selecting the radio button next to "User-defined item", the user can define his/her own data identifier. Other options become available, as shown below.



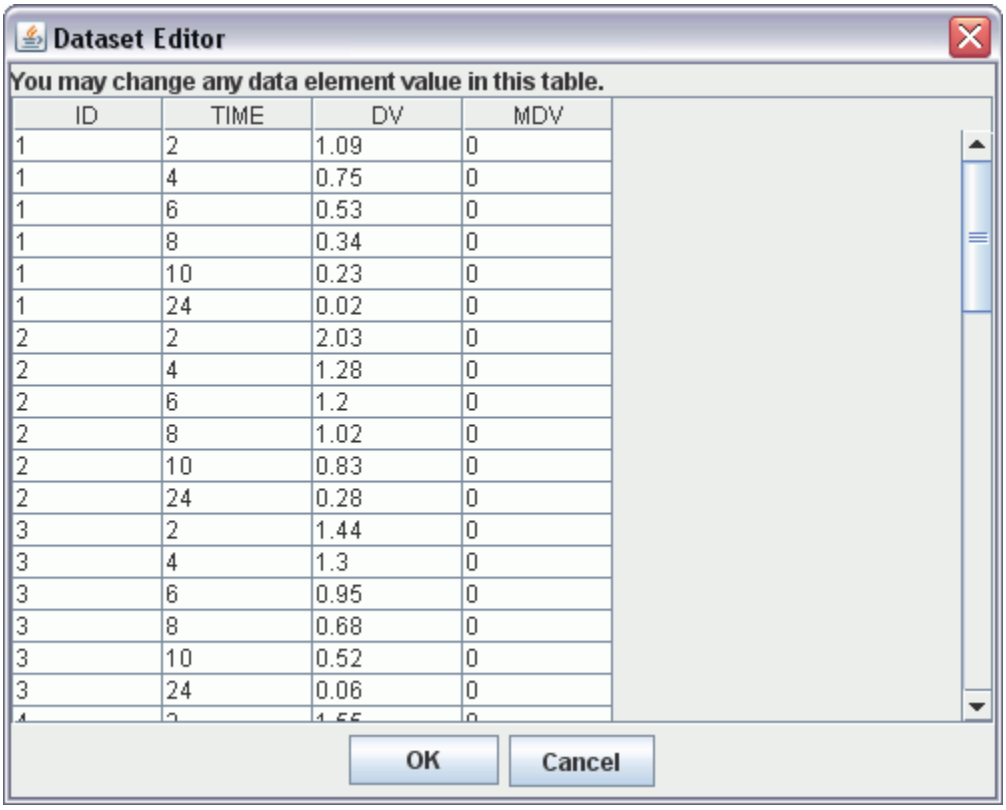
The user can also elect to "Drop data column" by selecting the appropriate radio button. Whatever the action, after the selection the user has to click on the "Enter" button to associate the data label with the relevant column. In the instance below, we have selected TIME for column 2, and clicked on "Enter", and DV for column 3, and clicked on "Enter". Note that the column that is being modified will be highlighted in red. In this case, the data items were predefined.



Now, all the columns in the data file should be associated with identifiers, and you can proceed to the next step in building your model for the data. "Edit Data" will first prompt you whether you want to add a data column as MDV:



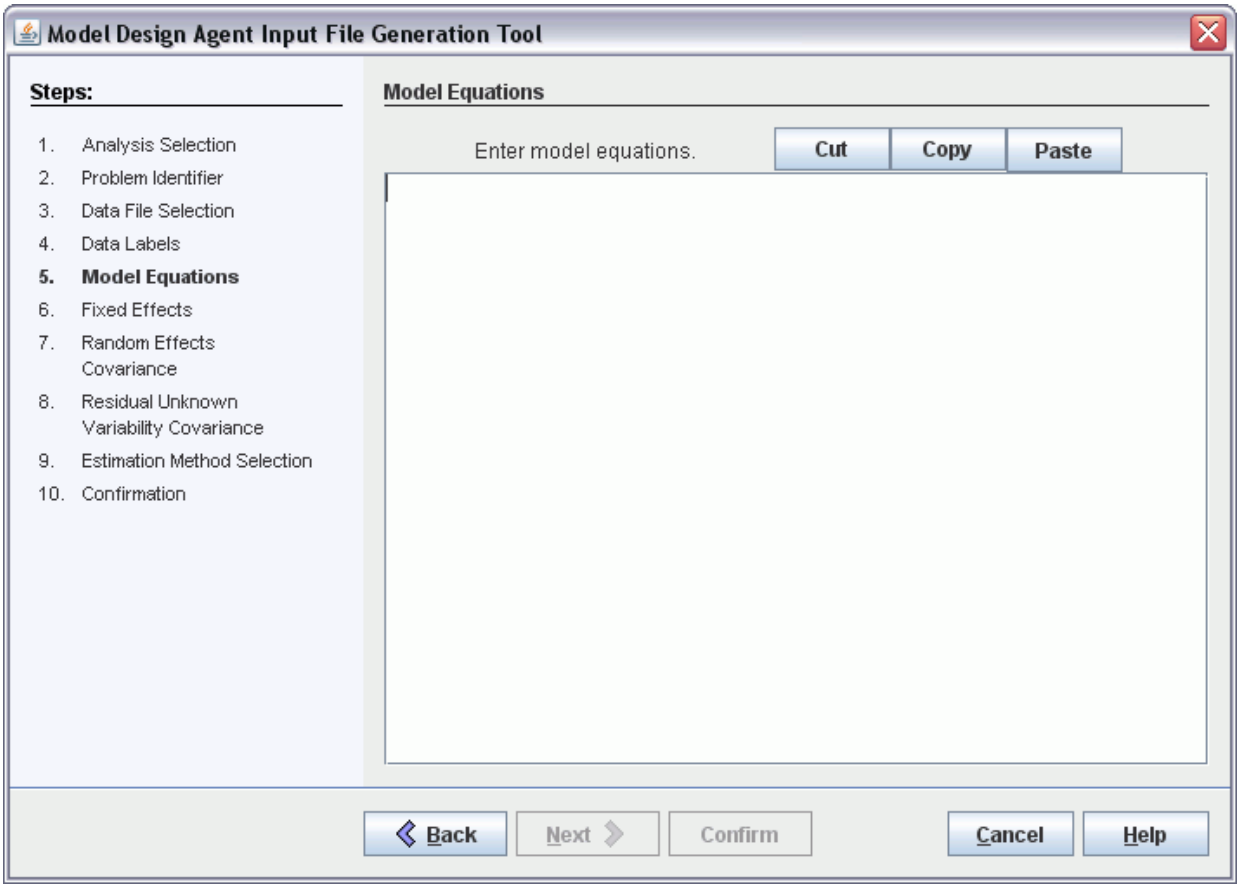
This is a useful option when one or more data points should be neglected or otherwise unweighted in the analysis. After answering this, a Dataset Editor window will open where any element in the dataset can be changed (note that this will also require the generation of another version of the dataset).



After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Model Equations

This is where the mathematical-statistical model to be used for data analysis is defined, assuming the user has selected an algebraic model for the data analysis. The screen in question should be as follows:



The model equations associate the data column marked with a DV identifier with the output of a statistical model. Assuming the data come from a population, the statistical model explicitly represents both between-subject (BSV) and residual unknown (RUV) variation. On the other hand, individual analysis only models RUV. The model parameters are defined using NONMEM(R) compatible notation as follows:

- THETA(1), THETA(2), ... indicate the fixed effects of the mean, i.e. the model parameters that do not change between individuals. They are often the center of mass of the statistical distributions of the model parameters. They are deterministic;
- ETA(1), ETA(2), ... have two different meanings. For population analysis, they indicate the BSV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance of the random effects OMEGA. For individual analysis, they are used to model the RUV specific to the measurement.
- EPS(1), EPS(2), ... indicate the RUV random effects, i.e. random sources of variation at the between-subject level. They are random

variables assumed to be Gaussian with mean zero and covariance SIGMA. They are used in population analysis only;

- F is the model for the population data, i.e. the model variable which is being measured and associated with the DV time course.
- Y is the statistical model for the measurements in the DV data column; this is the variable that is directly associated with the data in the DV column. The association needs to be defined.

For example, a single exponential time course in an individual subject with Gaussian variation on the measurement would be modeled as:

LAMBDA = THETA(1)

F = EXP(LAMBDA*TIME)

Y = F + ETA(1)

A single exponential time course with linear Gaussian variation on the exponent and Gaussian variation on the measurement would be modeled as:

LAMBDA = THETA(1) + ETA(1)

F = EXP(LAMBDA*TIME)

Y = F + EPS(1)

Note that in the first example ETA(1) models RUV, while in the second ETA(1) models BSV and EPS(1) is used for RUV. This is done to make SPK consistent with NONMEM(R) notation.

A single compartment pharmacokinetic model following a unitary pulse dose with Gaussian variation on the apparent volume of distribution, log-normal variation on the clearance and Gaussian variation on the measurement would be modeled as:

CL = THETA(1)*EXP(ETA(1))

V = THETA(2) + ETA(2)

F = EXP (-CL/V*TIME)

Y = F + EPS(1)

The same model with proportional error on the measurement would read:

CL = THETA(1)*EXP(ETA(1))

V = THETA(2) + ETA(2)

F = EXP (-CL/V*TIME)

Y = F * (1 + EPS(1))

In this instance, we chose to implement a single compartment model with clearance/volume parametrization, log-normally distributed parameters and a dose of 30 mg for all subjects:

D = 30

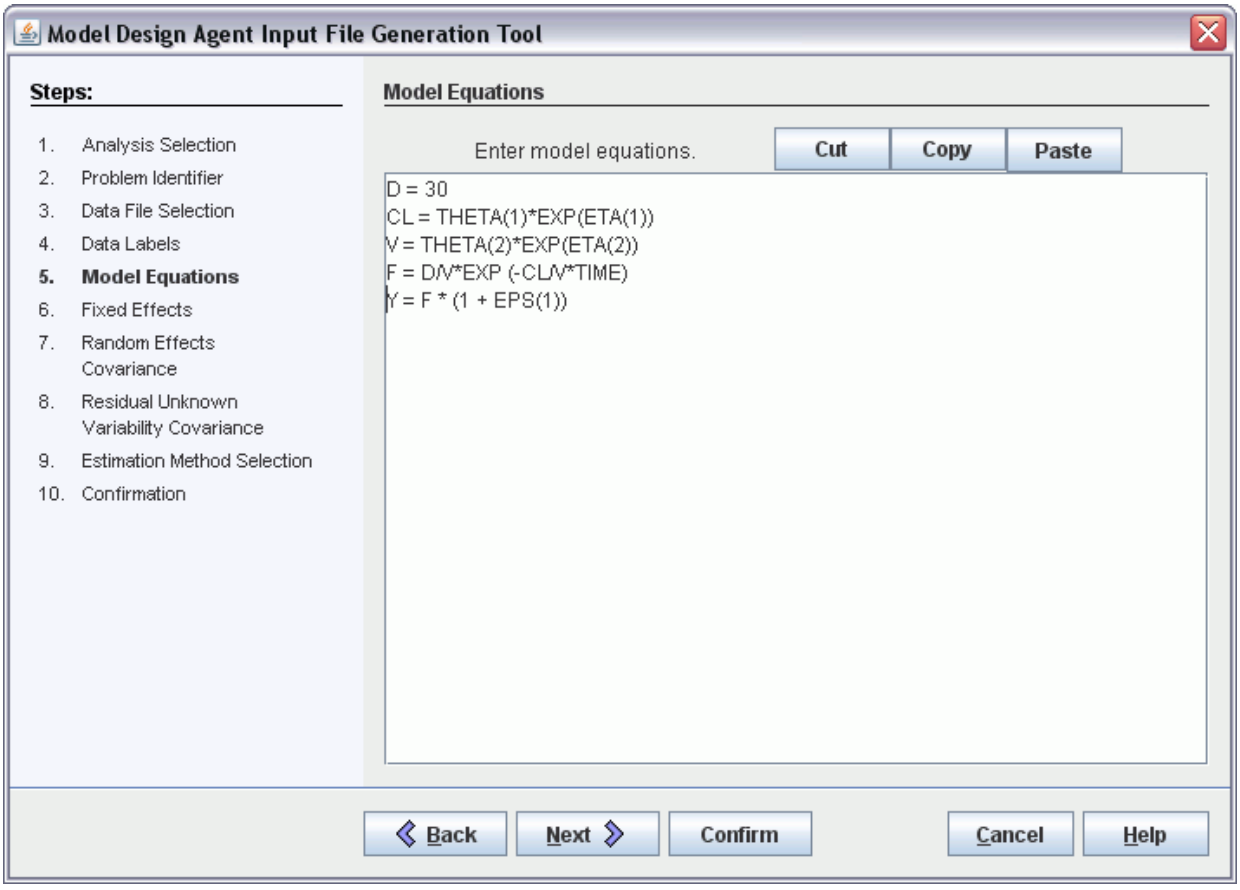
CL = THETA(1)*EXP(ETA(1))

V = THETA(2)*EXP(ETA(2))

F = D/V*EXP (-CL/V*TIME)

Y = F * (1 + EPS(1))

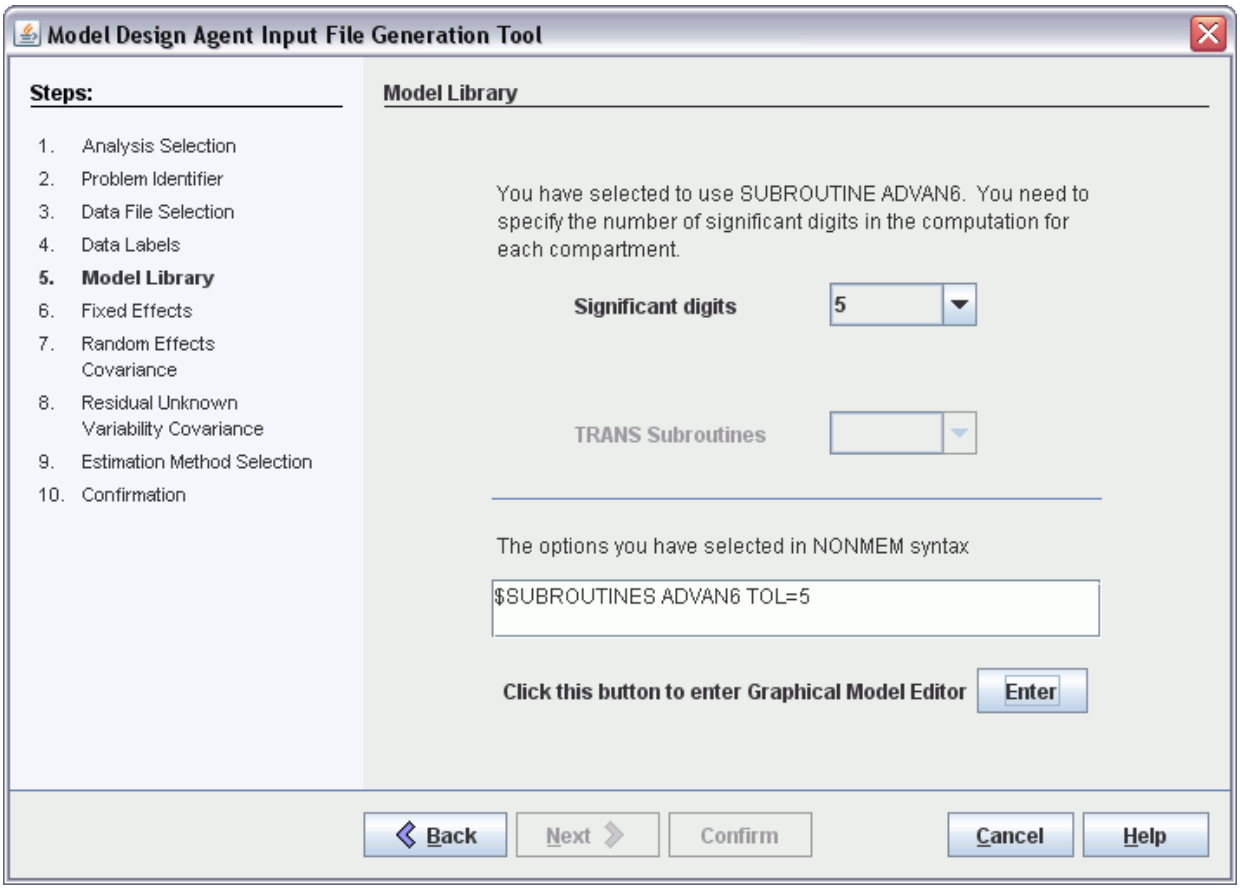
This is the resulting screen:



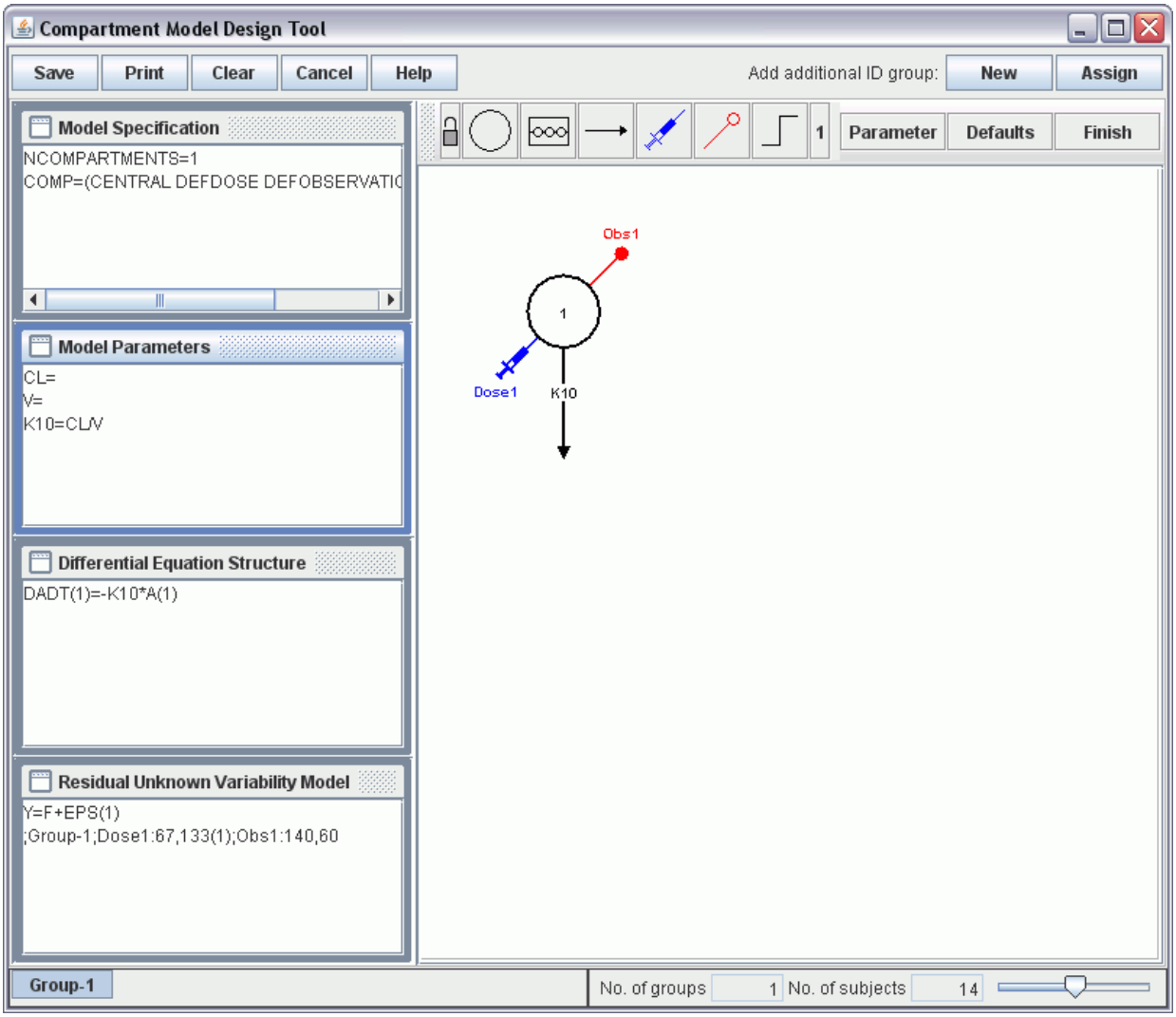
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Compartment Model Design Tool

If you have selected **Graphical Model Editor** in the Analysis Selection window, you can now click on the Enter button to be able to define your model graphically.



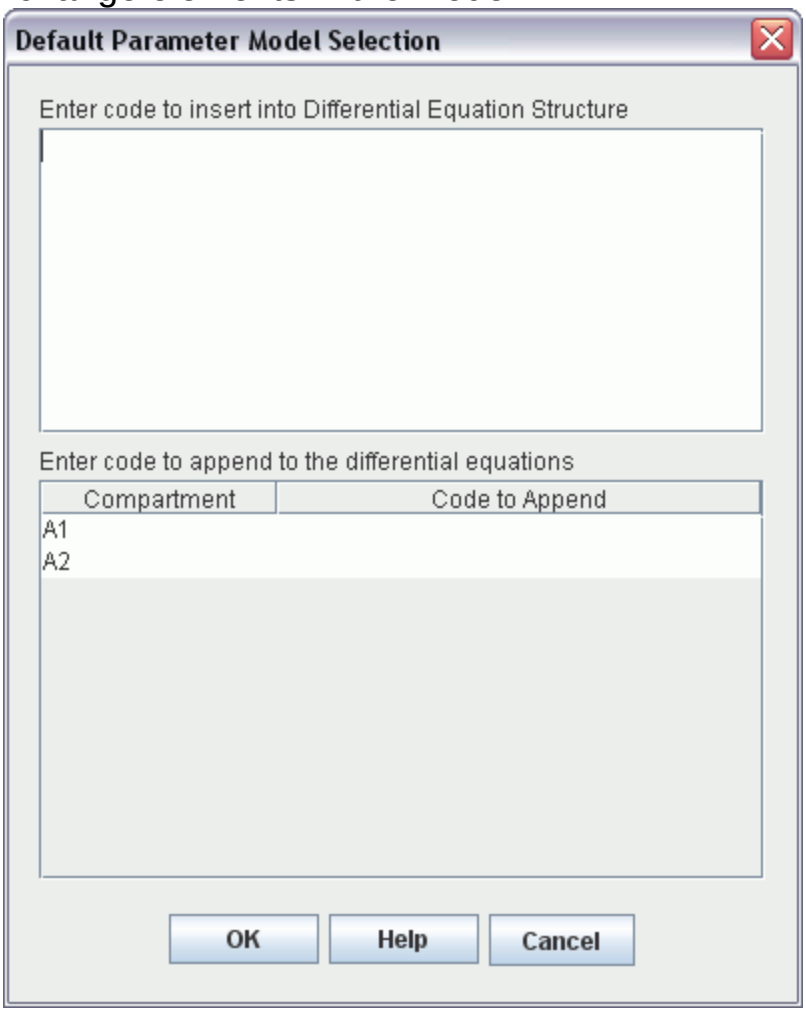
The Graphical Model Editor will be pre-filled with the model you have selected at the beginning. Various model features can be defined. In particular: the model can be saved (**Save**), its structure can be printed (**Print**), the canvas can be cleared for a new model (**Clear**), or control can be returned to the MDA (**Cancel**).



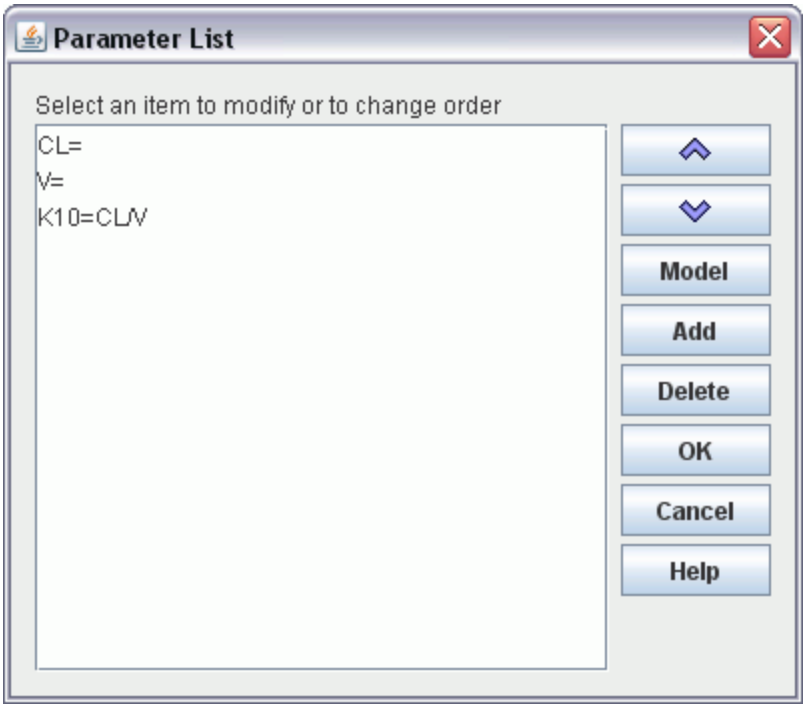
The four windows on the left (**Model Specification**, **Model Parameters**, **Differential Equation Structure** and **Residual Unknown Variability Model**) cannot be changed, rather they visualize model features that were defined elsewhere in the system. The sequence of buttons on the top row allows the user to:

- *Lock*: place in the model several compartments, or transfer rates, without having to select a compartment or transfer rate every time;
- *Compartment*: clicking on the compartment icon and then on the canvas places a compartment on the canvas;
- *Delay*: clicking on the delay icon and then on the canvas places a delay unit on the canvas;
- *Transfer Rate*: clicking on the transfer rate icon and then on the origin and destination compartment defines a transfer rate between those two compartments;

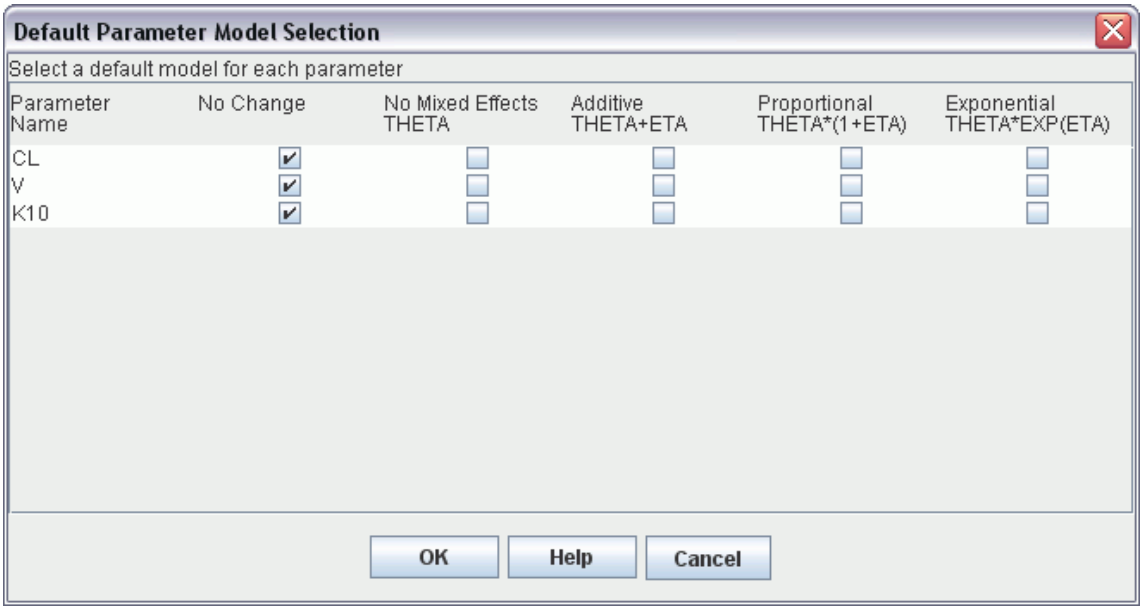
- *Input*: clicking on the input syringe icon and then on the input compartment and on the canvas defines an input function in the input compartment;
- *Measurement*: clicking on the measurement icon and then on the output compartment and on the canvas defines a measurement in the output compartment;
- *Change Condition*: clicking on the change condition button allows the user to access the change condition definition window, to change elements in the model.



- *Toggle*: clicking on the toggle button (marked with a [1]) allows the user to toggle between compartment number and name in the model canvas.
- *Parameter*: clicking on the parameter button displays the model parameters in a separate window:



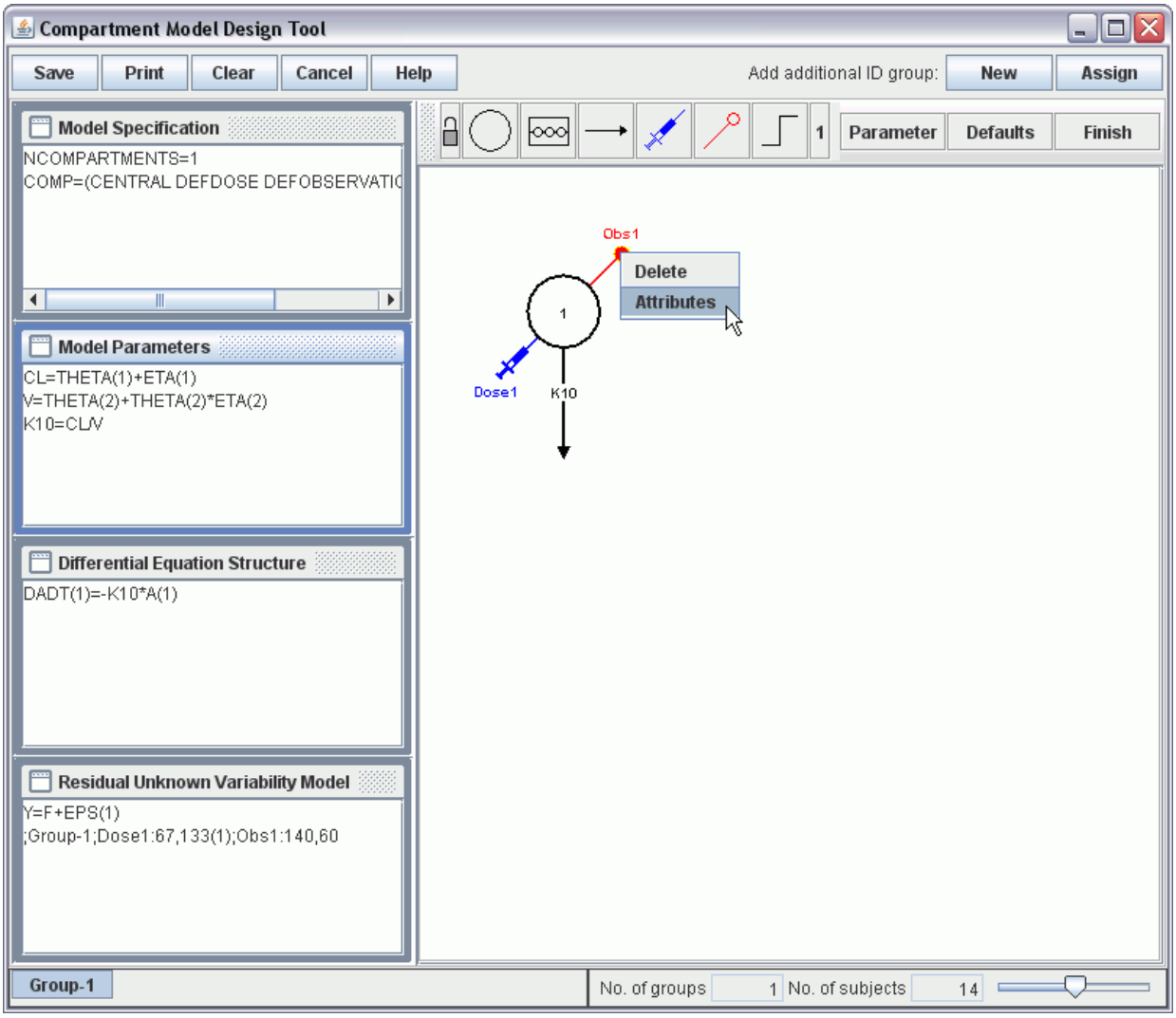
- *Defaults*: this allows the user to display various widely used defaults for population models:



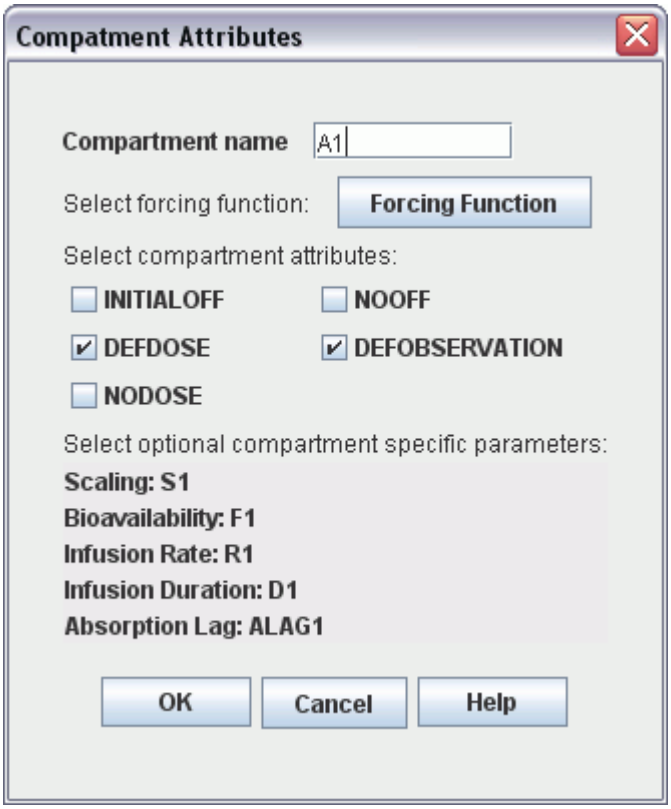
- *Finish*: clicking on the Finish button allows the user to leave the Graphical Model Editor.

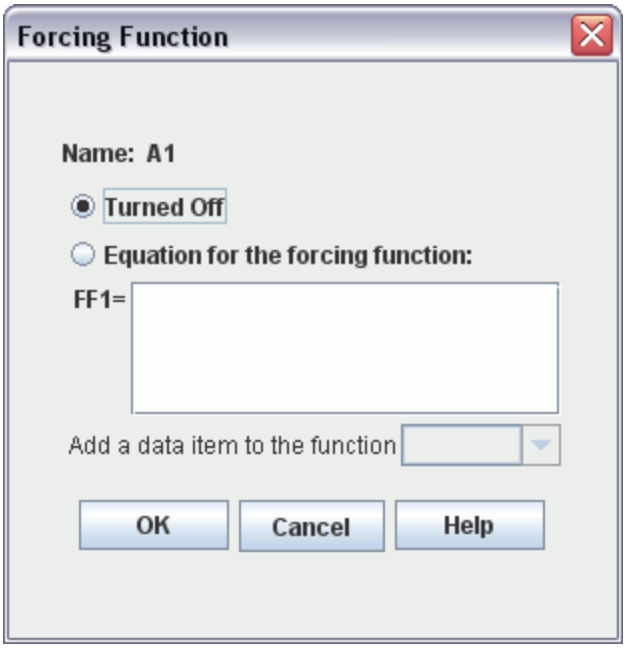
Right-clicking on the various elements of the canvas (**compartments**, **transfer rates**, **measurements** and **inputs**) allows the user to access various elements of the model. For example, right-clicking on the

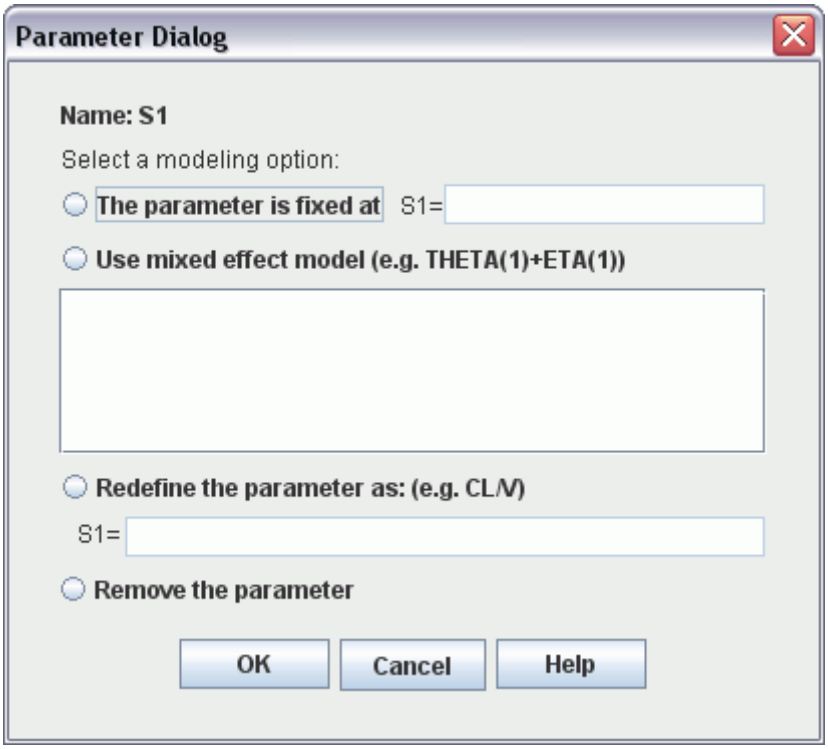
measurement icon allows the user to either delete it or access its attributes:



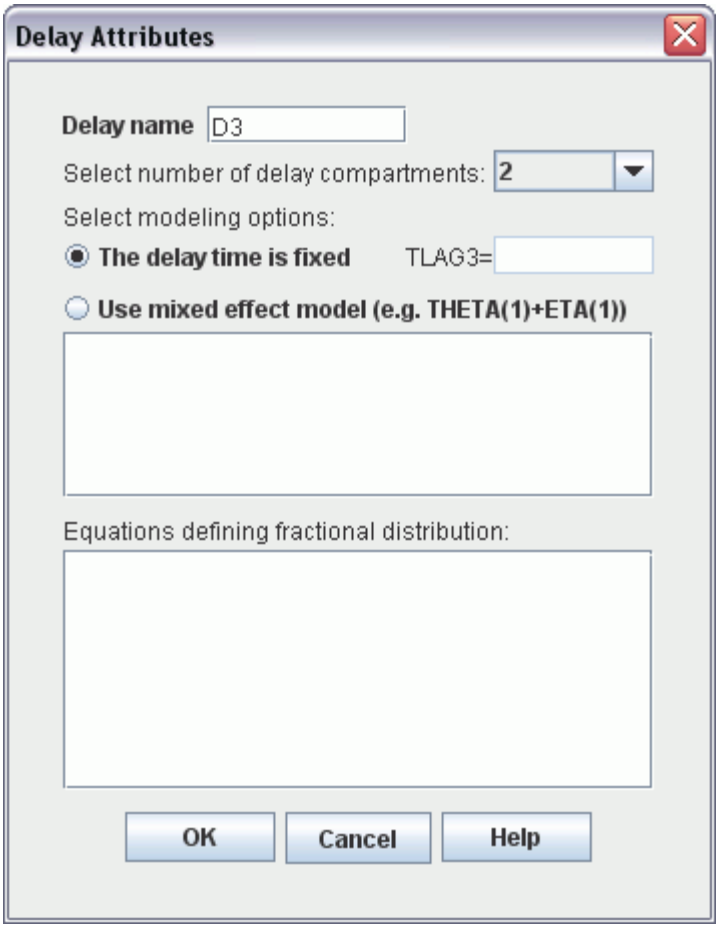
- The Compartment attributes allow the user to specify forcing function,compartment attributes and optional compartment specific parameters.


Compatment Attributes
Compartment name
A1
Select forcing function:
Forcing Function
Select compartment attributes:
INITIALOFF
NOOFF
DEFDOSE
DEFOBSERVATION
NODOSE
Select optional compartment specific parameters:
Scaling: S1
Bioavailability: F1
Infusion Rate: R1
Infusion Duration: D1
Absorption Lag: ALAG1
OK
Cancel
Help

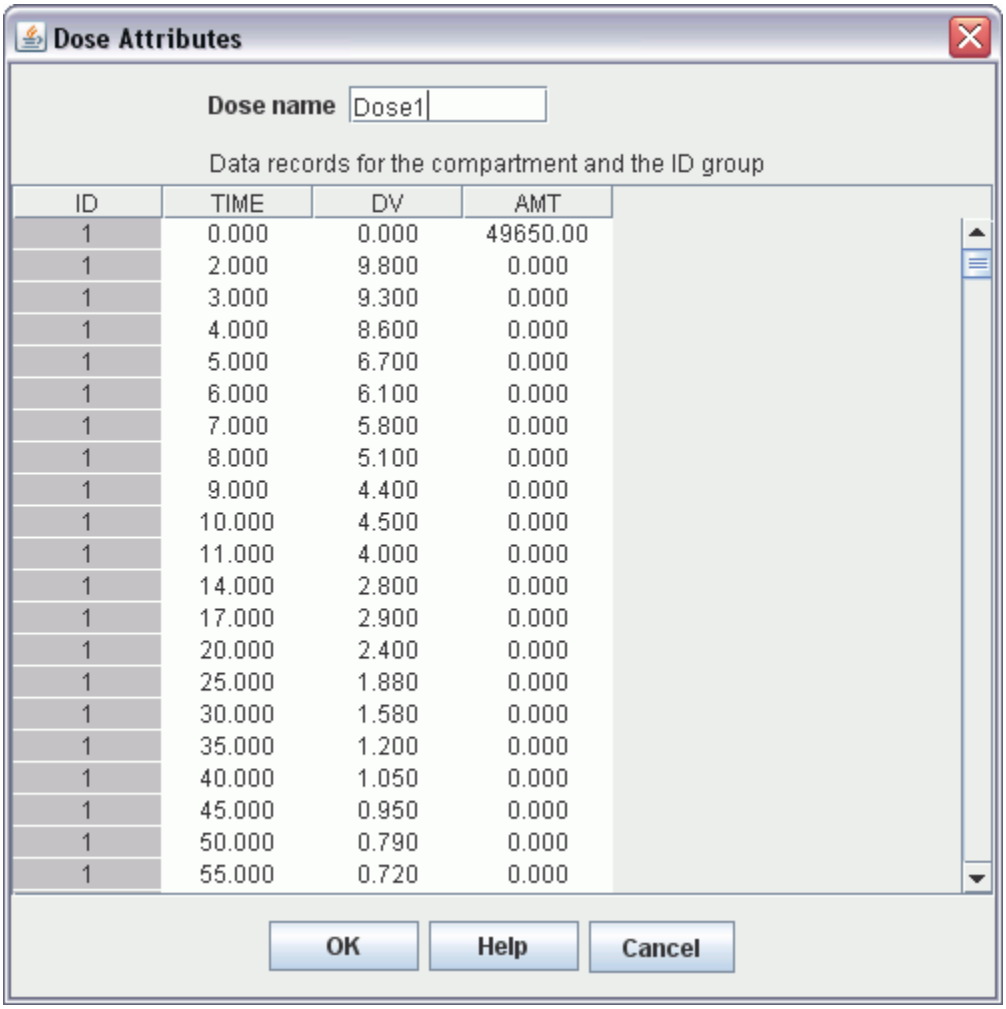

Forcing Function
Name: A1
Turned Off
Equation for the forcing function:
FF1=
Add a data item to the function
OK
Cancel
Help



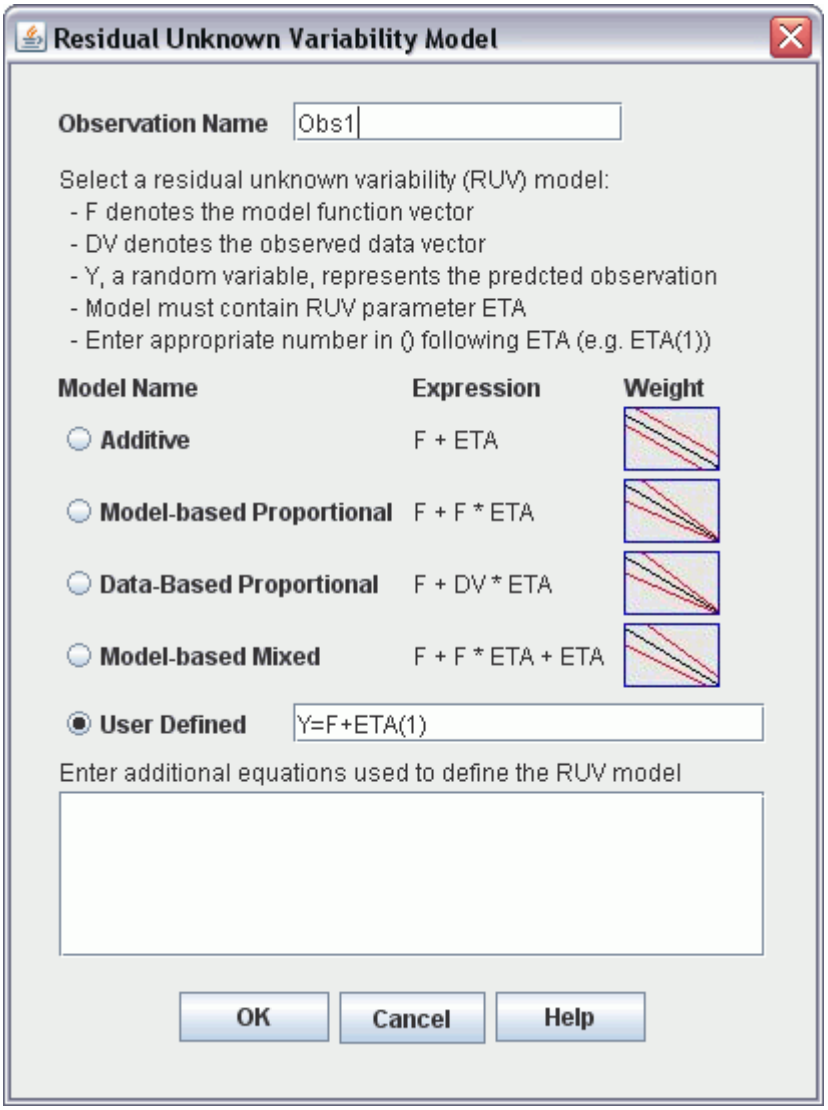
- The Delay attributes allow the user to specify number of compartments to simulate the delay, delay time and equations defining fractional distribution.



- For the Input, you can enter a new name and edit data for the compartment and the ID group:

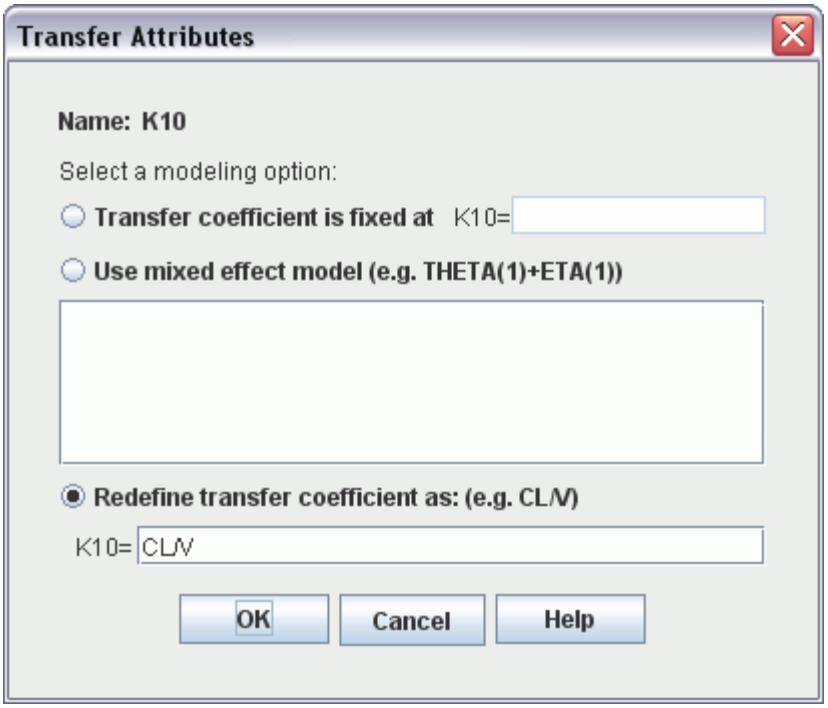


- The Measurement attributes allow the user to define various attributes of the Residual Unknown Variability for the experiment:



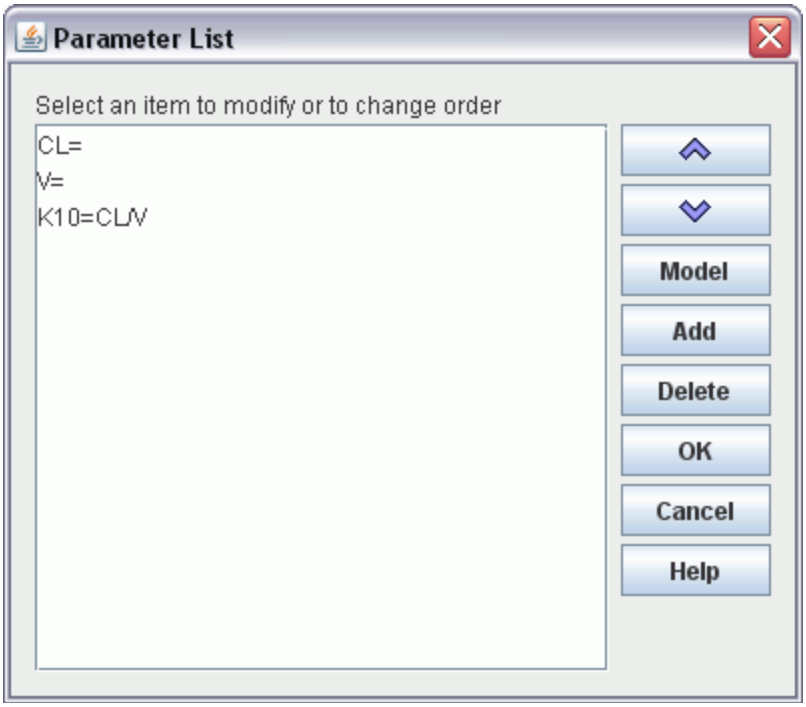
Possible attributes for the RUV model are: Additive, Model-based Proportional, Data-Based Proportional and Model-based Mixed. Moreover, the user can enter a general error model as well.

- The Transfer attributes allow the user to enter specific mixed effects modeling characteristics for the Transfer Rate. More sophisticated mixed effects models can be entered as well.

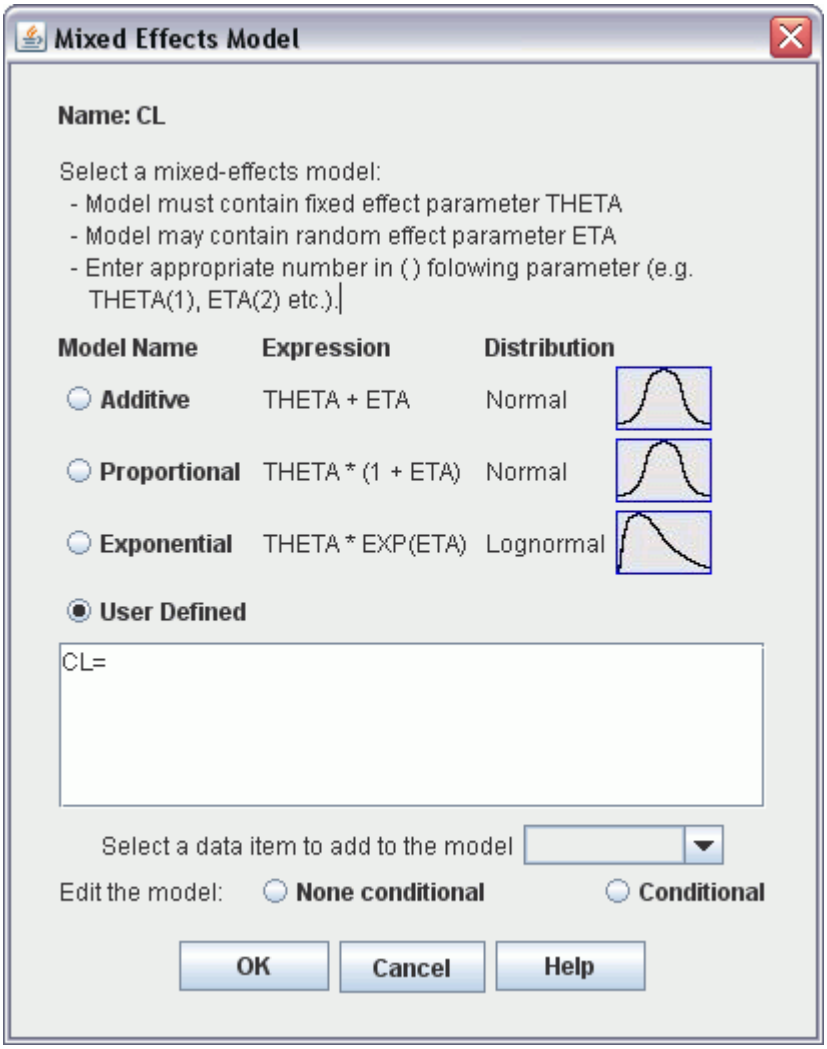


Parameters

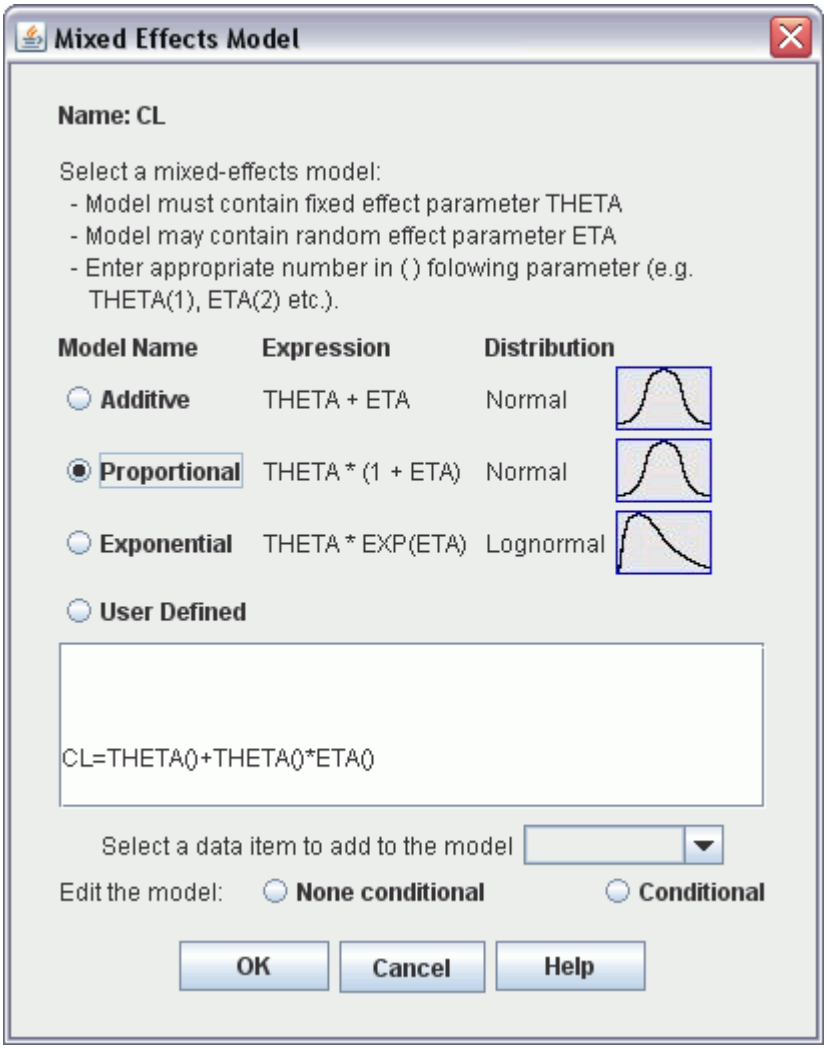
The Parameter List window displays a list of the undefined parameters in the model. The assumption is that these parameters now need to be associated with fixed and/or random effects, or covariates. The parameters need to be selected first, by clicking once on the corresponding line:



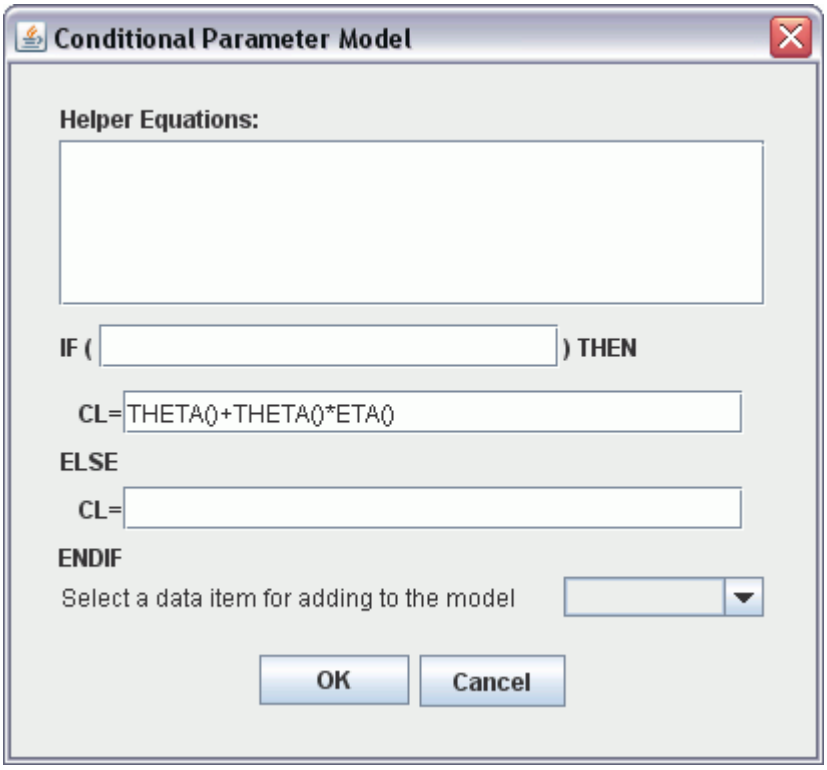
Next, by clicking on Model, a model definition window appears where the mixed effects model for the specific parameter can be defined for a population analyses:



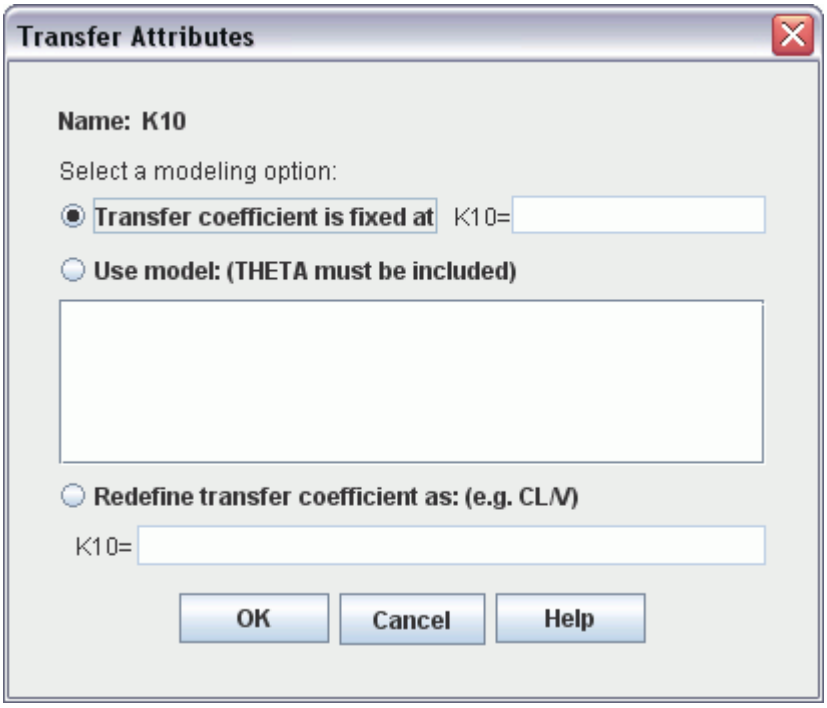
The available models are: **Additive**, **Proportional**, **Exponential** and **User Defined**. For example, by selecting Proportional, the following definition appears, and can be modified by the user:



Note that numerals indicating the sequence order of the fixed and random effects need to be specified. Lastly, if a conditional statement is associated with the model, the Conditional radio button must be selected. When this is done, the following window appears:

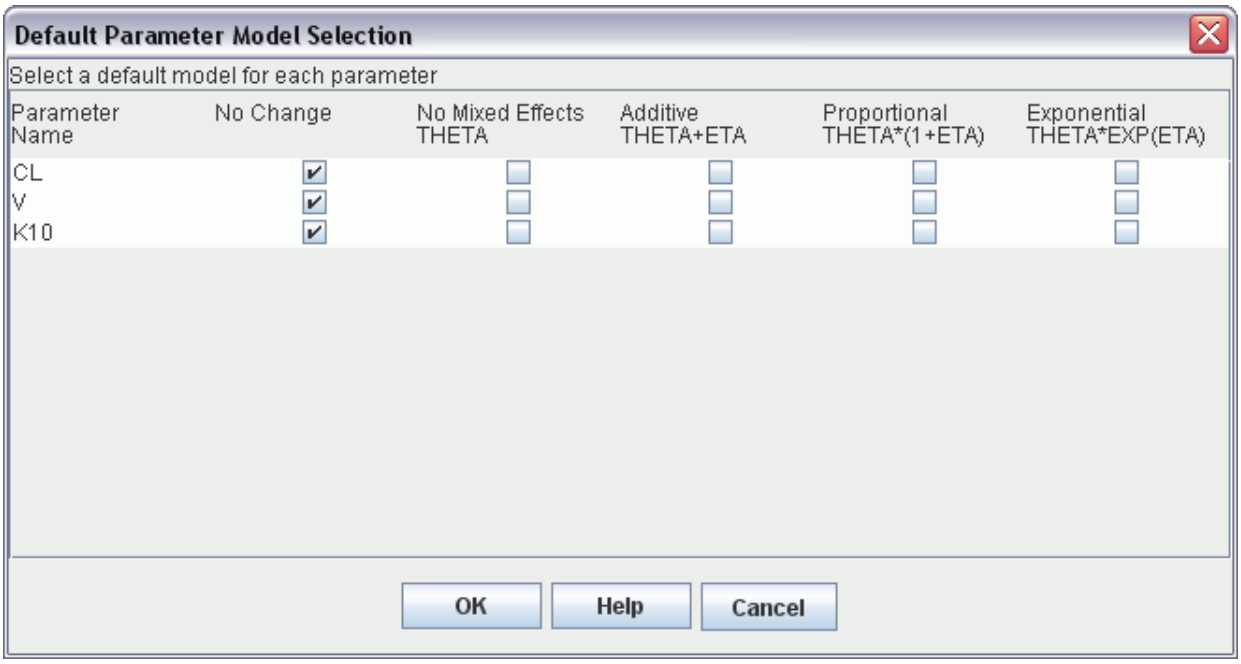


General conditional statements can then be defined. For an individual analyses the model definition window appears when a model is selected in the Parameter List window.

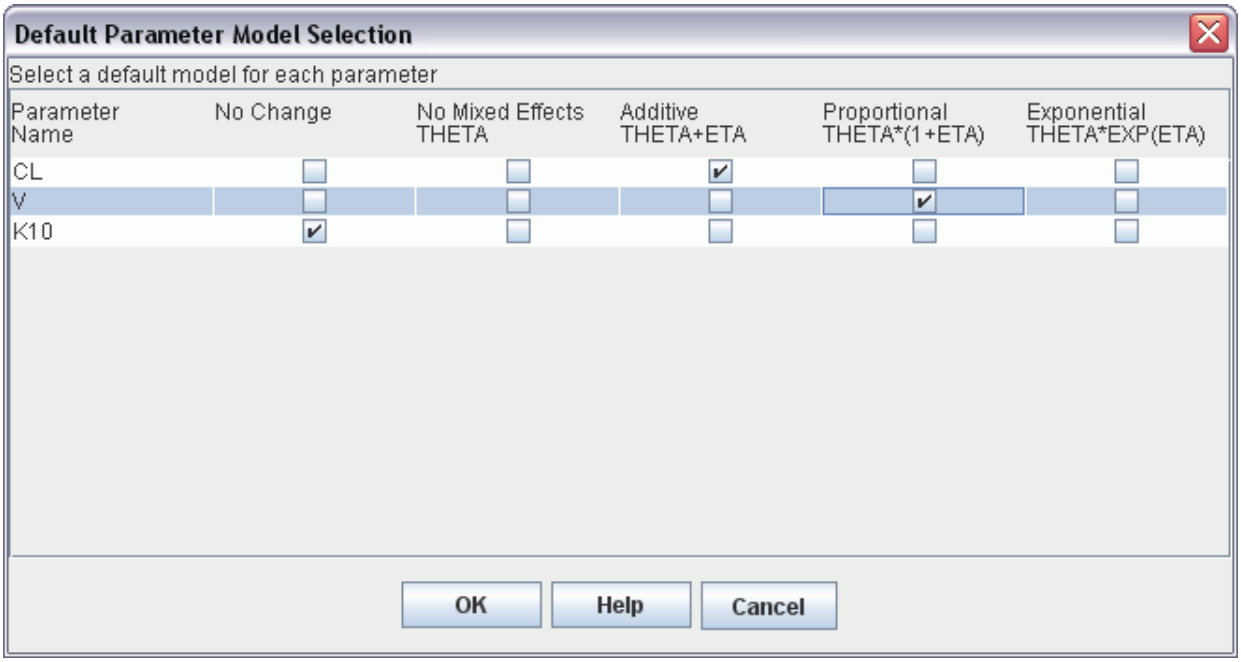


Defaults

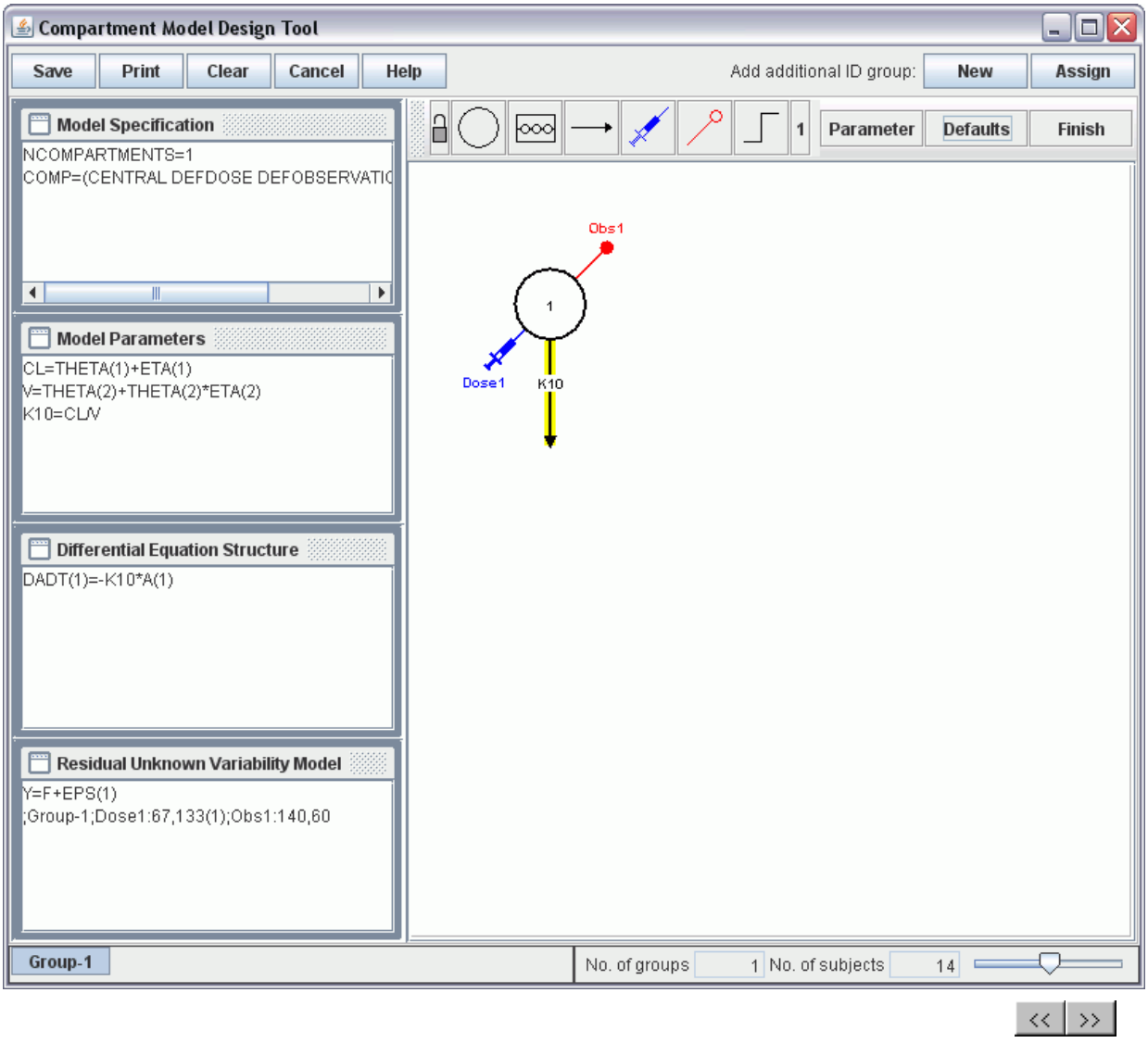
The Defaults window allows the user to quickly and efficiently define standard mixed effects models. The window looks like this:



Mixed models can be defined quickly and are updated automatically in the Graphical Model Editor. For example, to define an additive model for CL and a proportional model for V, the corresponding boxes need to be selected:

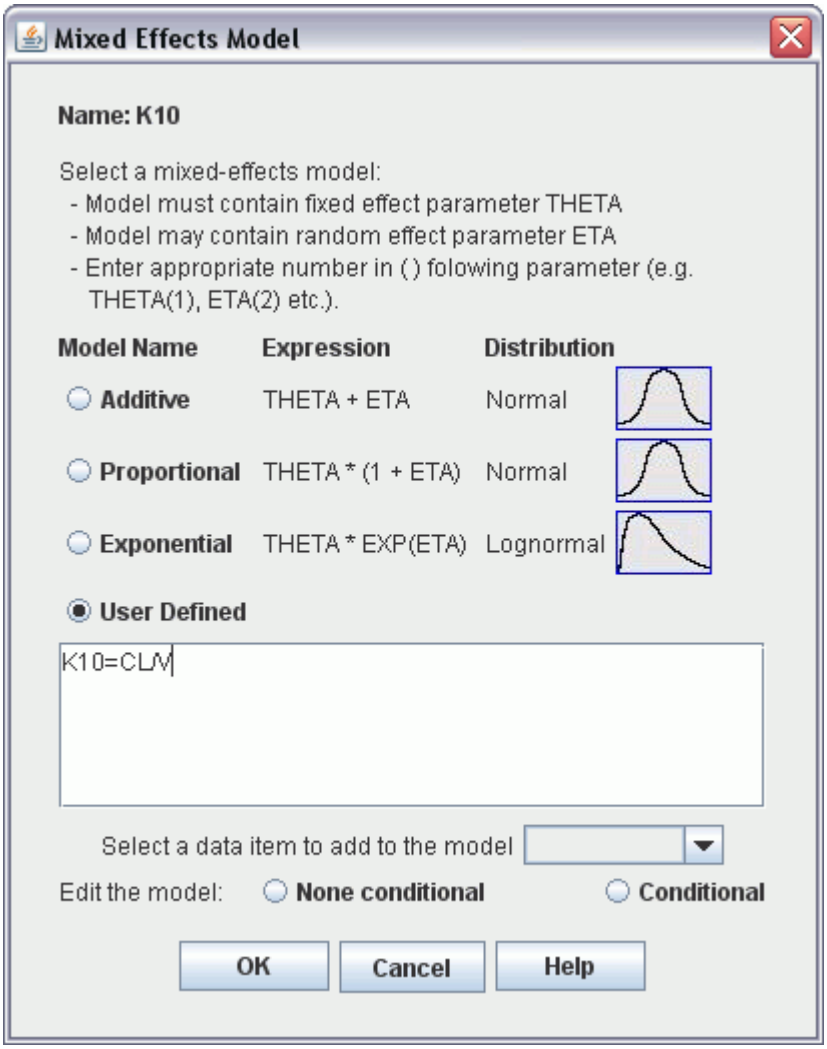


The model is automatically replicated in the Model Parameters window, where it is available for inspection.



Mixed Effects Model (Graphical Editor)

The statistical model to be defined in this window can be used to explicitly represents between-subject (BSV) variation. Options for defining a mixed effects model are accessed by clicking on relevant radio buttons. Pictorial representations of the associated probability densities assist the user in choosing a specific statistical model.



The model parameters are defined using NONMEM(R) compatible notation as follows:

- THETA(1), THETA(2), ... indicate the fixed effects of the mean, i.e. the model parameters that do not change between individuals. They are often the center of mass of the statistical distributions of the model parameters. They are deterministic;
- ETA(1), ETA(2), ... indicate the BSV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance of the random effects OMEGA;

For an individual subject, the BSV random effects, ETA(1), ETA(2), ... are not used.

For example, population linear Gaussian variation on a parameter LAMBDA would be modeled as:

LAMBDA = THETA(1) + ETA(1)

Gaussian variation on the apparent volume of distribution and log-normal variation on the clearance would be modeled as:

CL = THETA(1)*EXP(ETA(1))

V = THETA(2) + ETA(2)

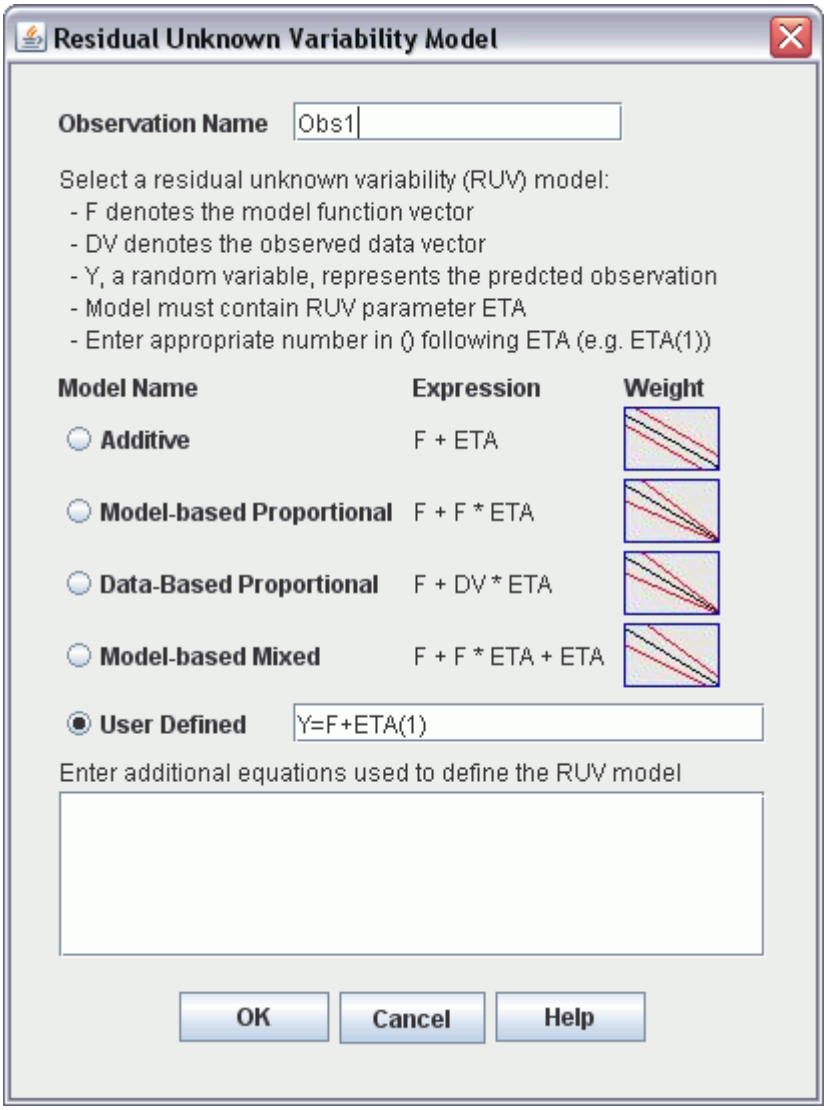
As an example, we could build a log-normal model for population between-subject variation by entering the following equations:

CL = THETA(1)*EXP(ETA(1))

V = THETA(2)*EXP(ETA(2))

Residual Unknown Variability Model (Graphical Editor)

There are various possibilities for defining a Residual Unknown Variability model. These are accessed by selecting various radio buttons.



The model is defined using NONMEM(R) compatible notation as follows:

- EPS(1), EPS(2), ... indicate the RUV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance SIGMA;
- Y is the statistical model for the measurements in the DV data column; this is the variable that is directly associated with the data in the DV column. The association needs to be defined.
- F is the model for the population data, i.e. the model variable which is being measured and associated with the DV time course.

For example, Gaussian additive variation on the measurement would be modeled as:

Y = F + EPS(1)

Gaussian proportional error on the measurement would read:

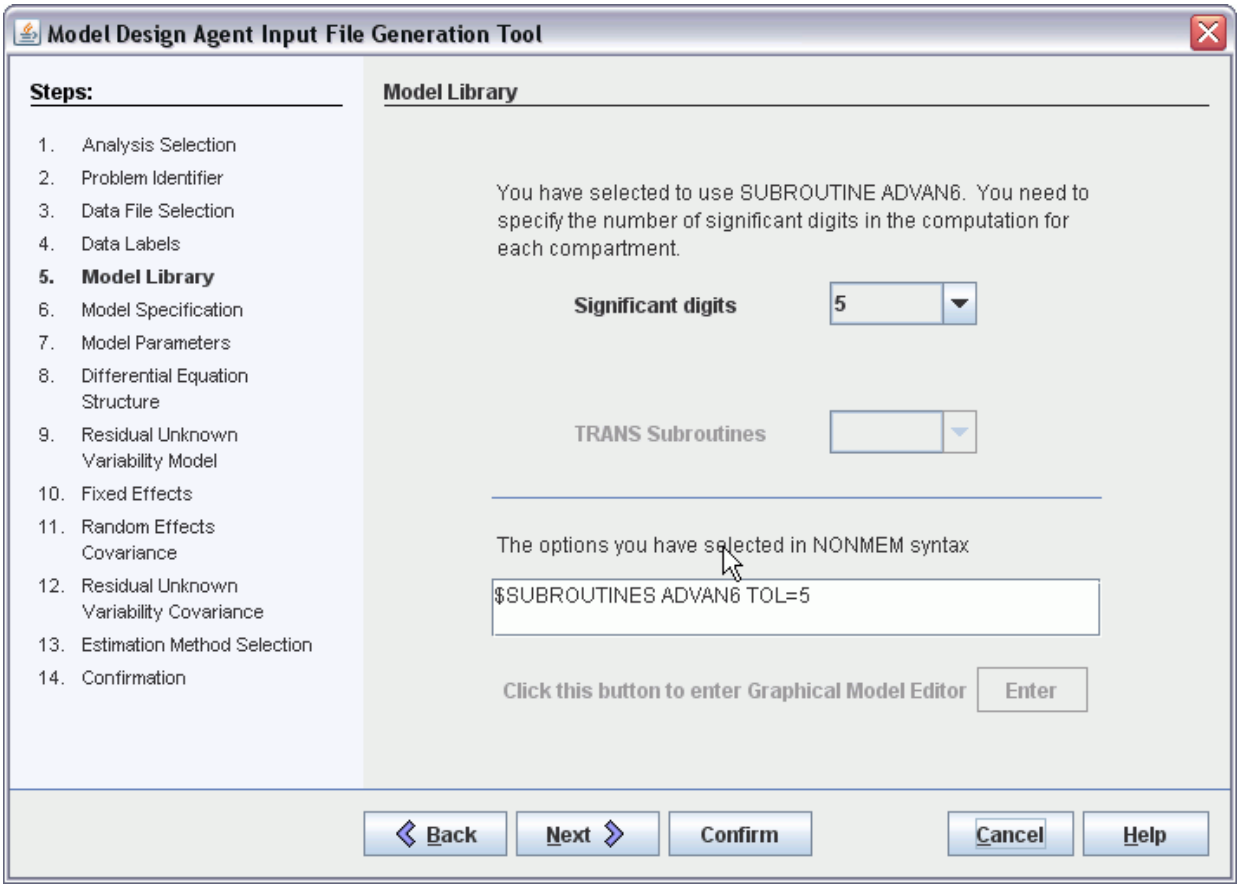
Y = F * (1 + EPS(1))

In this particular instance, we have chosen an additive Gaussian error model. Other statistics are also possible, such as an exponential error model:

Y = F *EXP(EPS(1))

Prepare Input: Model Numerics from the Model Library

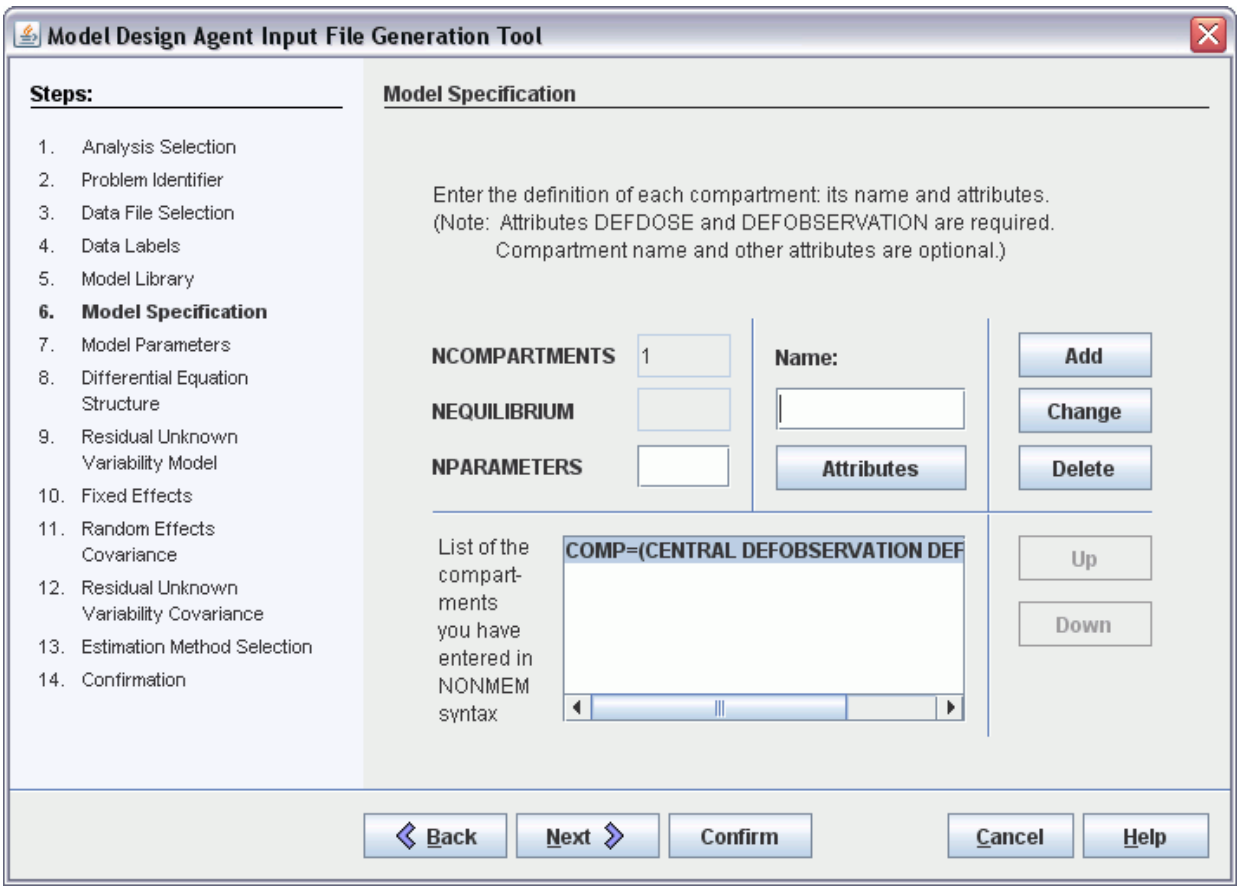
SPK allows the user to select models using the NONMEM(R) notation for compartmental pharmacokinetic models. For example, assume that we have selected ADVAN1, TRANS2 from the initial Analysis Selection window. This implies a one-compartment model parameterized as clearance and volume, where the rate constant is a derived variable. Note that all ADVANs except ADVAN8 are implemented in SPK as differential equations and are translated as ADVAN6, i.e. the differential equations are explicitly defined. At this point, all the user has to do is select the number of significant digits required in the computation of the model output. The default is five.



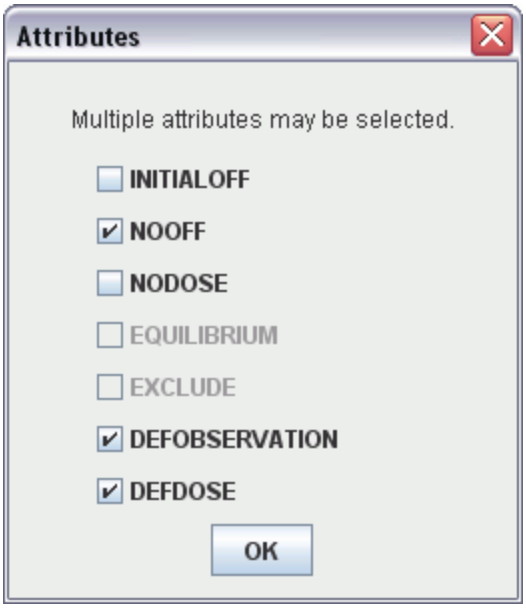
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Model Specification

The Model Specification window allows the user to select specific attributes for the compartmental model. The content is already pre-filled if a library model is used. Otherwise, the user should click the "Attributes" button to select compartment attributes and then "Add" or "Change". Note that the default compartment for dosing (DEFDOSE) and the default compartment for the measurement (DEFOBSERVATION) have to be provided.



Clicking on **Attributes** will bring up a window where the compartmental attributes can be selected.

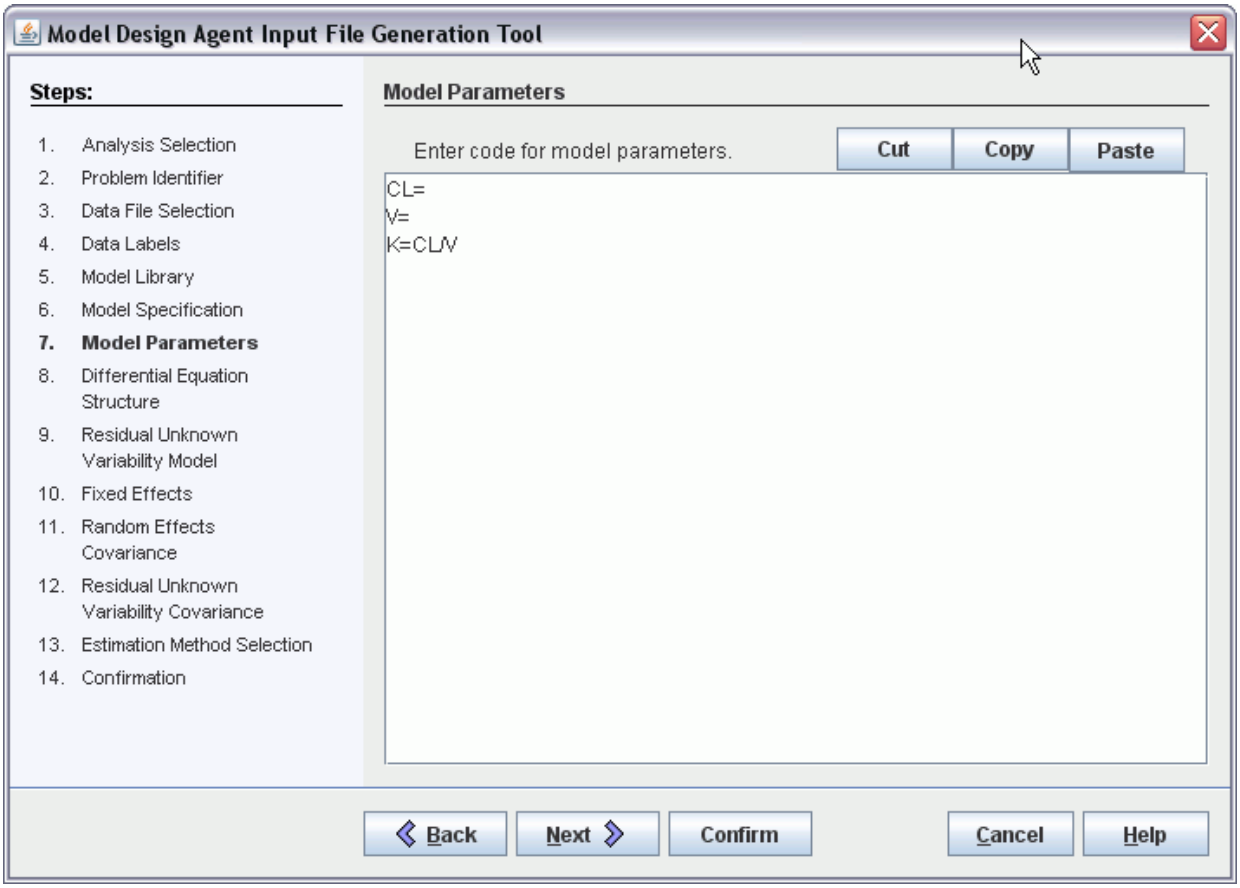


After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The

"Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Model Parameters

This window allows the user to specify the model parameterization and the relationships between fixed and random effects and the kinetic parameters of the ODE model (to be defined on the following screen). if a model from the library was selected, the editor window will be already pre-filled with the left-hand side of the algebraic equations linking (in the example below) clearance and volume with fixed and random effects.



The statistical model to be defined in this window can be used to explicitly represents between-subject (BSV) variation. The model parameters are defined using NONMEM(R) compatible notation as follows:

- THETA(1), THETA(2), ... indicate the fixed effects of the mean, i.e. the model parameters that do not change between individuals. They are often the center of mass of the statistical distributions of the model parameters. They are deterministic;
- ETA(1), ETA(2), ... indicate the BSV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance of the random effects OMEGA;

For an individual subject, the BSV random effects, ETA(1), ETA(2), ... are not used.

For example, population linear Gaussian variation on a parameter LAMBDA would be modeled as:

LAMBDA = THETA(1) + ETA(1)

Gaussian variation on the apparent volume of distribution and log-normal variation on the clearance would be modeled as:

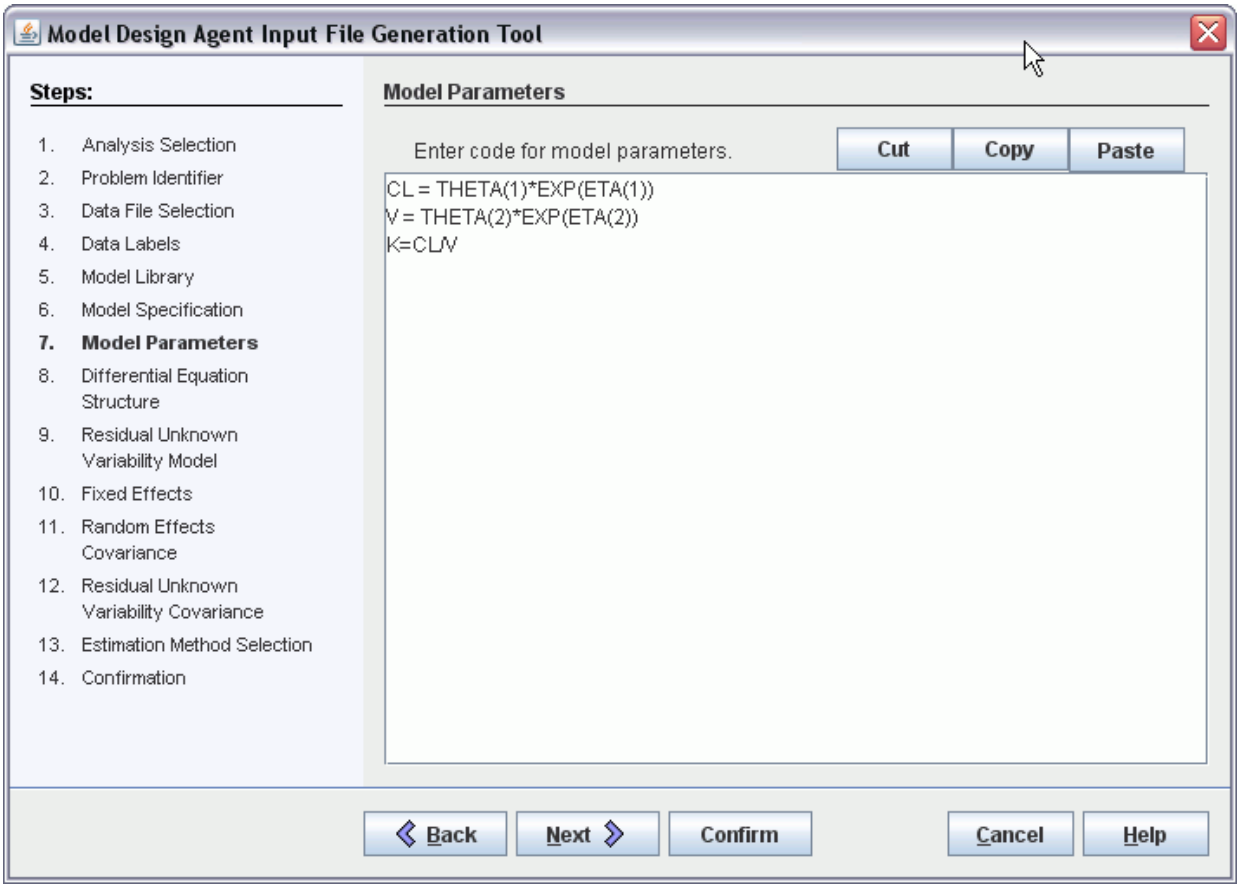
CL = THETA(1)*EXP(ETA(1))

V = THETA(2) + ETA(2)

As an example, we could build a log-normal model for population between-subject variation by entering the following equations:

CL = THETA(1)*EXP(ETA(1))

V = THETA(2)*EXP(ETA(2))

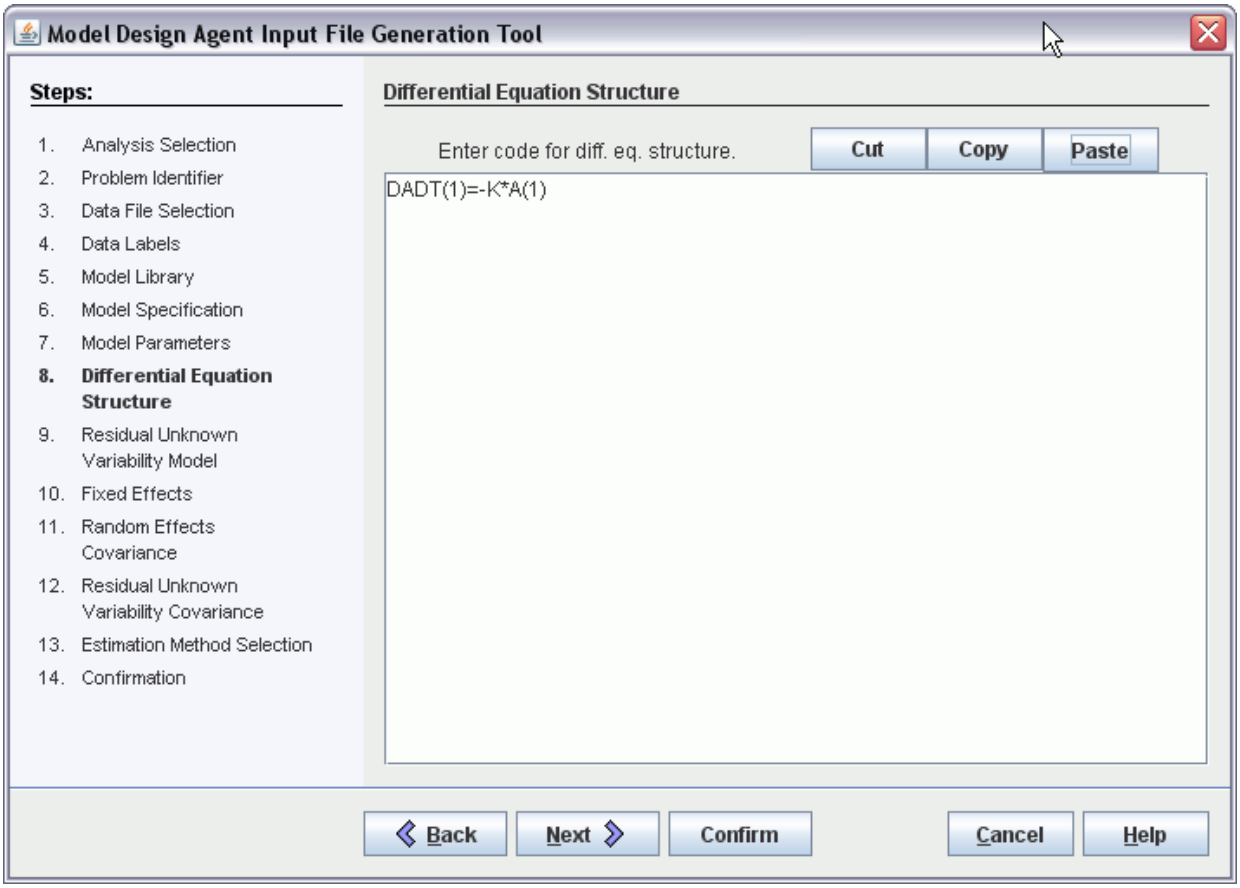


Other between-subject variation models are also possible. Note that the rate constant K is already defined as the ratio of clearance and volume.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Differential Equation Structure

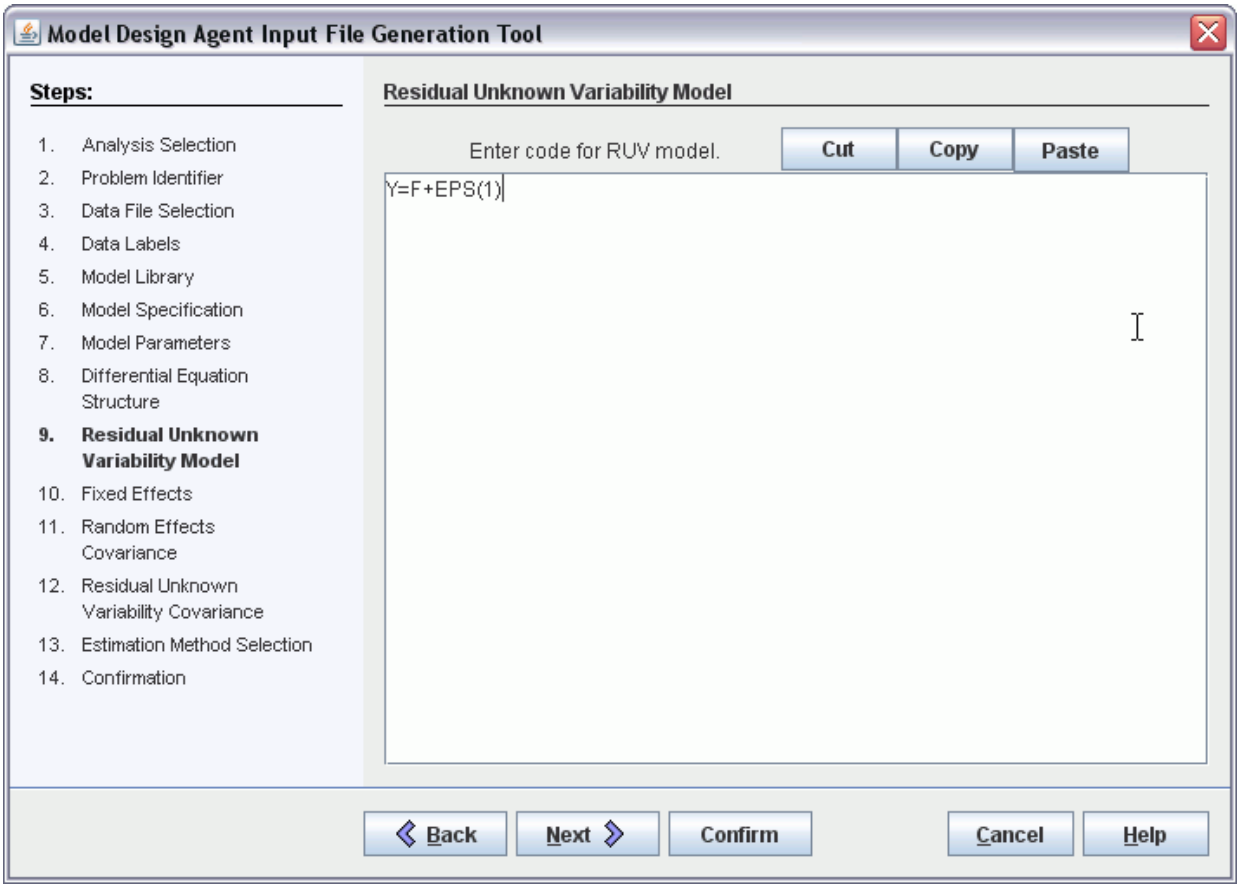
This window allows the user to define the differential equations for the model, assuming a model was selected from the library and/or ADVAN6 was used. If a model comes from the library, then the differential equations are pre-filled and all the user needs to do is check them to make sure they meet the needs of the analysis.



After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Residual Unknown Variability Model

This window allows the user to define a model for the measurements that takes into account residual unknown variation (RUV).



The model is defined using NONMEM(R) compatible notation as follows:

- EPS(1), EPS(2), ... indicate the RUV random effects, i.e. random sources of variation at the between-subject level. They are random variables assumed to be Gaussian with mean zero and covariance SIGMA;
- Y is the statistical model for the measurements in the DV data column; this is the variable that is directly associated with the data in the DV column. The association needs to be defined.
- F is the model for the population data, i.e. the model variable which is being measured and associated with the DV time course.

For example, Gaussian additive variation on the measurement would be modeled as:

Y = F + EPS(1)

Gaussian proportional error on the measurement would read:

Y = F * (1 + EPS(1))

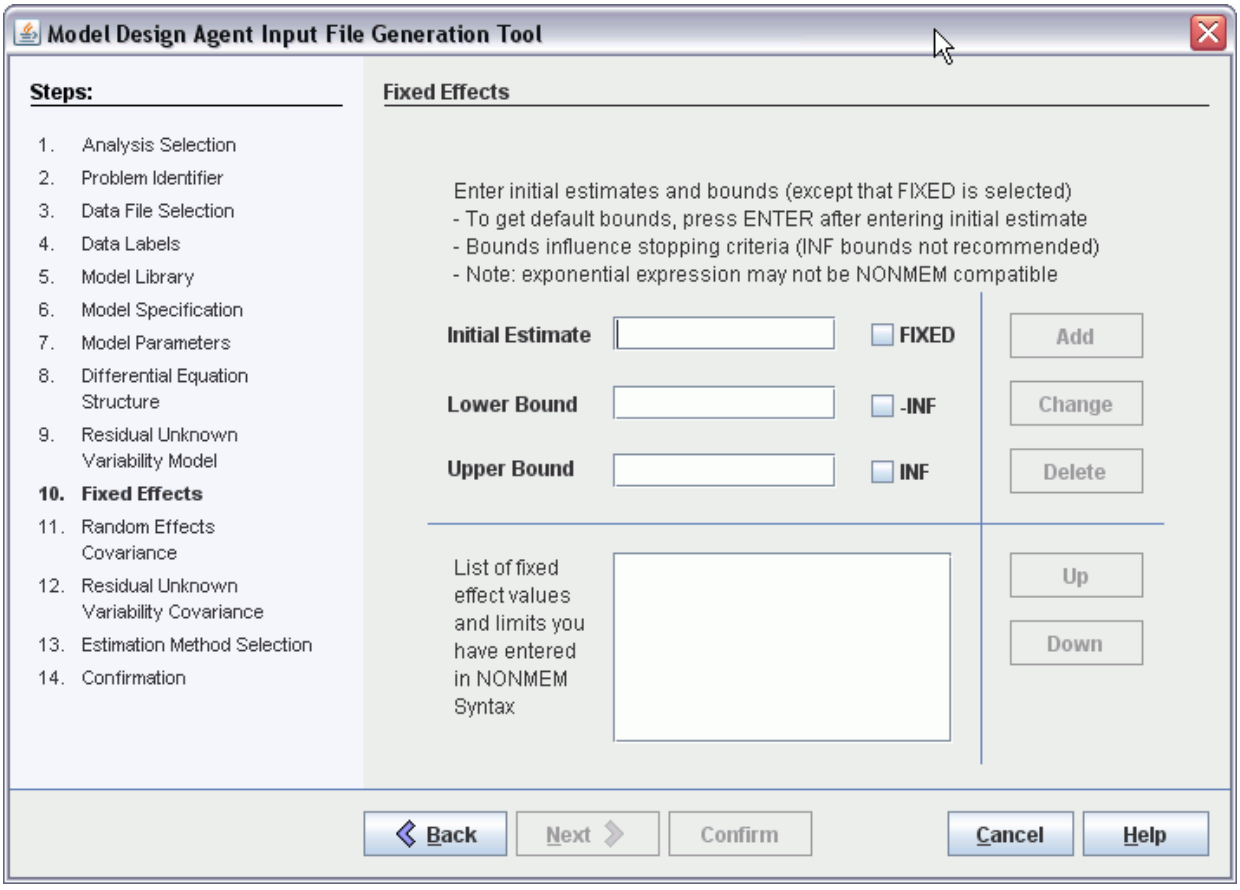
In this particular instance, we have chosen an additive Gaussian error model. Other statistics are also possible, such as an exponential error model:

Y = F *EXP(EPS(1))

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

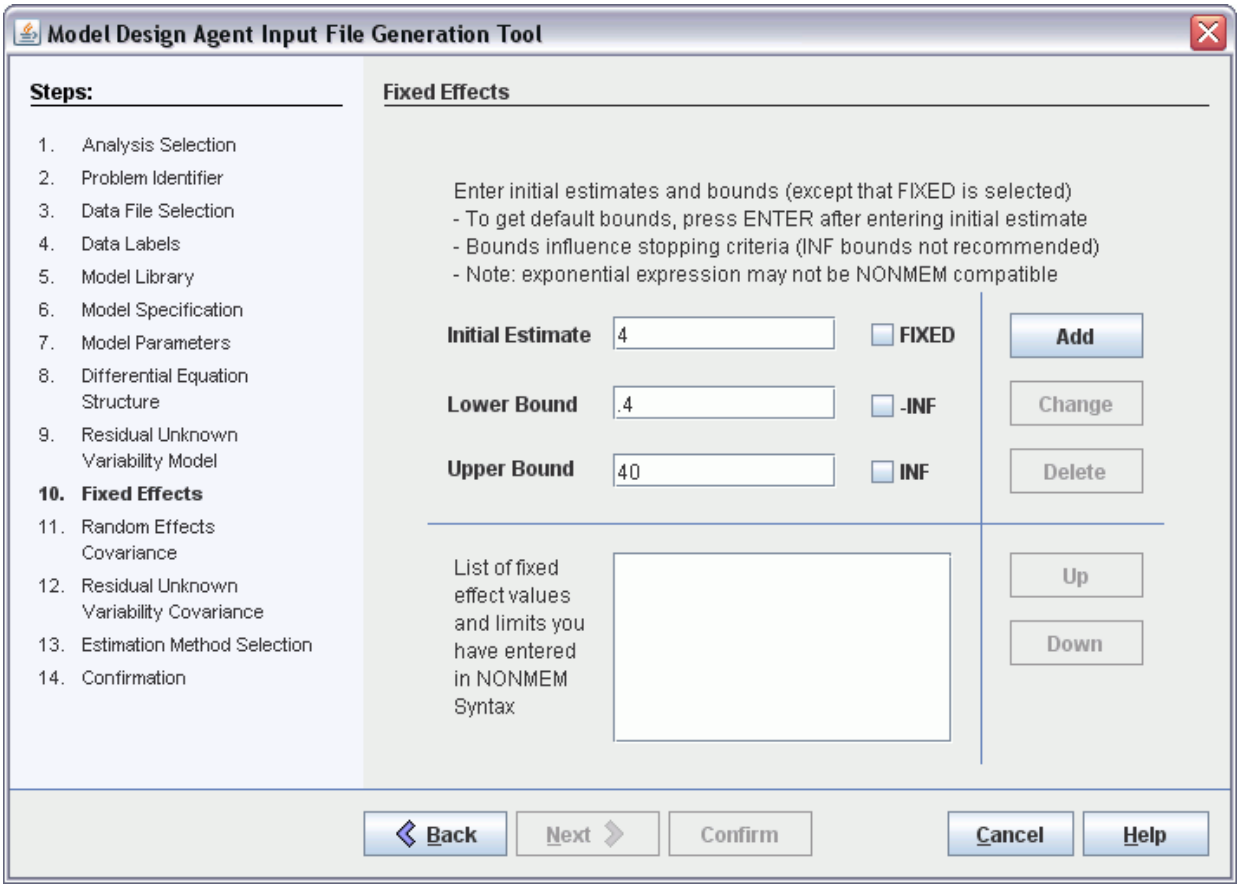
Prepare Input: Fixed Effects

This step requires you to enter initial estimates for the fixed effects across the population. These are the THETA(1), THETA(2), ... parameters that you have entered earlier in the model equations. They represent model parameters that do not change across your population of subjects. This is the screen shot in question:

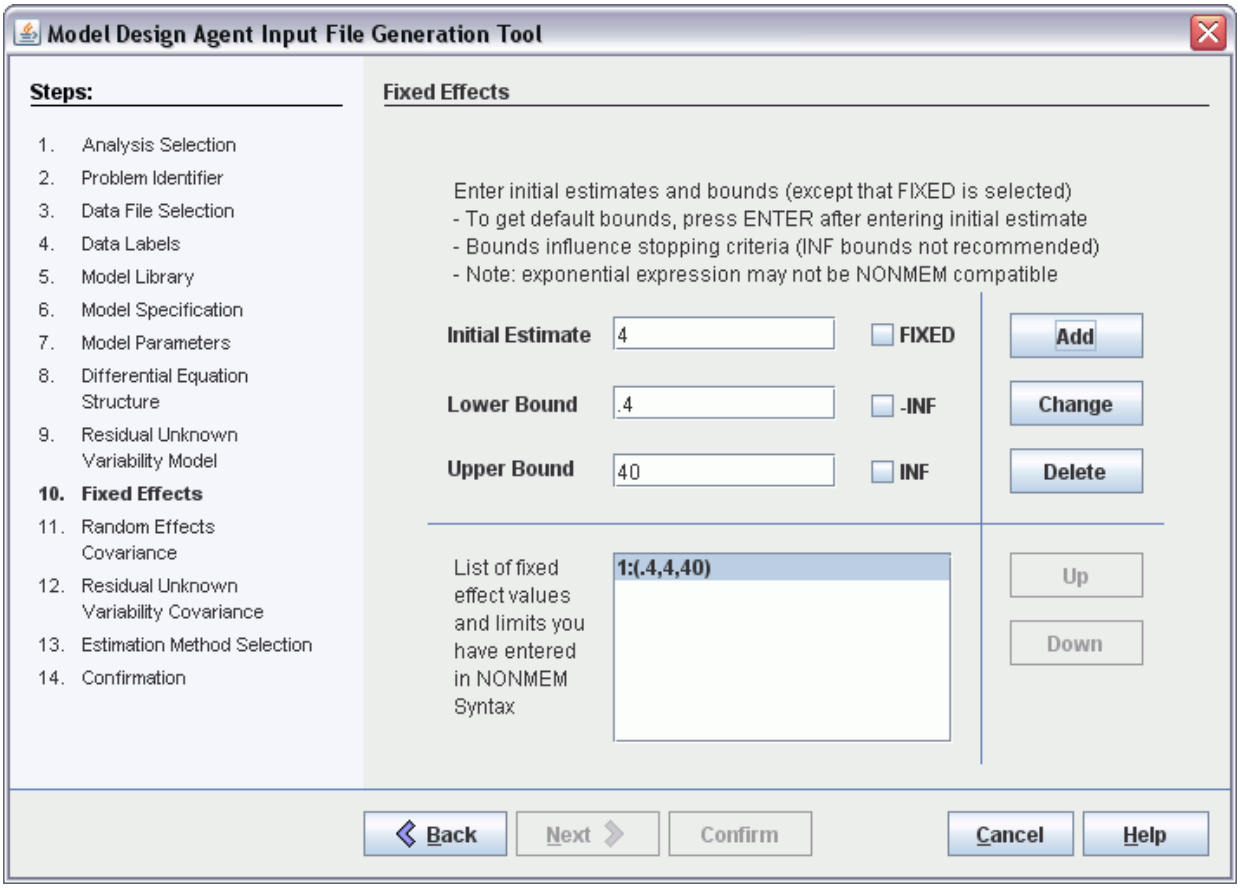


You can enter initial estimates and bounds for the fixed effects across the population. Initial estimates, lower bound and upper bound must be entered separately for each fixed effect. The bounds are required, except when a fixed effect is designated as FIXED (which will cause it not to be adjusted during model optimization).

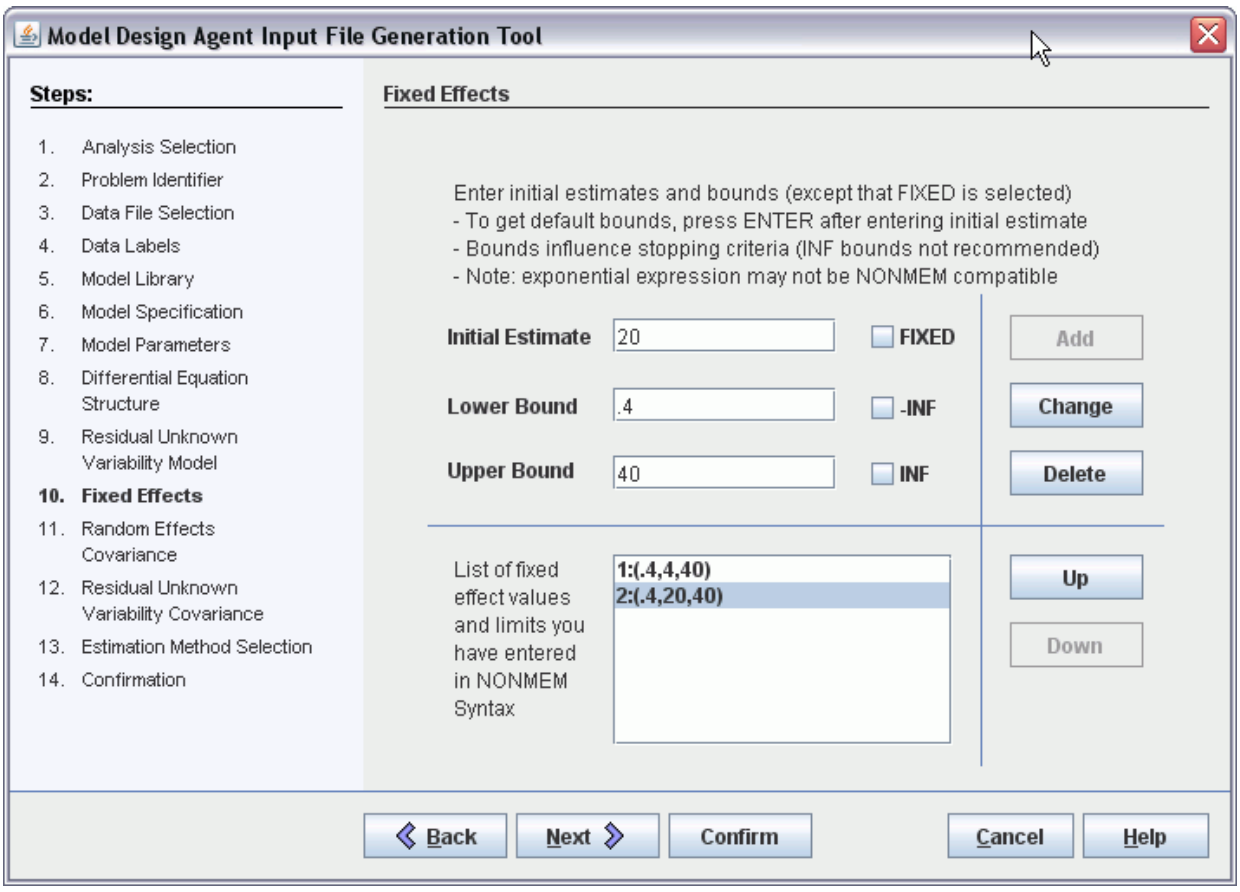
Note that, if you enter the value for the initial estimate and press the "Enter" key, default lower and upper bounds will appear equal to 1/10 and 10 times the initial estimate respectively, as shown below.



You will be asked to enter this information once for each fixed effect you have defined in the model equations. After entering Initial Estimate, Lower Bound and Upper Bound, you must press "Add". This will save your choices and associate them with the right fixed effect, as can be seen below:



You need to enter these values for all fixed effects. If you wish to change a set of values, you must highlight it in the list and then press "Change". At the end, the list of fixed effects will contain the required information, and the "Next" button will highlight to signal that it is time to move on to the next step. Double-clicking on a fixed effects list item will bring the values back up, so that changes can be made to either the initial value, or the bounds, or both.



The bounds on the fixed effects determine (together with the user-requested number of significant digits) the stopping criteria for optimization. Bounds that are too wide can result in solutions that are less accurate, so it may be appropriate to use the default or make sure that the bounds do not increase too much.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Random Effects Covariance

This section is where the covariance of the random effects ETA (which model the between subject variation, BSV) is defined and initial values chosen. Remember that ETA models RUV in individual analysis. There can be many ETA parameters, and their covariance structure can be

quite general. For example, a single exponential time course with Gaussian variation on the exponent proportional to 30% of the typical value would be modeled as:

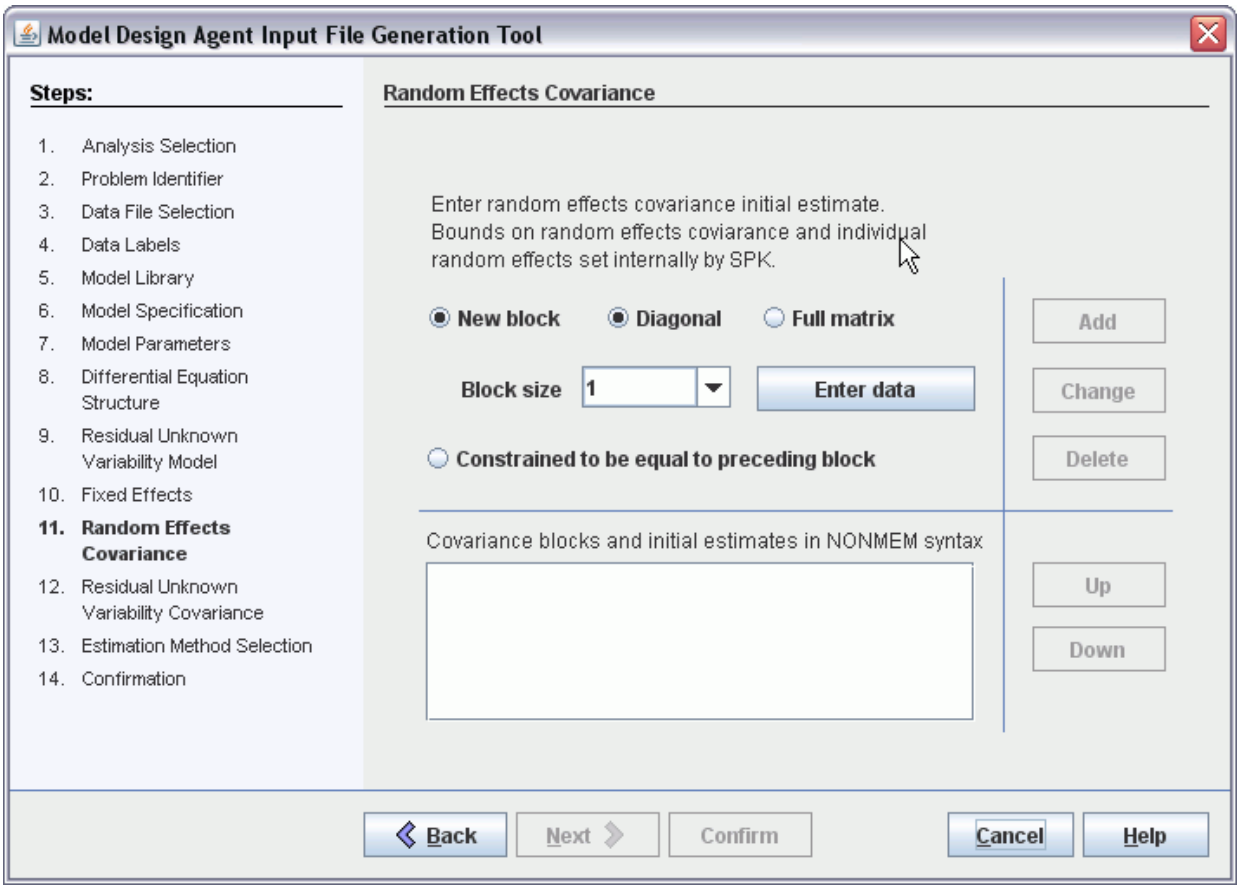
LAMBDA = THETA(1) *(1+ ETA(1))

and the corresponding OMEGA value (in this case, OMEGA is a scalar) would be 0.09 (which is the square of 0.3). A single compartment pharmacokinetic model following a unitary pulse dose with linear Gaussian variation on the apparent volume of distribution equal to 50 volume units, and log-normal variation on the clearance proportional to 30% of the clearance typical value would be modeled as:

CL = THETA(1)*EXP(ETA(1))

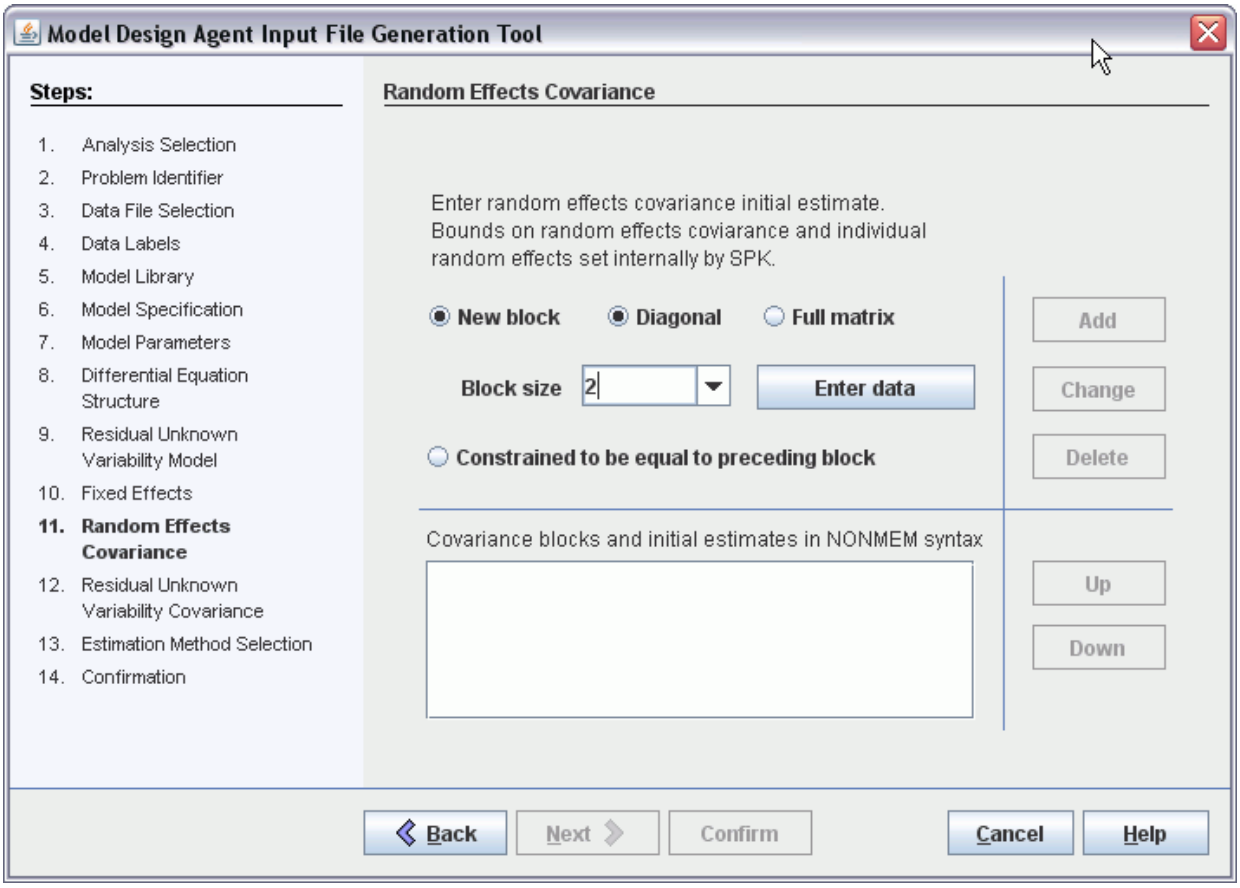
V = THETA(2) + ETA(2)

where the corresponding OMEGA matrix would be diagonal 2 by 2 in the case of uncorrelated variations, and full 2 by 2 in the case of correlated variations. The OMEGA values would be OMEGA(1,1)=2500 (which is the square of 50) and OMEGA(2,2)=0.09.

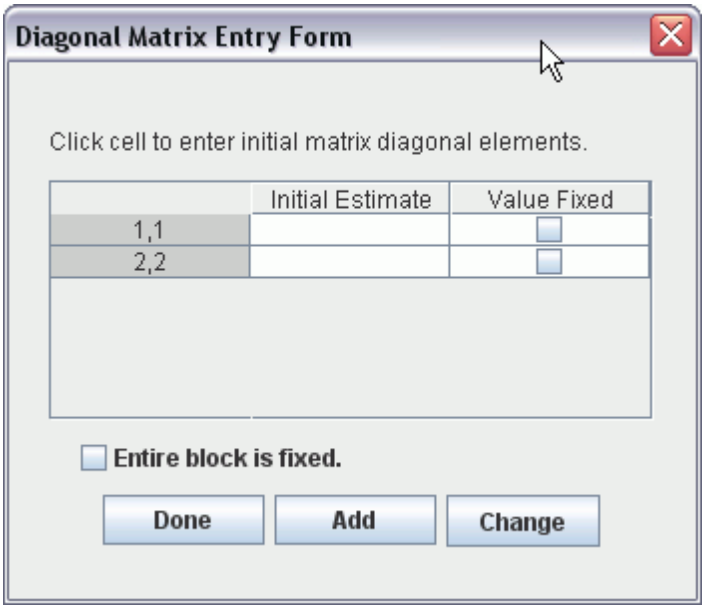


Every new OMEGA matrix is a new "block" (again in keeping with the NONMEM(R) notation). To start, one selects the "New block" radio button

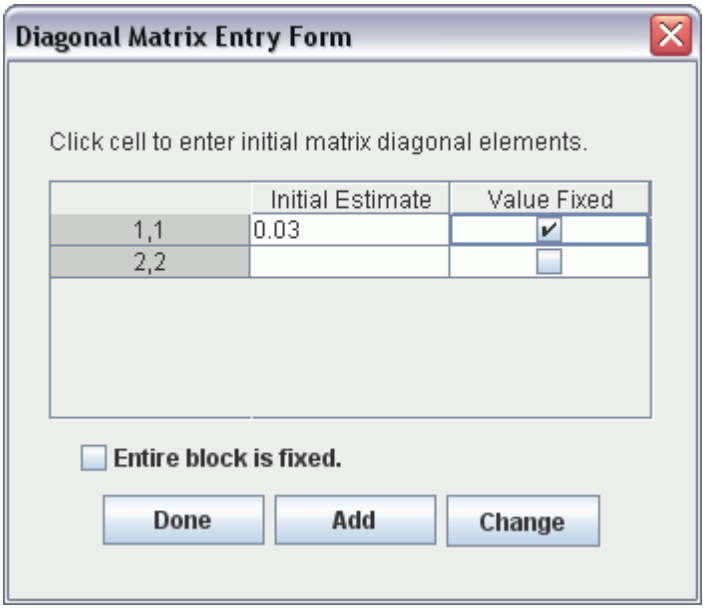
and whether the matrix is "Diagonal" or "Full matrix". The next thing to do is to select the Block size, i.e. the size of the matrix. In this case, we are going to select a block of size 2 (since we have defined two random effects), and a diagonal matrix (which implies that the random effects are uncorrelated).



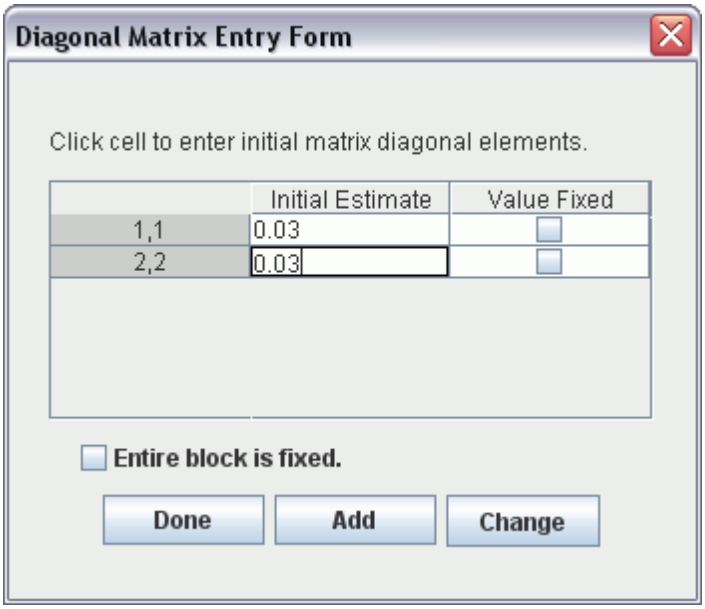
After the size of the block has been selected, the user should click on the "Enter data" button. The Matrix Entry Form appears.



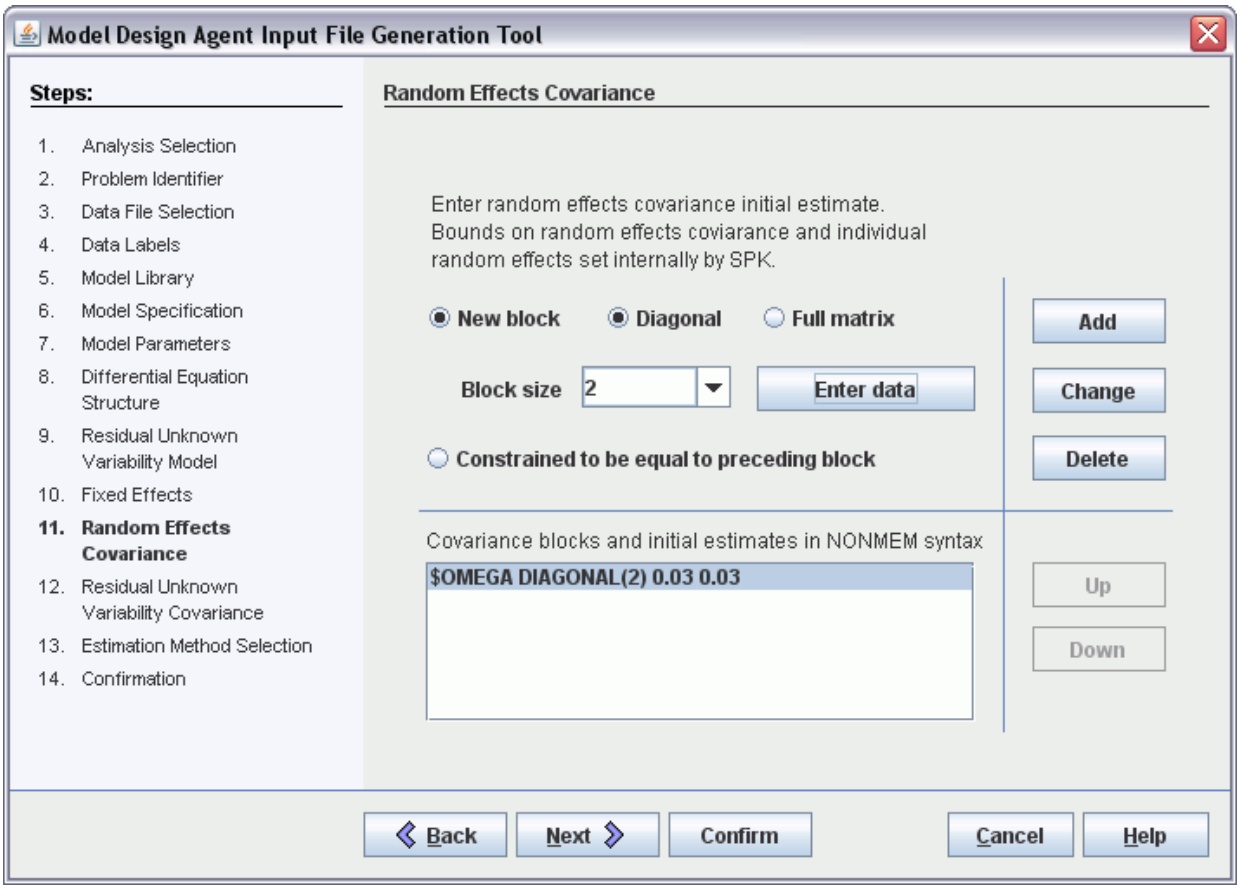
Note that the form will be different depending on the size of the matrix. In this case, there are two rows corresponding to the 1,1 and 2,2 elements. These two numbers completely define the matrix. Note that the OMEGA values can also be fixed by checking the box next to the value, as shown below.



Your chosen values for OMEGA can be entered by clicking on the corresponding cell and typing in the value.



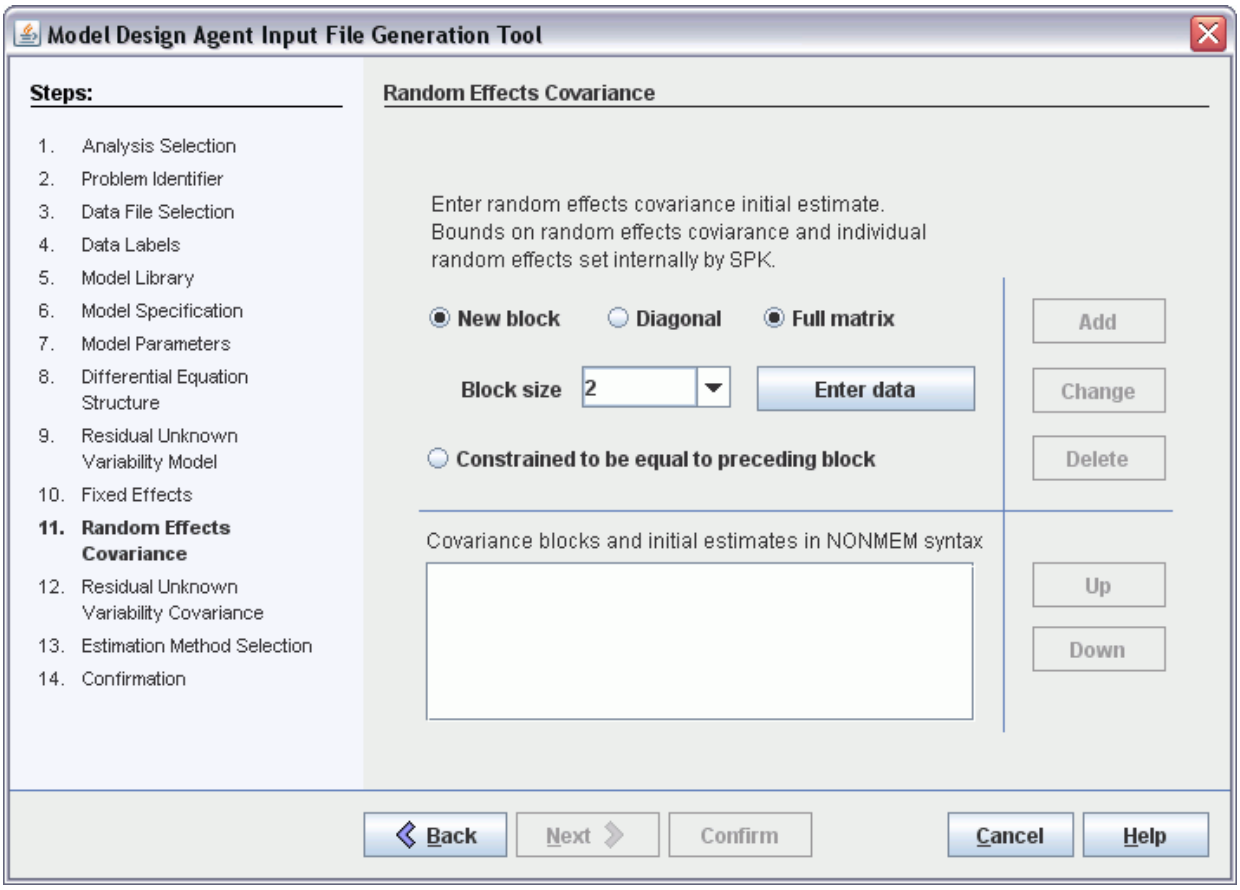
After doing this, you need to press "Add" or "Change" to add or change these initial values:



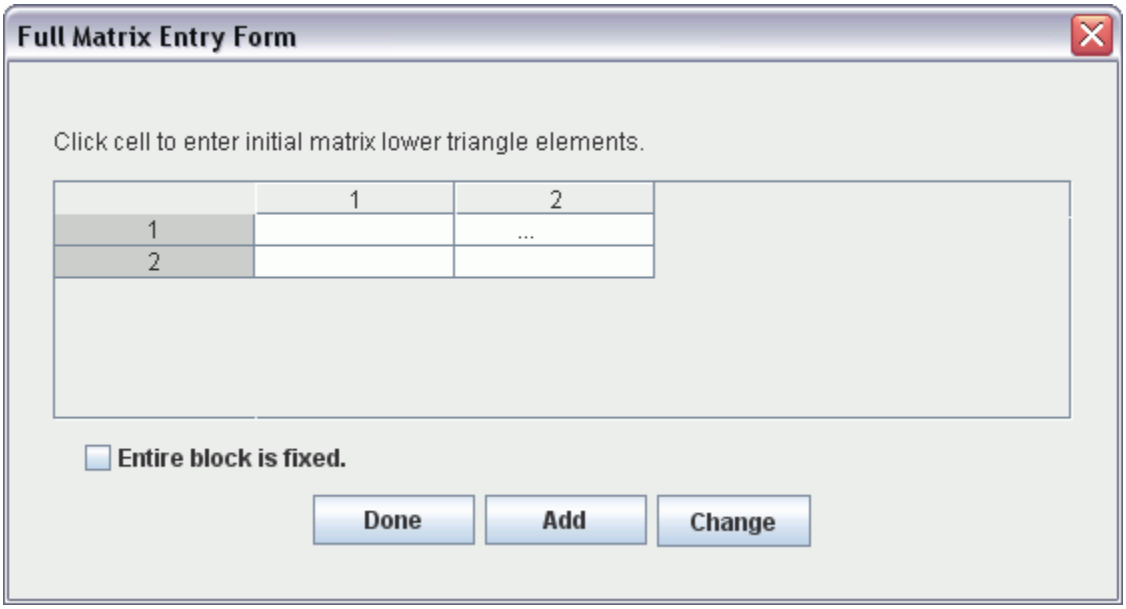
As can be seen, the screen below the entry buttons has displayed a description of the random effects covariance you have entered in NONMEM(R) syntax. In this case, we have entered an OMEGA matrix

which is size 2, diagonal and with elements 1,1 and 2,2 both equal to 0.03.

We could also have chosen to enter a full two by two matrix. To do that, we would have to have selected a block of dimension two and we would check the radio button next to "Full matrix".

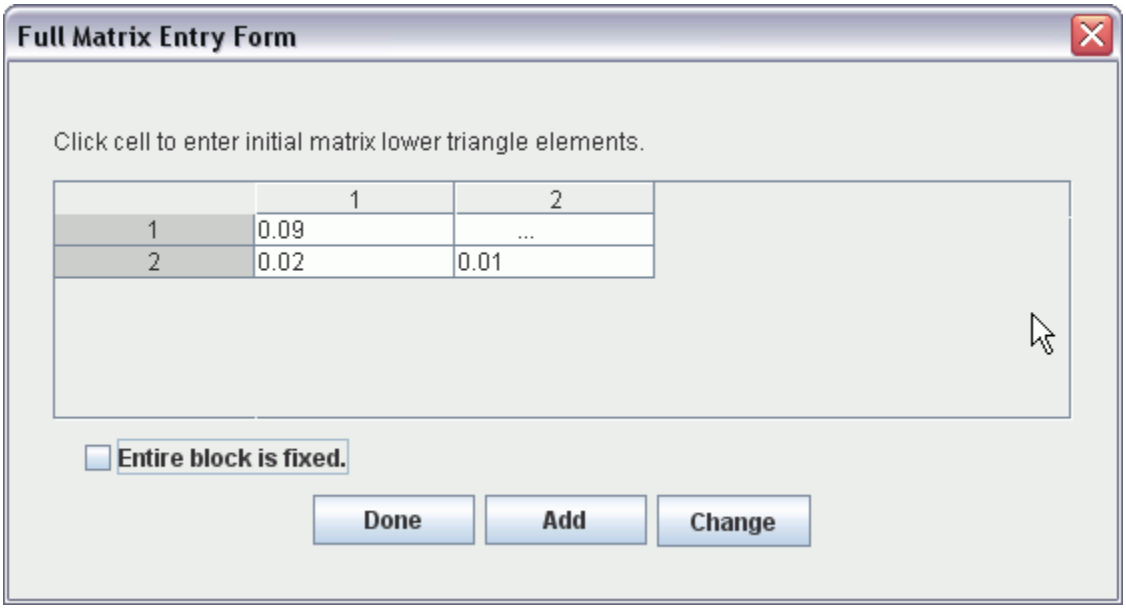


The user then clicks the "Enter data" button, as before. The Matrix Entry Form appears.

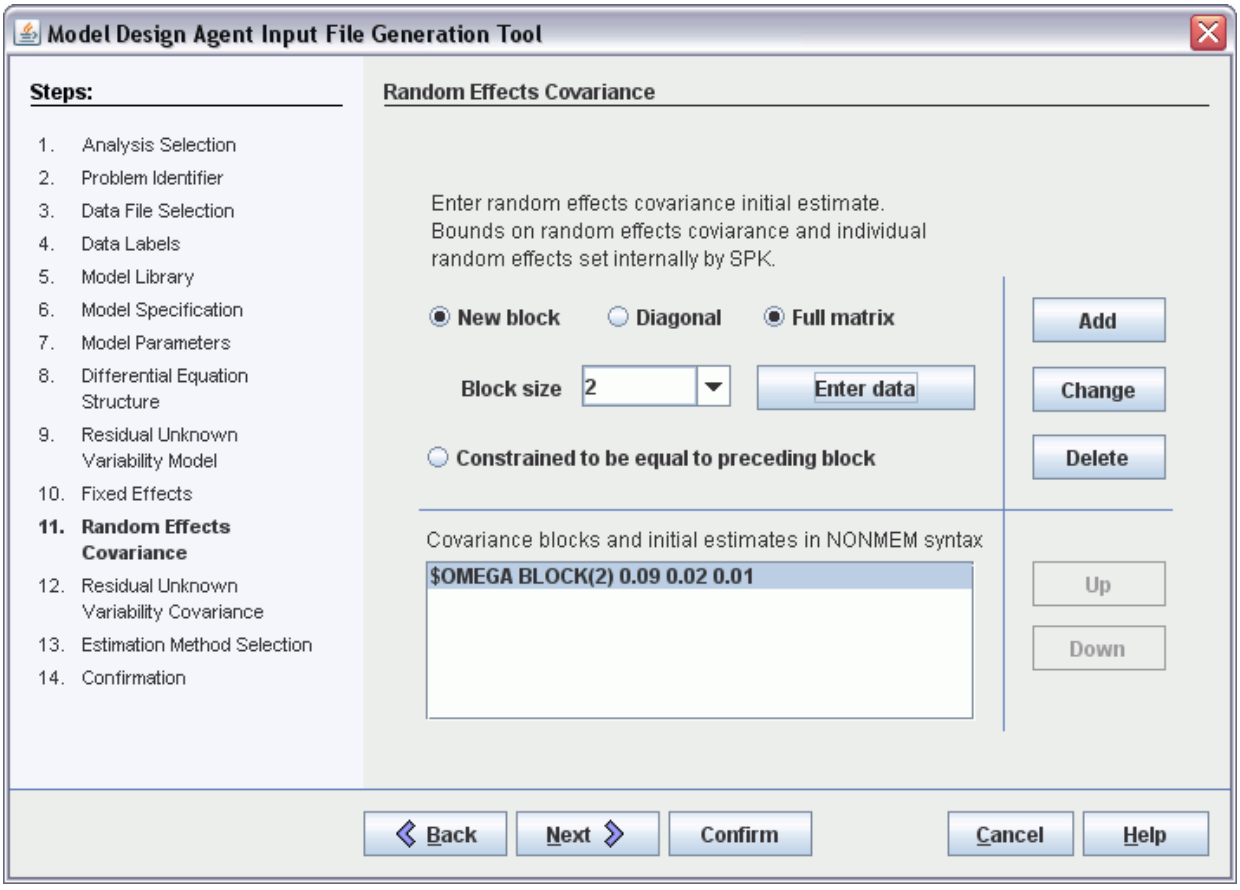


As before, the form will be different depending on the size of the matrix. In this case, there are two rows and two columns, and space to enter the (1,1), (2,1) and (2,2) elements (since the matrix is symmetric, the (2,1) element is identical to the (1,2) element). These three numbers completely define the matrix.

As before, the chosen values for OMEGA can be entered by clicking on the corresponding cell and typing in the value.



After doing this, you need to press "Add" or "Change" to finalize your entry.



As it can be seen, the screen below the entry buttons has displayed a description of the random effects covariance you have entered in NONMEM(R) syntax. In this case, we have entered an OMEGA matrix which is size 2, full and with elements 1,1 equal to 0.09, 2,1 equal to 0.02 and 2,2 equal to 0.01.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Residual Unknown Variability Covariance

This section of the MDA is where the matrix describing the residual unknown variation (RUV) can be defined and initial values chosen. This

is the covariance of the random effects EPS (which model the residual unknown variation, RUV).

The RUV appears at the level of the measurements, while the BSV appears at the level of the model parameters (although changes to this may be possible).

There can be many EPS parameters, and their covariance structure can be quite general. As with the OMEGA matrix, this is a covariance matrix, and it can be diagonal or full. For example, Gaussian, additive RUV on the measurement with constant variance would be modeled as:

Y = F + EPS(1)

On the other hand, Gaussian, additive RUV on the measurement with variance proportional to the magnitude of the measurement would be:

Y = F * (1 + EPS(1))

Lognormal RUV would be defined as:

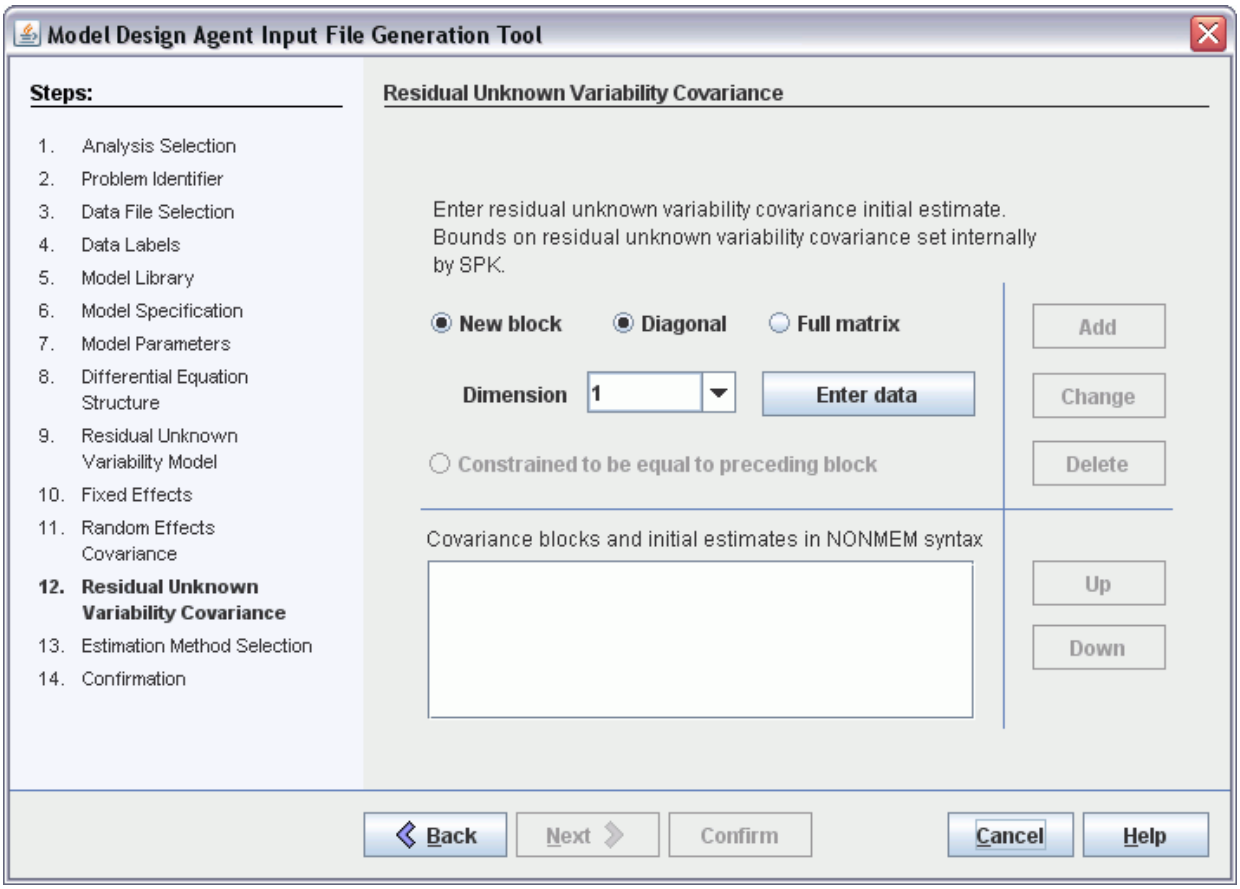
Y = F * EXP(EPS(1))

Note that, when using the First Order approximation when fitting, the proportional and lognormal RUV are equivalent, since the exponential would be approximated by a proportional term. The SIGMA matrix defines the covariance of the RUV. For the examples above, the SIGMA matrix has different interpretations. For example, Gaussian, additive RUV on the measurement with constant standard deviation equal to 100 would be modeled as: Y = F + EPS(1), and SIGMA would be equal to 10000 (the square of 100, since SIGMA is in variance units). An additive RUV with standard deviation proportional to 10% of the measurement would be modeled with a SIGMA equal to 0.01 (which is the square of 0.1). When fitting, these values are only starting (initial guesses) values, to be modified during and after data fitting, and when simulating they are taken as the true value for the population to be simulated. Note also that SIGMA is a full matrix, so more complicated error structures are feasible as well. For example, a RUV structure with error that is characterized by both a proportional and a linearly additive term would be modeled as:

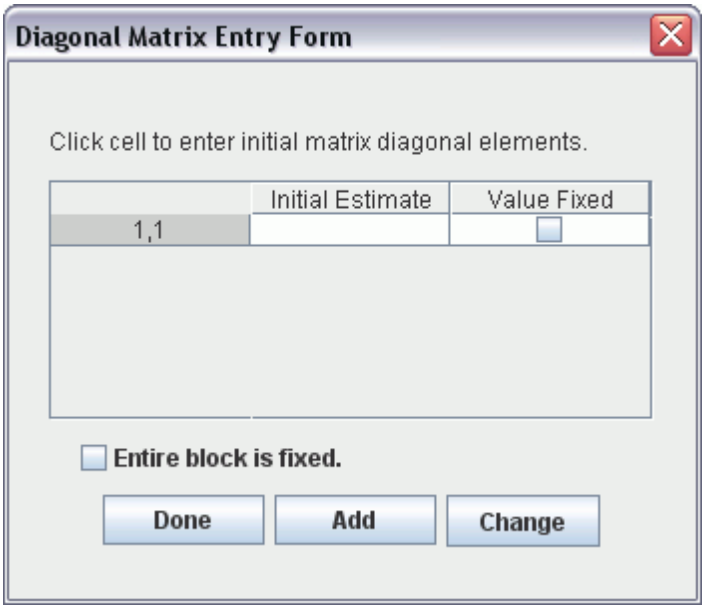
Y = F * (1 + EPS(1)) + EPS(2)

In this case, the SIGMA matrix is going to be 2 by 2 and with values determined by the magnitudes of the error terms. For example, if the RUV is proportional to 10% of the measurement and has a noise "floor" of standard deviation equal to 100, then SIGMA(1,1) is going to be 0.01 and SIGMA(2,2) is 10000. The cross-covariance term, SIGMA(1,2) or

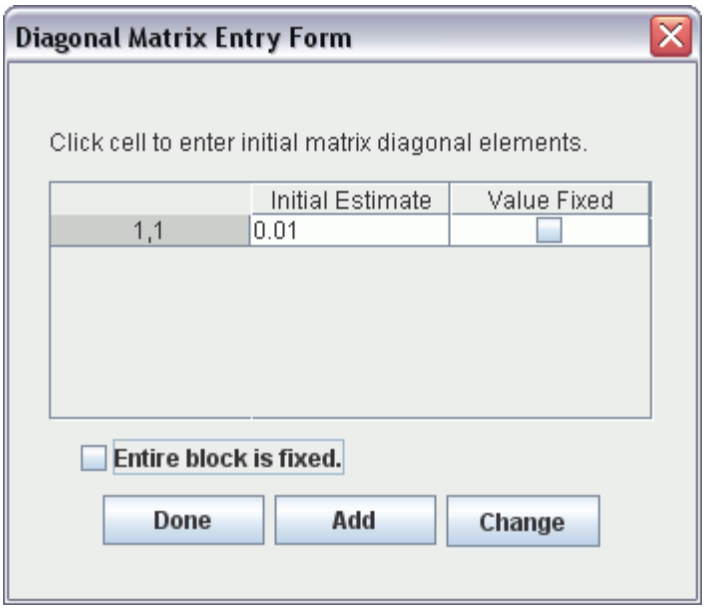
SIGMA(2,1), can be zero in case of uncorrelated noise or nonzero in case some information is available from the data and the model can be fit.



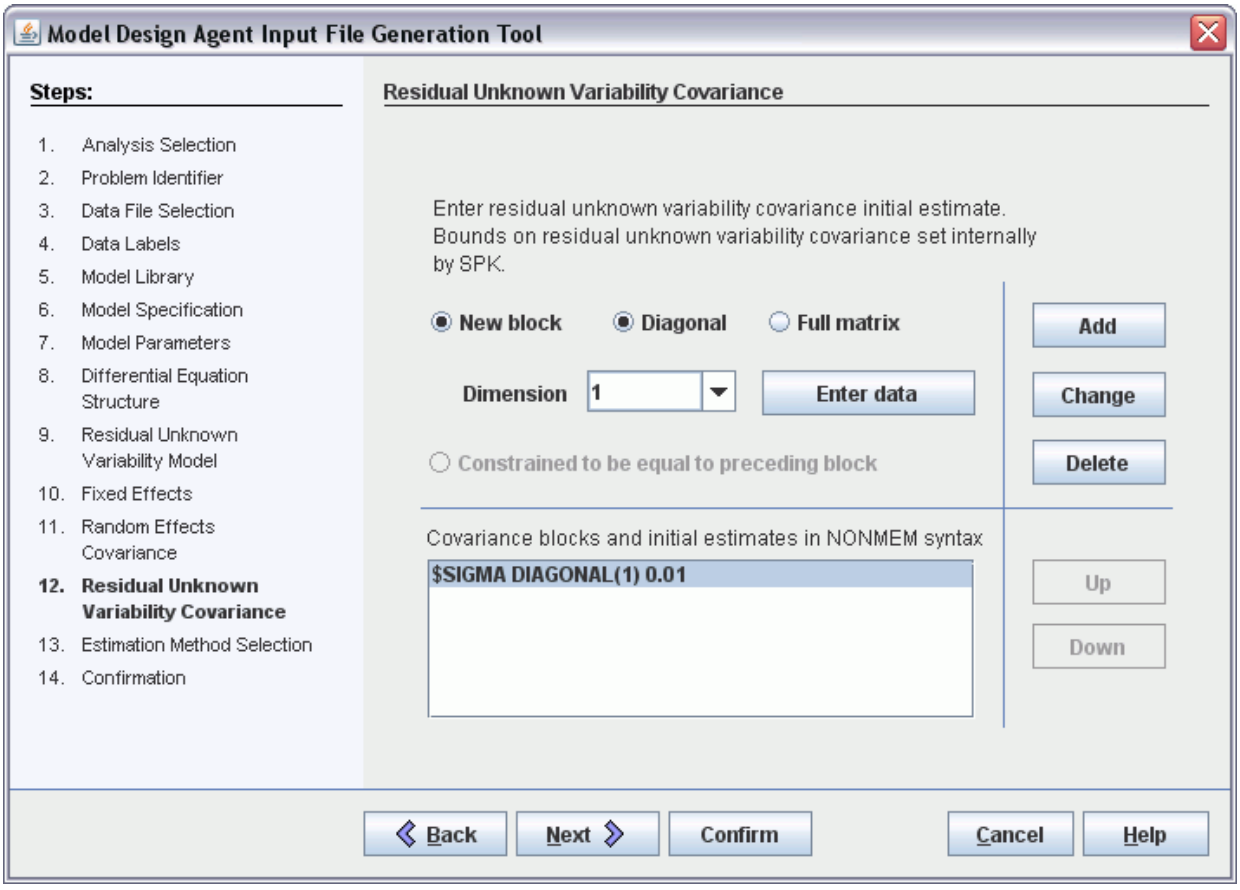
As we have seen for the OMEGA matrix, every new SIGMA matrix is a new "block" (in keeping with the NONMEM(R) notation). To start, one selects the "New block" radio button and whether the matrix is "Diagonal" (only non diagonal elements are nonzero) or "Full matrix" (all matrix elements are nonzero – note that SIGMA is symmetric). The next thing to do is to select the Block size, i.e. the size of the matrix. In this case, we are going to select a block of size 1, and a diagonal matrix. The Entry Form will appear:



Note that the form will be different depending on the size of the matrix. In this case, there is only one row, corresponding to the only SIGMA element to be defined. This number will define the matrix completely. Note that the SIGMA values can also be fixed by checking the box next to the value. Fixing the values will cause them not to be changed during estimation. Your chosen values for SIGMA can be entered by clicking on the corresponding cell and typing in the value.



After doing this, press "Add" or "Change" to finalize your entry.

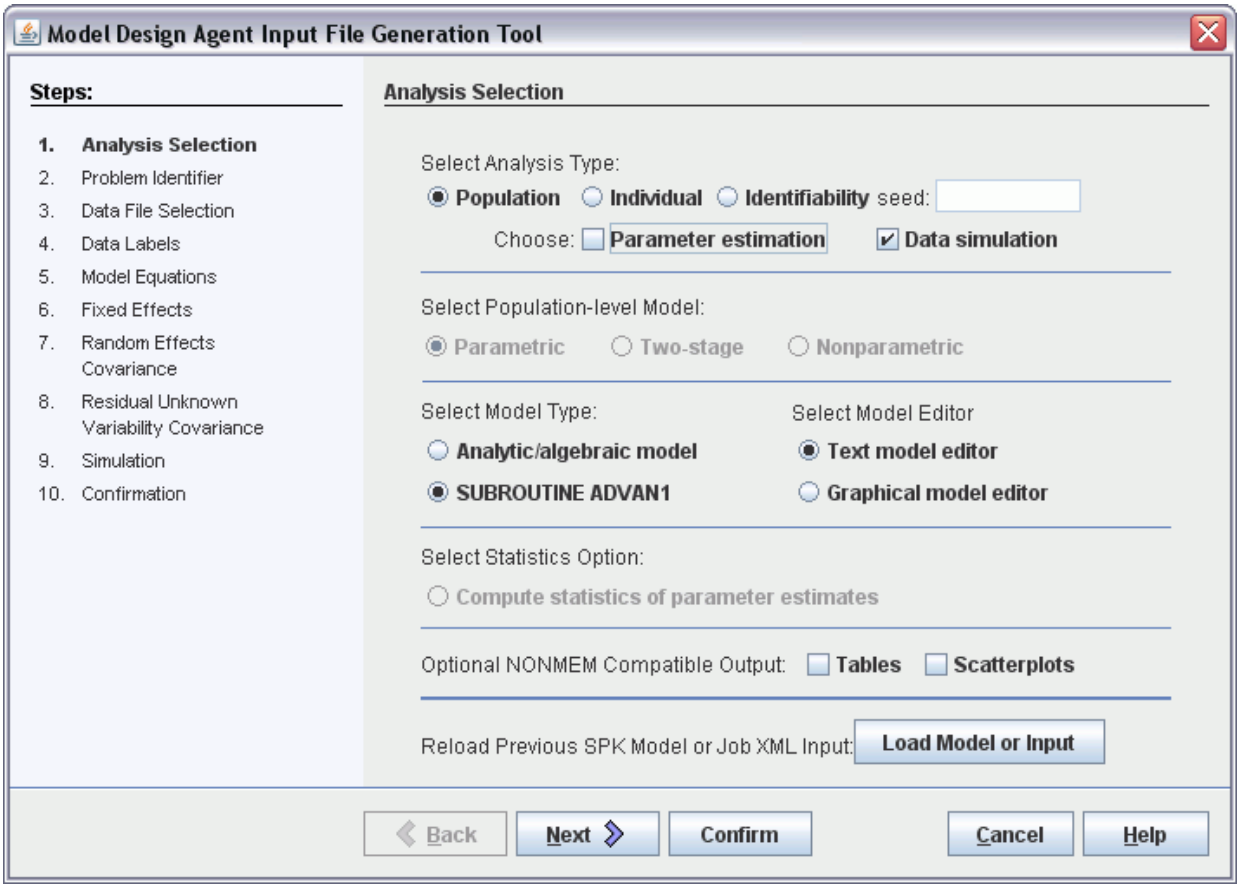


As can be seen above, the screen below the entry buttons displayes a description of the residual unknown variability covariance you have entered in NONMEM(R) syntax. In this case, we have entered a SIGMA matrix which is size 1 (scalar) and with element 1,1 equal to 0.01. Again, for comparison, a SIGMA values of 0.01 in the case of proportional error implies a standard deviation of 0.1, or 10%, on the measurements.

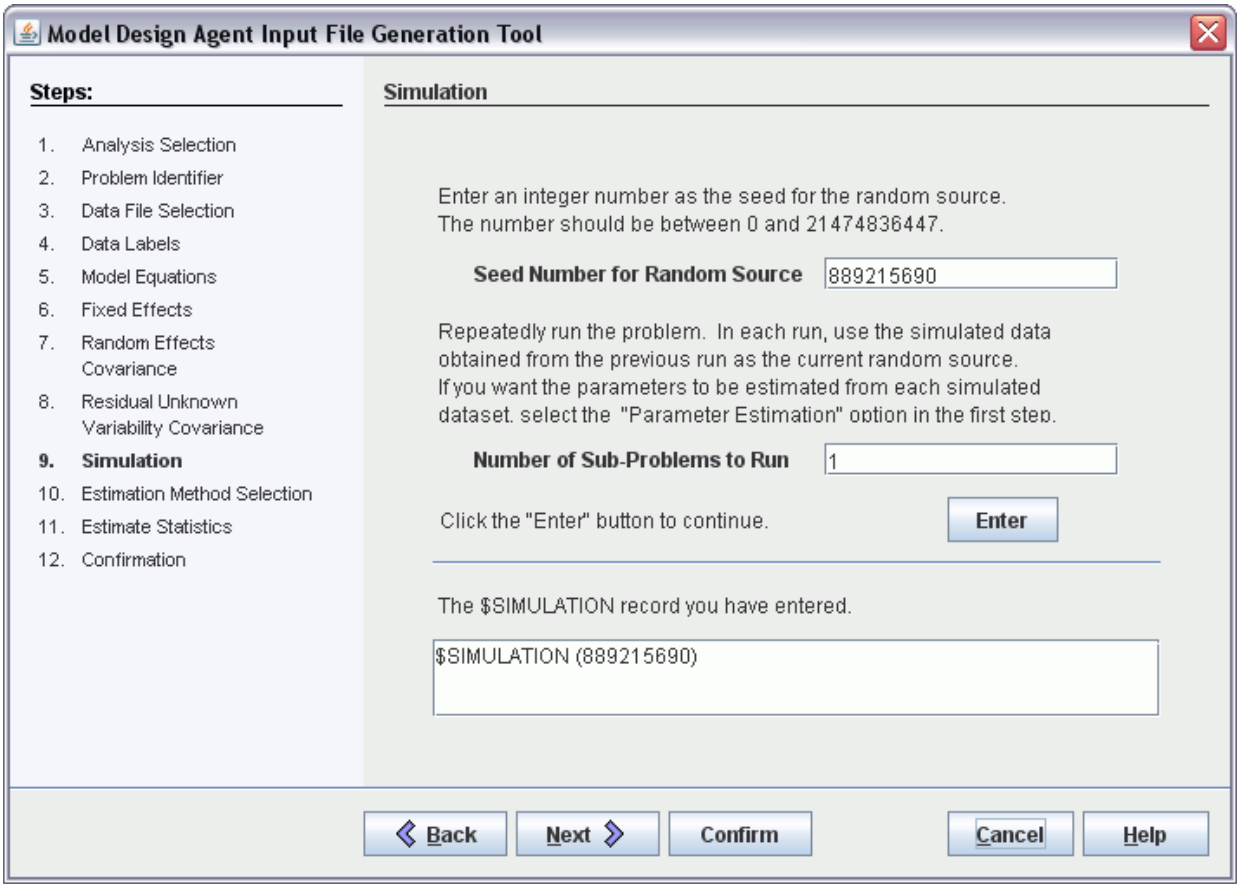
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Simulation

SPK allows the user to simulate data conditional on a model. If Simulation has been selected at the start (under Analysis Selection):



then the following screen will be shown instead of the Method Selection screen:



The user is required to select a seed number (to replicate the run if needed) and a subproblem number.

After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

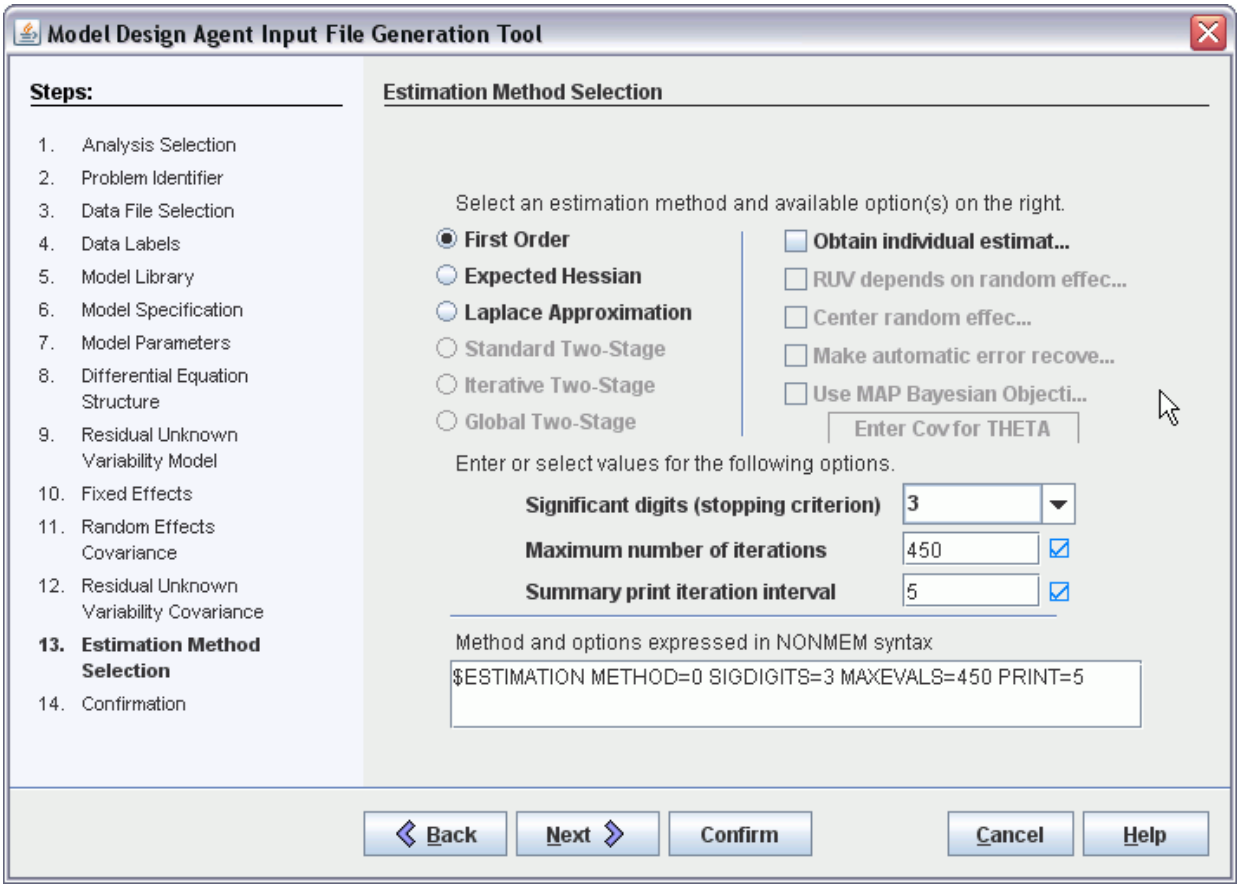
Prepare Input: Estimation Method Selection

The Method Selection screen allows you to select various methods for estimation of the fixed effects and the BSV and RUV covariances. The presence of many methods is due to the fact that the maximum likelihood problem for nonlinear mixed effects does not have a closed-form solution with respect to the unknown parameters, due to the nonlinear fashion in which the fixed and random effects enter the problem. Thus,

approximation methods have to be used to linearize the model function and approximate the likelihood function w.r.t. the original problem. If you have selected **Parametric** in the opening window, the methods available from the computational server include, in increasing order of accuracy:

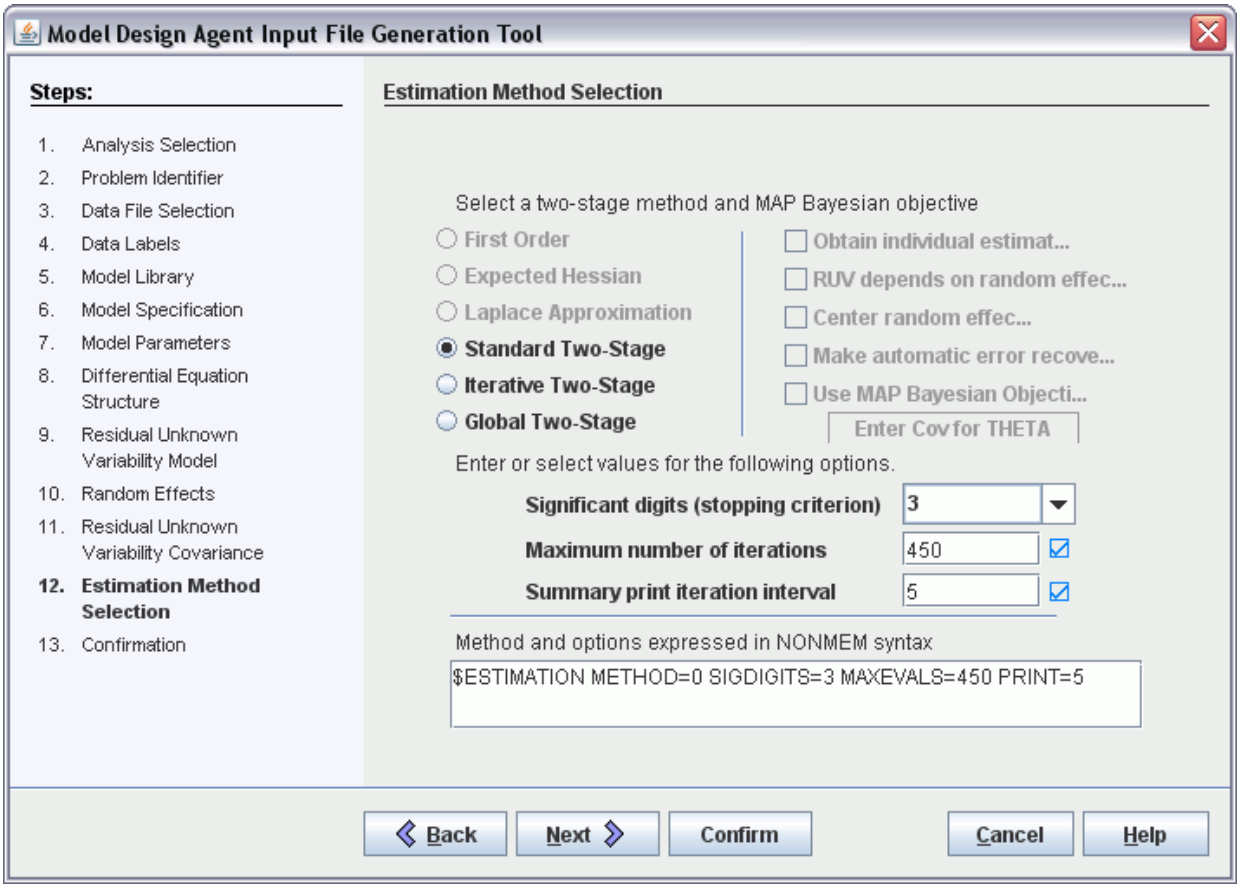
1. The **First Order method** linearizes the mathematical model of the measurements around a value of zero for the BSV random effects. While the approximation to the expected value of the measurement is linear, the approximation to the second order moment (RUV) is zero order. This is considered a rather crude approximation, but it is very computationally efficient, and so it is still widely used in practice. The First Order method is equivalent to the NONMEM(R) First Order, or FO, method.
2. The **Expected Hessian method** linearizes the model for the expected value of the measurements around a suitable individual estimate for the BSV random effects. In principle, a linear approximation (the default method) or a zero-order approximation (this approach is not currently available in the SPK system) can be used for the RUV. Expected Hessian is more accurate than the First Order method, but also more computationally expensive. The Expected Hessian method is equivalent to the NONMEM(R) First Order Conditional Estimation (FOCE) method with INTERACTION.
3. The **Laplace approximation** turns the integration problem of the marginal likelihood into an optimization problem using Laplace's approximation to the integral. It is considered marginally more accurate than the Expected Hessian method, but it is also considerably more computationally expensive. The Laplace approximation is equivalent to NONMEM(R)'s conditional estimation method with selection of the LAPLACIAN option.

The selection of the desired method is done by clicking on the corresponding radio button. Checking "Obtain individual estimates" will also return the individual parameter estimates for the random effects (POSTHOC option in NONMEM(R)). Checking "Make Automatic Error Recovery" will instruct SPK to gracefully recover from errors such as failure in parametric optimization or integration (it roughly has the same effect as NONMEM(R) NOABORT option).



If you have selected Two Stage on the opening window, your choices include:

1. The **Standard Two Stage** approach, where every subject's data are fit separately and the population parameters are defined as the sample average (THETAs) and sample covariance (OMEGAs) of the individual estimates. The SIGMAs are calculated as the sample averages of the individual SIGMAs estimates.
2. The **Iterative Two Stage** approach, where every subject's data are fit separately, but the population parameters (again defined as the sample average (THETAs) and sample covariance (OMEGAs) of the individual estimates) are used as population priors for the individual estimation, using a Maximum A Posteriori (MAP) approach.
3. The **Global Two Stage** approach, where every subject's data are fit separately, and an iterative scheme similar to the Iterative Two Stage is applied to the individual parameter estimates and the individual asymptotic covariance matrices, thus returning refined population estimates.



Other estimation variables that can be set in this screen include:

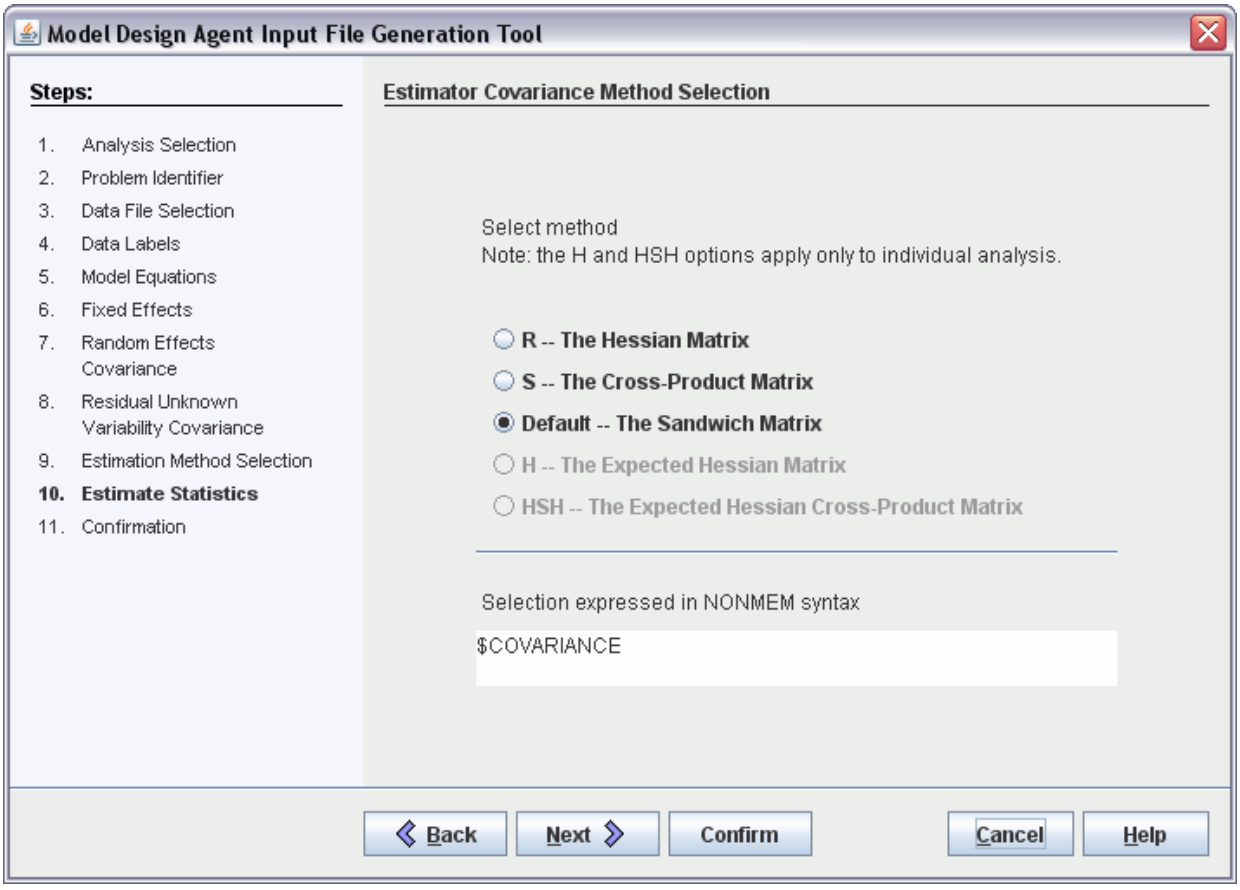
- The number of significant digits in the estimate: the default number is 3. A choice of a higher number will require longer computation time, while a lower number will sacrifice accuracy for computational speed.
- The maximum allowable number of function evaluations: these are the evaluations of the maximum likelihood functions to be performed by the computational engine. This number can be varied at will. In general, noisier, less reliable data may require more function evaluations for the estimation to be successful, while better data may not require as much computational effort. This may not hold for all data sets.
- The Iteration summaries print out interval steps number indicates the number of iterations after which a report should be given to the user. Usually, this choice is 5, meaning that a report should be given about the optimization status every 5 function evaluations.

Note that, after you have entered the required variables, you will see that the screen below the entry buttons has displayed a description of the requirements you have entered (method and other variables) in NONMEM(R) syntax. This is meant to facilitate comparison between SPK and NONMEM(R) output. In the case displayed in the screen shot above, we have selected the First Order method and have requested 3 significant digits, at most 450 function evaluations and a printout of the optimization status every 5 function evaluations. If the method you selected is not available in NONMEM(R), then the First Order estimation is displayed.

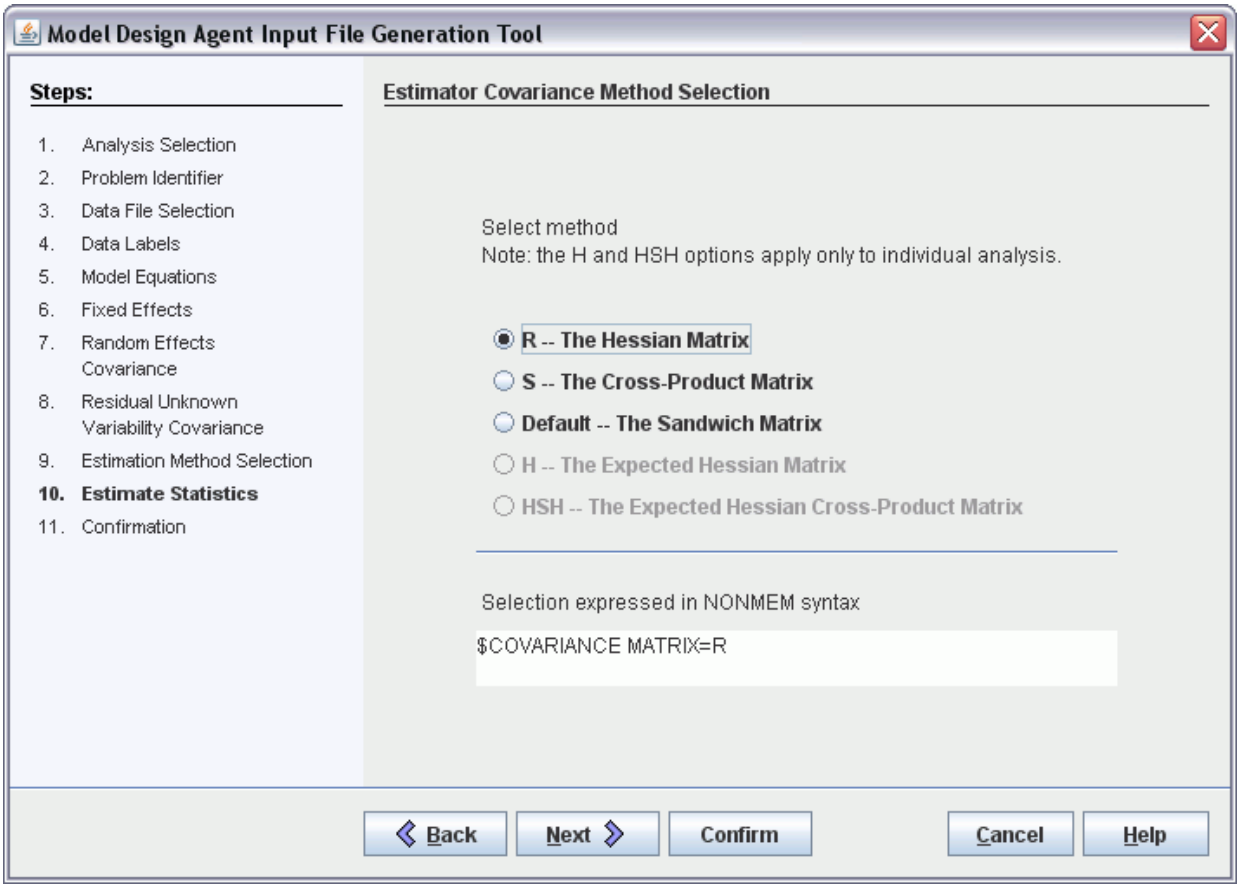
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Estimator Covariance Method

The Estimator Covariance Method Selection screen is where the user selects the procedure to be employed when calculating the reliability of the parametric estimate. This applies to THETA, OMEGA and SIGMA estimates since they are all estimated together and simultaneously. Just like with the optimization problem, there is not a single way to calculate the estimate precision. Thus, three methods are provided, which the user can select. Note that no method is absolutely reliable, and one method may provide well-defined answers while another may not. Serious divergence between methods usually indicates that the precision of the estimates is not well determined.



The screen shot above and the one below indicate the result (in NONMEM(R) syntax) of selecting two different options for the calculation of the covariance. In the estimation report, covariance information will be given as standard errors of the estimates.



After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

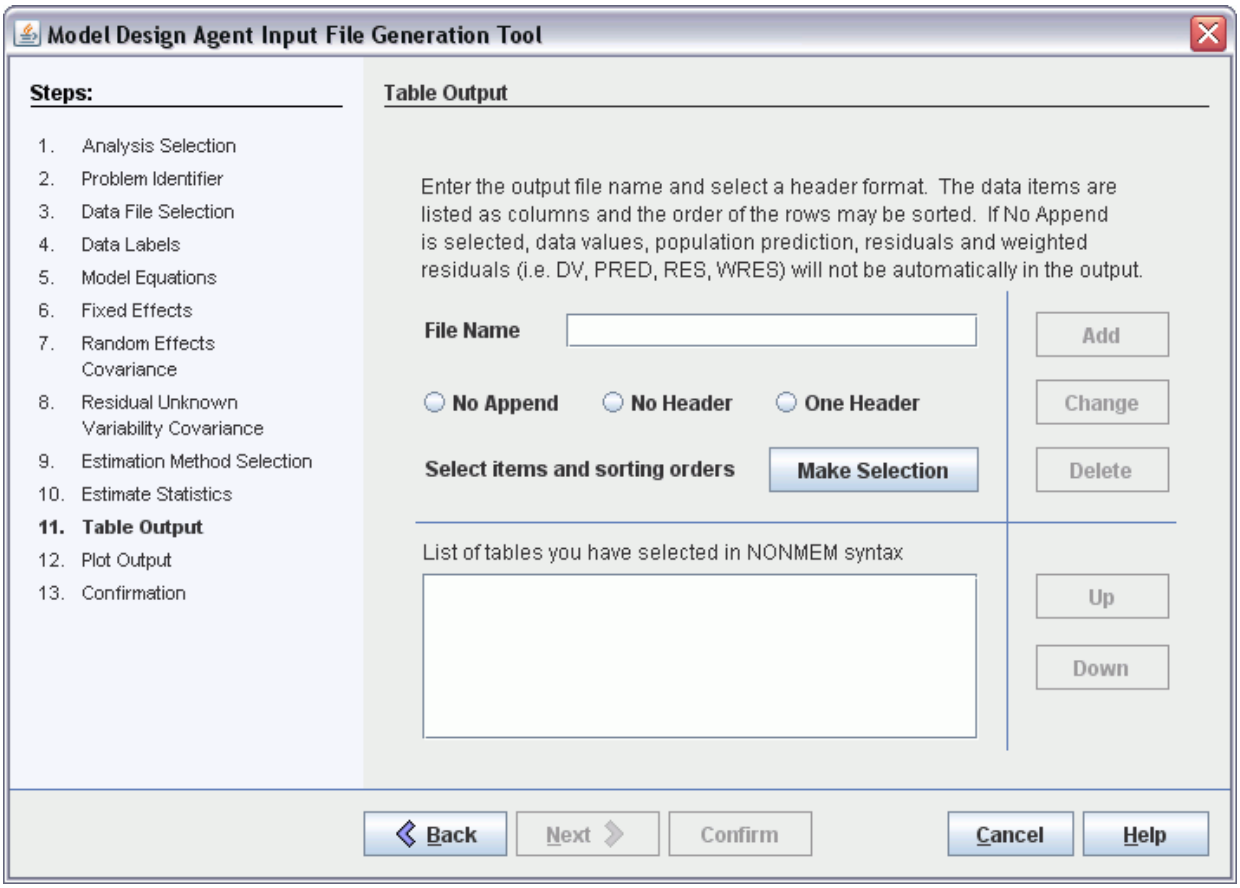
Prepare Input: Table Output

In this section, the user can specify which kind of tabular output the system should return after the estimation step is completed. The options in this window apply only if one wants to generate NONMEM(R)-compatible tables, since SPK tables can be usually generated from the report window.

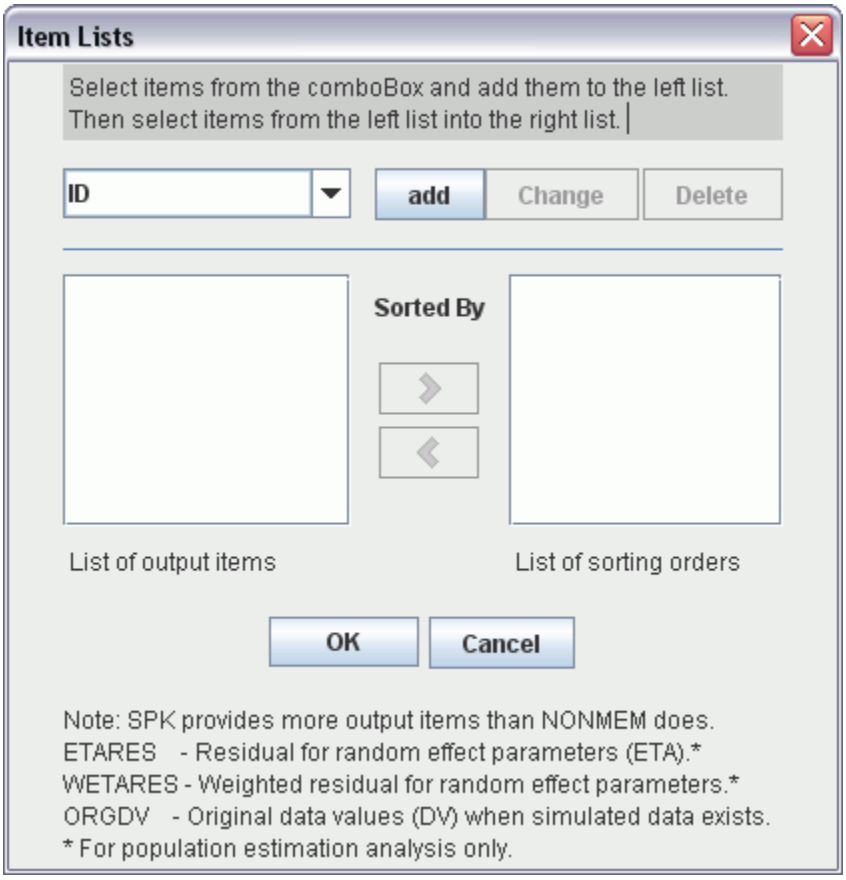
Normally, data values (DV), population predictions (PRED), residuals, i.e. the difference between data and model (RES) and weighted residuals

(i.e. the difference between data and model weighted by the covariance of the measurements) are appended to the output table by default.

This is the starting screen for the Table Output definition:



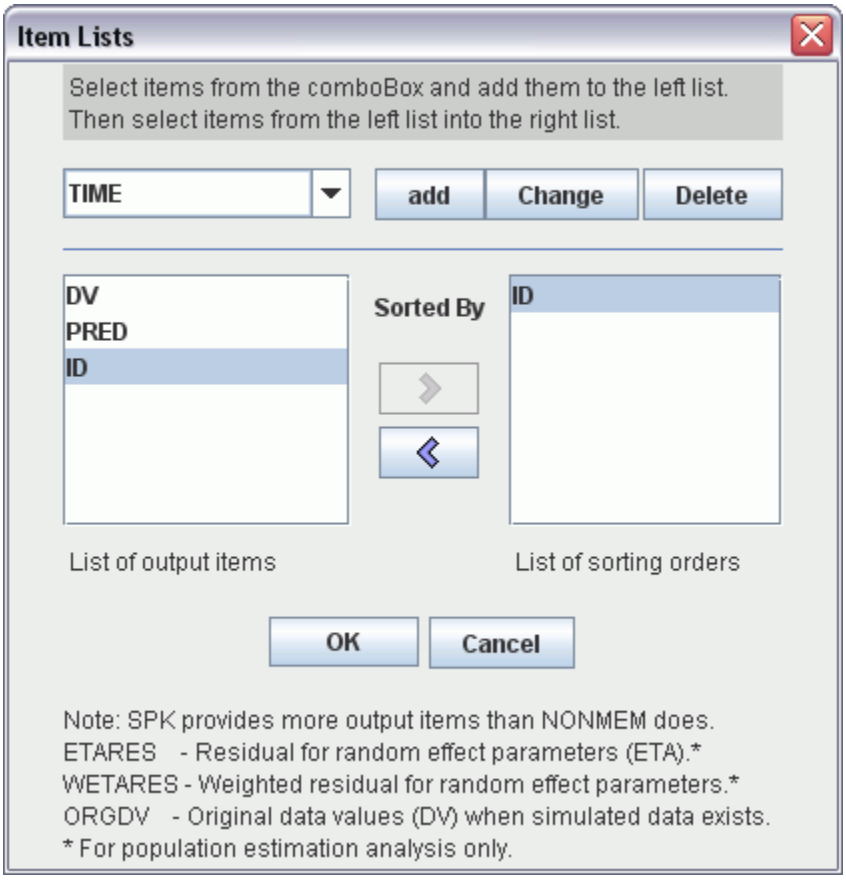
By clicking on **Make Selection**, items to be plotted and their sorting orders can be defined. This is the screen that becomes available when Make Selection is invoked:



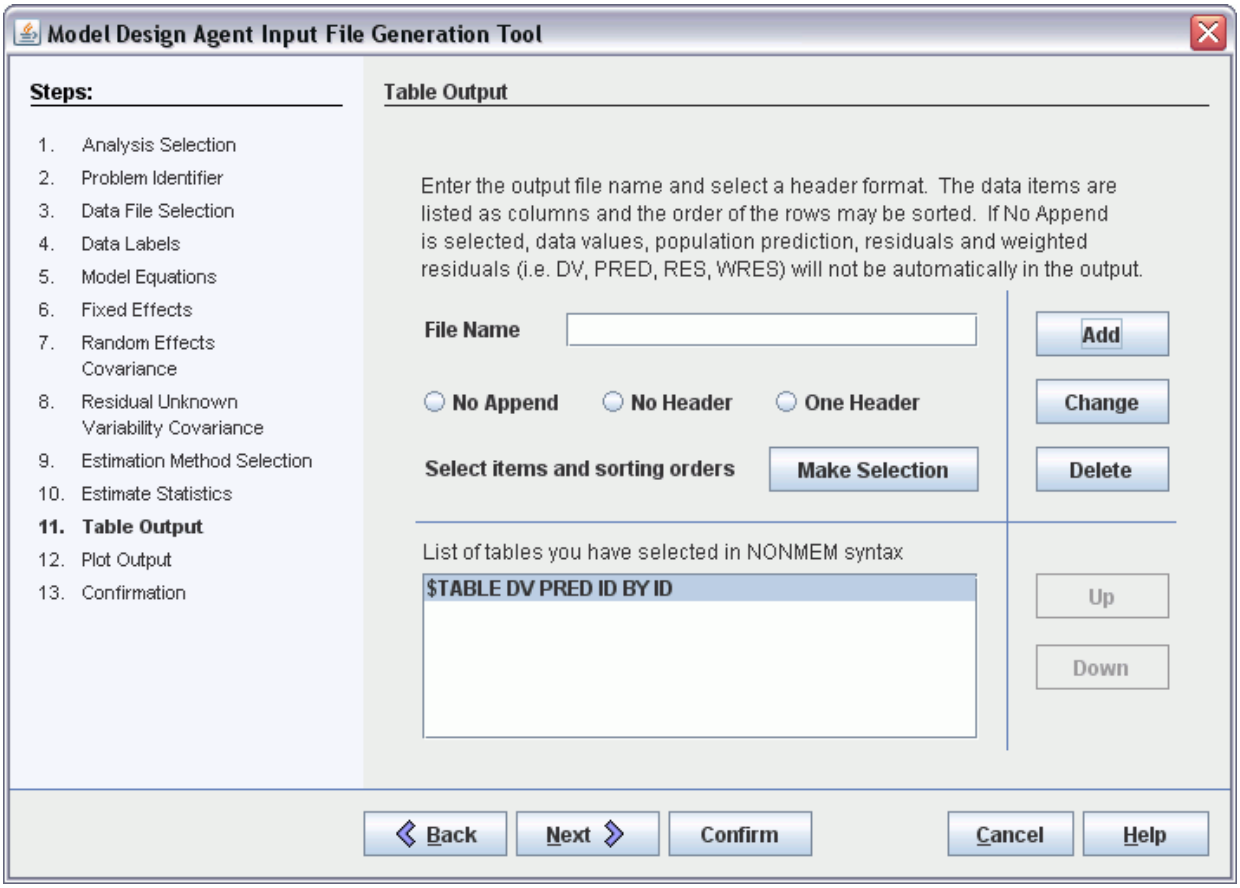
In addition to DV, PRED, WRES and RES, SPK also provides:

- ETARES, the residuals for the random effect parameters. These are the differences between the individual ETAs (random effects) and their average;
- WETARES, the weighted residuals for the random effect parameters. These are the differences between the individual ETAs (random effects) and their average, weighted by the corresponding OMEGA elements;
- ORGDV, the original data values (DV) in the data file when simulated data are generated.

Any combination of input and output variables can be selected. For example, in the screen shot below, we have selected to return DV and PRED, sorted by subject ID:



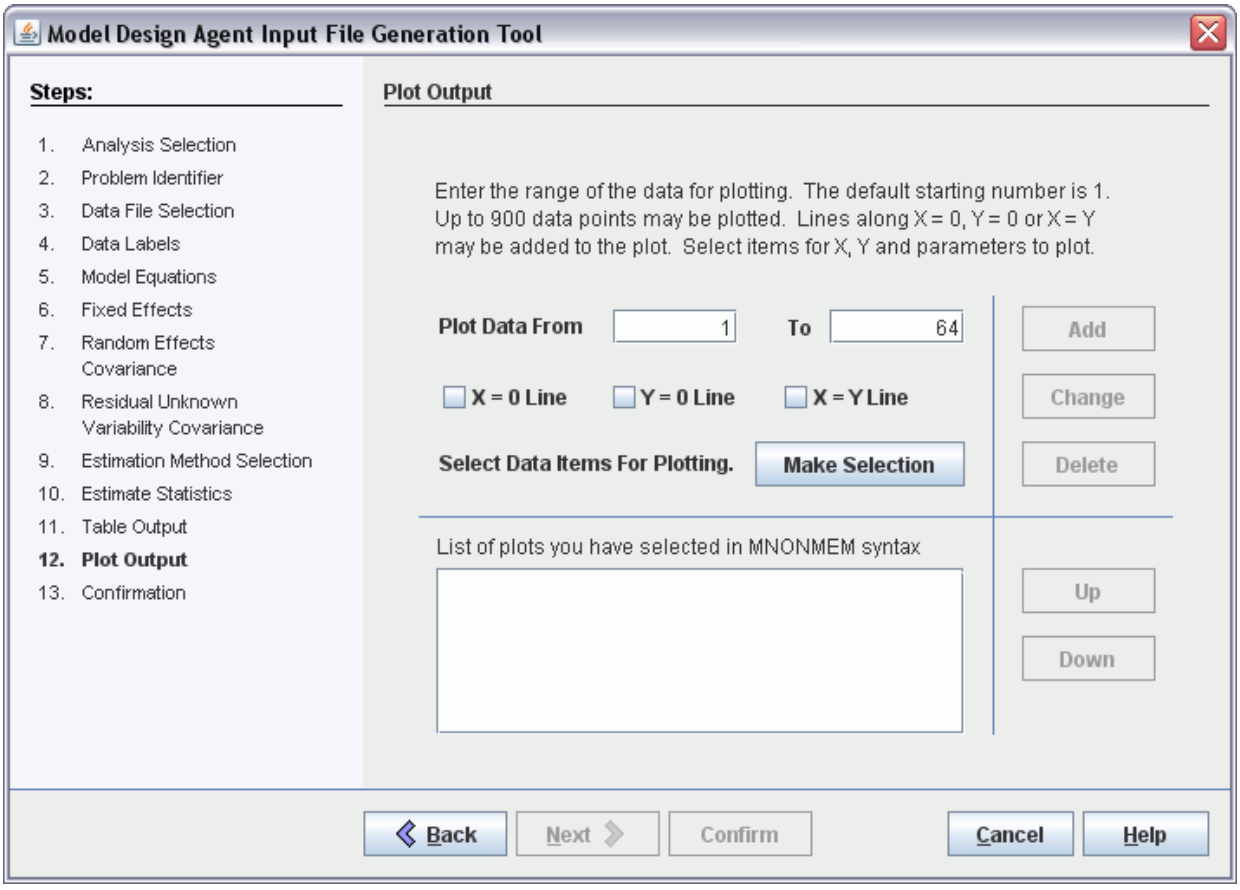
After selecting OK, we are returned to the screen below – one still needs to select **Add** for the table output to be saved and be displayed in NONMEM(R) format.



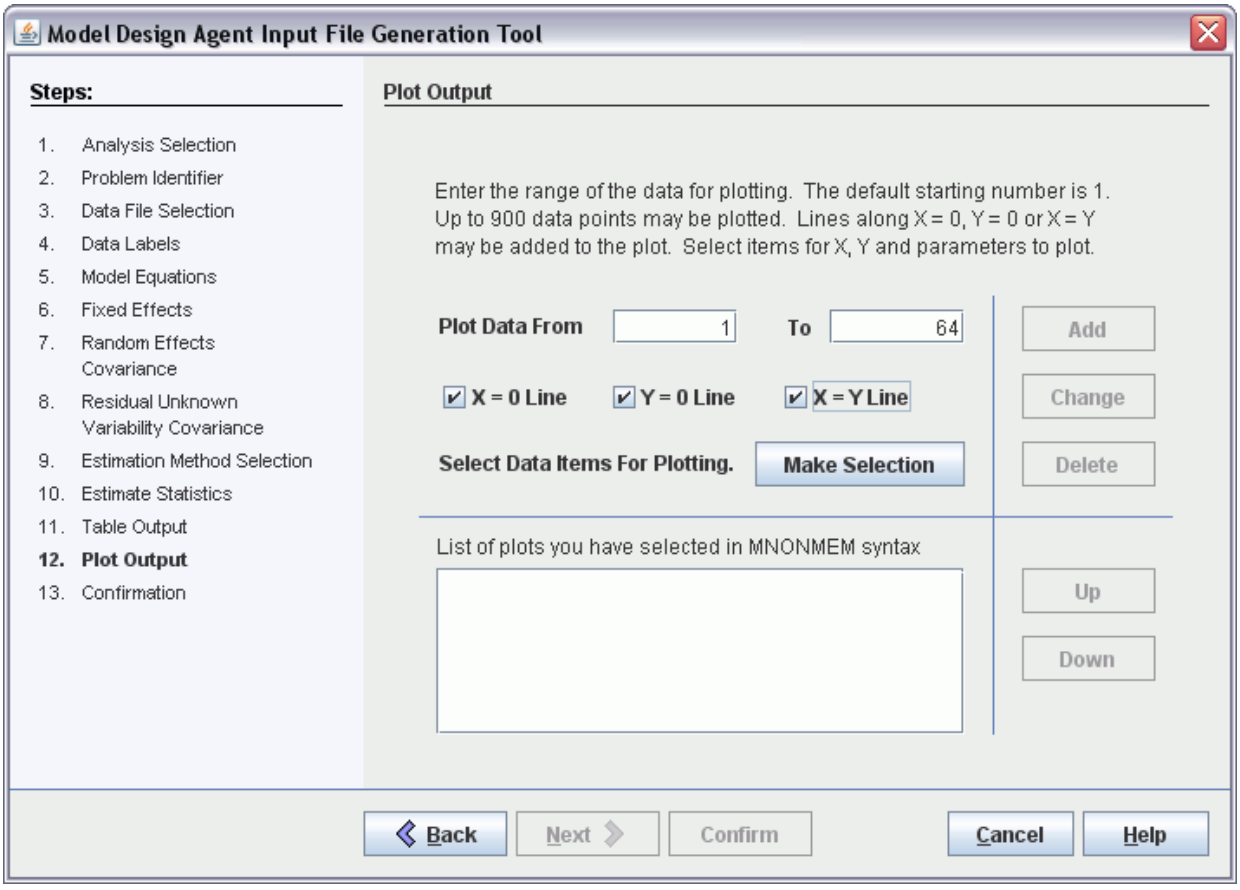
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Plot Output

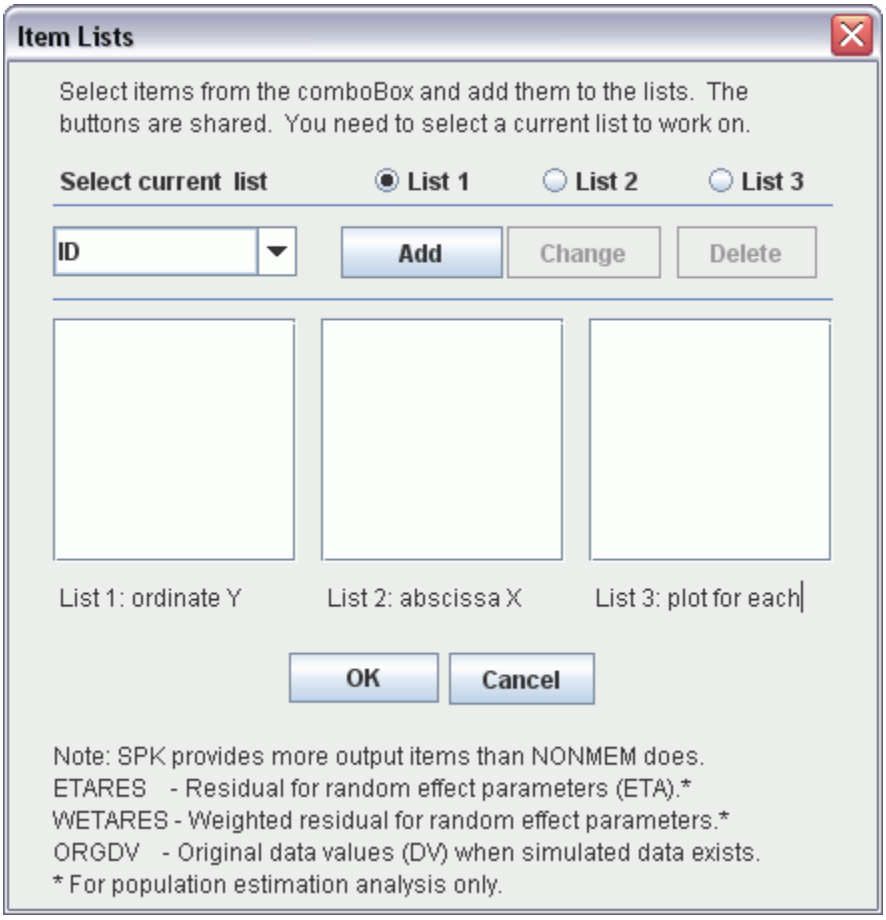
SPK offers basic and extended plotting capabilities. The options in this window apply only if one wants to generate NONMEM(R)-compatible plots, since SPK plots can be usually generated from the report window. The screen below is the starting point to define plot output following the Estimation step:



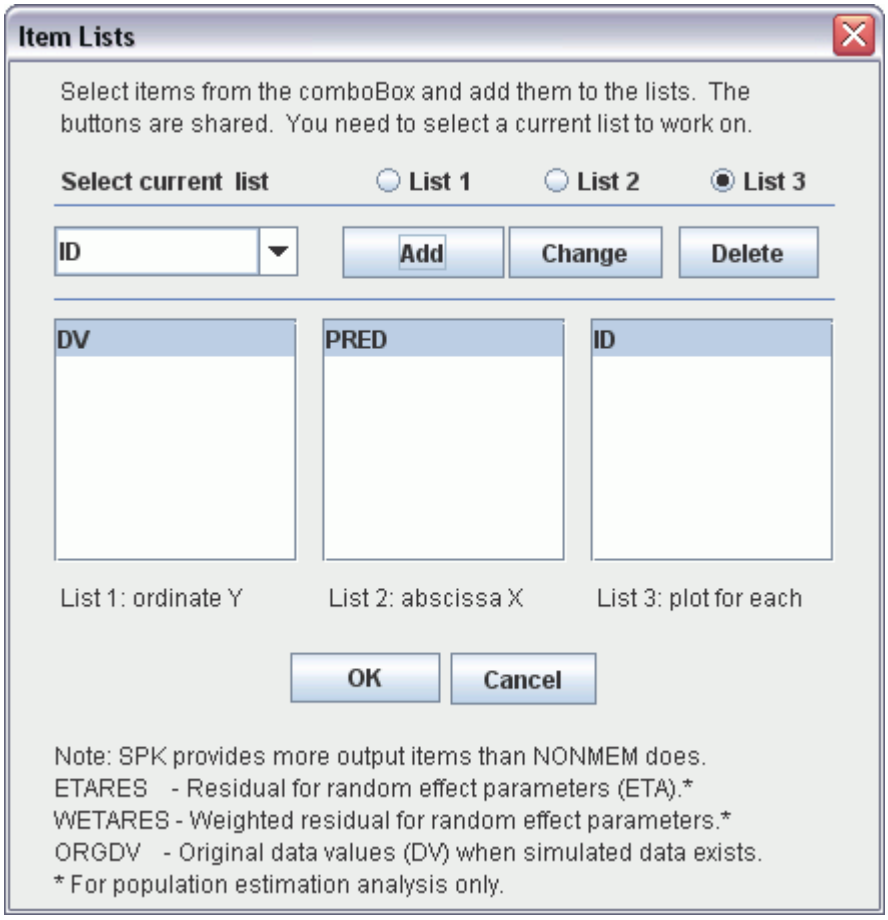
In the instance below, the data are plotted from 1 to 64 (the maximum number of data records in this instance), and we have asked for the x-axis, the y-axis and the identity line to be displayed.



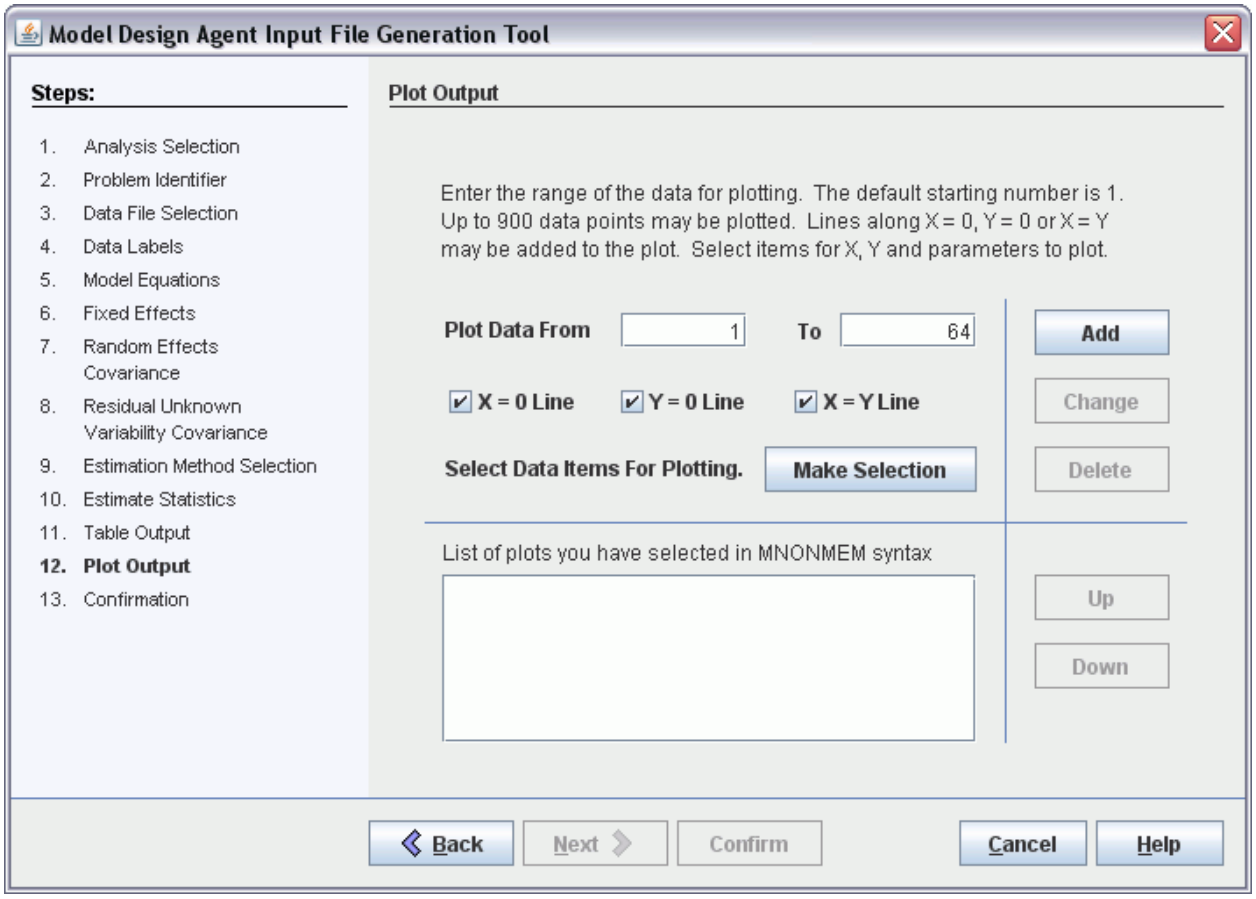
Plotting variables are selected similarly to the tabular output variables by clicking on Make Selection. The following screen appears:



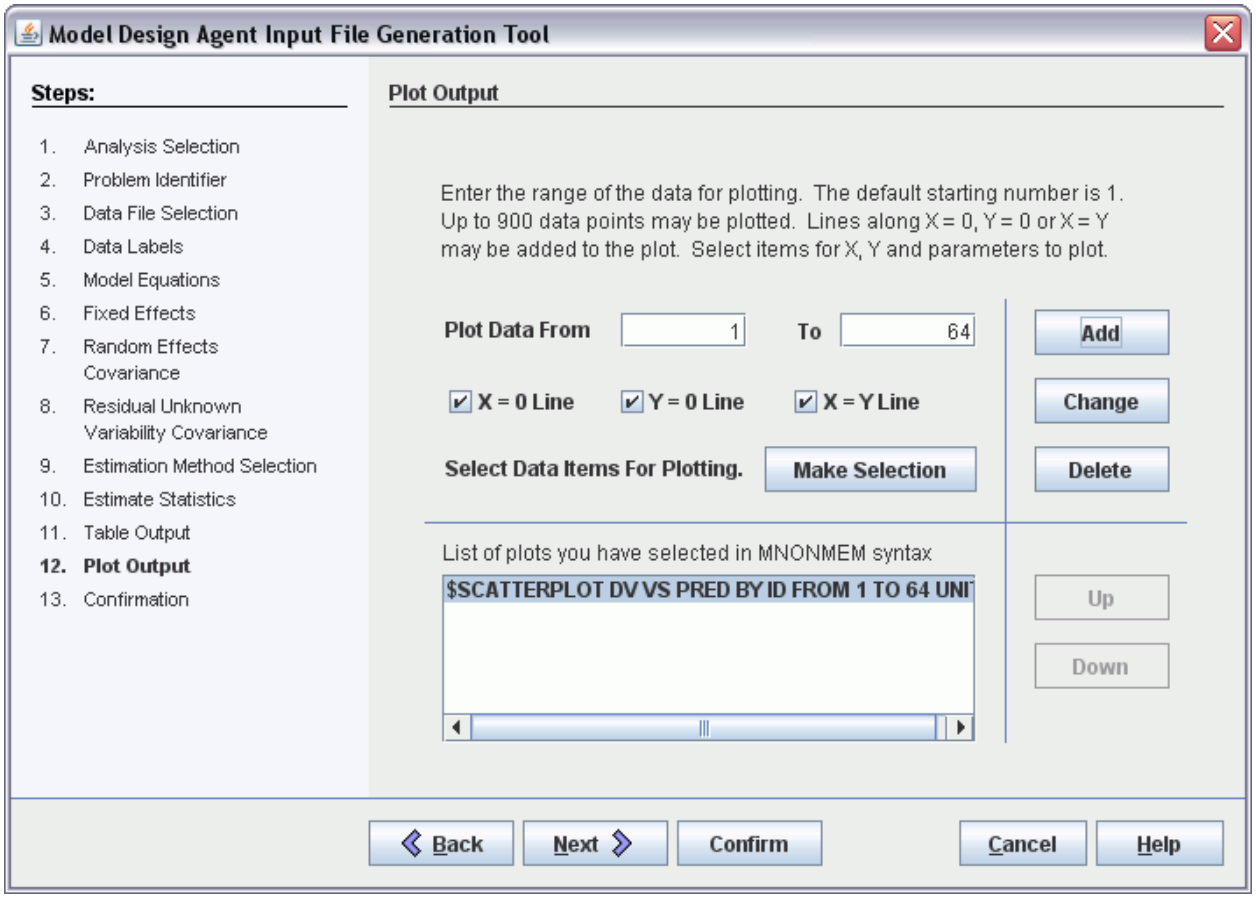
For example, one can ask to plot the predictions (PRED) on the x-axis and the data values (DV) on the y-axis, plotted for each subject ID:



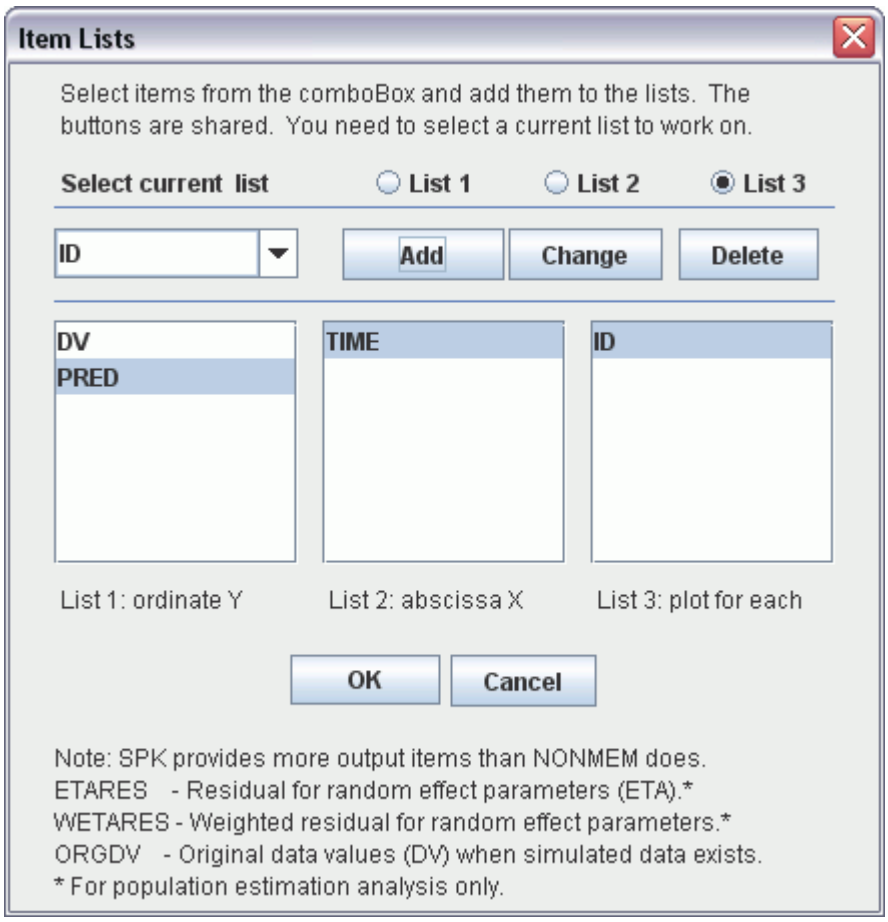
In the example above, "List 1", "2" and "3" correspond to the ordinate, abscissa and splitting variable respectively. After clicking on OK, one is returned to the screen below:



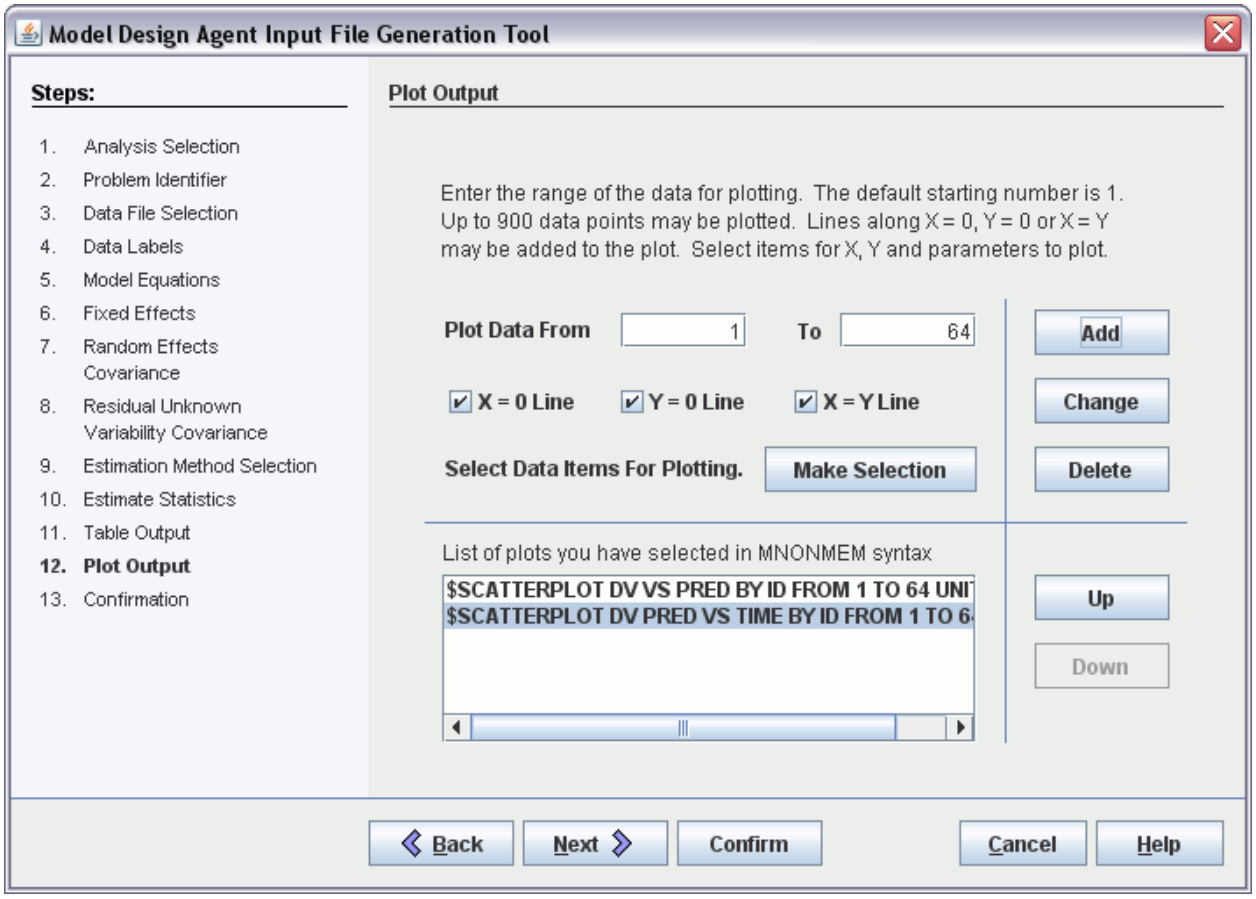
After clicking "Add", the plot variables are saved and displayed in NONMEM(R) syntax:



Another plot can be added, for example, by selecting to plot DV and PRED against TIME, splitted by ID:



The resulting selection is as follows:



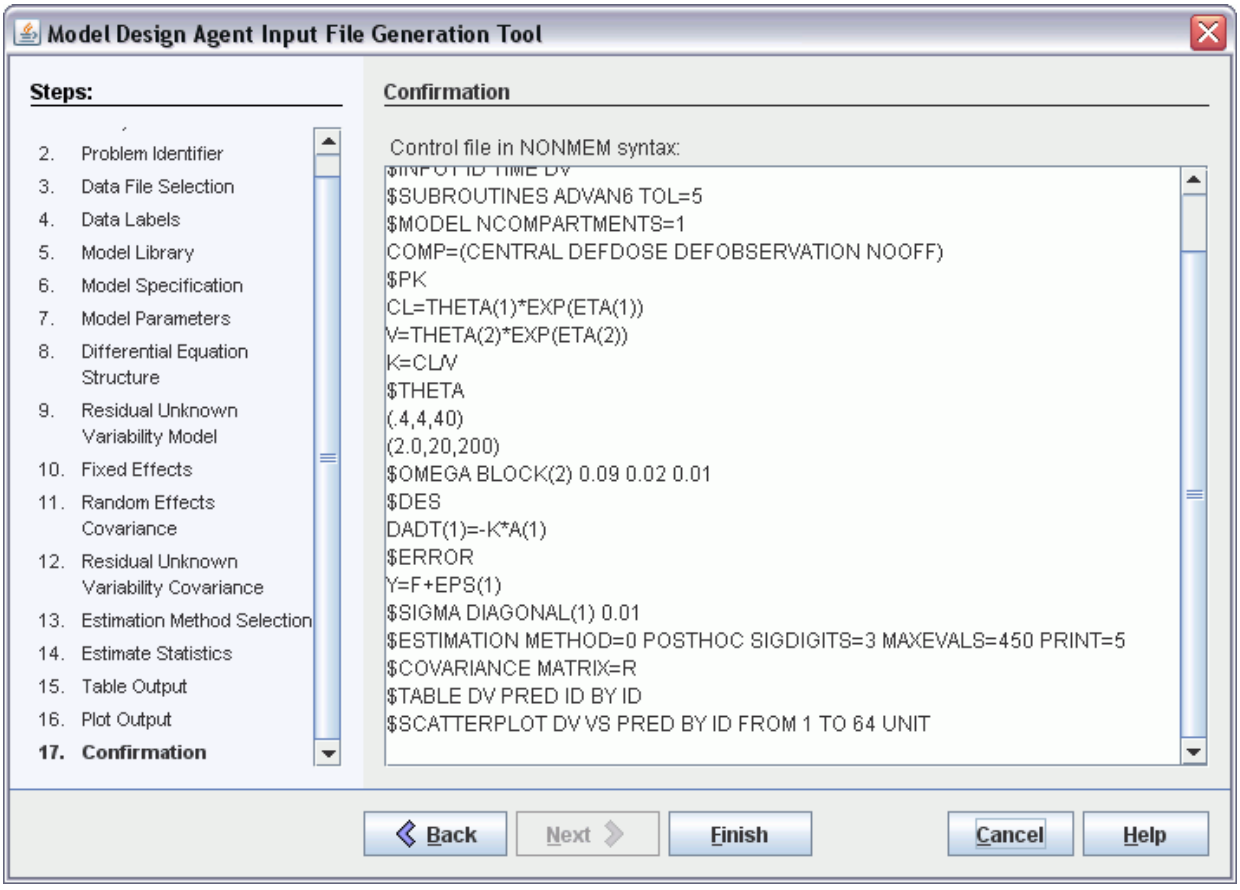
After you have performed the requested operations, the "Next" button will highlight and you can select it and continue. You can navigate back and forth in the MDA interface using the "Back" and "Next" buttons. The "Confirm" button displays the NONMEM(R) control file generated by the MDA up to this step in the process. Clicking "Cancel" will abort the model definition, while selecting "Help" will bring you to the relevant Help topic.

Prepare Input: Confirmation

The problem has now been completely defined, and if you reached this step your model has all the required information.

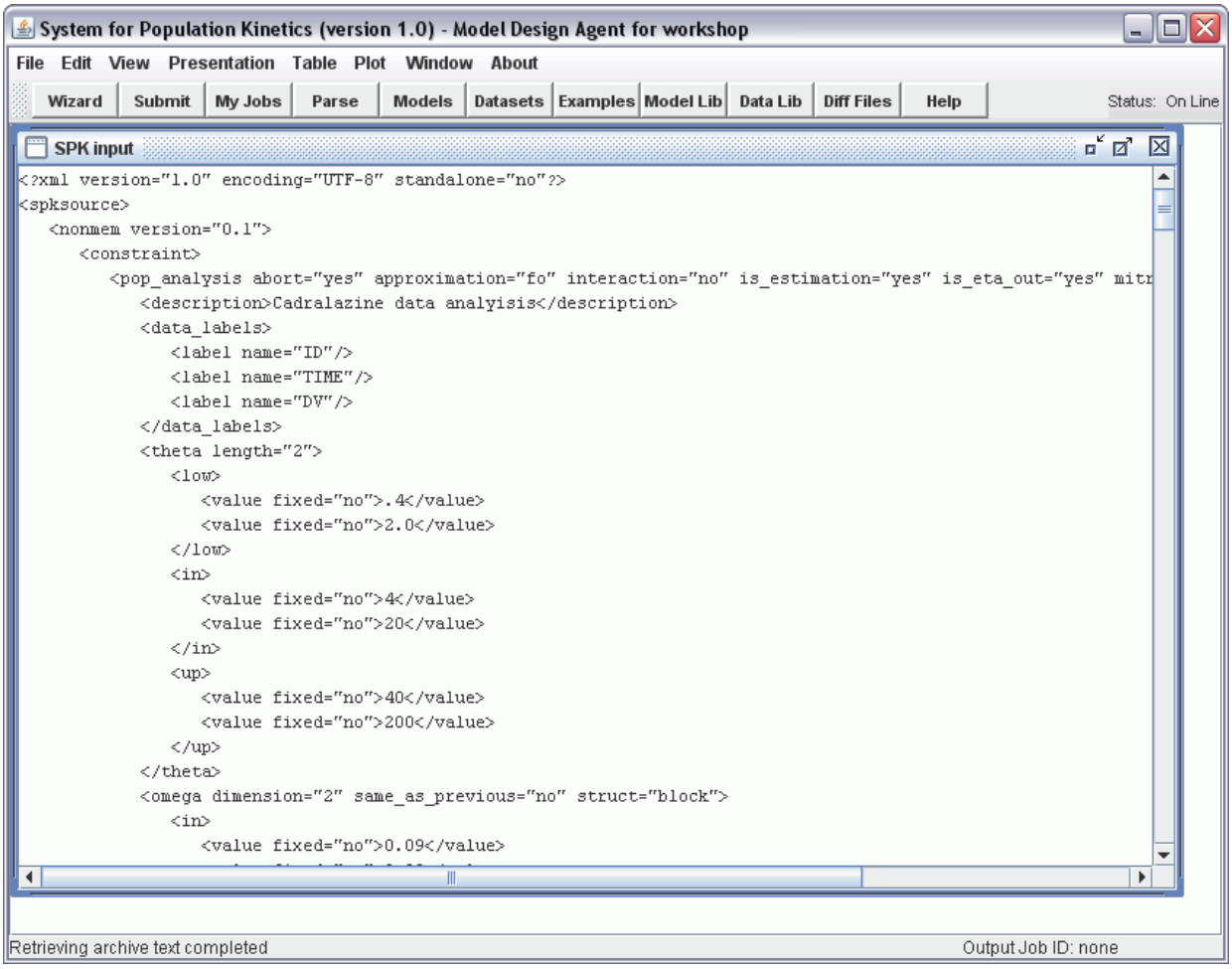
It is time now to finalize the model structure before submission to the computational library.

The model information is shown in NONMEM(R) format, since at this time system functionality is comparable to NONMEM(R). Commands which are not compatible with NONMEM(R) will be flagged in future versions.



If you would like to change the model specification, simply use the "Back" button to return to the appropriate screen.

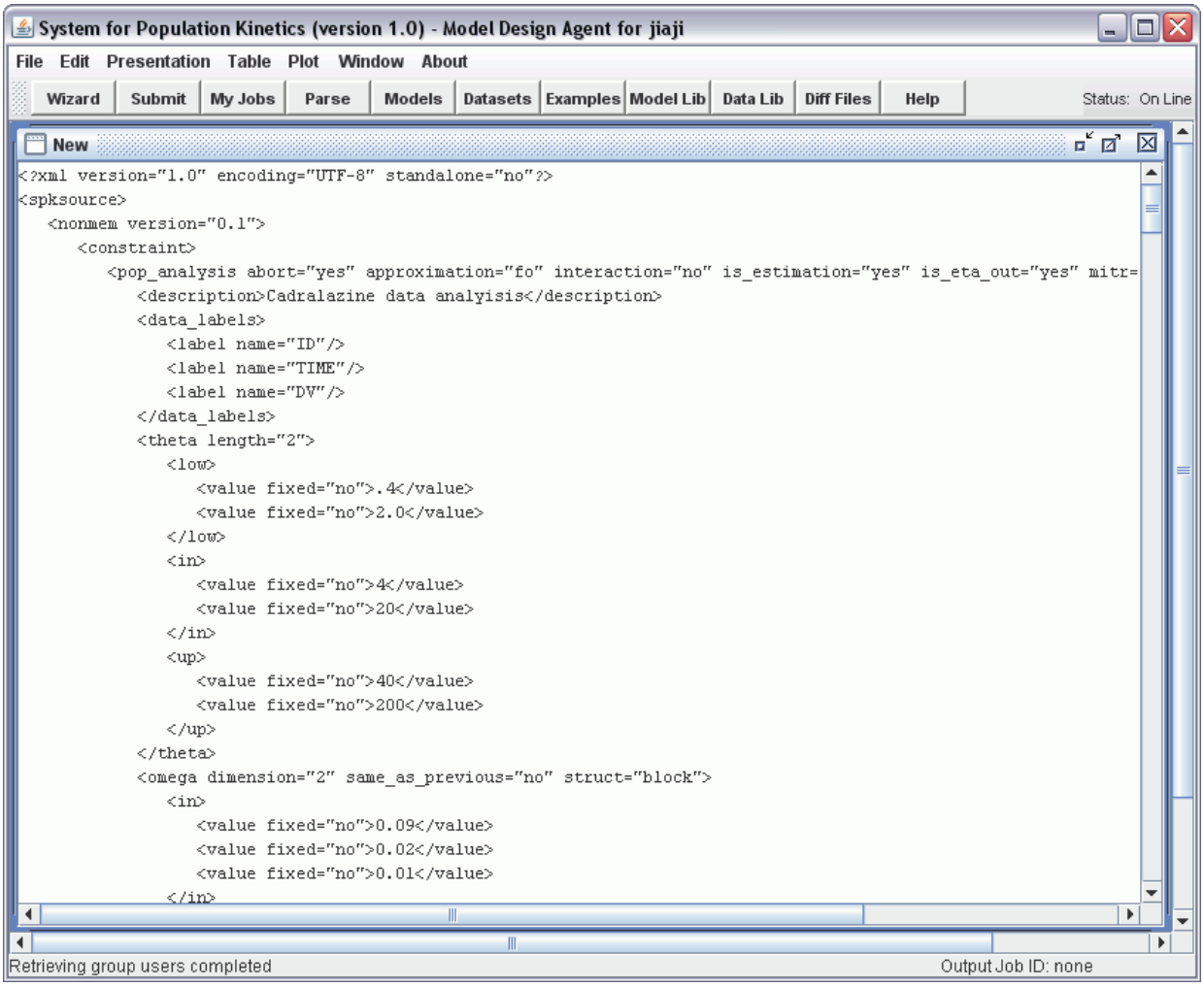
If the model is satisfactory, you should click the "Finish" button, which finalizes the model structure and starts the translation in XML, which is the modeling language spoken by the computational kernel. Then, the system will present the XML translation of your model file.



At this point, the model file is ready to be submitted to the computational library by clicking on "Submit Job" (the second button from the top left). Please note that you should now either submit the job or save it locally, or the whole process will be lost.

Submit Job

This action sends the XML model code to the computational server for execution. Submit is the second button from the left in the MDA main window.



This button, when activated, brings up a dialog box, the **Job Submission Dialog**.

In this dialog there are three tabbed panes for "Model", Dataset" and "Job", respectively.

The "Model' and the "Dataset" panes allow the user to specify the names and descriptors of the model and the dataset used in the job.

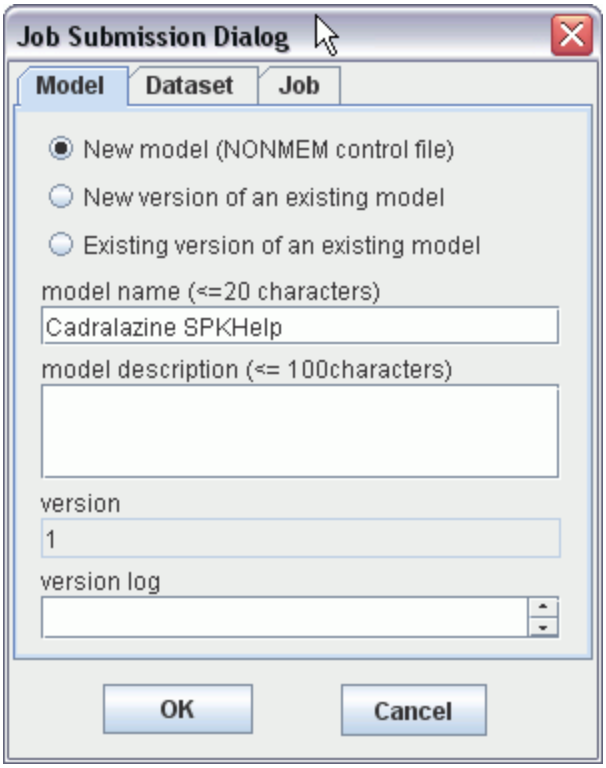
The "Job" pane displays the analysis method for the job and allows the user to enter a short job abstract.

More specifically, you are asked whether the job you are submitting contains:

- A new model (as defined by the NONMEM(R) control file), which applies when the model you have defined is completely new and it has not been derived from a previous model (a model name must be entered if this is the case);

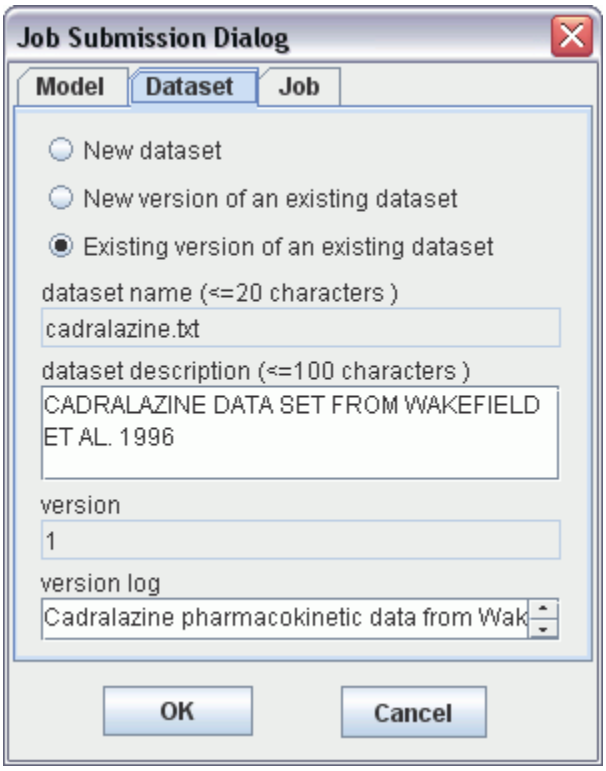
- A new version of an existing model, which applies when your model has been derived from a previous model by changing some options (e.g., the between-subject variability options, the initial parameter values, etc.). The most common case when this may occur is when the same dataset is analyzed with different models, to compare modeling strategies. You will be asked to select the model of which this one is a derivative version, and the version number is automatically updated by the system.
- An existing version of an existing model: this may apply, for example, when the model is exactly the same as a previous model, and the dataset being analyzed is changed.

If the job is a likelihood evaluation job, only the job pane appears (since the parent job's model and dataset are used automatically). In this case, the user must choose among the available likelihood integration methods. Each integrator provides a different approximation to the negative logarithm of the likelihood near the (approximate) optimal value provided by the estimation method.

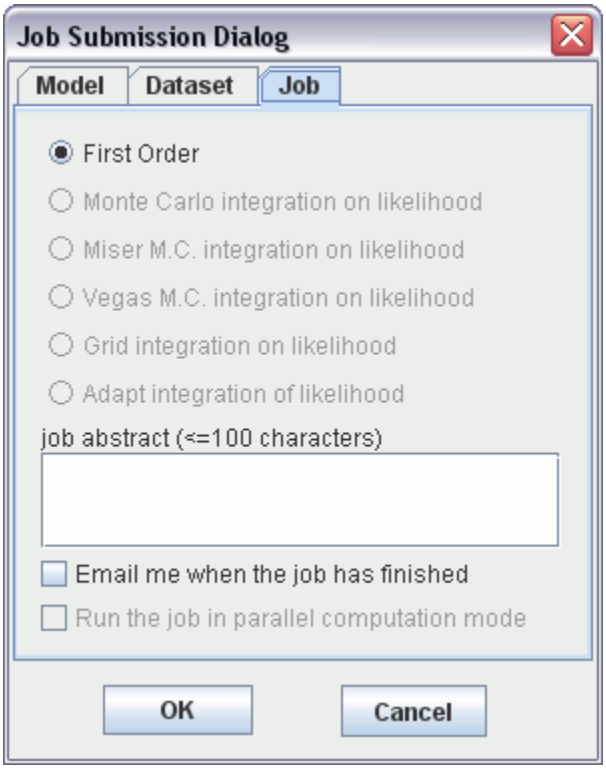


The second tab of the Job Submission Dialog regards the dataset which is associated with the job you are submitting. Again, there are three cases:

- A new dataset: this situation applies when the dataset you wish to analyze is completely new and it has not been derived from a previous dataset;
- A new version of an existing dataset, which applies when your dataset has been derived from a previous dataset by changing some data (e.g., removing a sample value, or a subject, or modifying input rates, etc.). The most common case when this may occur is when your purpose is to measure the effect of removing outlying observations. You will be asked to select the dataset of which this one is a derivative version, and the version number is automatically updated by the system.
- An existing version of an existing dataset: this applies, for example, when this dataset is exactly the same as a previous dataset, and you are analyzing it with a new model.

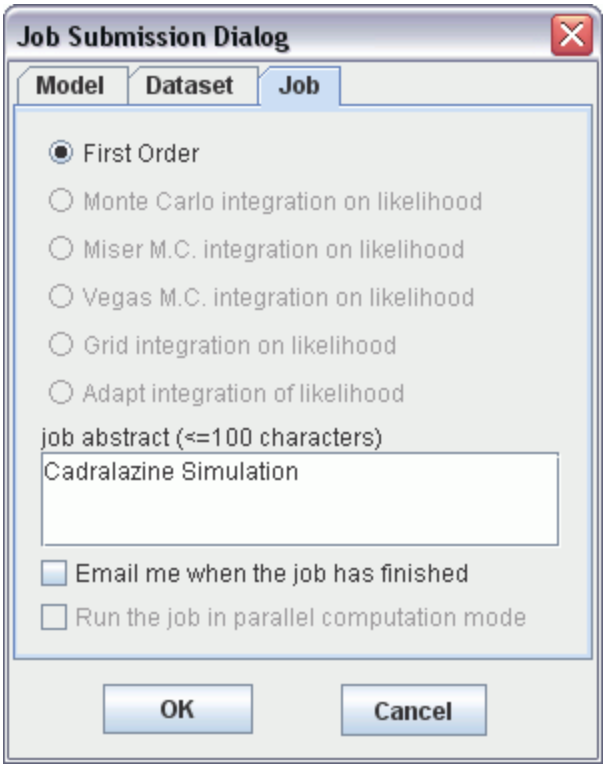


For new models and datasets, you will be asked to enter a descriptive name and a short description. It pays to be as descriptive as possible.

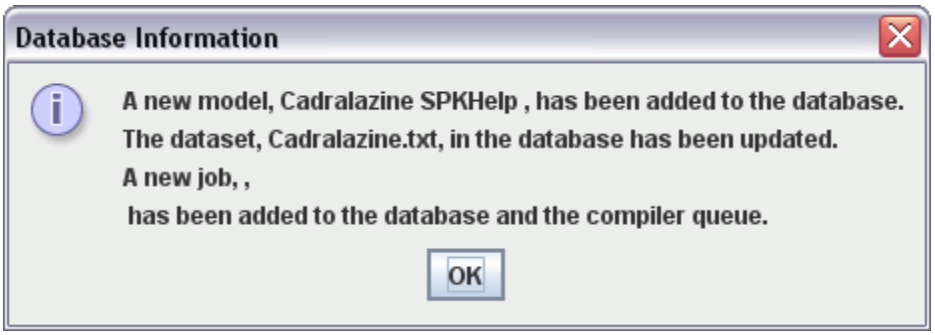


The Job Description you provide here will be visible when you access the database (see under **My Jobs**). It will be editable later from the Job information page (again, see under **My Jobs**).

If the job had been a simulation job, then the following would appear:



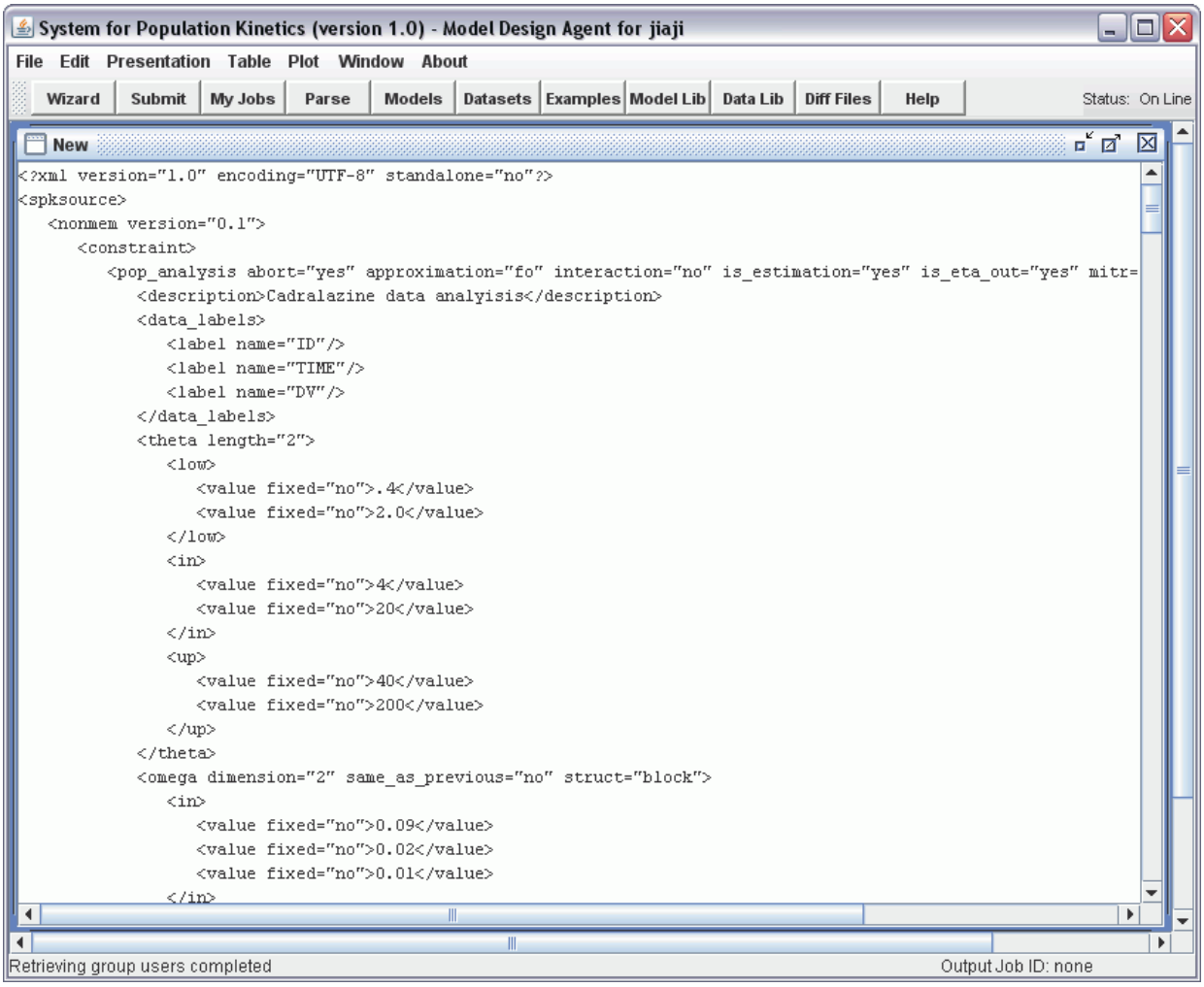
After you click OK on the Job Submission Dialog, the job is sent to the computational kernel. Lastly, you are told that your model is queued for execution:



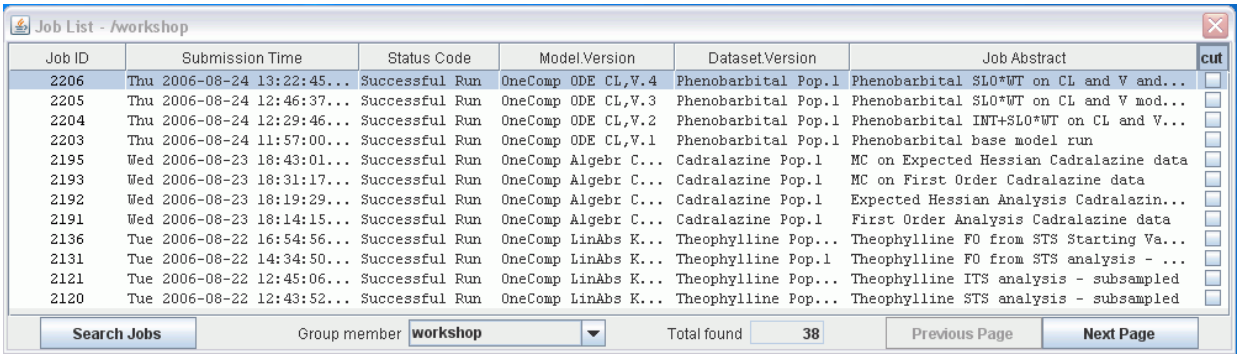
Congratulations! You have completed your SPK run submission! When you click OK, you are returned to the MDA.

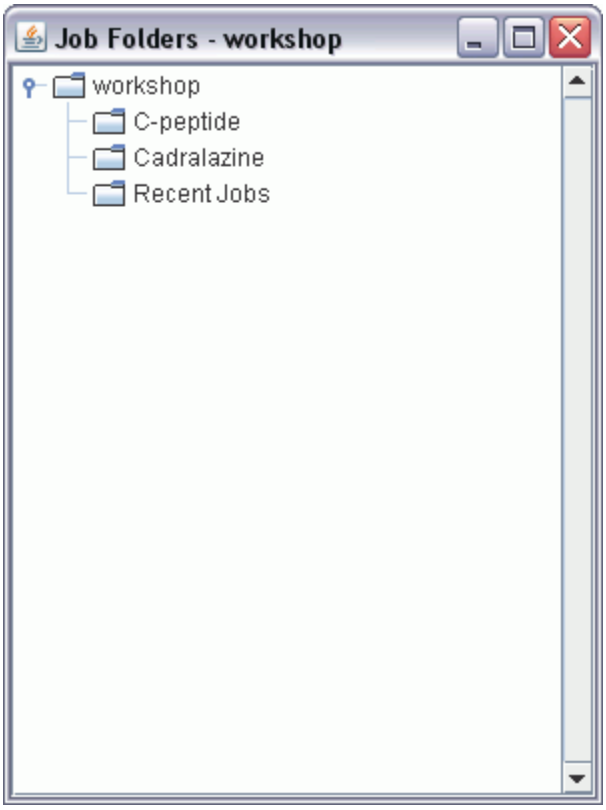
My Jobs and Job Information Page

Every job sent to the SPK computational server through the MDA is logged in the user's personal database. This database can be accessed by clicking on **My Jobs**. This is the third button from the left in the MDA main window.



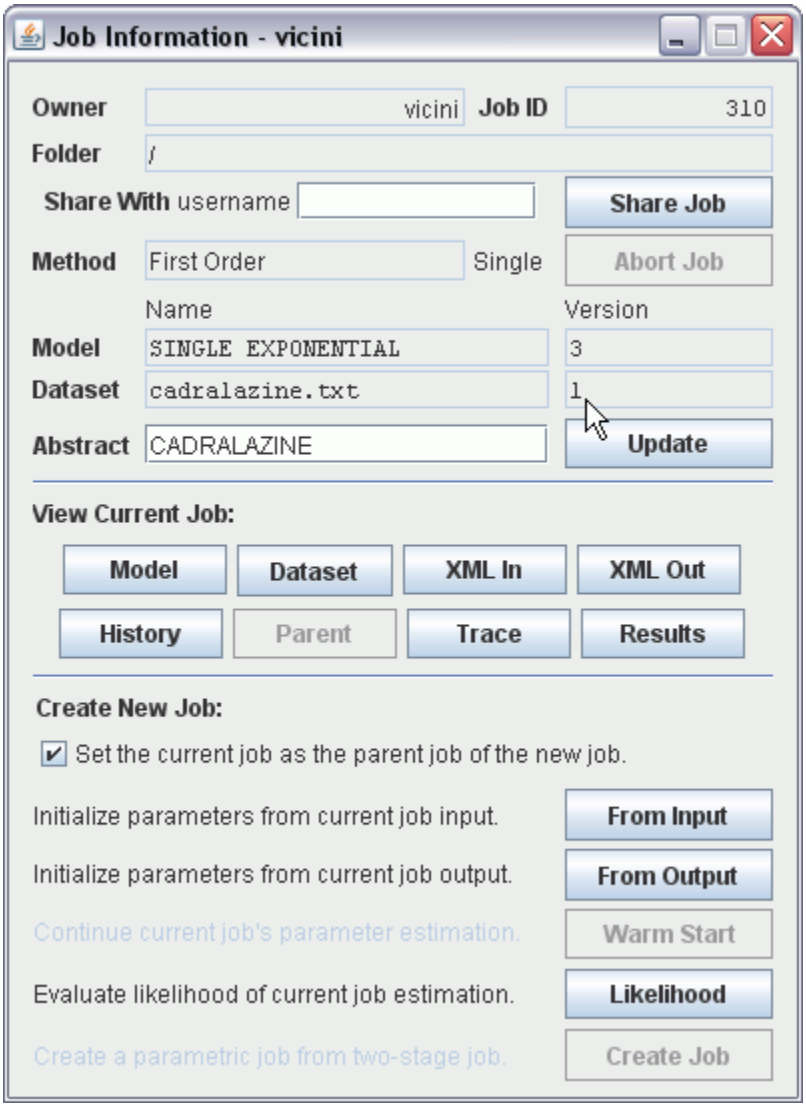
By clicking on **My Jobs**, the user accesses a personal database where every job is stored and assigned a Job ID, a Submission Time, a Status Code, a Model Version, a Dataset Version and a Job Abstract.





The **Search Jobs** button allows the user to refine the job list by specifying search terms or job numbers. The **Group member** drop-down menu allows one user to see jobs that belong to other members of the Group. Users can establish groups by contacting the SPK administrator.

Users can select jobs on the list by clicking on the corresponding line. Selecting, for example, Job ID 310, a Job Information window is accessed:



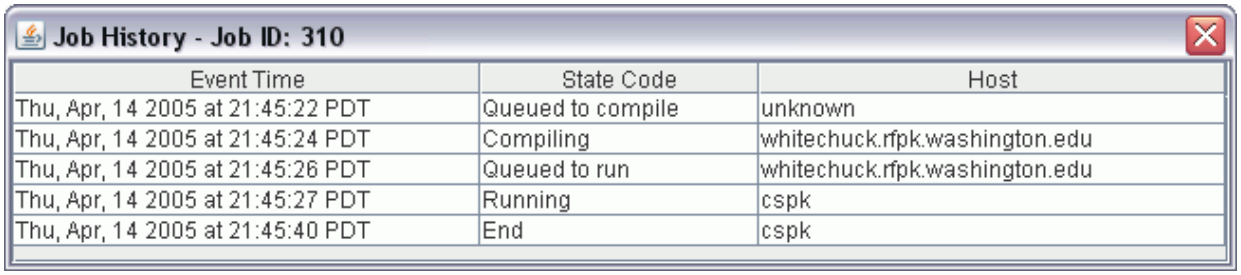
Various information regarding the job is displayed in this window. In addition, the job can be shared with another user (a blue-tinted job number will appear in that user's job list). The Model and Dataset used in the job appear (with a version number) and the job abstract is also listed (this can be edited).

There are eight options for viewing information related to the current job and up to five options for creating a new job from the current job:

Information retrieval options are:

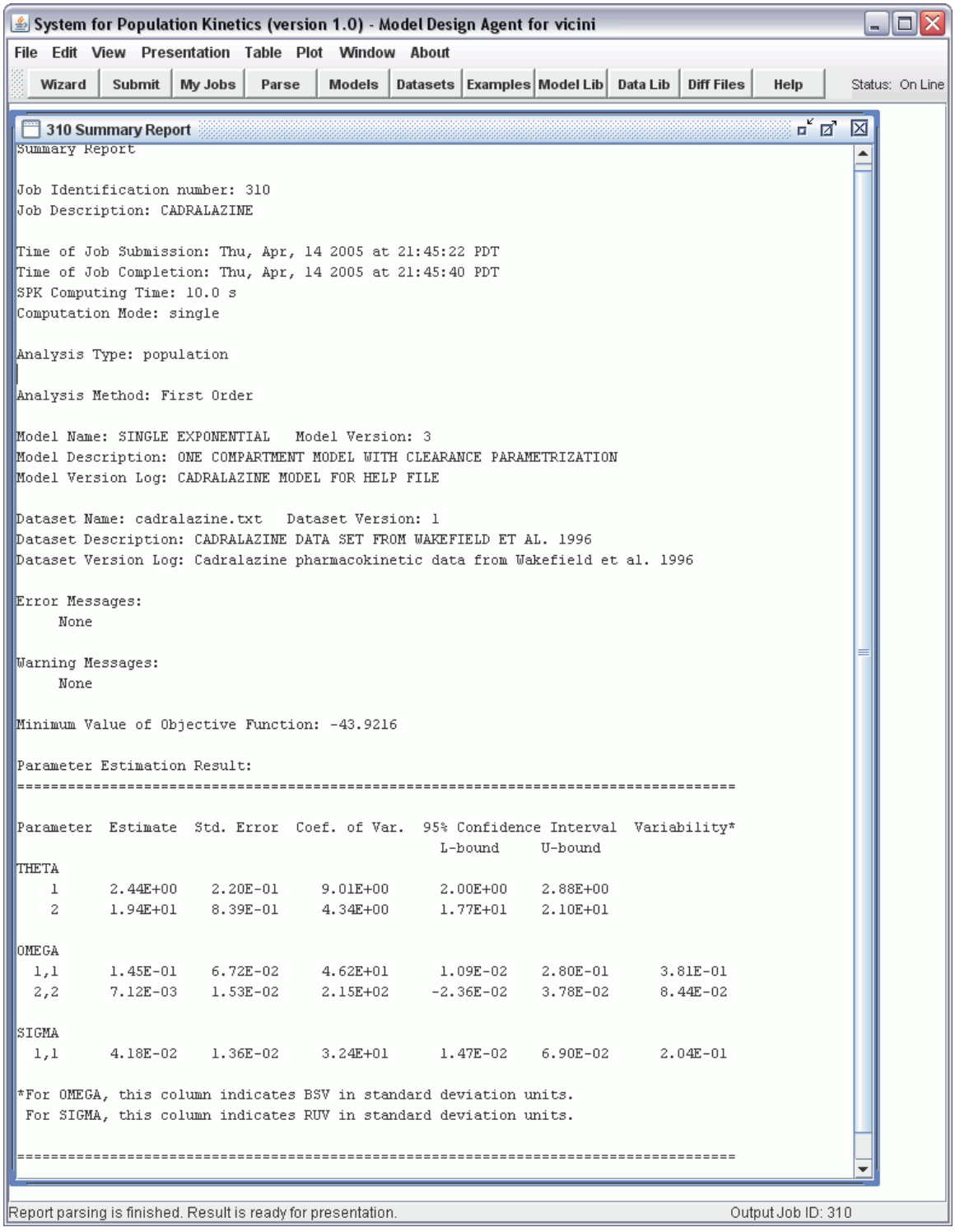
- **Model**: clicking on this button brings up the NONMEM(R) control file for this job in the MDA editor window.
- **Dataset**: selecting this option visualizes the data file in the MDA editor window.

- **XML In**: selecting this option visualizes the input XML file in the MDA editor window.
- **XML Out**: selecting this option visualizes the output XML file in the MDA editor window.
- **History**: selecting this option visualizes the time history of the job from submission to completion, and allows to determine how much time was spent in the compilation and execution of the job.



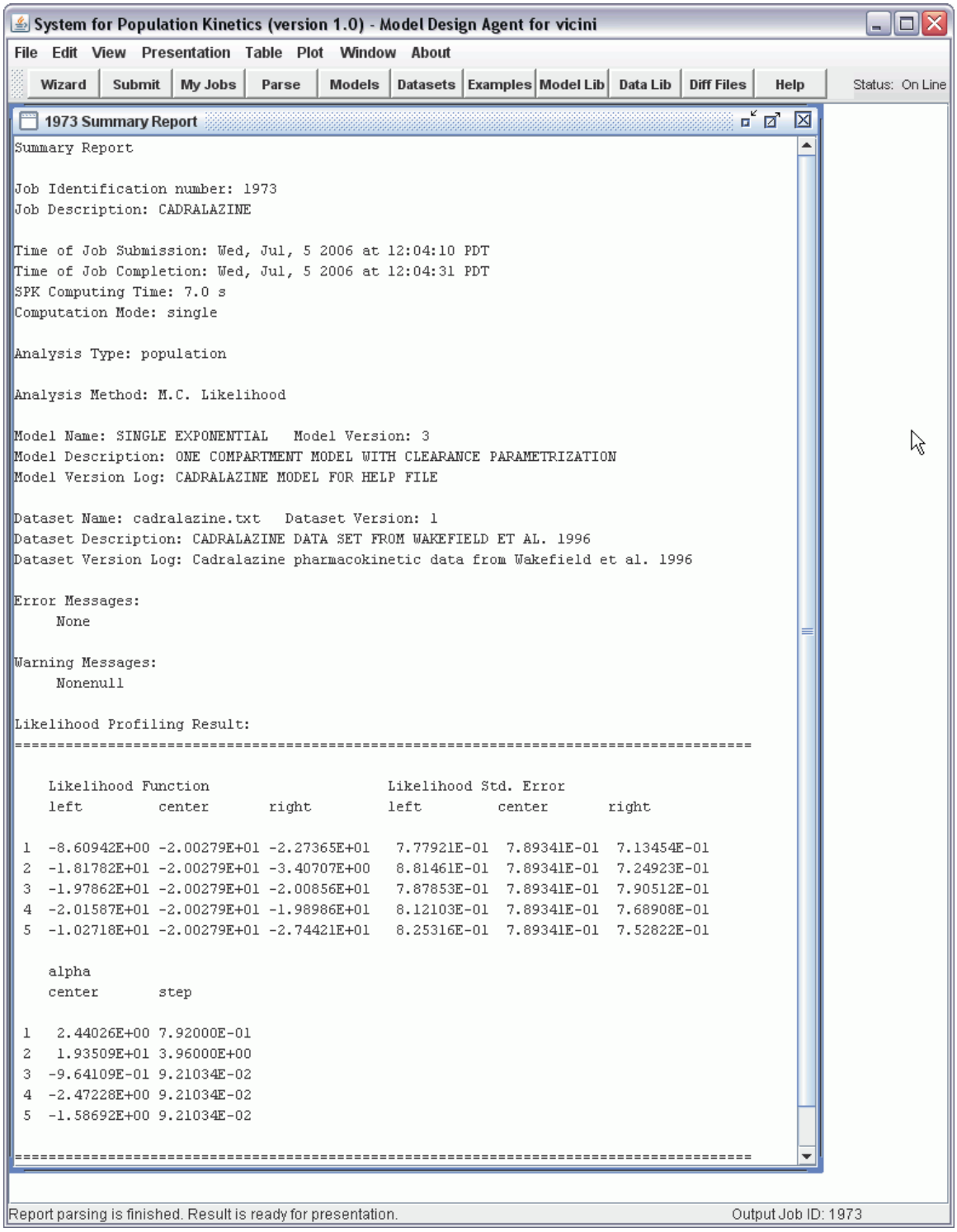
Event Time	State Code	Host
Thu, Apr, 14 2005 at 21:45:22 PDT	Queued to compile	unknown
Thu, Apr, 14 2005 at 21:45:24 PDT	Compiling	whitechuck.rfpk.washington.edu
Thu, Apr, 14 2005 at 21:45:26 PDT	Queued to run	whitechuck.rfpk.washington.edu
Thu, Apr, 14 2005 at 21:45:27 PDT	Running	cspk
Thu, Apr, 14 2005 at 21:45:40 PDT	End	cspk

- **Parent**: this option opens the Job Information Window of the corresponding parent job, if one exists.
- **Trace/Status**: trace allows user to watch real-time optimizer trace for parameter estimation jobs, or status allows user to watch job completion progress for likelihood profiling jobs.
- **Results**: this option requests the MDA to load the output values (parameter estimates, model predictions) from the current job. After parsing the job output XML, the Summary Report is displayed first. The Summary Report for the file we have defined is below:

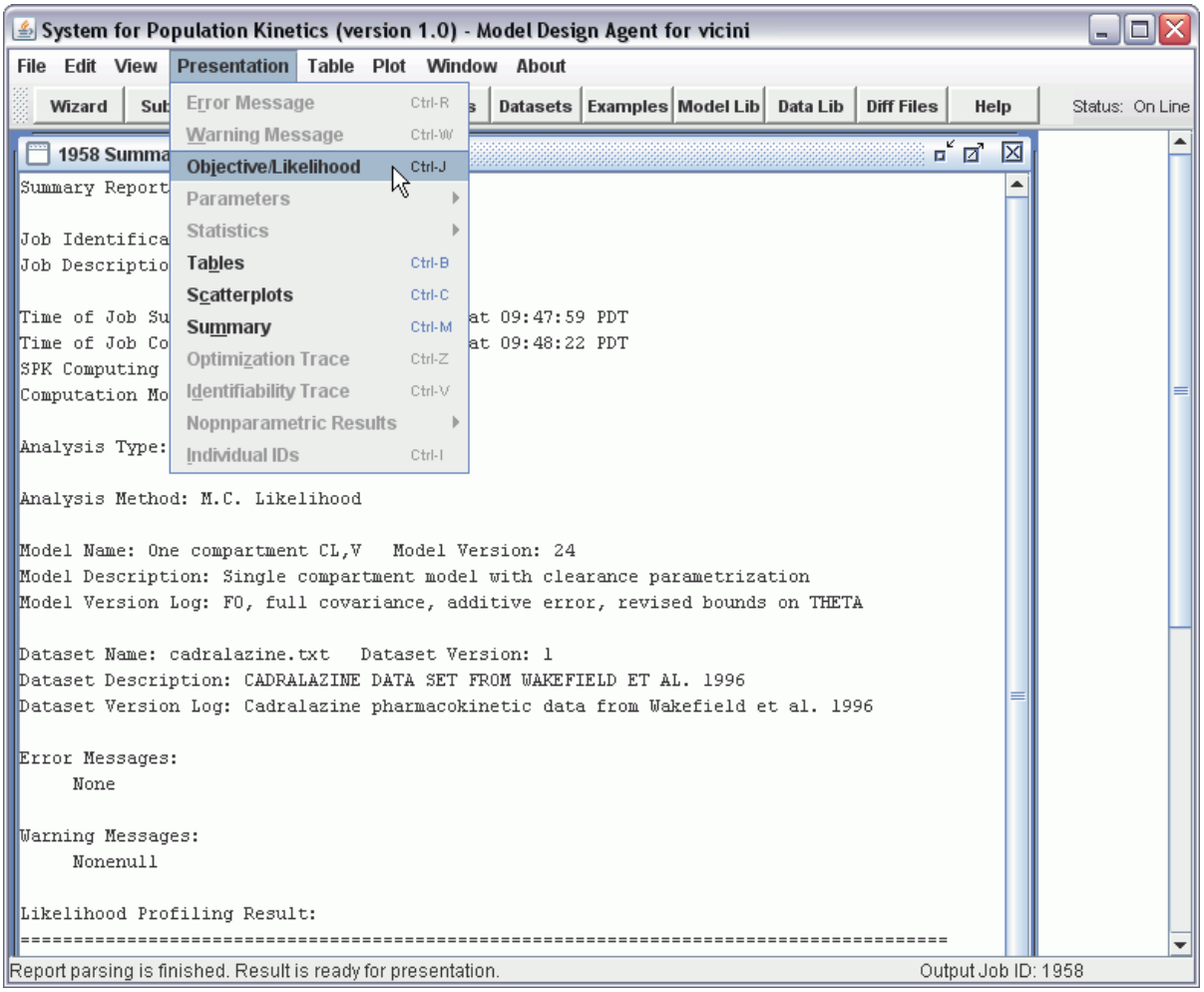


The Summary Report displays important information about the job, such as optimal parameter estimates, their coefficients of variation, lower and upper bound of the 95% confidence interval, and so on. If the job was a likelihood evaluation job, then the report only shows the

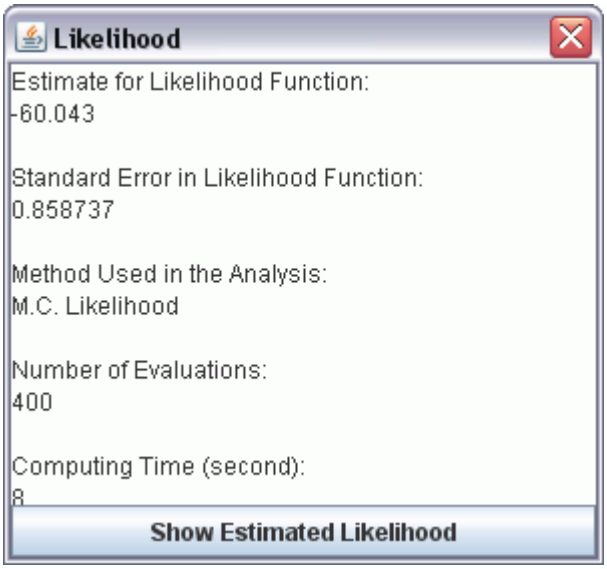
value of the integrated likelihood and its standard error from the Monte Carlo analysis, as shown below.



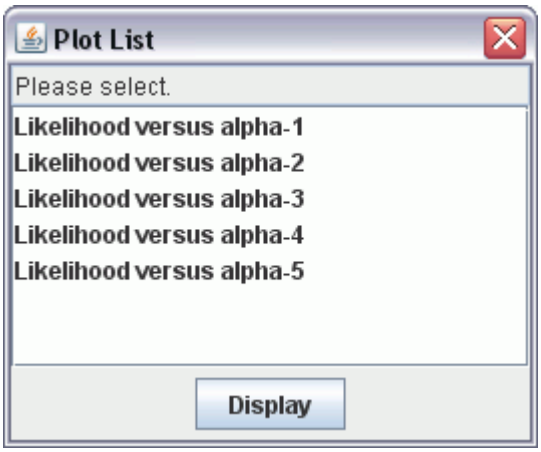
Graphical output from a Monte Carlo run can be accessed by going to the "Presentation" menu and selecting "Objective/Likelihood":



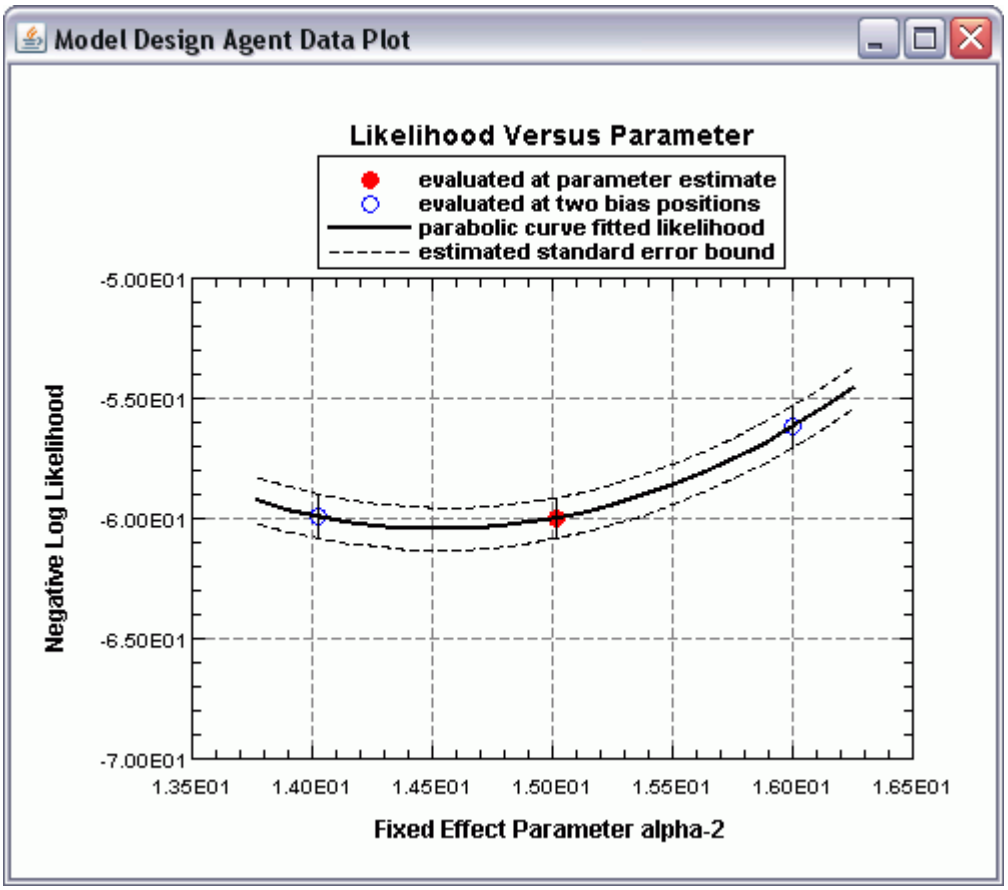
This opens a window that summarizes the results of the likelihood evaluation job, an example of which is shown below.



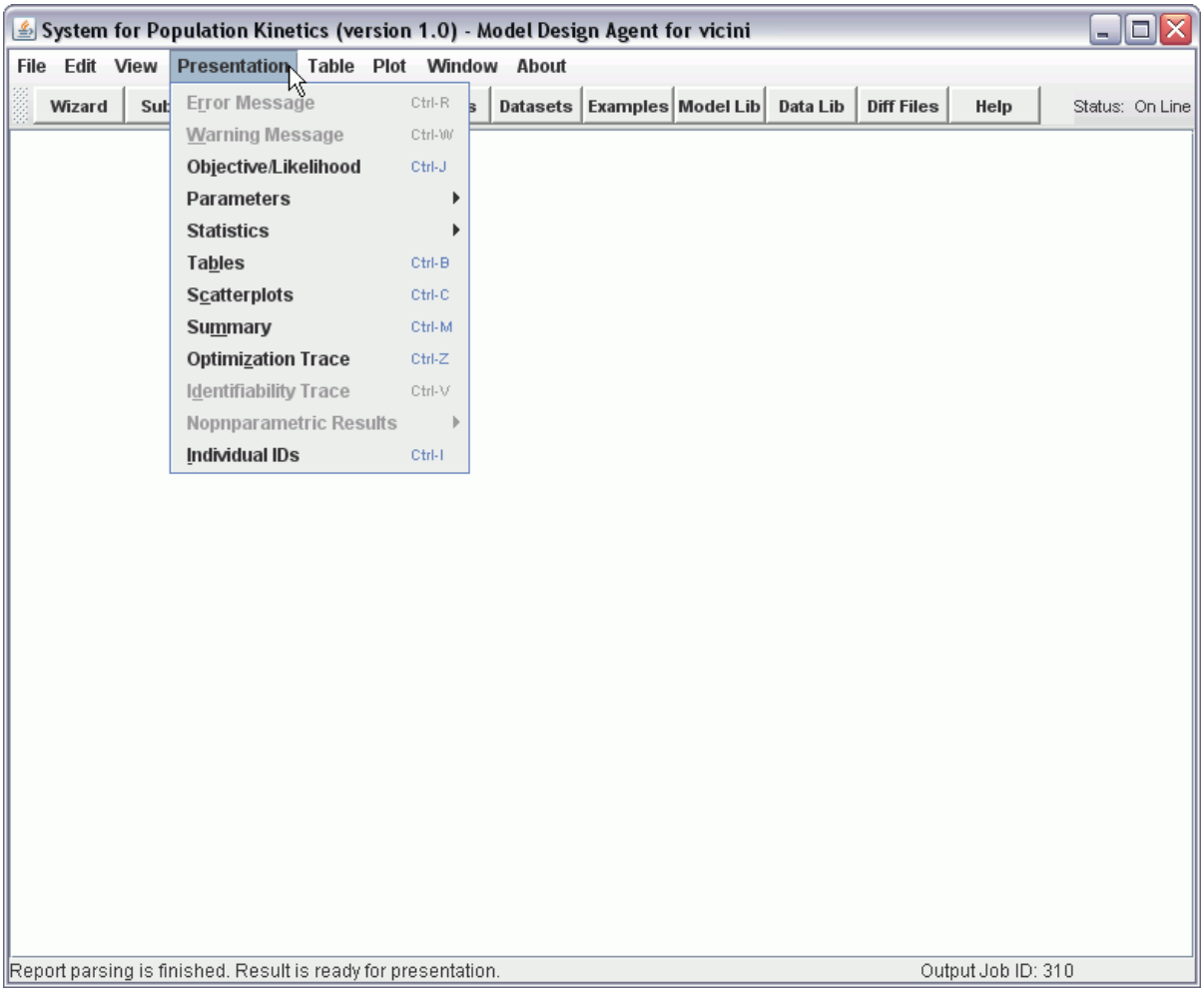
Clicking on "Show Estimated Likelihood" provides access to a series of plots that profile the Monte Carlo likelihood against each one of the fixed effects:



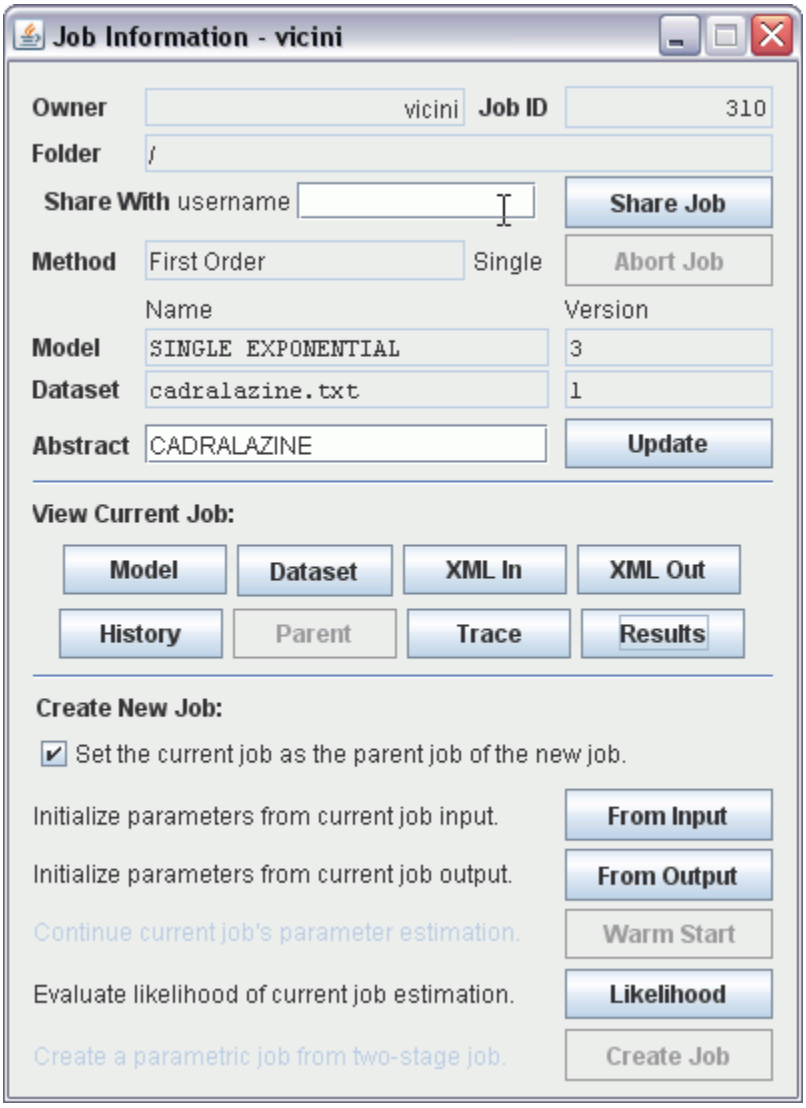
The user can select one or more of these plots. An example of profiling is shown below.



Other elements of the computational output can be accessed using the Presentation menu from the MDA:

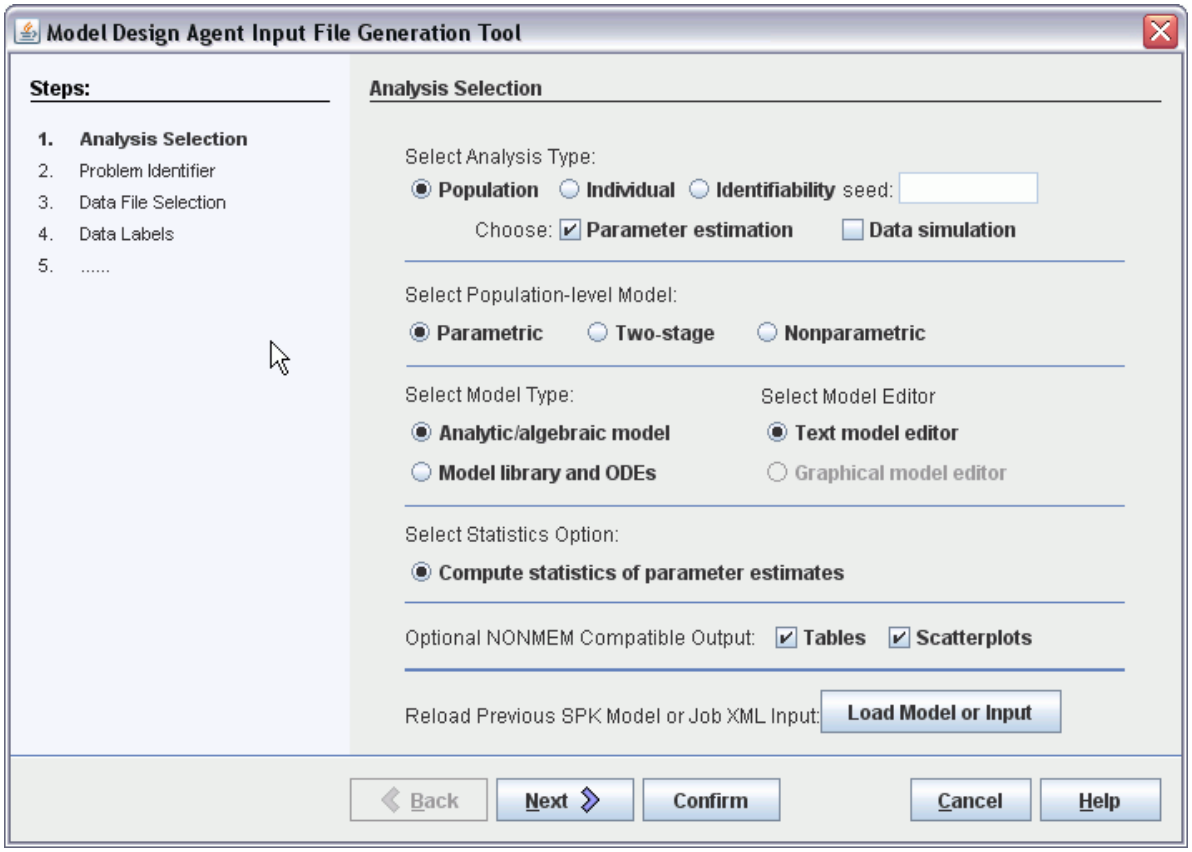


The MDA allows to create new jobs from the Job Information page, which is shown below.

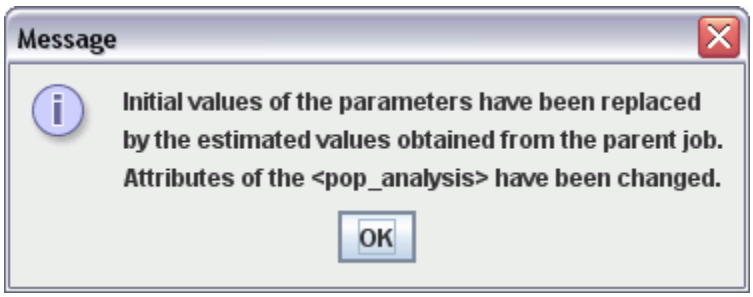


Under **Create New Job** there are a series of possibilities for the user to create a new job using elements of an existing job. Checking next to "Set the current job as the parent job of the new job" keeps track of which job was used to generate (is the parent) of the new job.

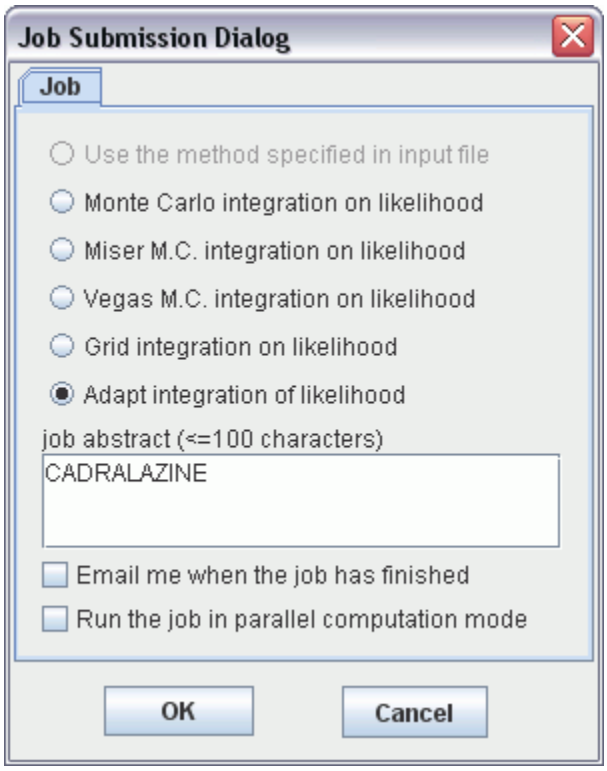
- **From Input**: this option allows you to generate a new job using the existing job as a template. When selecting this option, the Input File Generation Tool opens up, and all fields are pre-filled with the corresponding elements from the current job:



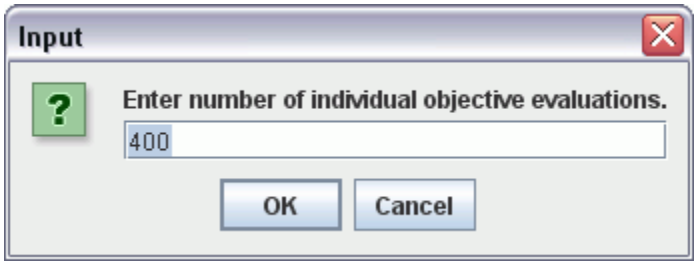
- **From Output**: same as "From Input", except that this option allows you to generate a new job using the results of the existing job as a template. When selecting this option, the Input File Generation tool opens again, but the fields are pre-filled with the output of the preceding job.
- **Warm Start**: this option restarts a job that has been aborted or has used its maximum number of function evaluations. Values relating to the current state of the optimization are periodically saved and used to restart the job if this option is used.
- **Likelihood**: this option allows for Monte Carlo integration of the likelihood following a successful job run. After selecting this option, the user will see this window:



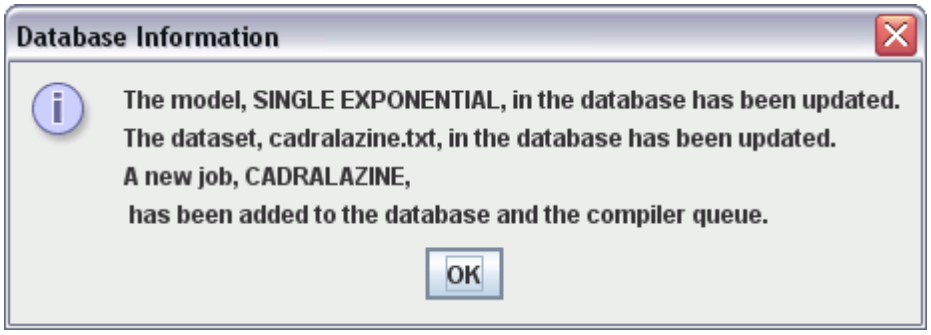
The purpose of this window is to alert the user to the fact that the output of the job is going to be used to initialize a likelihood integration routine that will provide the profile of the likelihood function at the optimal parameter estimates for the job. This triggers a job submission, where the user is asked to select between various likelihood integration options:



The ADAPT integrator is usually selected as the default, since it is presumed to be faster and more reliable. By clicking OK, the user starts the submission process. The accuracy of the integration depends on the number of functions evaluations used in the calculations. The user can set this number in this window, which is pre-filled with values suggested from the size of the random effects:



The job can then be submitted just like any other job:



- **Create Job**: this option allows to seed a parametric population analysis from two-stage results. In other words, it initializes a population run by using output from a two-stage method parameter estimation. This is only available if the current job used a two-stage method.

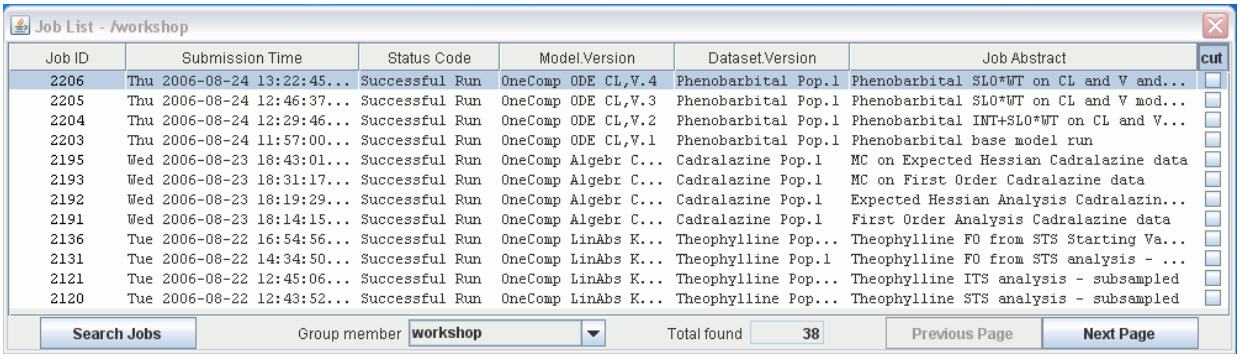
Parse Report

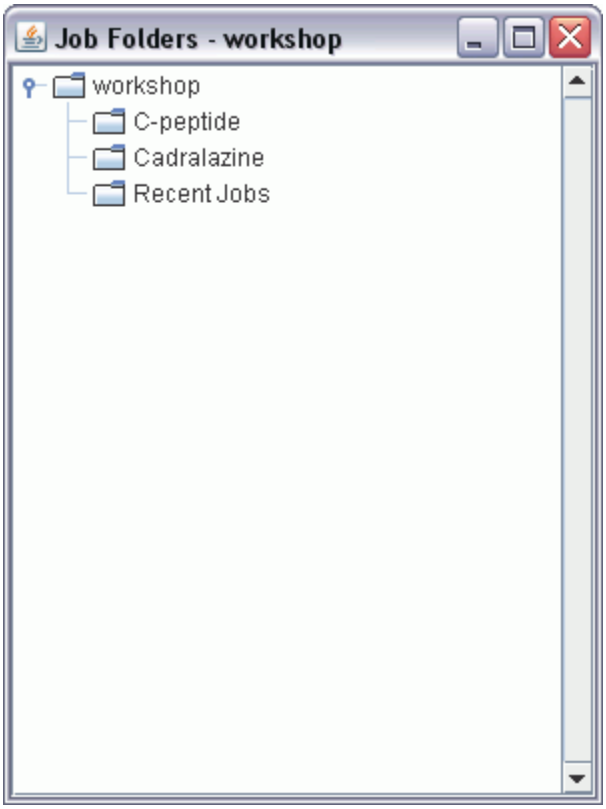
The MDA user has the option to view the output as an XML job file or to parse the output and view a summary report. Parsing the report also allows access to plotting and tabling functionality.

Every job is associated with an XML file that contains all information about that job. While the structure of these XML files is somewhat fluid, they are built and updated with compatibility in mind, so ideally the MDA should be able to process both old and new XML files.

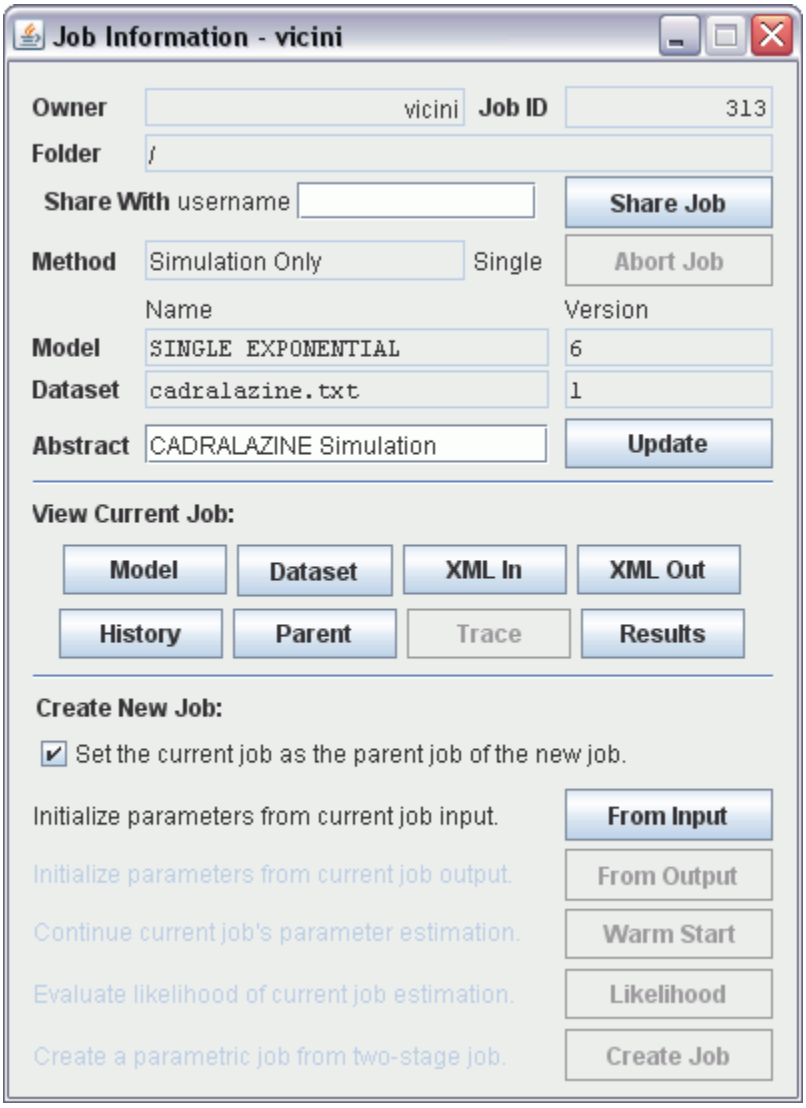
XML is a text-based format, so it can be exchanged using email and/or FTP (please note that some email clients format this file, so email may not always work reliably (compressing the file before email may work best).

Clicking the **Parse** button is a way to process and display the output or the input associated with a particular XML job file. Parse is the fourth button from the left in the MDA main window. When the user has selected My Jobs and the database list appears:





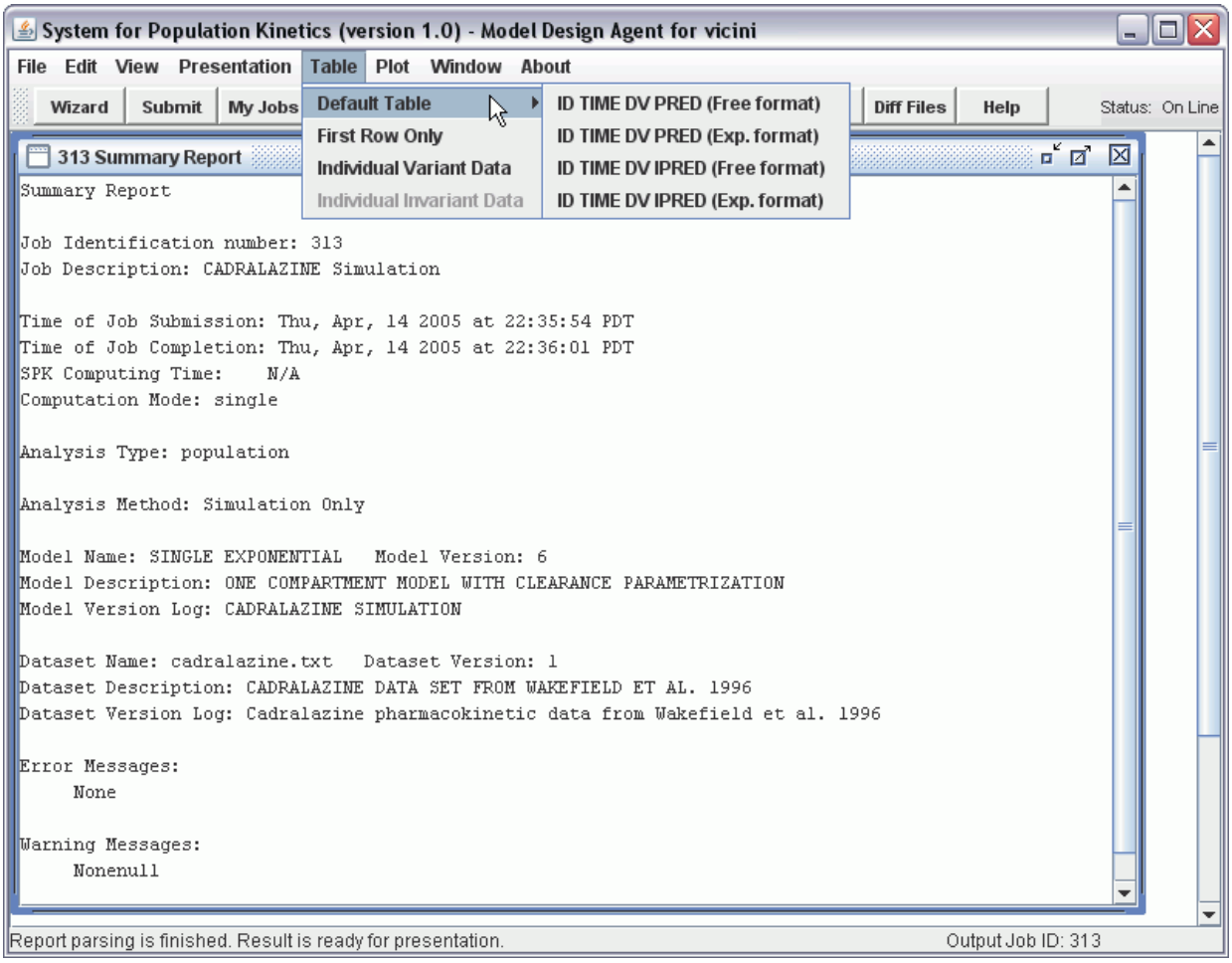
the user can select one job from the list. The following window (or a similar one) will appear:



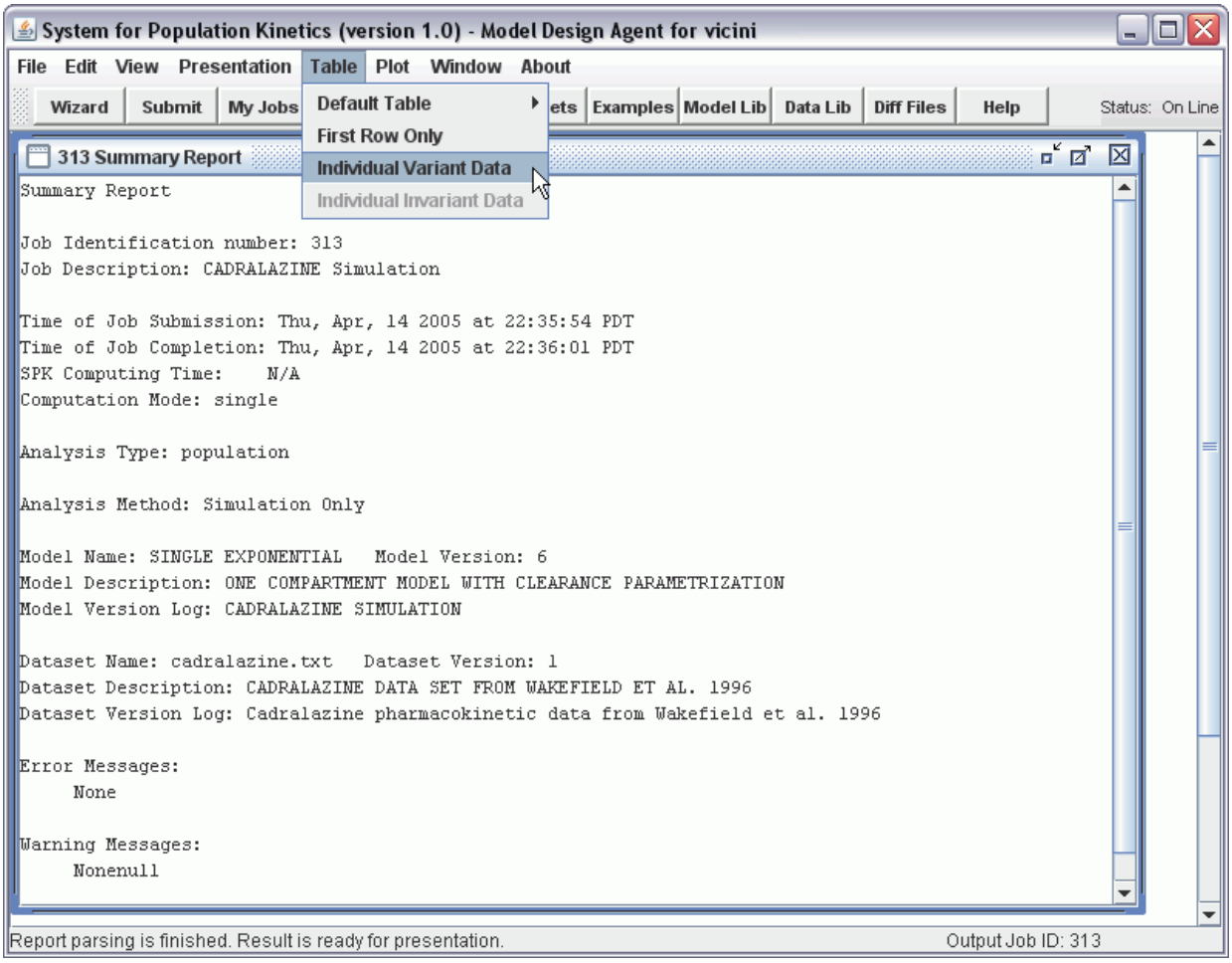
If one clicks on the "Output" button, the XML file describing this model's output will appear in the MDA's editor window, instead of being processed automatically. The user can then check the report for accuracy and inconsistencies that may be causing a problem with the MDA processing the output. Clicking on "Parse Report" will then load the results in memory for processing. This is also a possible way through which users can share models between themselves (they only need to email each other the XML file).

Tabular and plotting output are possible.

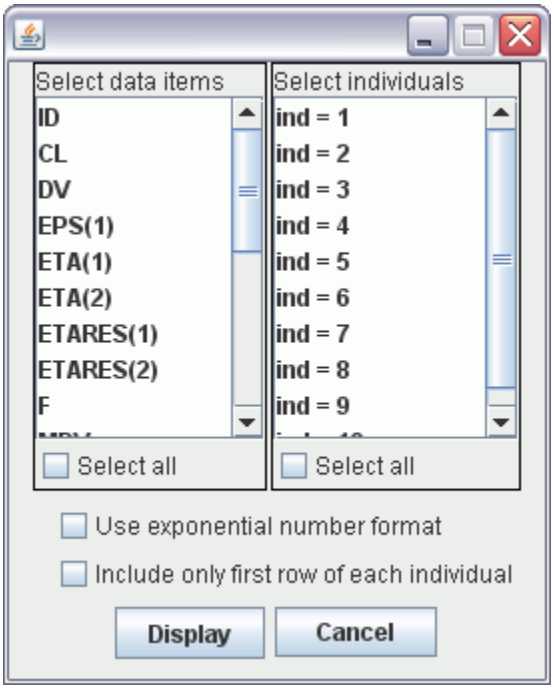
Tabular output: There are default tabular outputs or a custom table can be built using the entire report.



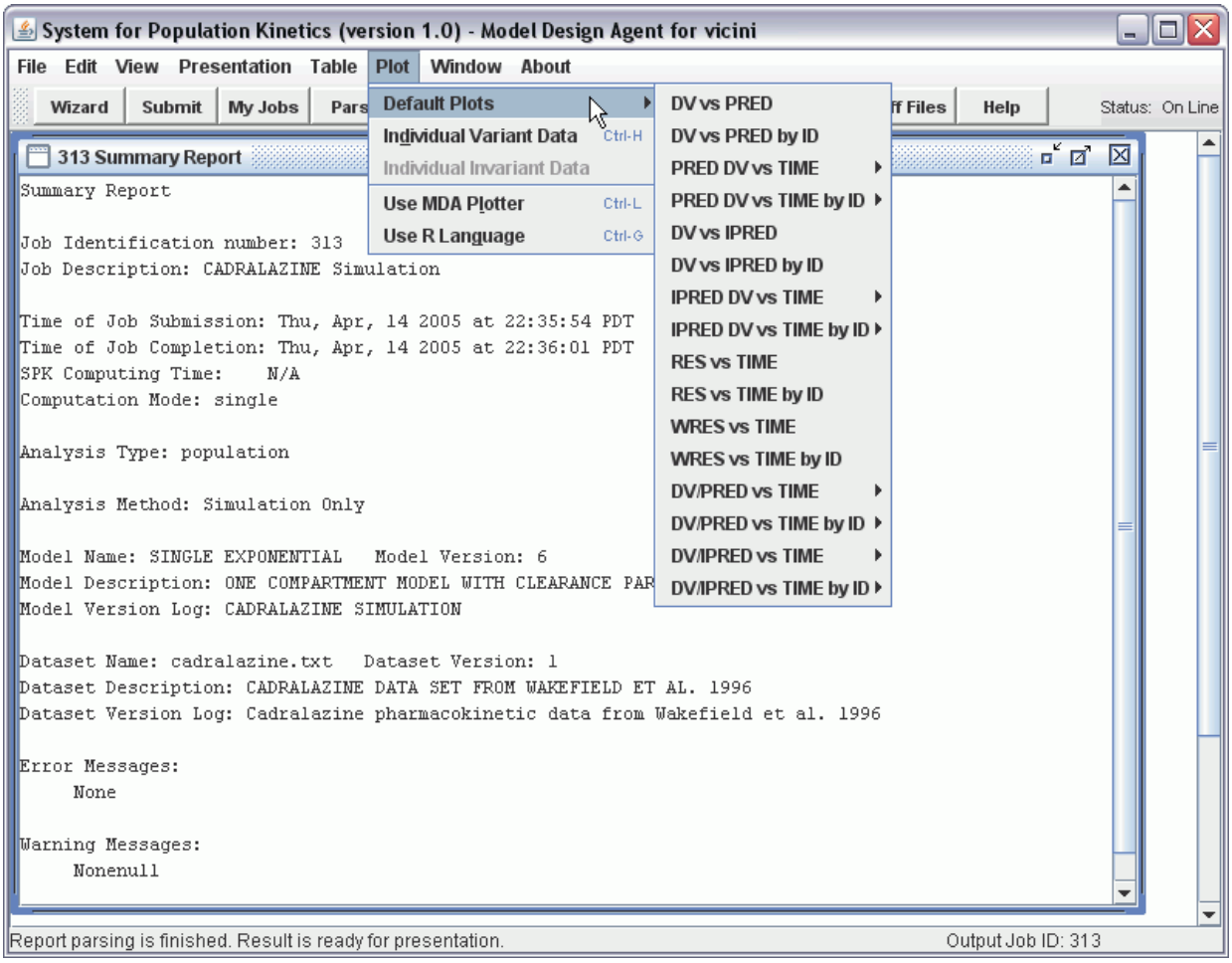
The "First Row Only" option is useful to display ID-specific information without repetition (if the variable of interest does not change between IDs).



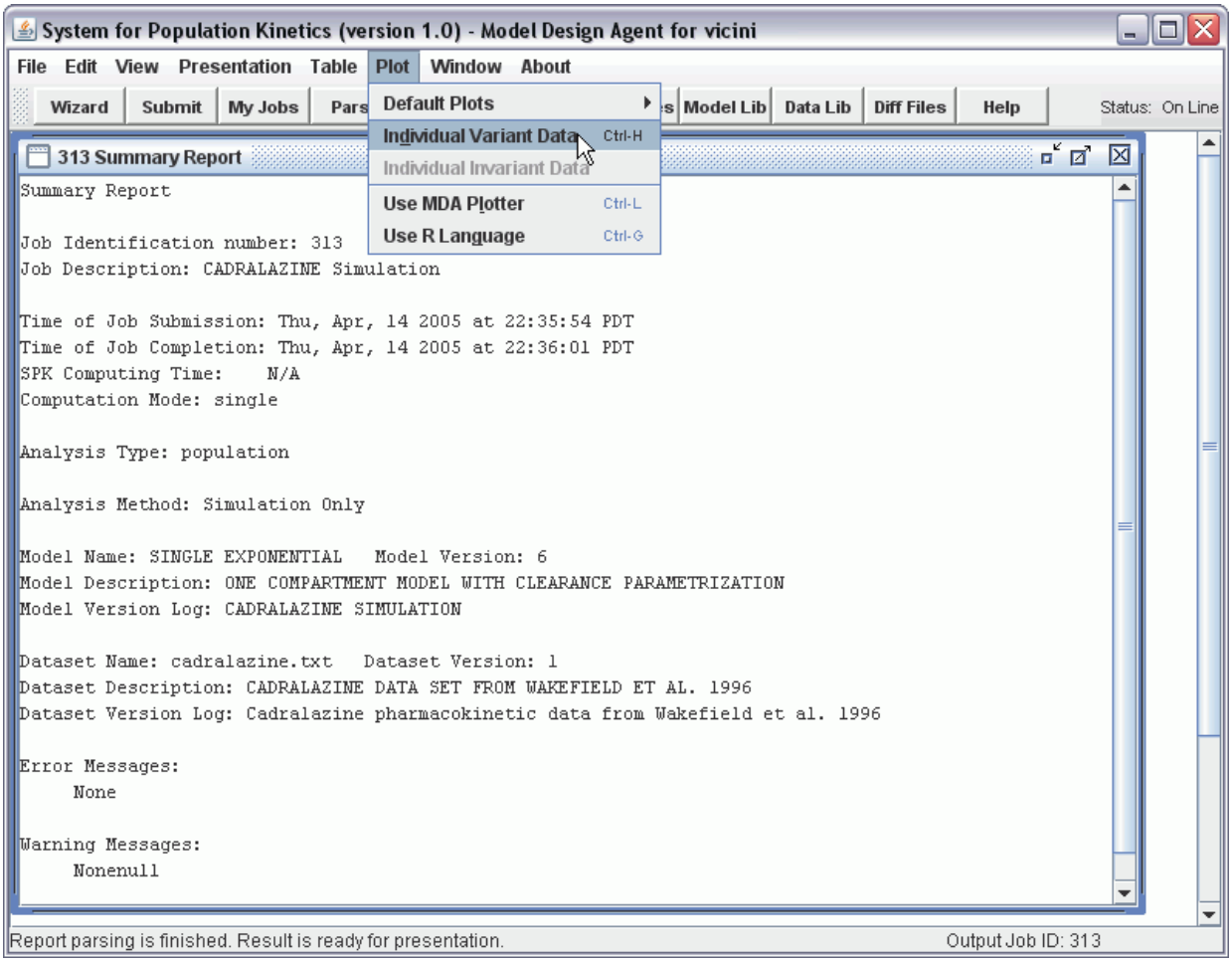
The "Individual Variant Data" option and the "Individual Invariant Data' option allow to build custom tables that may be specific to a certain ID or to a certain group of subjects or variables of interest.



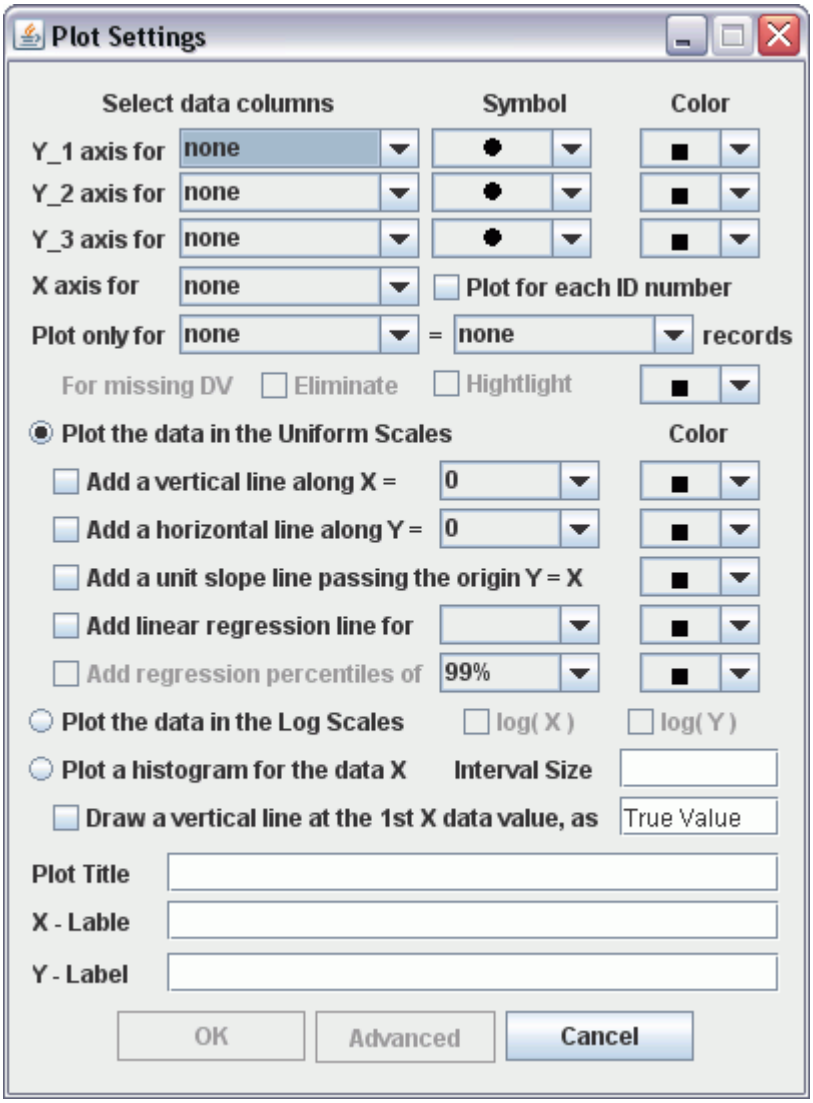
Plotting output: Default plots are available or a custom plot can be built using the entire report.



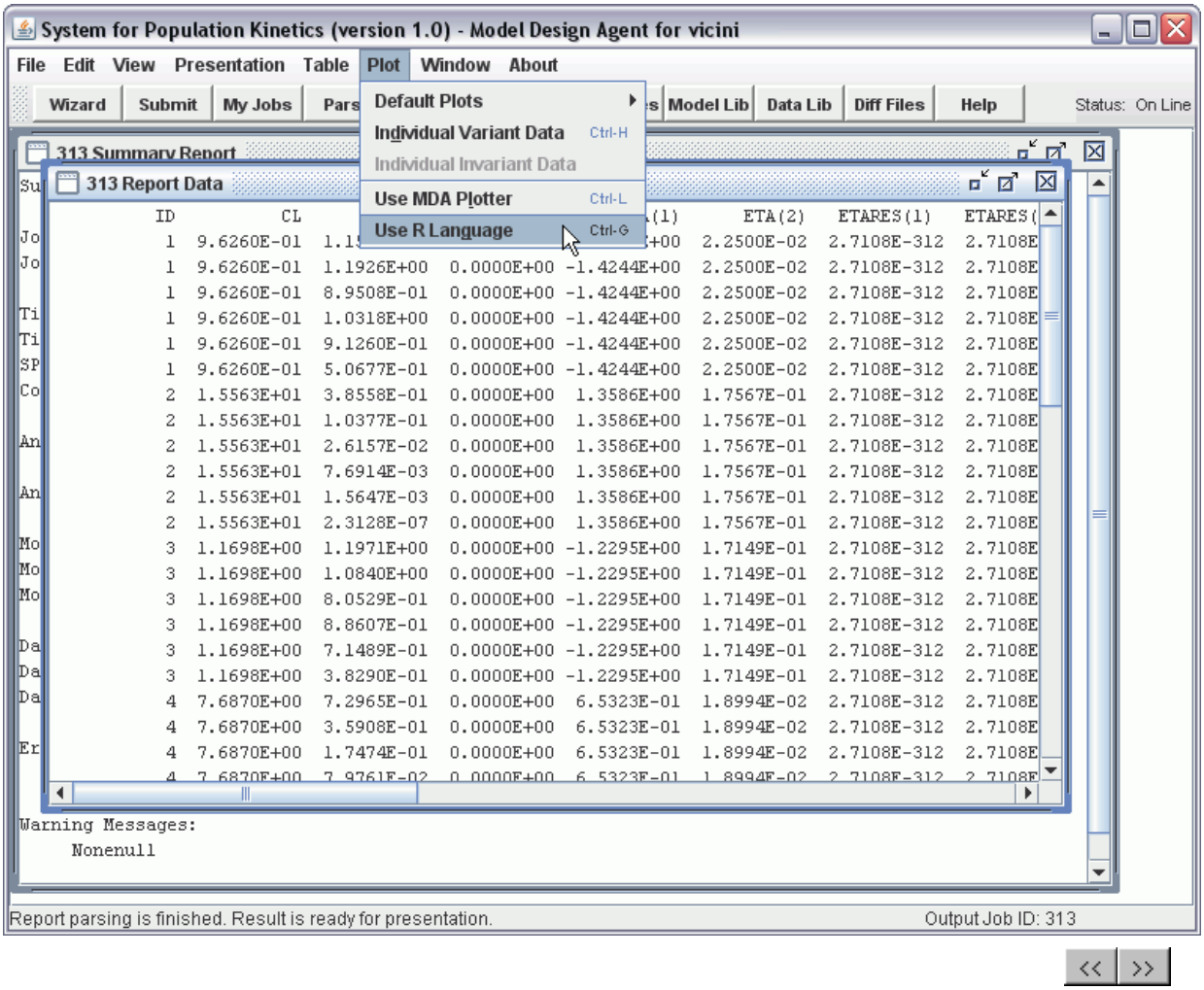
The "Individual Variant Data" option and the "Individual Invariant Data" option display the values for all the variables defined in the entire job. If a default variable has not been modified, its value is not displayed.



The "Use MDA Plotter" option allows the user to build custom plots that may be specific to a certain ID or to a certain group of subjects or variables of interest.

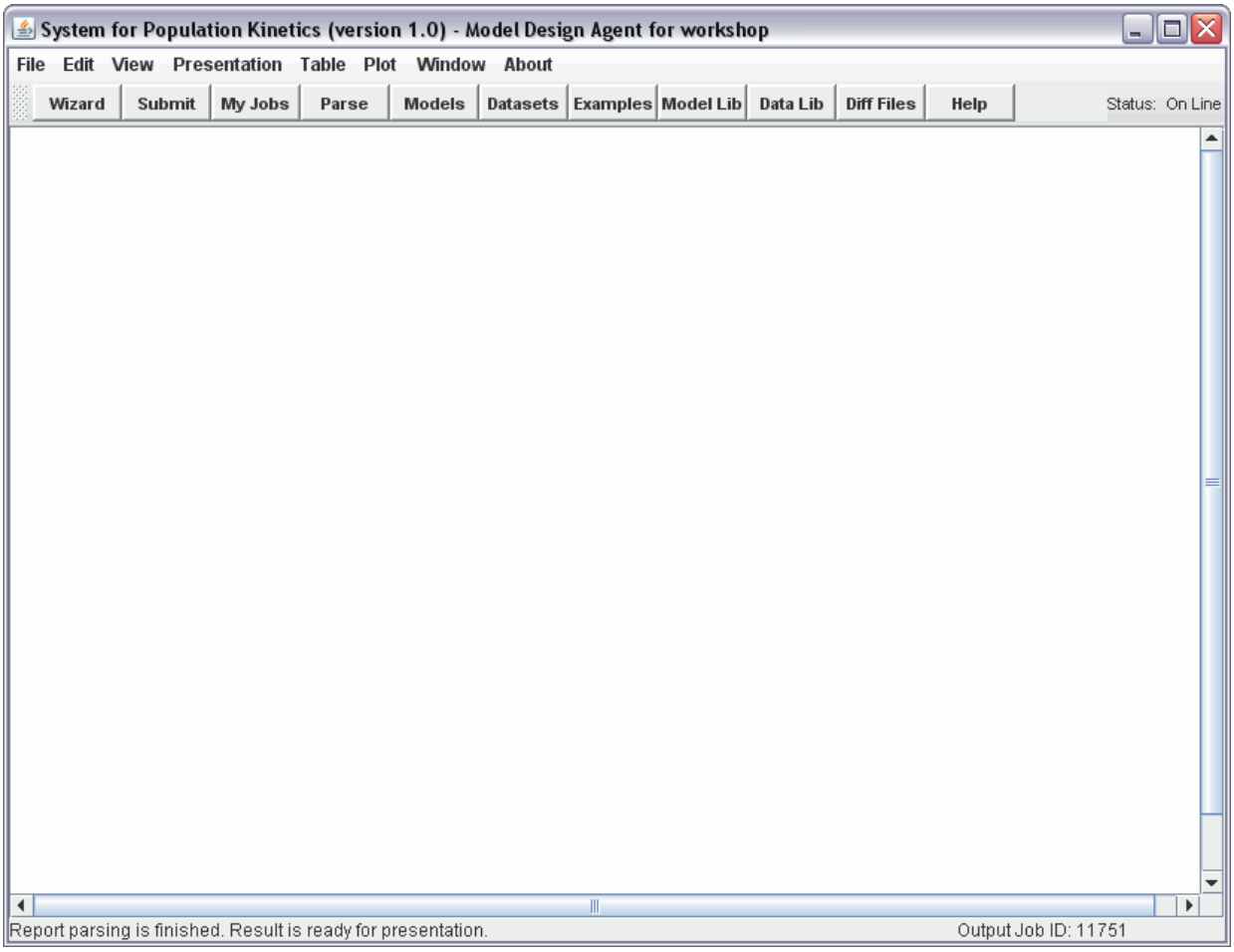


The "Use R Language" option provides an escape to the R programming environment. The login page at MySPK has instructions for installing R.

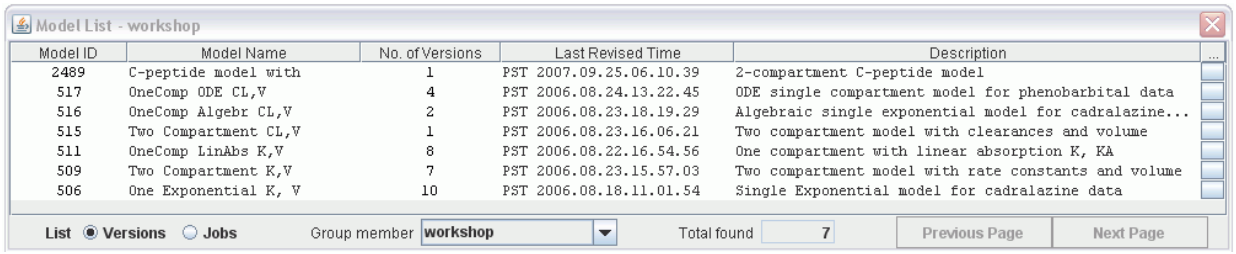


My Models

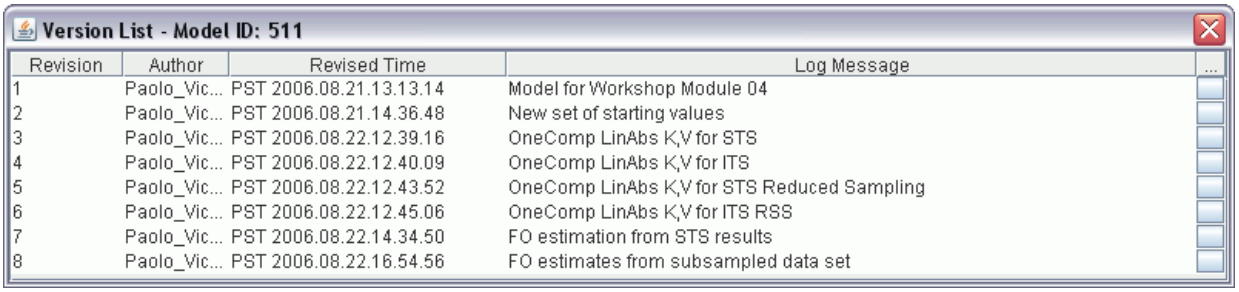
Normally, the user will want to access full jobs from the database via the **My Jobs** button. There are some instances when the user would like to inspect models or datasets separately. Clicking on the **Models** option (the fifth button from the left in the MDA main window) allows the MDA user to select models from the database.



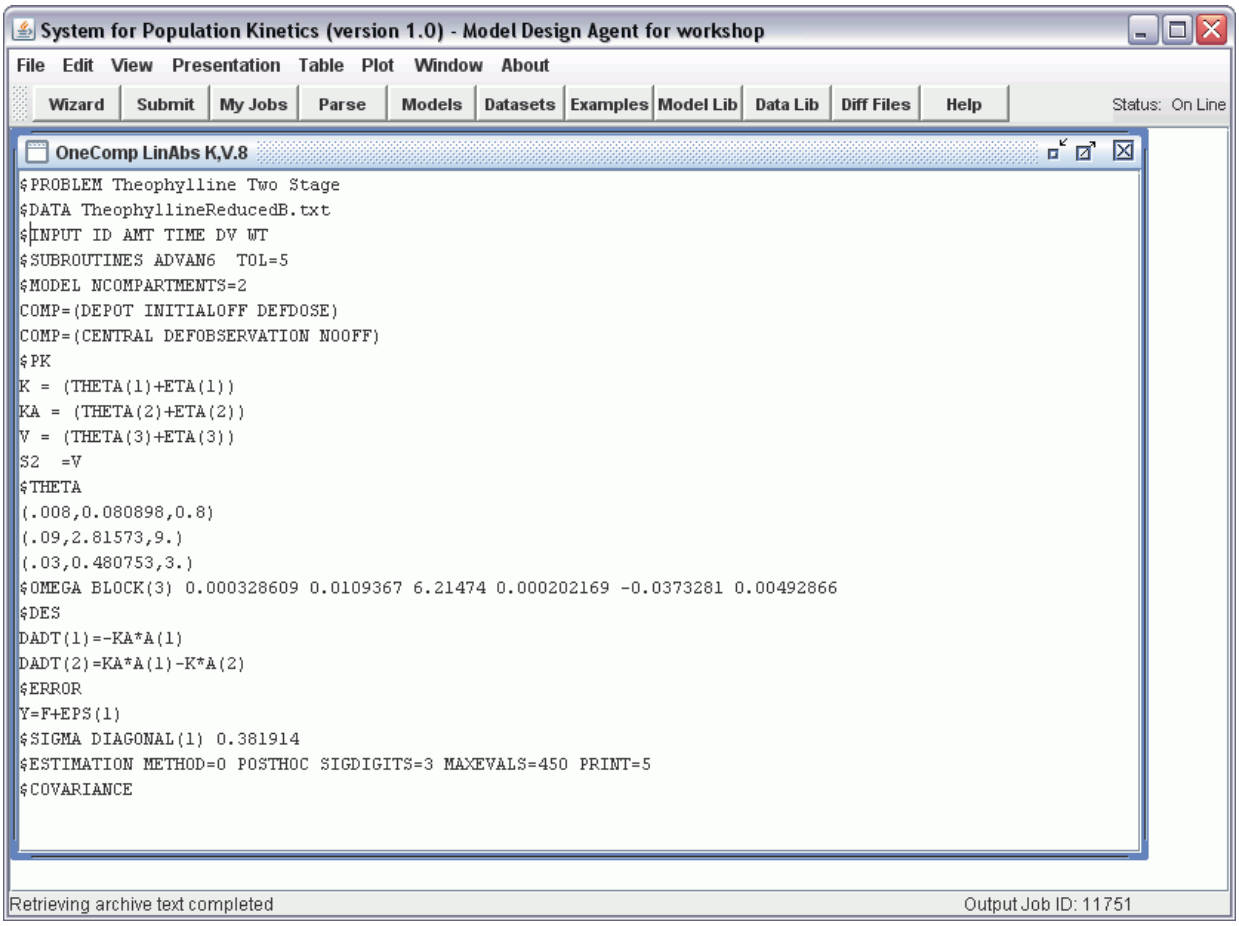
When selecting My Models, a list of all models generated by a user appears:



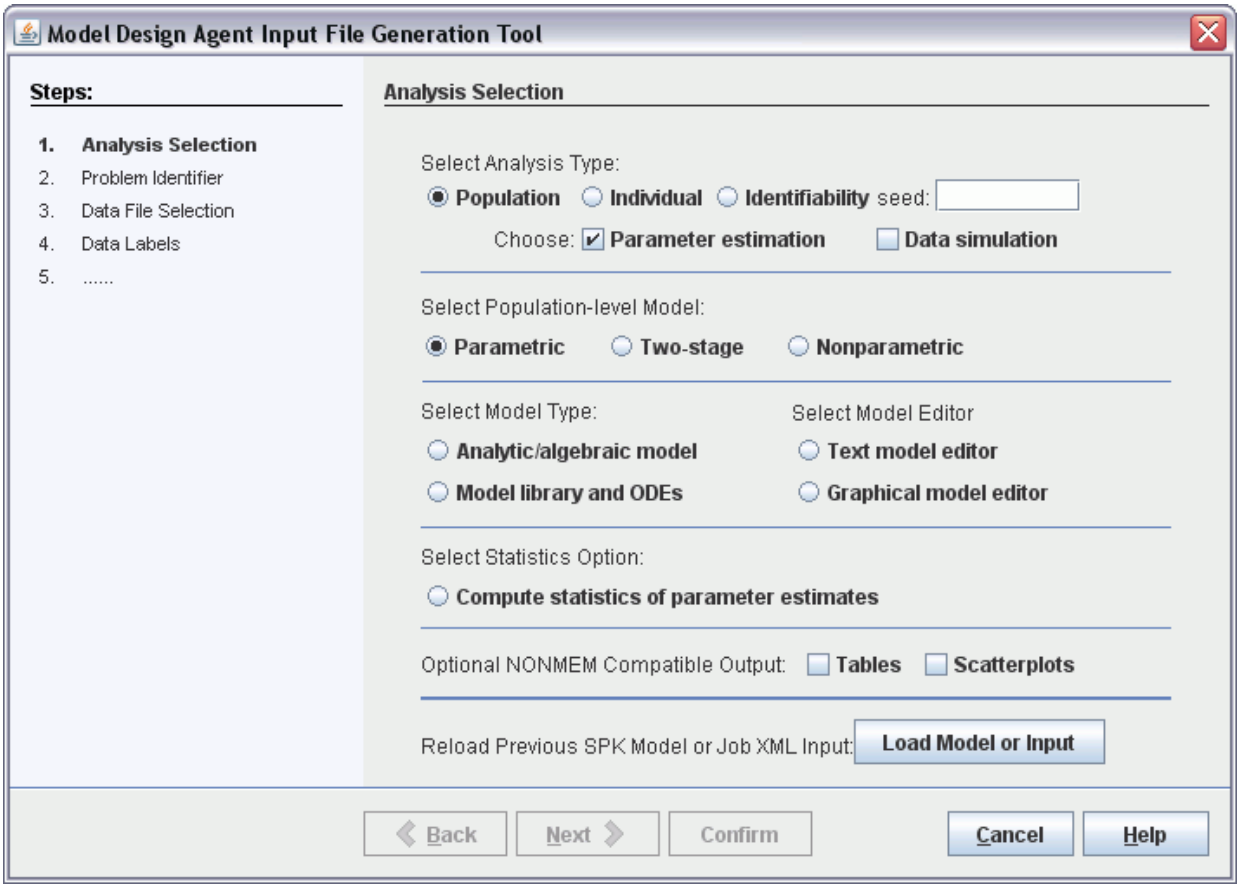
Every version of each model is stored separately in the database. Details referring to each model can be displayed in two ways. When the **Jobs** bullet is chosen and a model is selected, all jobs that have used that model are displayed in the Job List window. When the **Versions** bullet is chosen and a model is selected, all versions of that model are displayed. For example, this model has five versions:



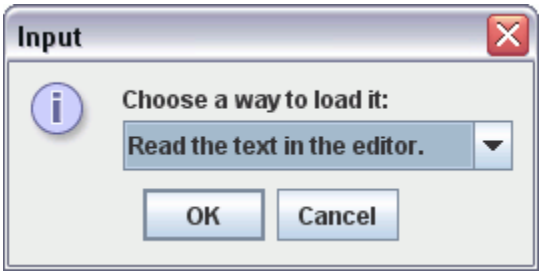
Every version is described by a log and has a revision time stamp associated with it. When a particular model is selected from the list, that model opens in the MDA editor window:



This model can be processed by clicking on **Prepare Input**:



and then selecting "Load Model or Input". The user will also be presented with choices about where the model information should come from (the alternatives are to read the text in the editor or load a model from the file system):



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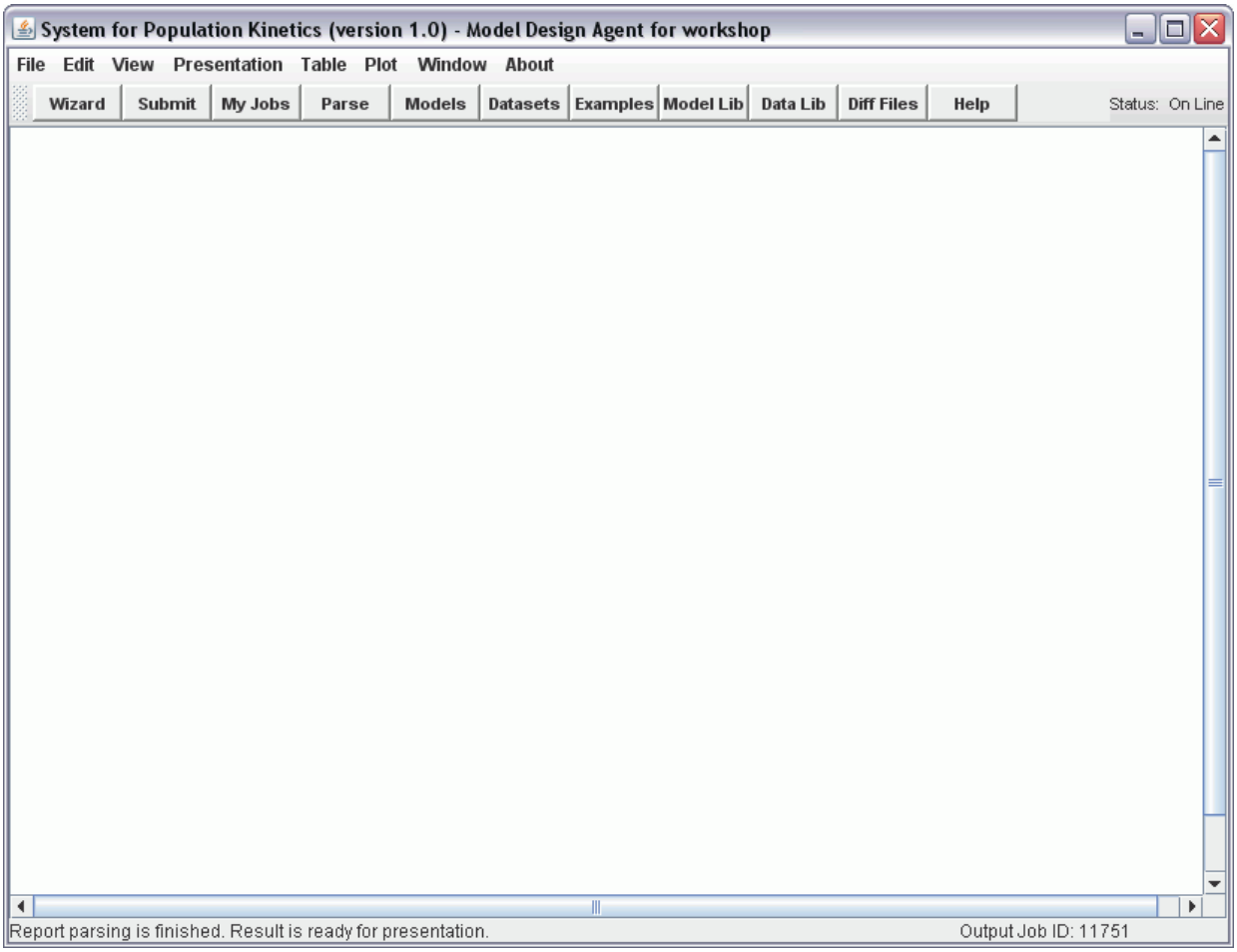
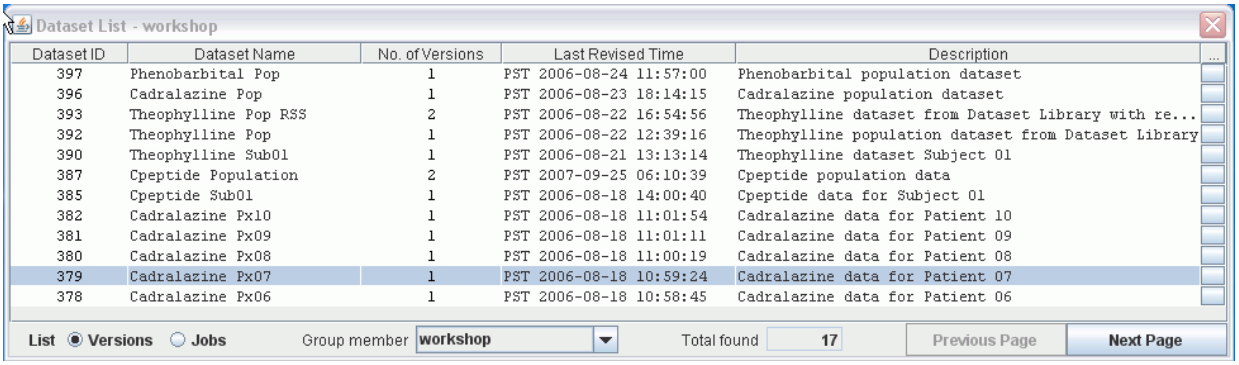
My Datasets

Normally, the user will want to access full jobs from the database via the **My Jobs** button. There are some instances when the user would like to inspect datasets separately. Clicking on the **Datasets** option (the sixth

button from the left in the MDA main window) allows the MDA user to select datasets from the database.

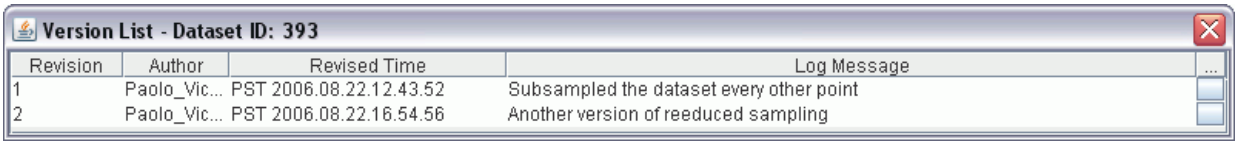


When selecting My Datasets, a list of all datasets belonging to a user appears:

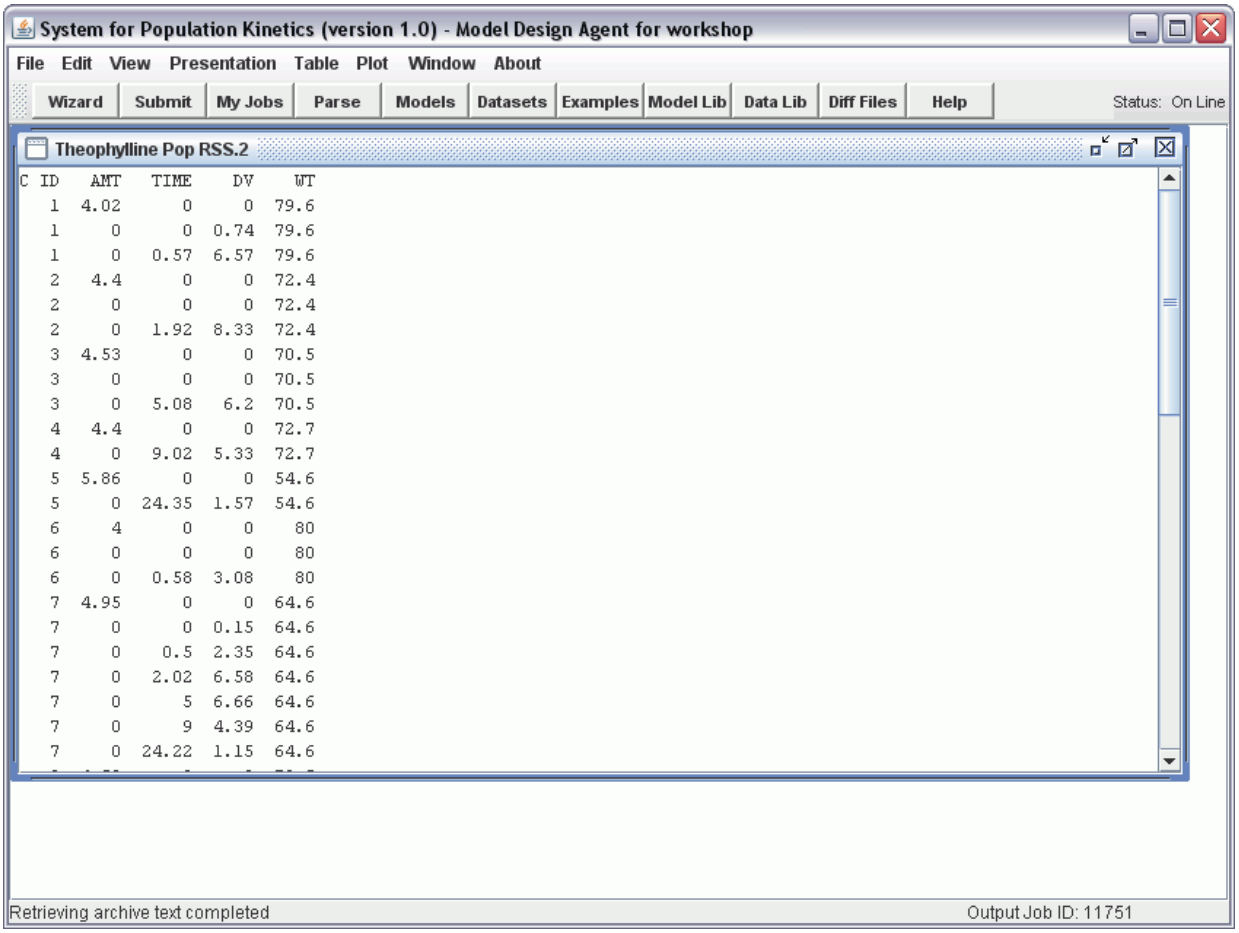


Every version of each dataset is stored separately in the database. Details referring to each dataset can be displayed in two ways. When the **Jobs** bullet is chosen and a dataset is selected, all jobs that have used that dataset are displayed in the Job List window. When the **Versions**

bullet is chosen and a dataset is selected, all versions of that dataset are displayed:



Every version is described by a log and has a revision time stamp associated with it. When a version is selected, that dataset becomes visible in the MDA editor window:



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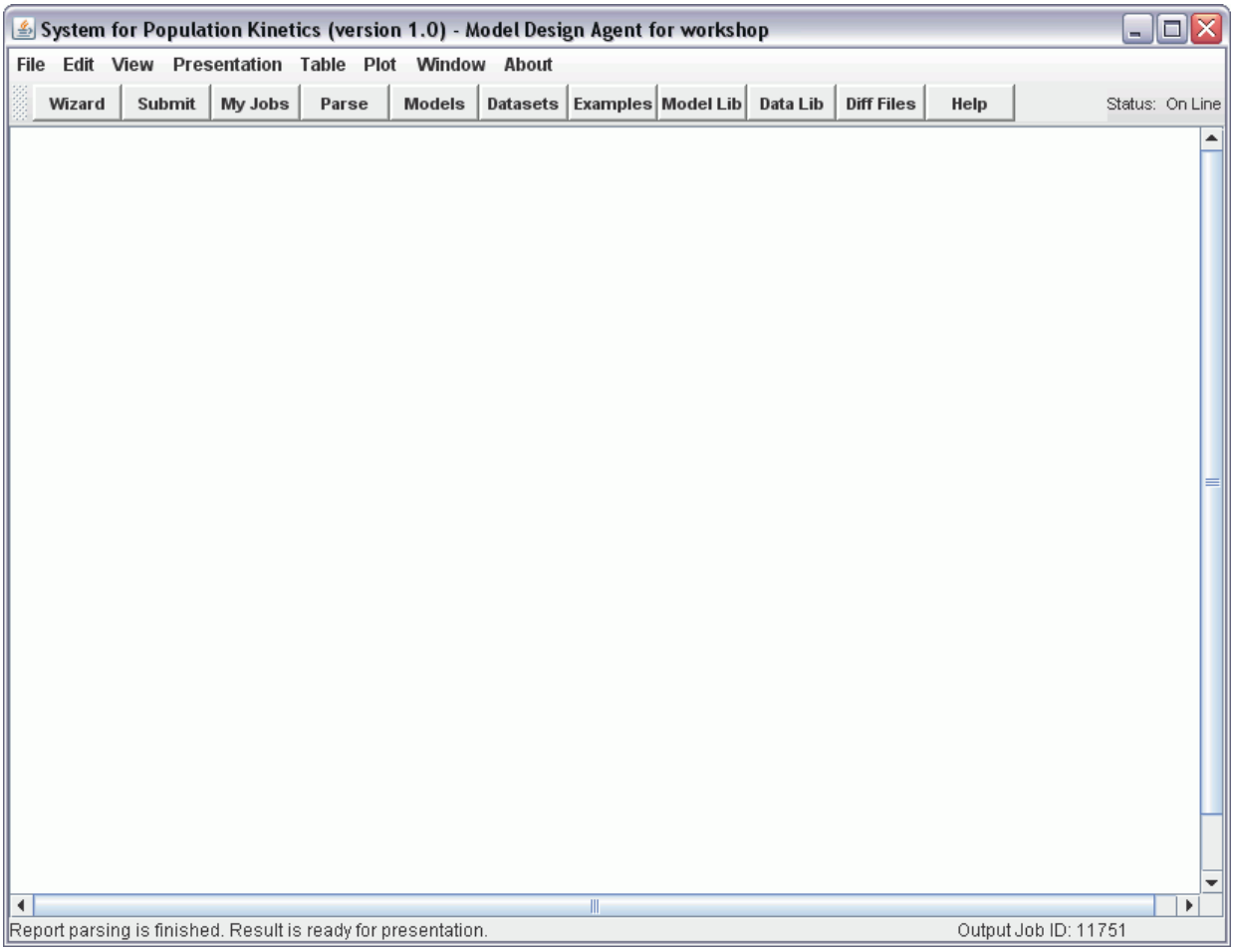
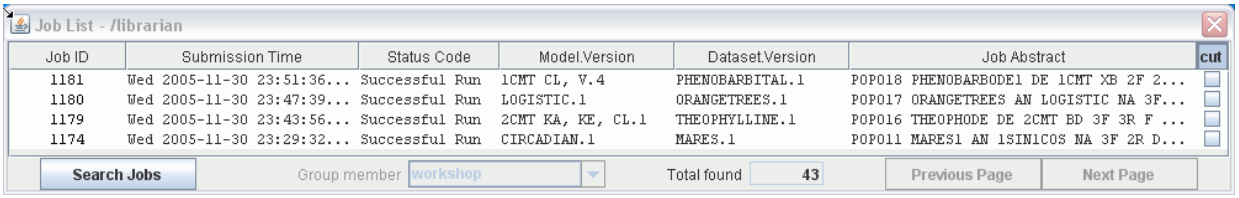
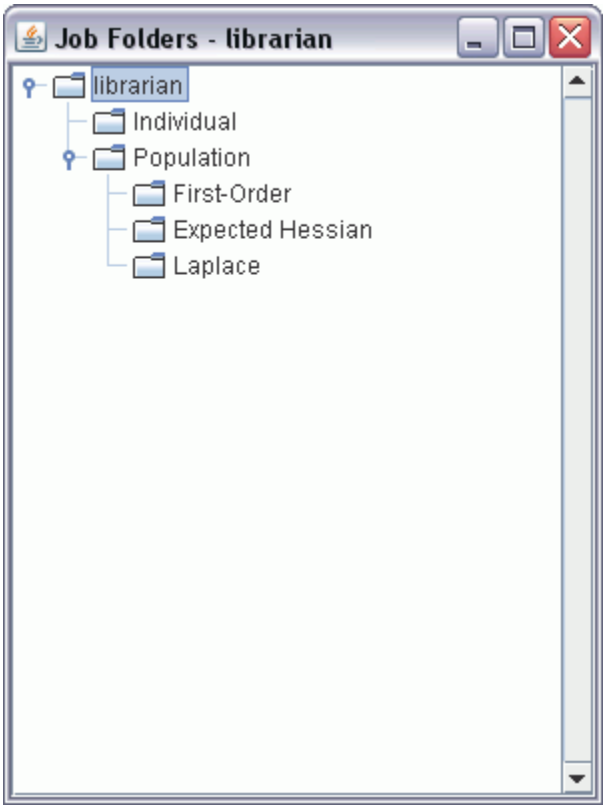
Job Examples

RFPK scientists have made available a series of sample jobs to familiarize users with the SPK system. These jobs are available to all users by clicking on the "Examples" button in the main MDA screen:



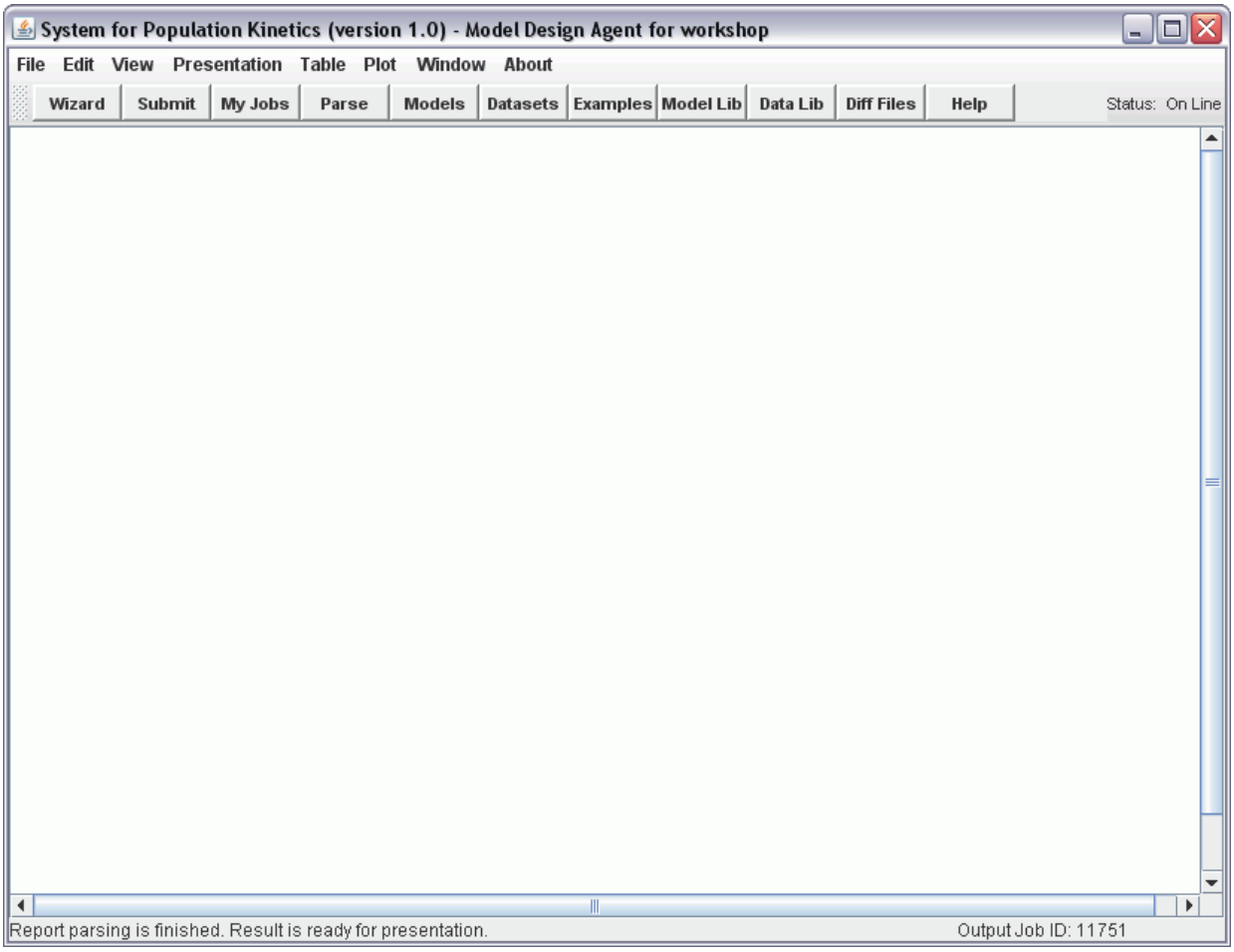
The examples are brought up and can be inspected or used to create new jobs. They are available to all users and can be modified by anyone (the modified version belongs to the user that modifies it).



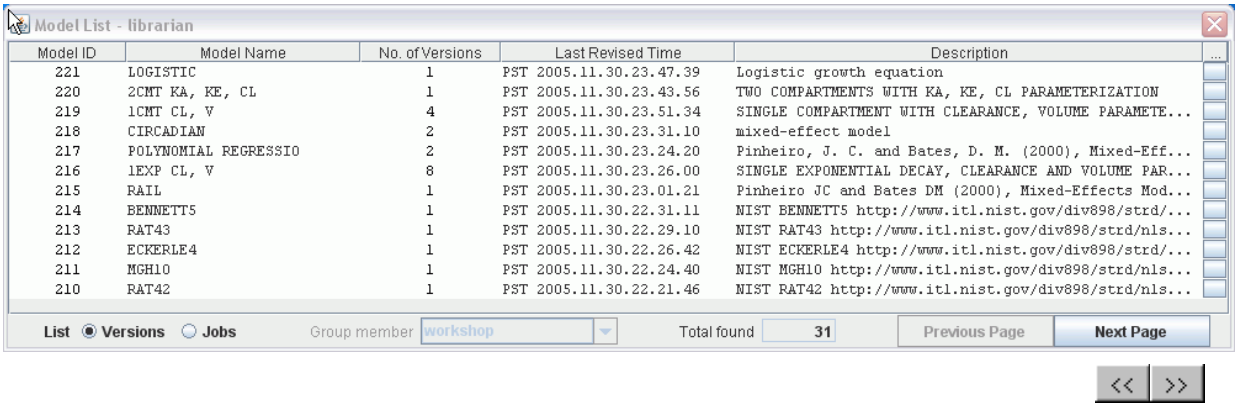


Model Library

RFPK scientists have made available a series of sample models to familiarize users with the SPK system. These models are available to all users by clicking on the "Model Lib" button in the main MDA screen:

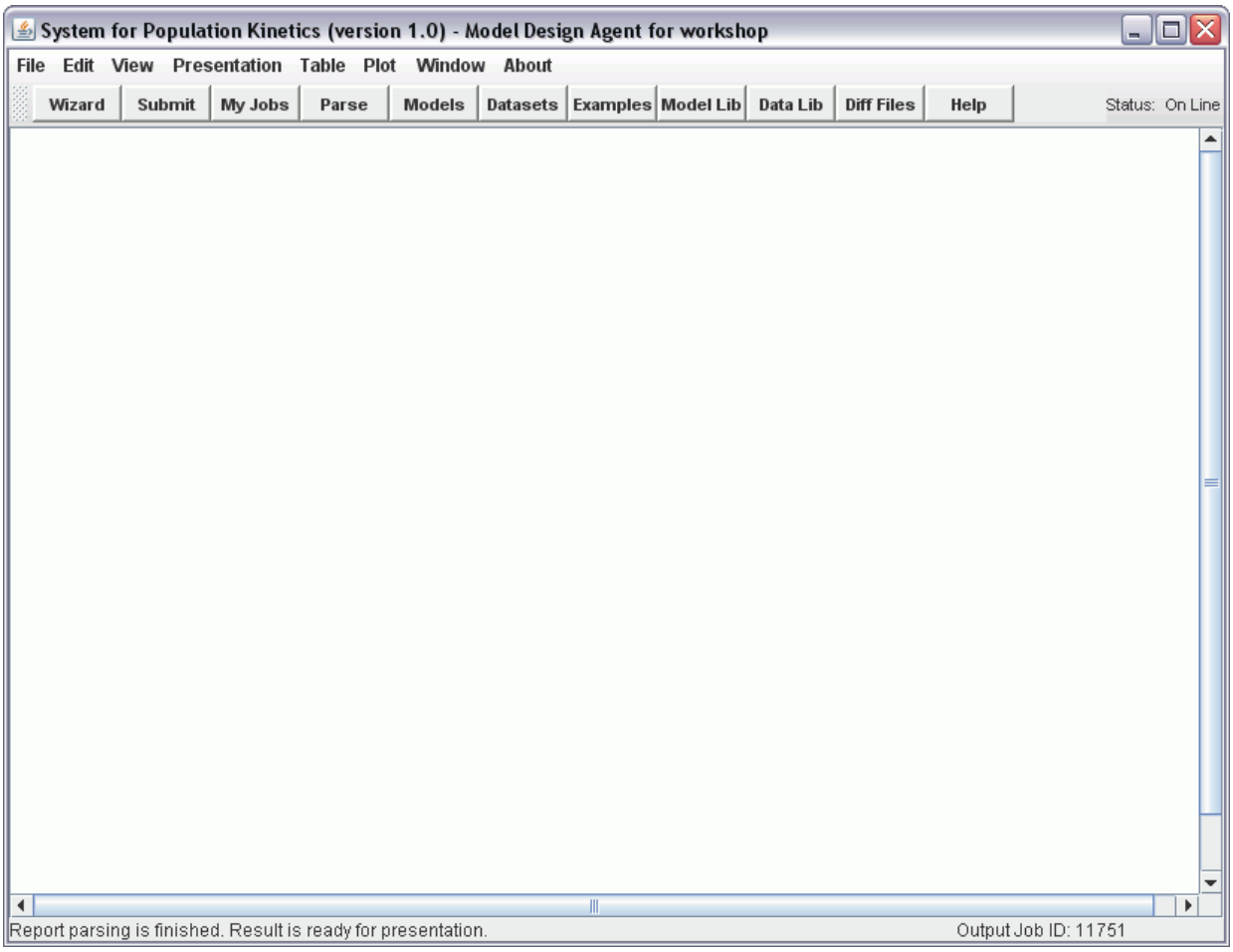


The examples are accessible and can be inspected or used to create new jobs as indicated elsewhere.

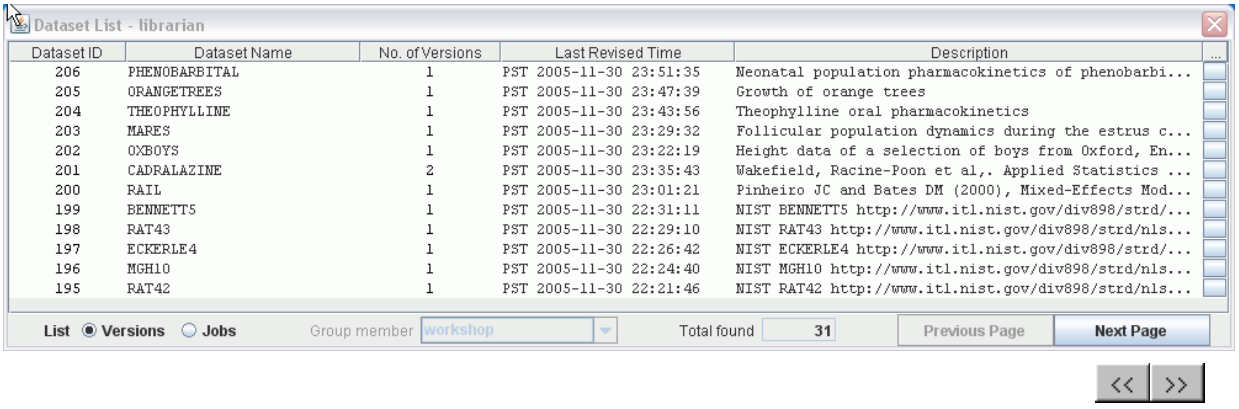


Dataset Library

RFPK scientists have made available a series of sample datasets to familiarize users with the SPK system. These datasets are available to all users by clicking on the "Dataset Lib" button in the main MDA screen:

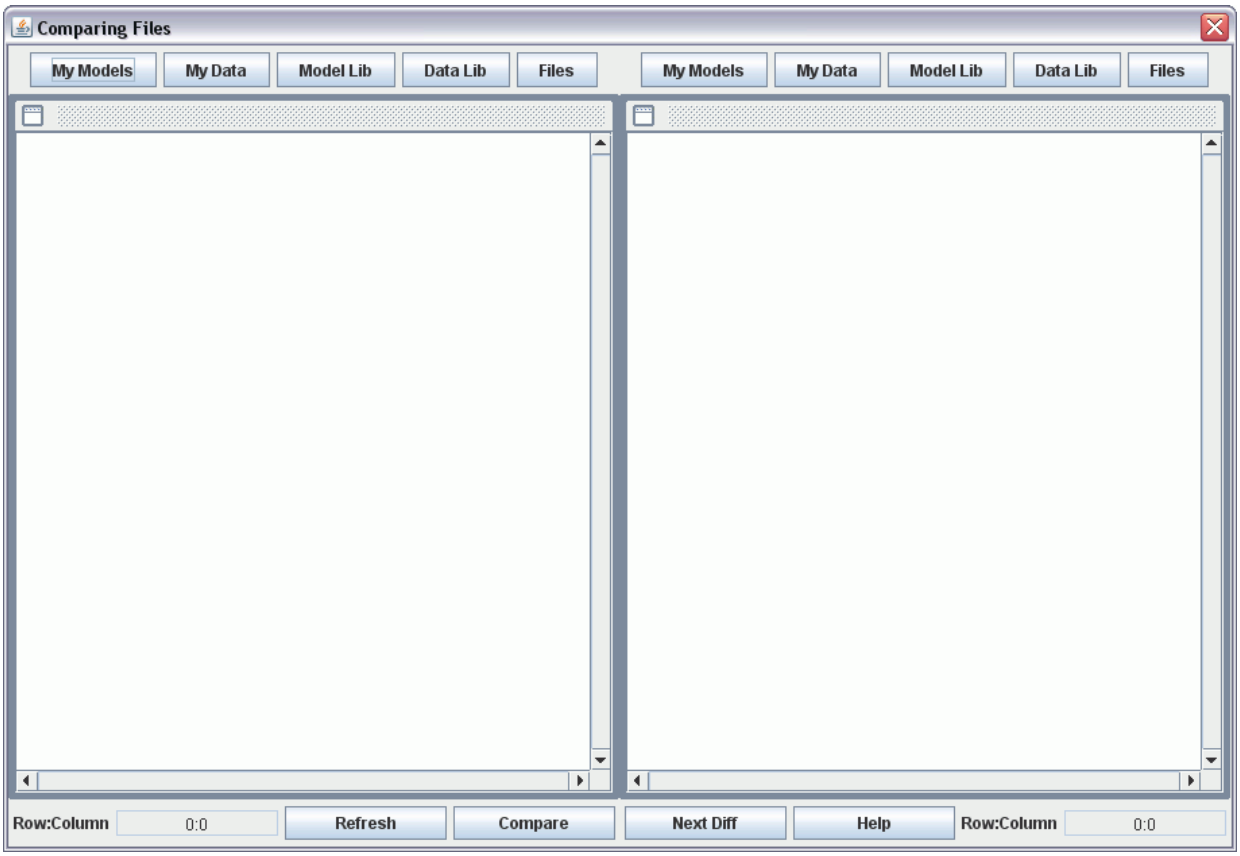


The examples are accessible and can be inspected or used to create new jobs as indicated elsewhere.



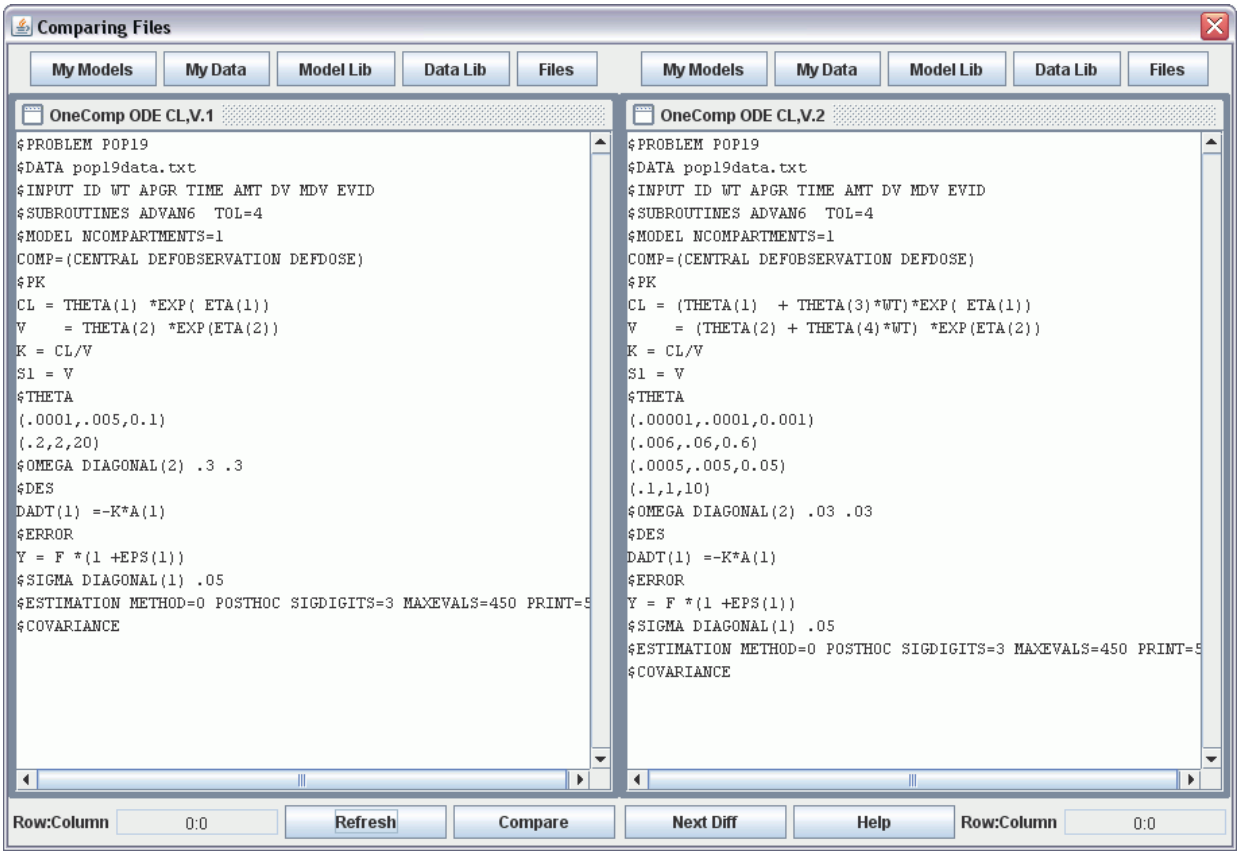
Compare Files

This option allows to compare files that are residing in different portions of the database. When clicking Diff Files button from the main MDA window, the following screen appears:

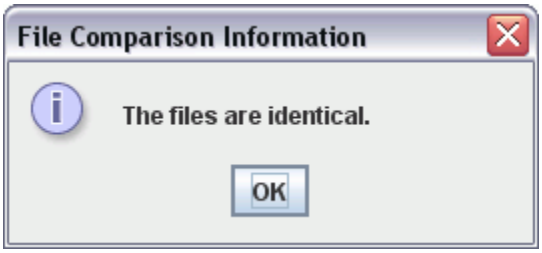


My Models and My Data select files in the individual (personal) sections of the database, Model Lib and Data Lib select files from the library while Files selects files from the local hard drive.

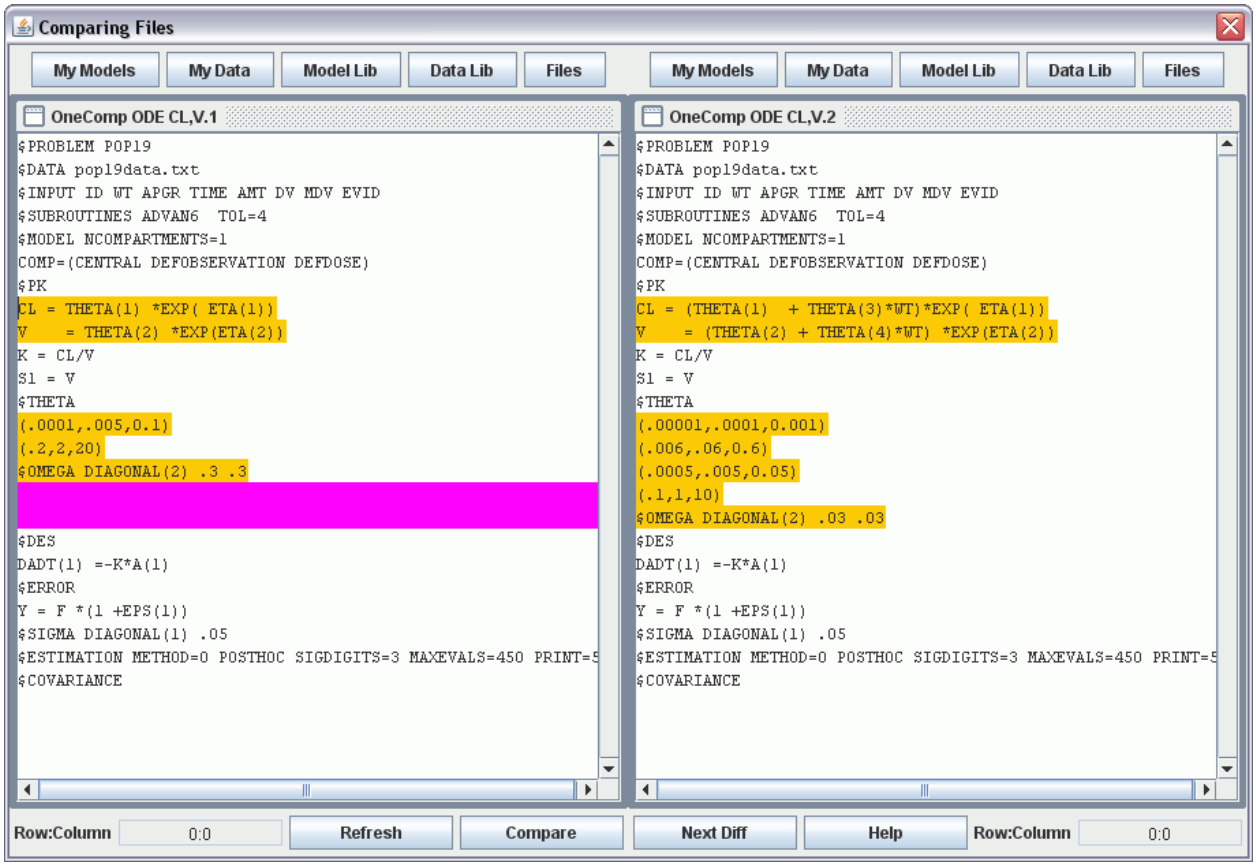
Selecting two files provides the following prompt:



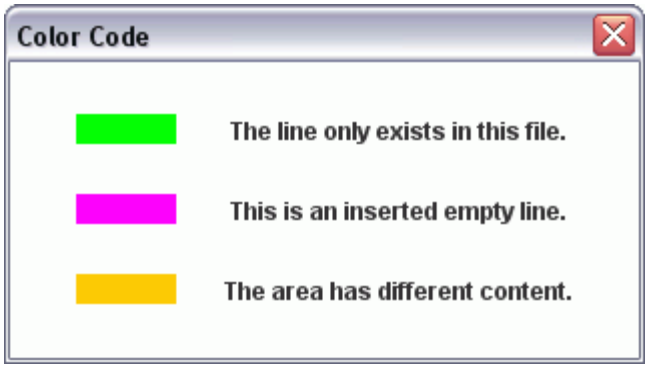
If two files are identical, then the result is:



If the files are different, like in this case, differences are highlighted:

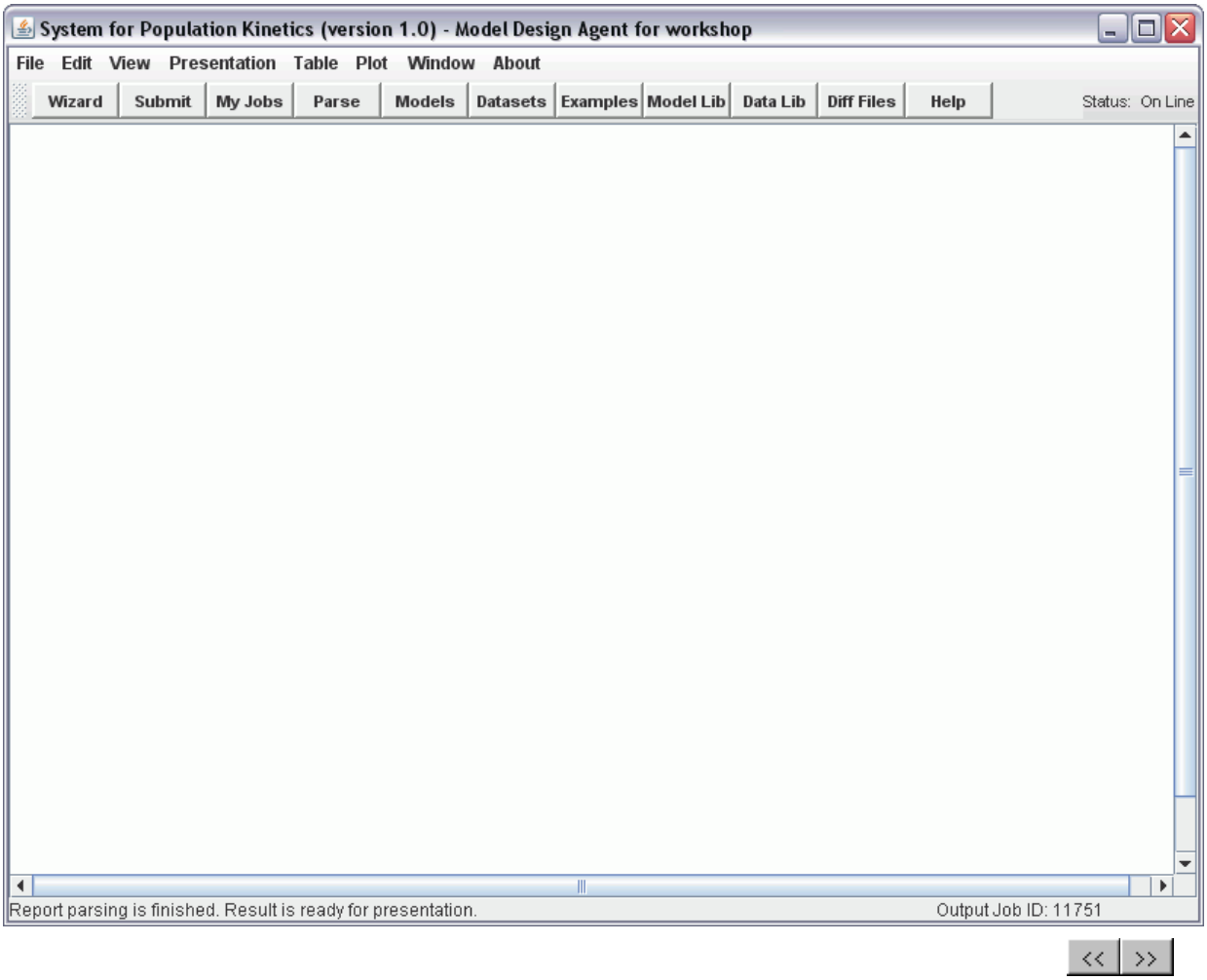


The color code is as follows:



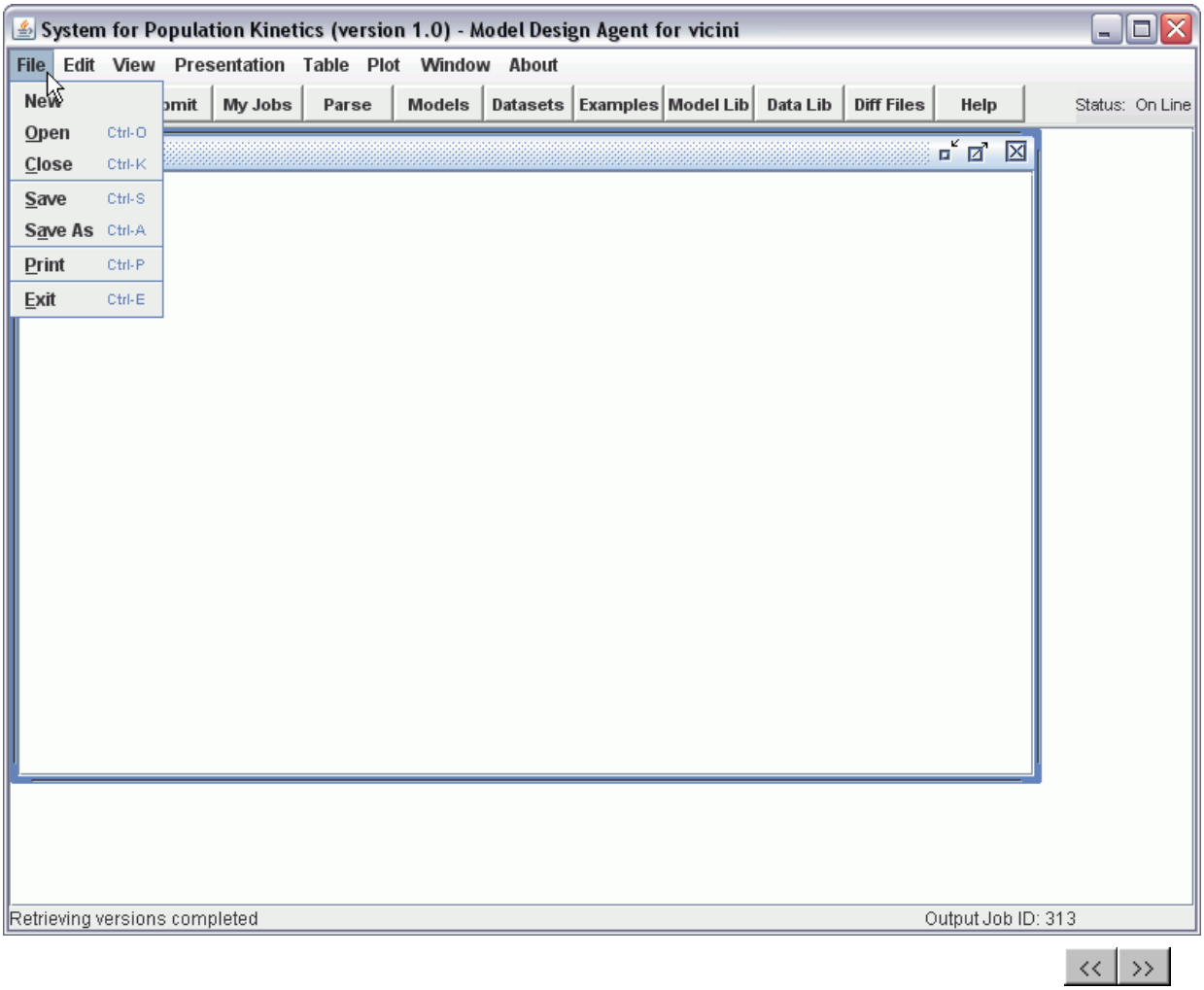
Help

Clicking on the Help button on the main screen brings up the main Introduction panel; clicking on the Help button from every other screen accesses the relevant help topic.



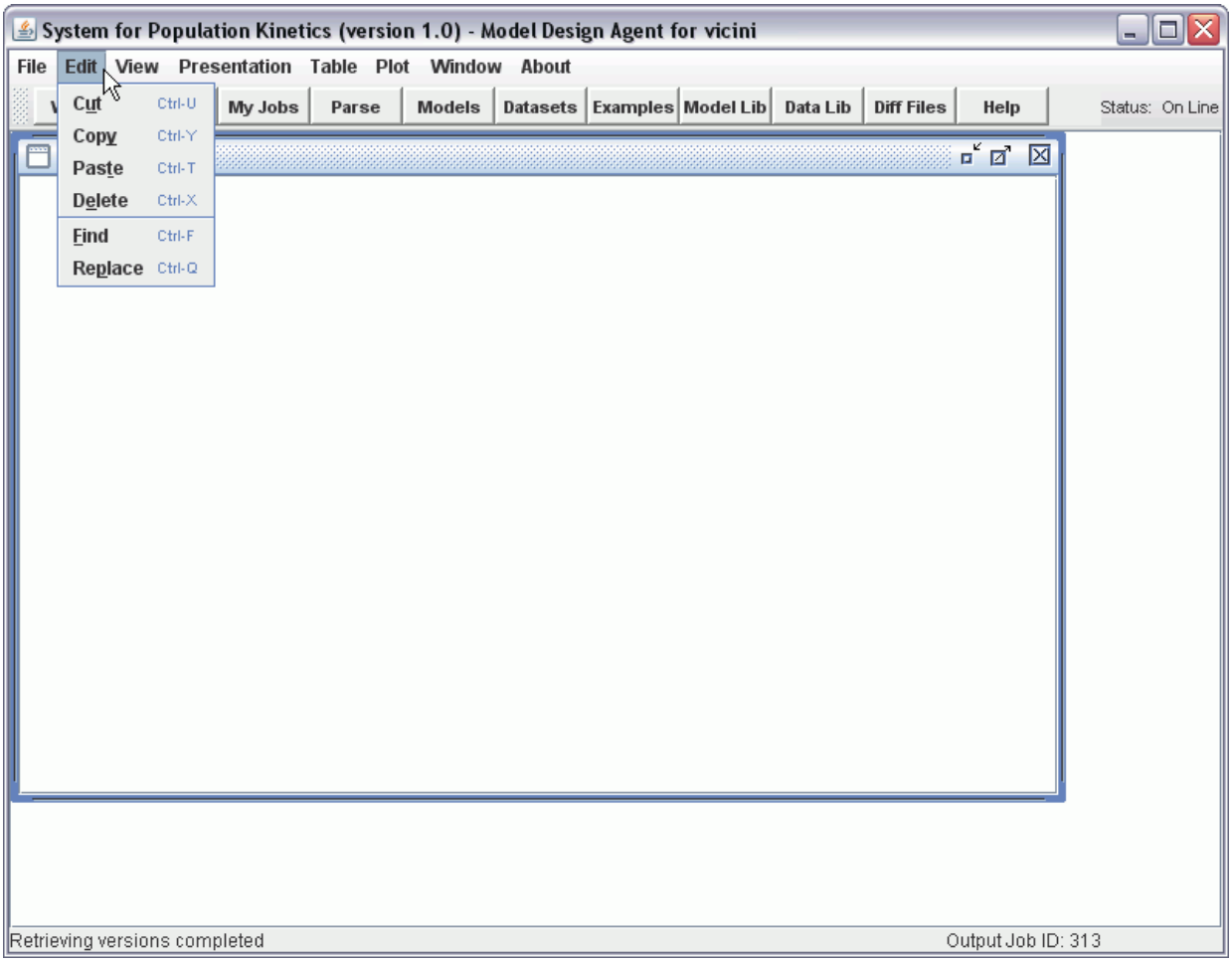
File

This option in the MDA editor window provides the basic file editing capabilities (New, Open, Close, Save, Save As, Print, Exit). Note that selecting Exit closes the MDA.



Edit

This option in the MDA editor window provides the basic file editing capabilities (Cut, Copy, Paste, Delete, Find and Replace):



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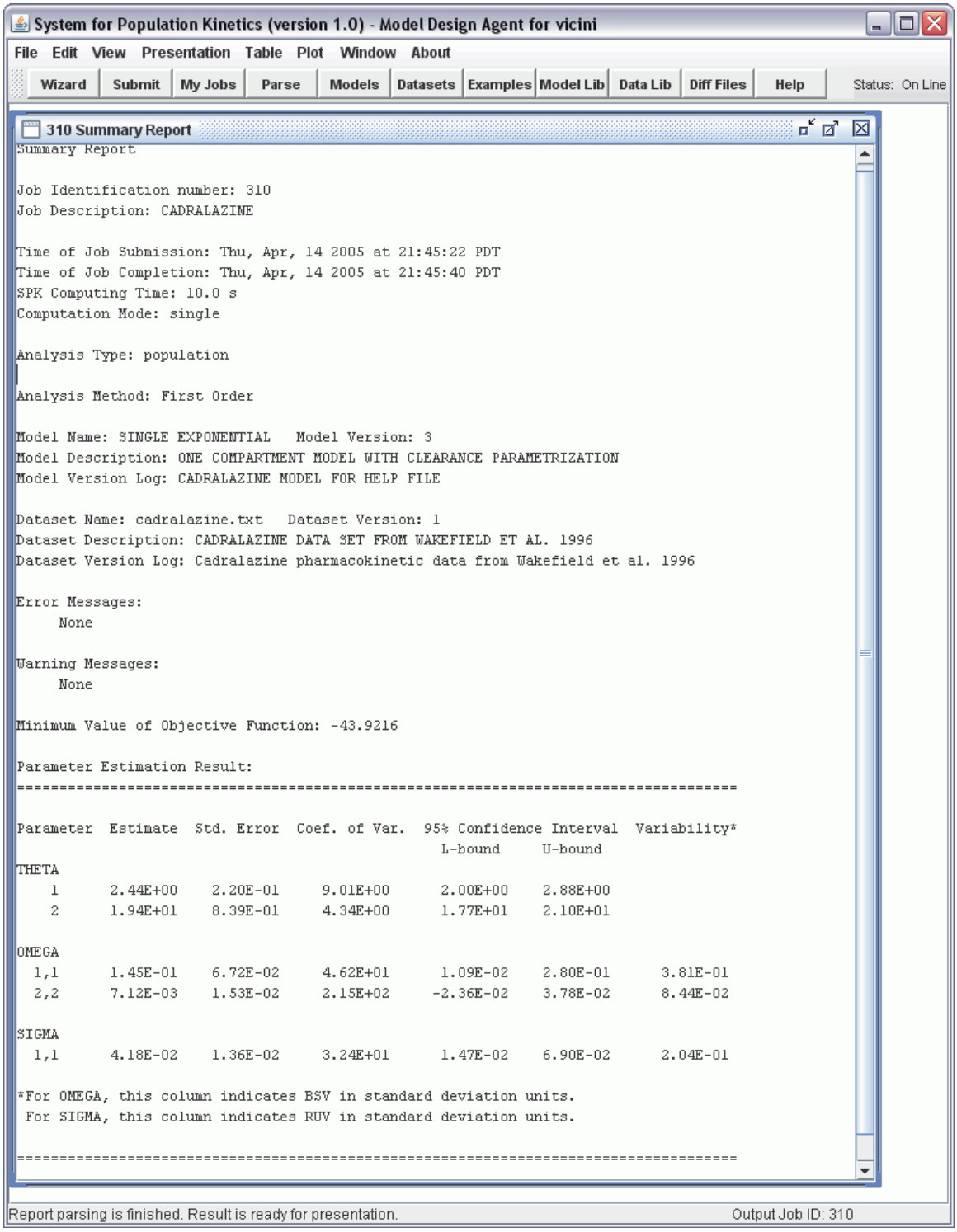
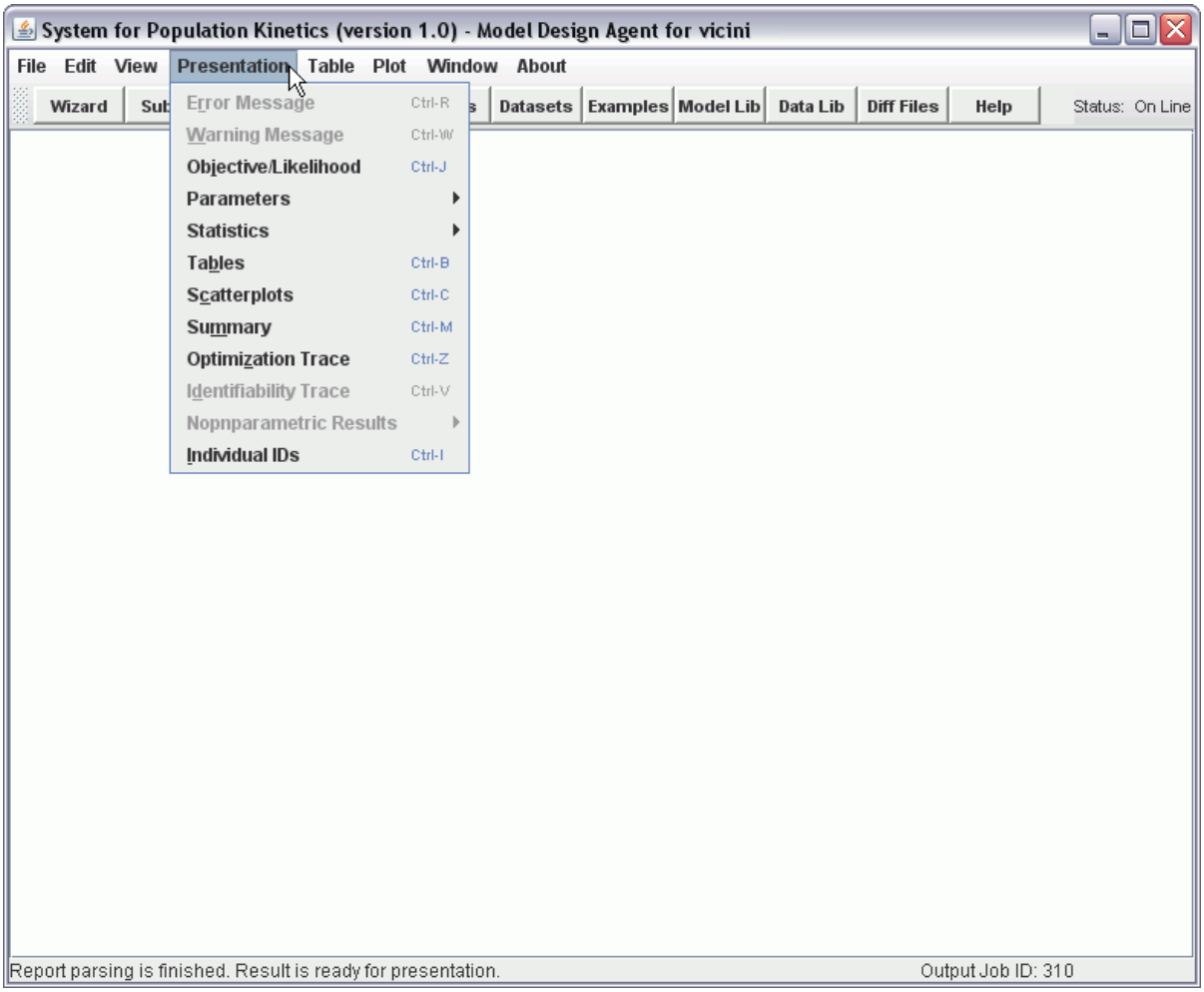
Presentation

An example Summary Report is shown below:



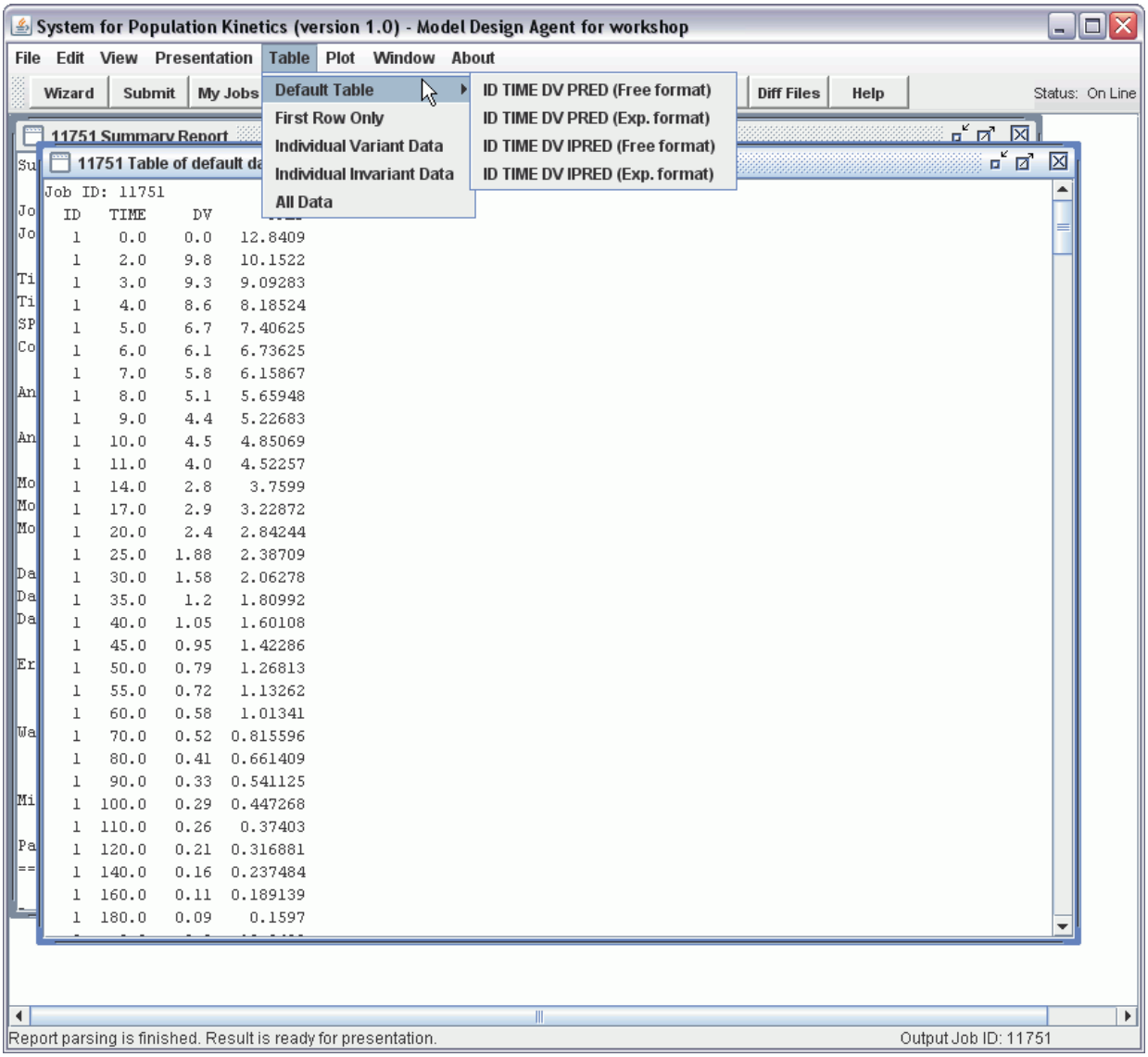
The Summary Report displays important information about the job, such as optimal parameter estimates, their coefficients of variation, lower and upper bound of the 95% confidence interval, and so on.

Other elements of the computational output can be accessed using the Presentation menu from the MDA:

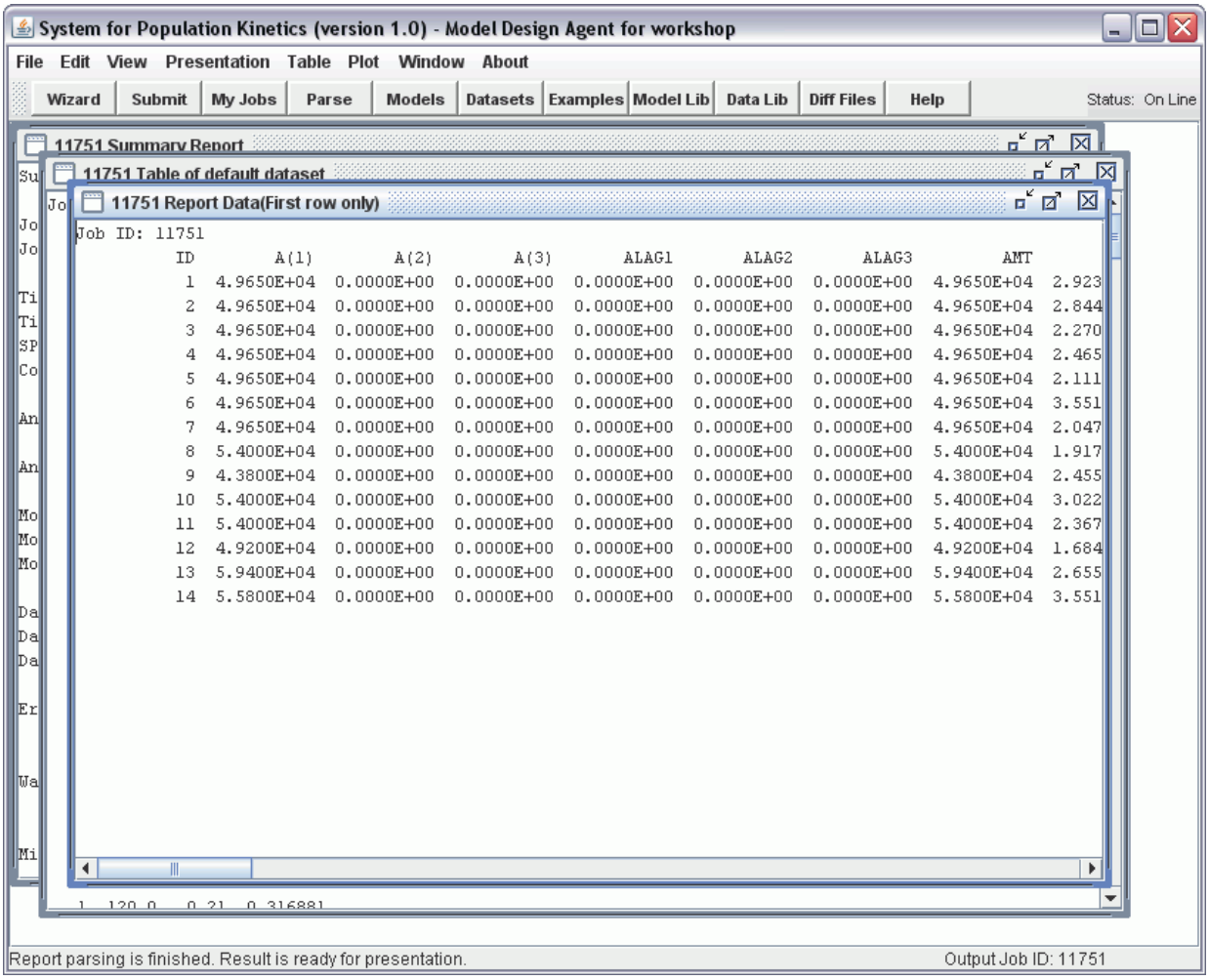


Table

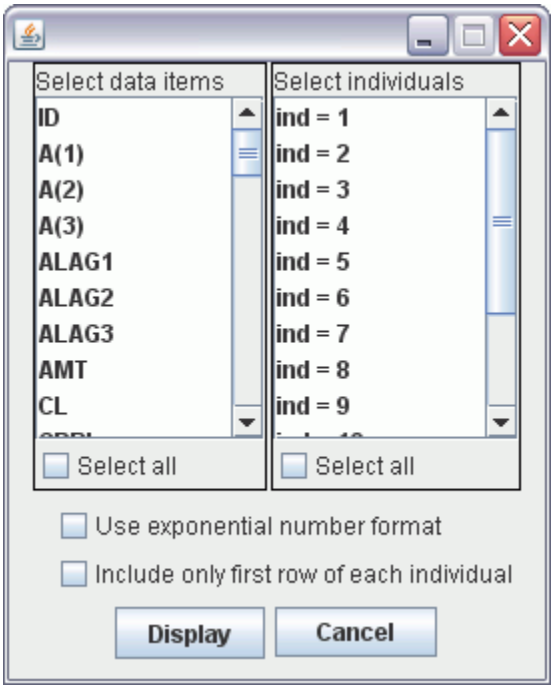
Default tables are available or a custom table can be built using the entire report. Tables can be requested once the report has been loaded. Default tables include TIME versus both PRED and IPRED for each ID. They are provided both in free format and exponential (scientific) format.



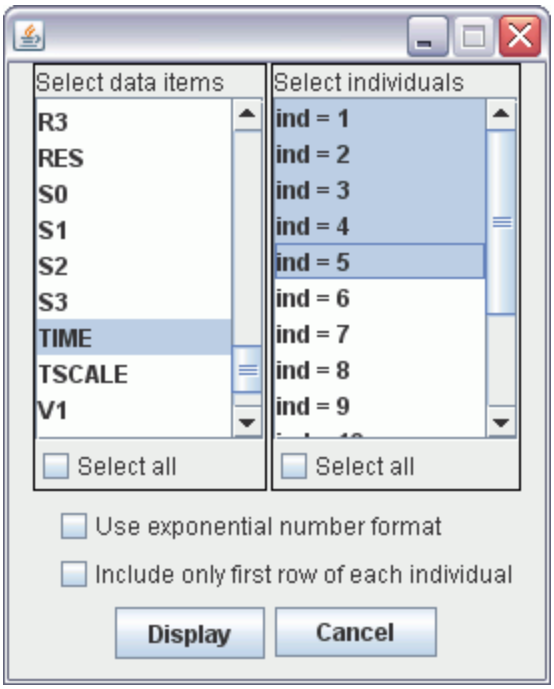
The option "First Row Only" provides values for each variable once for ID. It is useful when it is needed to display individual parameter values only once



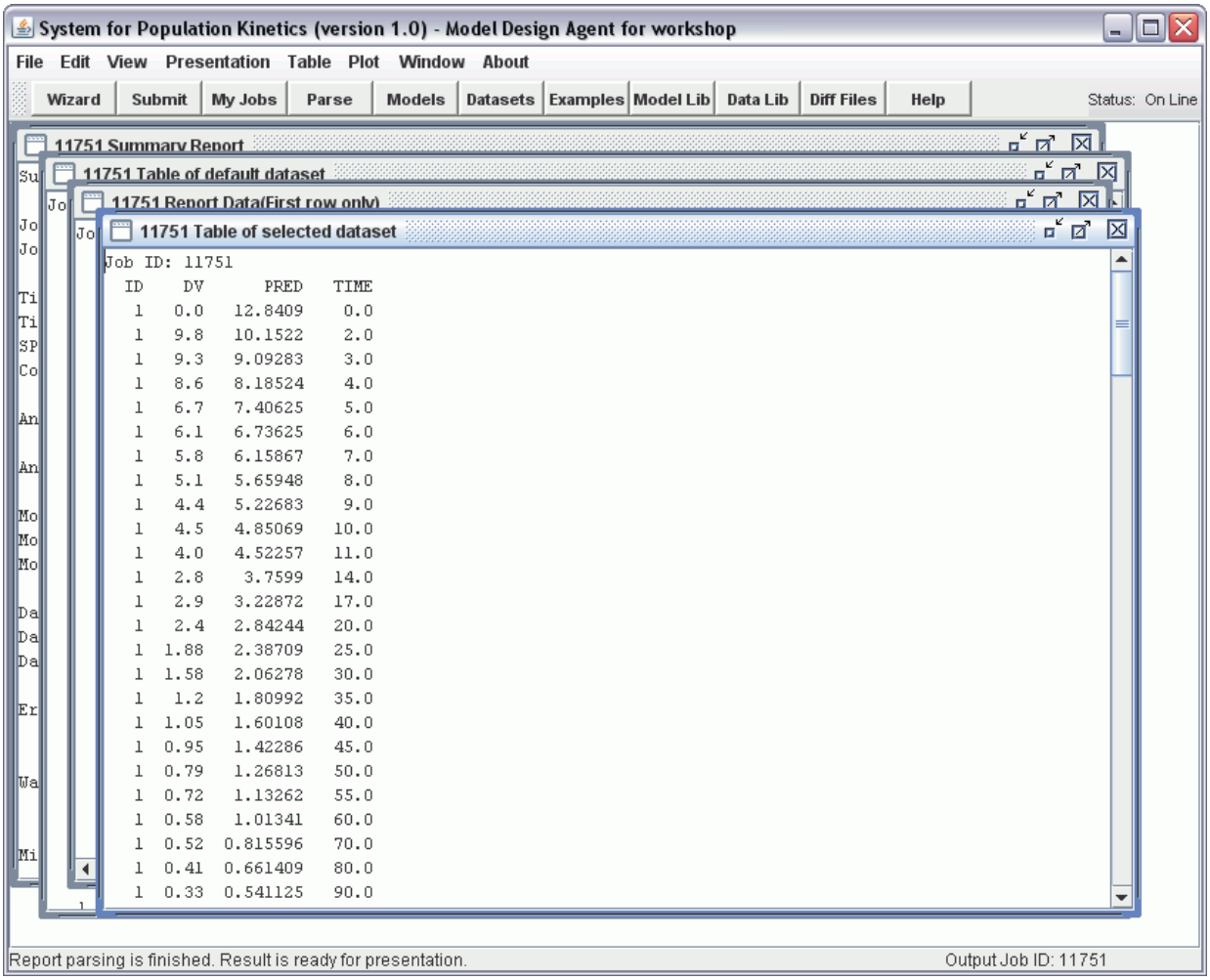
The "Selected Dataset" option allows the user to build custom plots that may be specific to a certain ID or to a certain group of subjects or variables of interest.



For example, the user could choose to plot the data (DV) and the predictions (PRED) for the first five individuals, listed by ID (the CTRL key should be used to select multiple items):

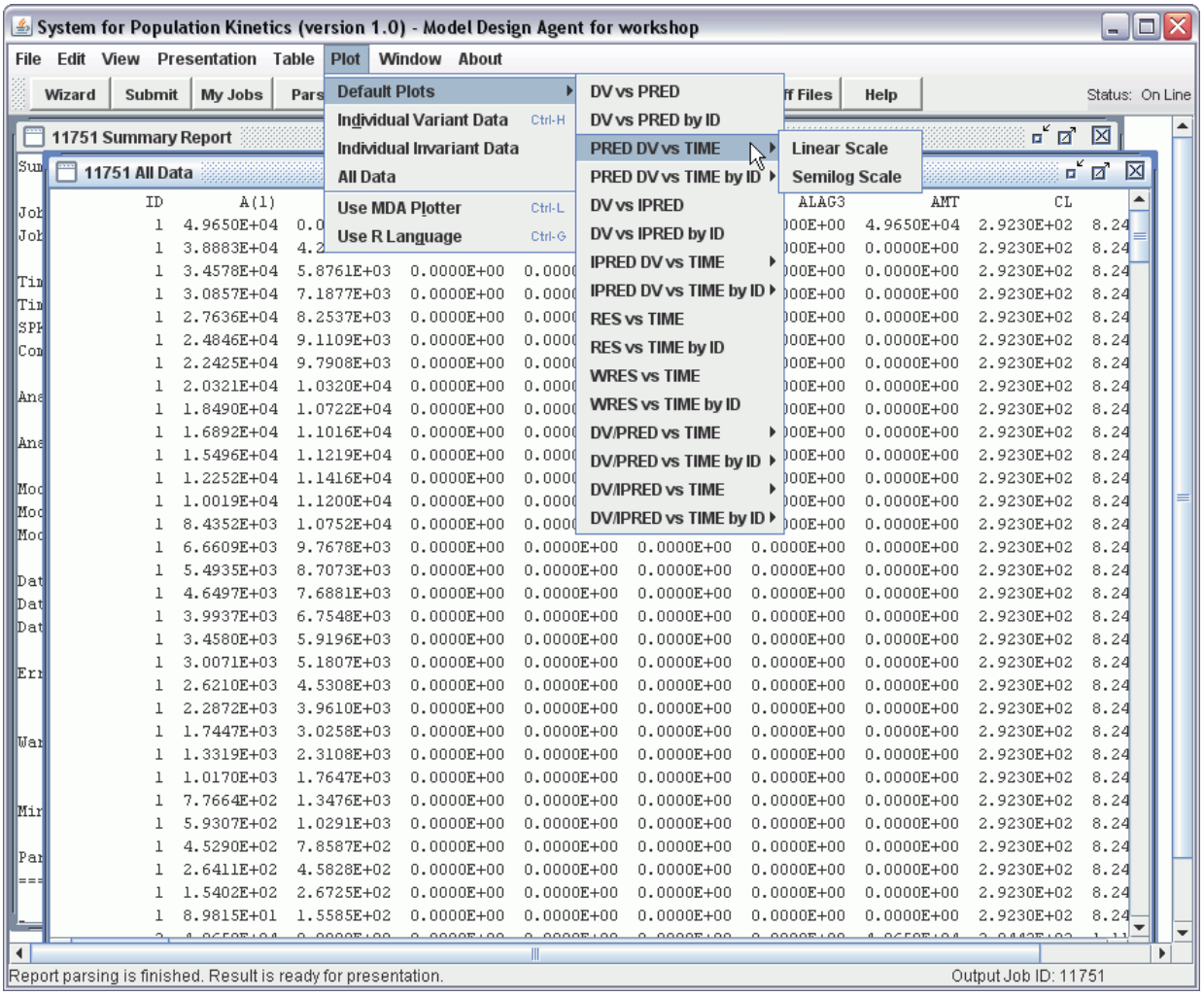


The result is displayed in the MDA window:

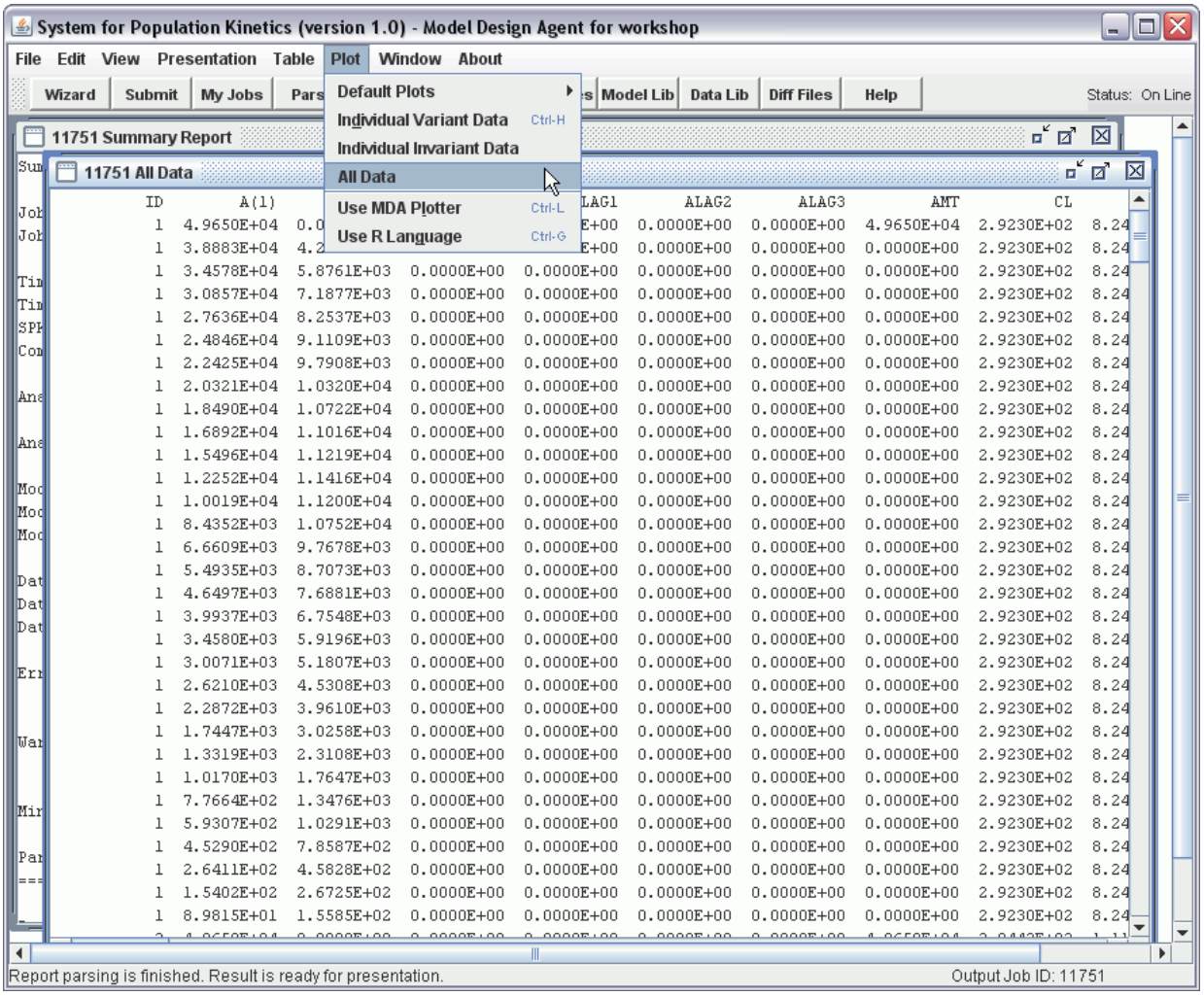


Plot

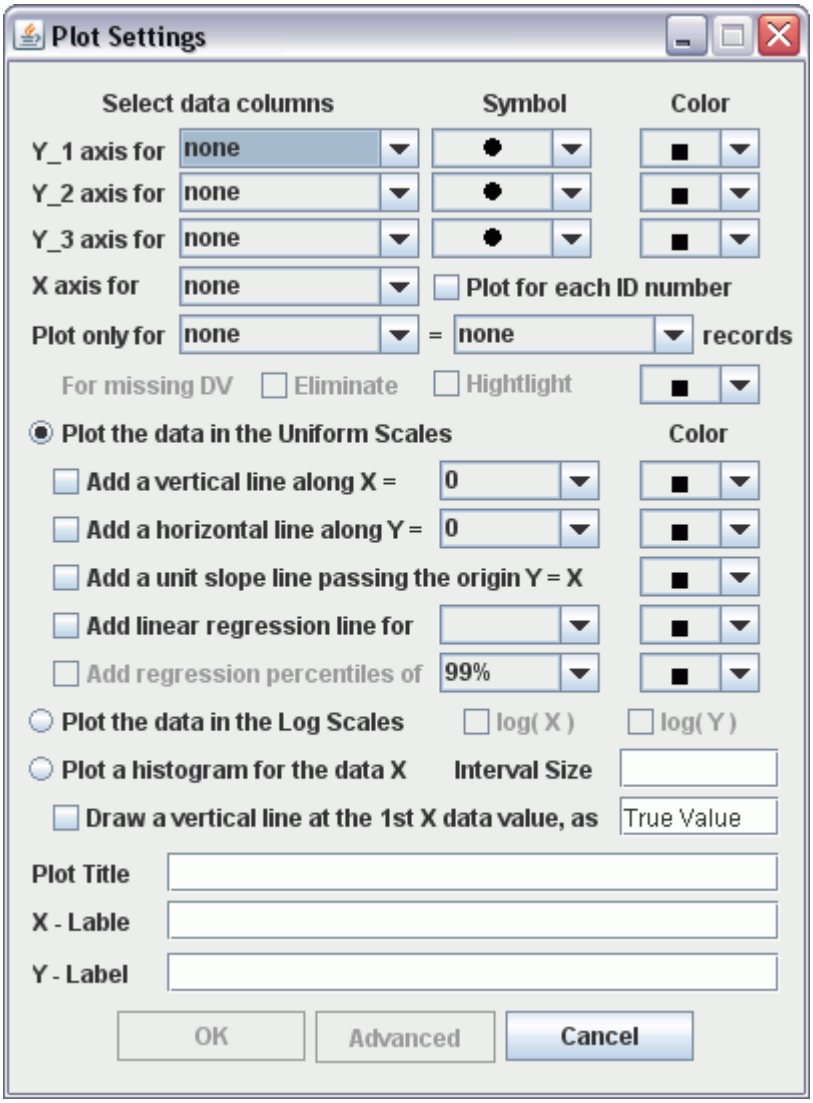
Default plots are available or a custom plot can be built using the entire report. The "Individual Variant Data", the "Individual Invariant Data" or the "All Data" should be selected before plots are requested.



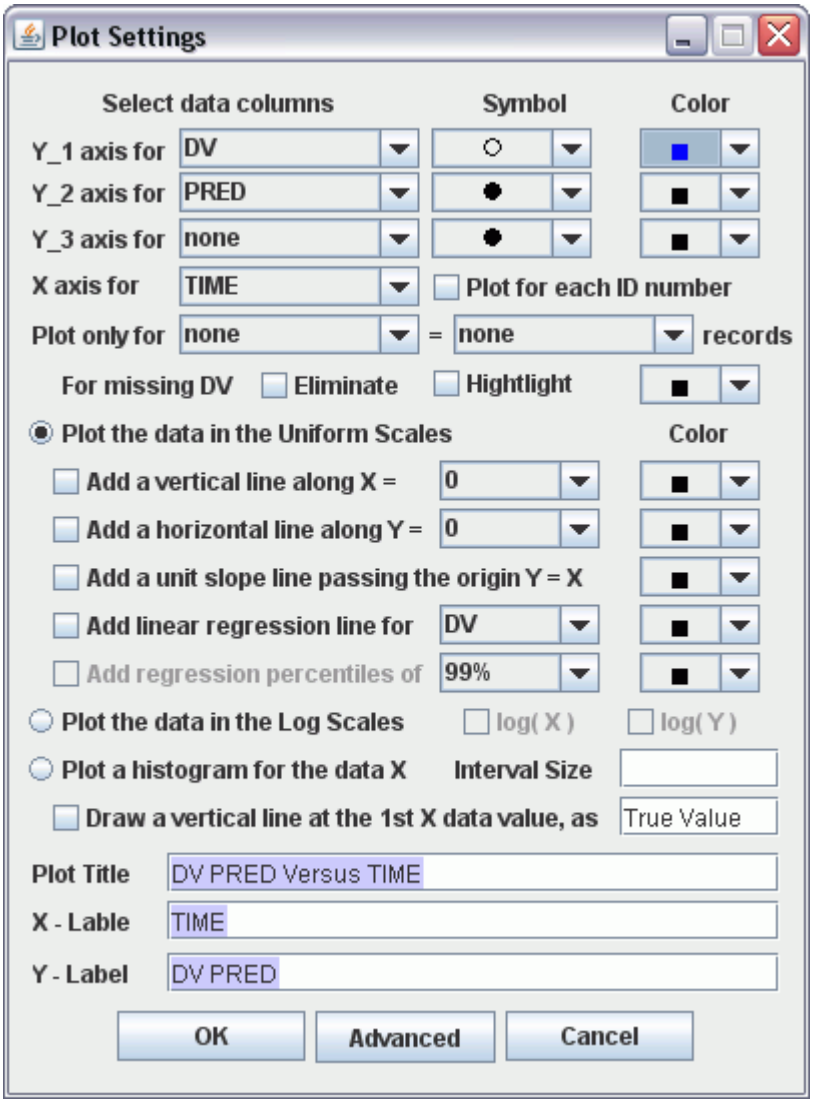
The "All Data" option displays the values for all the variables defined in the entire job. If a default variable has not been modified, its value is not displayed.



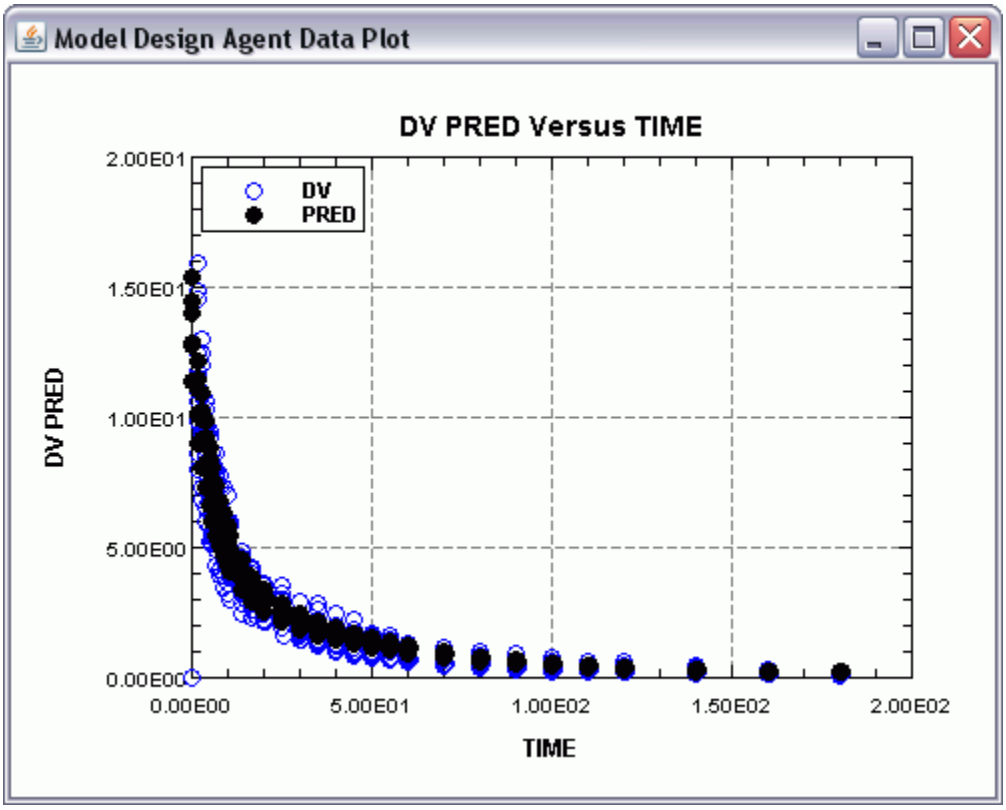
The "Use MDA Plotter" option allows the user to build custom plots that may be specific to a certain ID or to a certain group of subjects or variables of interest.



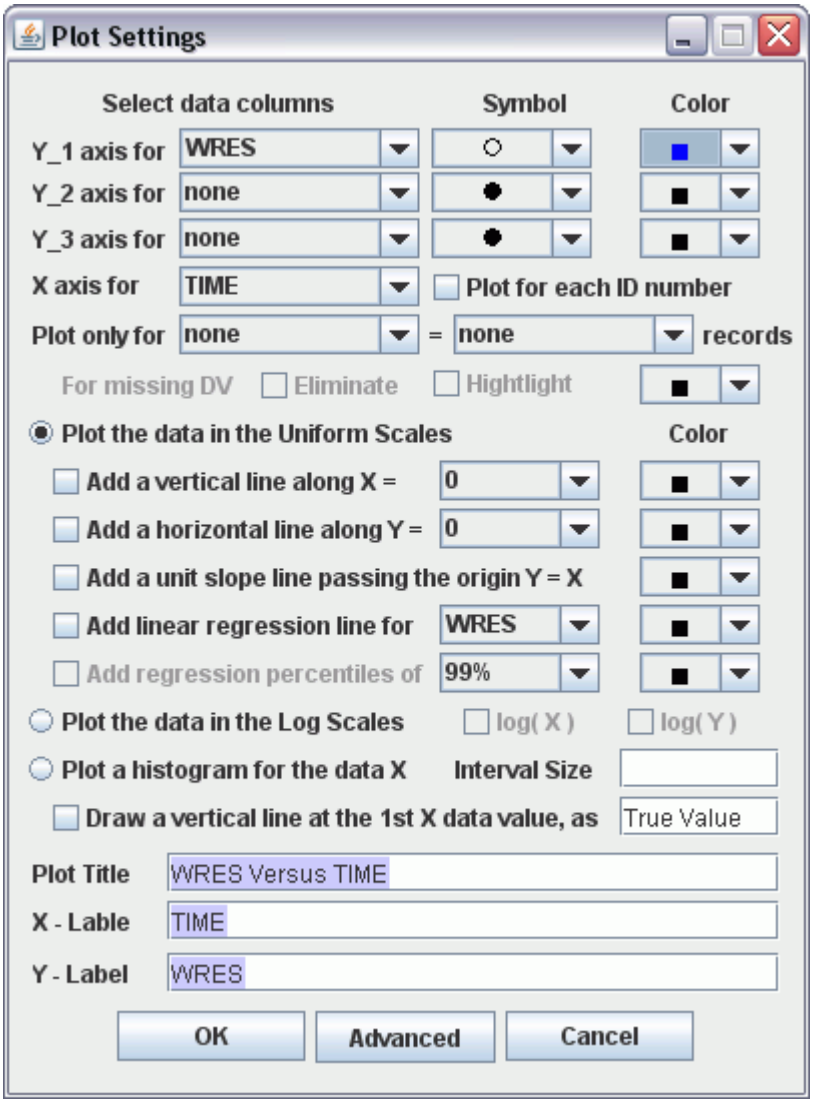
For example, the user could choose to plot the data (DV) as empty blue circles and the predictions (PRED) as black full circles, against TIME:

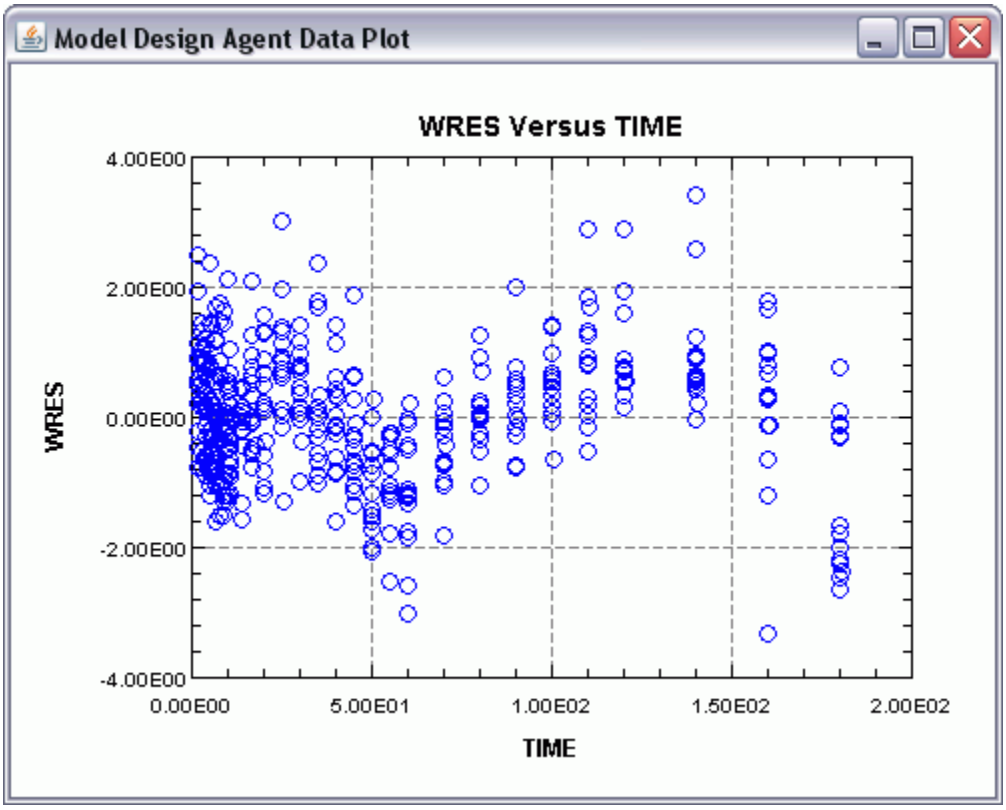


The result is as follows:



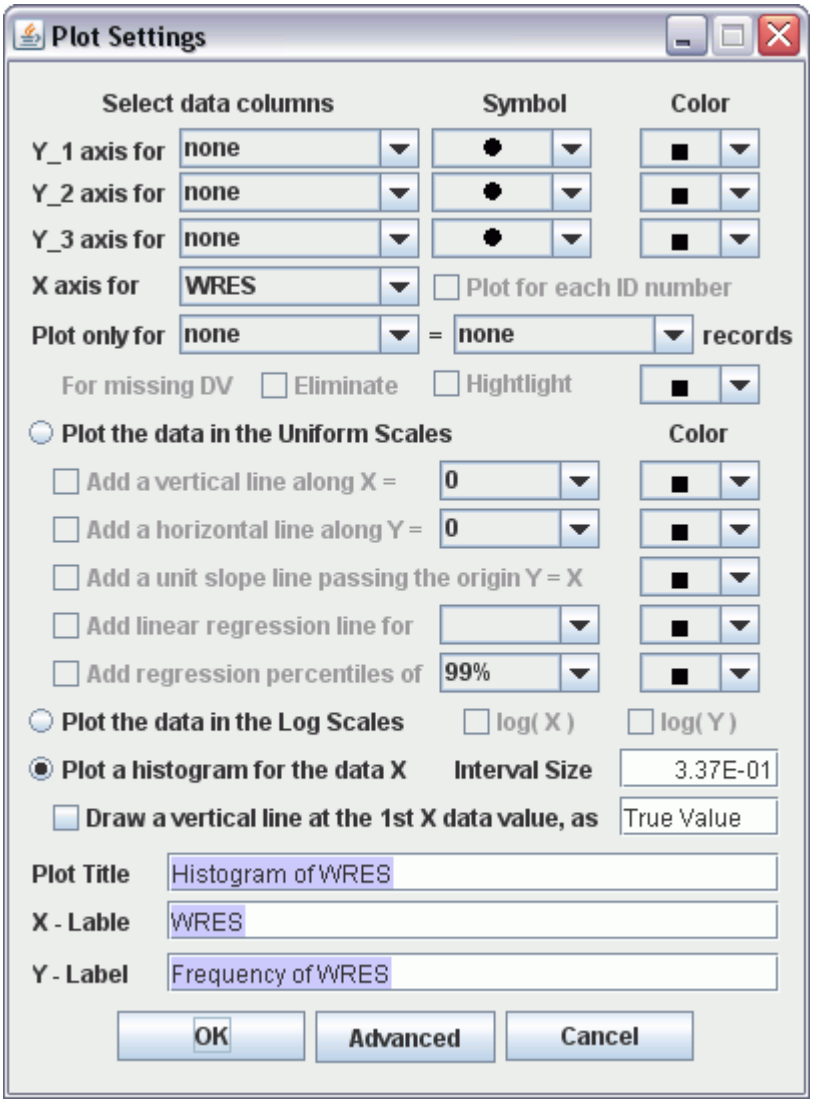
Another interesting plot could be WRES versus TIME:

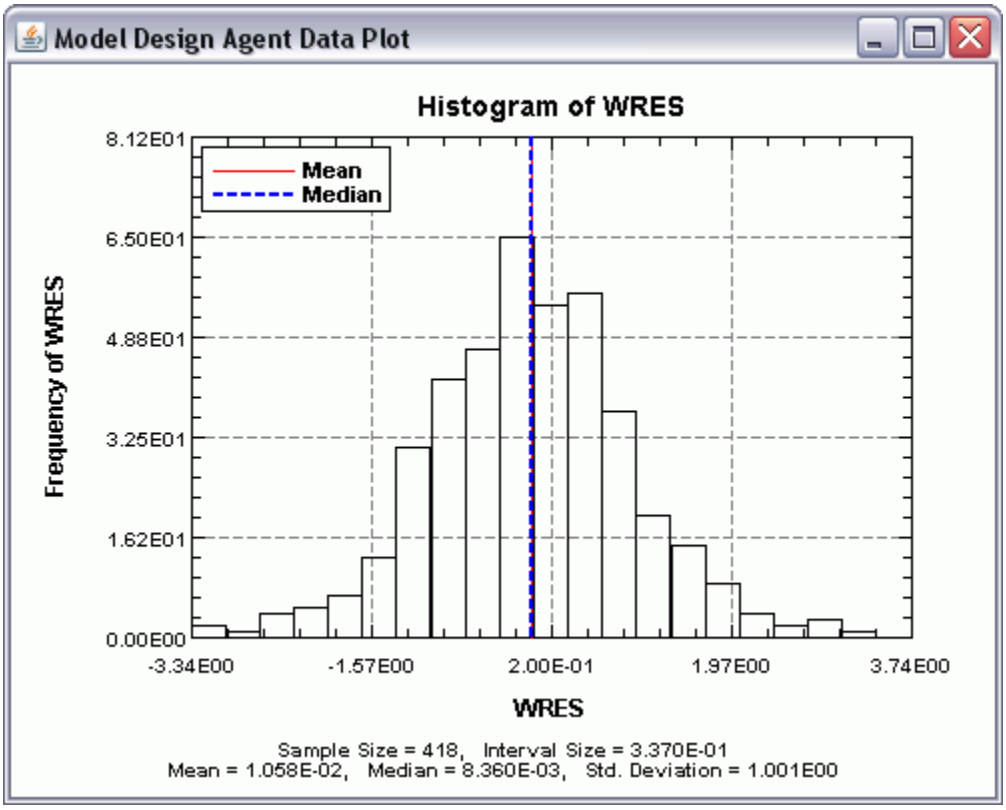

Plot Settings
Select data columns
Symbol
Color
Y_1 axis for
WRES
Y_2 axis for
none
Y_3 axis for
none
X axis for
TIME
Plot for each ID number
Plot only for
none
=
none
records
For missing DV
Eliminate
Hightlight
Plot the data in the Uniform Scales
Color
Add a vertical line along X =
0
Add a horizontal line along Y =
0
Add a unit slope line passing the origin Y = X
Add linear regression line for
WRES
Add regression percentiles of
99%
Plot the data in the Log Scales
log(X)
log(Y)
Plot a histogram for the data X
Interval Size
Draw a vertical line at the 1st X data value, as
True Value
Plot Title
WRES Versus TIME
X - Lable
TIME
Y - Label
WRES
OK
Advanced
Cancel



Plots can be sent to a printer by right-clicking on the plot window and selecting **Print**, or can be saved in either PNG or JPG format by right-clicking and selecting **Save**.

It is also possible to plot histograms, together with relevant statistics (mean, median, etc.):


Plot Settings
Select data columns
Symbol
Color
Y_1 axis for
none
Y_2 axis for
none
Y_3 axis for
none
X axis for
WRES
Plot for each ID number
Plot only for
none
=
none
records
For missing DV
Eliminate
Hightlight
Plot the data in the Uniform Scales
Color
Add a vertical line along X =
0
Add a horizontal line along Y =
0
Add a unit slope line passing the origin Y = X
Add linear regression line for
Add regression percentiles of
99%
Plot the data in the Log Scales
log(X)
log(Y)
Plot a histogram for the data X
Interval Size
3.37E-01
Draw a vertical line at the 1st X data value, as
True Value
Plot Title
Histogram of WRES
X - Lable
WRES
Y - Label
Frequency of WRES
OK
Advanced
Cancel


Model Design Agent Data Plot
Histogram of WRES
Mean
Median
8.12E01
6.50E01
4.88E01
3.25E01
1.62E01
0.00E00
Frequency of WRES
-3.34E00
-1.57E00
2.00E-01
1.97E00
3.74E00
WRES
Sample Size = 418, Interval Size = 3.370E-01
Mean = 1.058E-02, Median = 8.360E-03, Std. Deviation = 1.001E00

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