

MONOLIX

Version 4.3.0

JANUARY 2014

A software for the analysis of nonlinear mixed effects models

Maximum likelihood estimation

Model selection

Hypothesis testing

Graphical analysis

Data simulation

...

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I M P O R T A N C E S A H M P L I N G
C H A S M C
S I M U L A T E D A N N E A L I N G
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M E T R O P O L I S

MONOLIX[®](MOdèles NOn LInéaires à effets miXtes) is a platform of reference for model-based drug development. It combines the most advanced algorithms with unique ease of use.

Pharmacometricians of preclinical and clinical groups can rely on MONOLIX for population analysis and to model PK/PD and other complex biochemical and physiological processes. MONOLIX is an easy, fast and powerful tool for parameter estimation in non-linear mixed effect models, model diagnosis and assessment, and advanced graphical representation.

MONOLIX is the result of a ten years research program in statistics and modeling, led by INRIA (Institut National de la Recherche en Informatique et Automatique) on non-linear mixed effect models for advanced population analysis, PK/PD, pre-clinical and clinical trial modeling & simulation.

MONOLIX is based on the MATLAB scientific environment published by Mathworks. MONOLIX is also available as a full-featured standalone software compiled with MATLAB libraries, and therefore does not require to purchase MATLAB licences.

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Chapter 1

Introduction

1.1 The objectives

The objectives of MONOLIX are to perform:

1. Parameter estimation for nonlinear mixed effects models
 - computing the maximum likelihood estimator of the population parameters, without any approximation of the model (linearization, quadrature approximation, ...), using the Stochastic Approximation Expectation Maximization (SAEM) algorithm,
 - computing standard errors for the maximum likelihood estimator
 - computing the conditional modes, the conditional means and the conditional standard deviations of the individual parameters, using the Hastings-Metropolis algorithm
2. Model selection
 - comparing several models using some information criteria (AIC, BIC)
 - testing hypotheses using the Likelihood Ratio Test
 - testing parameters using the Wald Test
3. Easy description of pharmacometric models (PK, PK-PD, discrete data) with the MLXTRAN language
4. Goodness of fit plots
5. Data simulation.

MONOLIX handles a broad spectrum of models including models defined with differential equations, left censored data, discrete data models, repeated time to events, hidden Markov models, mixture models,...

Theoretical analysis of the algorithms used in this software can be found in [9, 10, 13, 14, 1]. Several application of SAEM in agronomy [19], animal breeding [12] and PKPD analysis [4, 17, 23, 25, 27, 28, 3, 29] have been published by several members of the MONOLIX group and other authors. Several applications to PKPD analysis and several extensions to complex models were also proposed during the last PAGE (Population Approach Group in Europe) meetings ([2, 16, 15, 20, 22, 24, 26, 8, 18, 7] as well as a comparison of estimation algorithms [11], (<http://www.page-meeting.org>).

The aim of the present User Guide is to help a MONOLIX beginner to discover the software abilities. **Chapter 2** contains the installation guide, **Chapter 3** explains how to use MONOLIX and its graphical interface. Advanced Features and examples are detailed in **Chapter 4**. And the use of the software without the graphical interface and batch mode is described in **Chapter 5**.

The statistical models handled by MONOLIX are given in **Appendix A** and a list of visual preferences for result graphics is given in **Appendix C**.

The user guide does not cover MLXTRAN programming in details, and is therefore completed by two additional documents:

- `modelMLXTRANtutorial.pdf` is a slidedeck tutorial on how to describe pharmacometric models with MLXTRAN .
- `ProjectMLXTRAN.pdf` presents how to easily program and customize complete MONOLIX projets with MLXTRAN .

Chapter 2

Installing and running MONOLIX[®]

2.1 Downloading packages

The MONOLIX packages can be downloaded through the download manager hosted at <http://download.lixoft.com>. The download manager is available for users provided with an access key. Different MONOLIX packages are available, depending on the MATLAB version and of the operating system. MONOLIX currently supports Windows XP/Vista/Seven 32bits, Linux (all common distributions) 32/64 bits.

Choice of MONOLIX versions

- MATLAB versions:
 - Linux 64 bits / Matlab R2009 to R2010a
 - Linux 64 bits / Matlab R2010bSP1 to R2013b
 - Linux 32 bits / Matlab R2009 to R2010a
 - Linux 32 bits / Matlab R2010b to R2013b
 - Windows 64 bits (XP, Seven, Vista and Windows 8.1) / Matlab R2009a to R2010a
 - Windows 64 bits (XP, Seven, Vista and Windows 8.1) / Matlab R2010bSP1 to R2013b
 - Windows 32 bits (XP, Seven and Vista) / Matlab R2009a to R2010a
 - Windows 32 bits (XP, Seven and Vista) / Matlab R2010bSP1 to R2013b recommended to use MATLAB 2010b-SP1.
- Standalone versions:
 - Linux (32 bits)

- Linux (64 bits)
- Windows (32 bits)
- Windows (64 bits)

2.2 Installation

2.2.1 Prerequisites

`perl` is required to run `perlScripts` and the validation suite; it is not required otherwise.

Linux specifics

- install `sharutils` : `uudecode` is required to uncompress the MONOLIX package;
- make sure you have `gcc/g++/make` installed or install them.

Windows 64bits specifics

The 32 bits *standalone* version of MONOLIX runs fine on Windows 7 64bits. You will need to install the 64 bits Windows version of MONOLIX in any of these situations:

- On other 64 bits versions of Windows (non Windows 7, or Windows 8.1);
- If you wish to use a MATLAB version of MONOLIX .
- If you simply prefer to use a 64bits version of standalone MONOLIX , although in practice this should not have an impact on the performance.

2.2.2 About Installer

- Linux : the installer is a self-extractable archive.
 - run the following command (depending on your os version):

```
#> sh Monolix-4.3.0-matlab2010a-linux32.bin
or
#> sh Monolix-4.3.0-matlab2010bSP1-linux32.bin
or
#> sh Monolix-4.3.0-standalone2008b-linux32.bin
or
#> sh Monolix-4.3.0-matlab2010a-linux64.bin
or
#> sh Monolix-4.3.0-matlab2010bSP1-linux64.bin
or
#> sh Monolix-4.3.0-standalone2008b-linux64.bin
```

- you can specify the target installation directory by giving the path as argument
 - a directory containing MONOLIX will be created in the directory installation path
- Windows
 - copy the installer on your Desktop or in your windows temporary directory
 - Double click on the executable and follow the instructions.

2.2.3 Directory structure

The MONOLIX directory structure is divided in two parts:

- the software directory containing the MONOLIX program (/Path/To/.../runtime)
- the personal user directory containing the MONOLIX workspace and documentation (/Path/To/.../lixoft)

Installation directory

```

Monolix.....MONOLIX ROOT DIRECTORY
├─ monolix430.....MONOLIX VERSION DIRECTORY
│  └─ bin.....TOOLS DIRECTORY
│  └─ config.....CONFIGURATION FILES
│     └─ graphics.....GRAPHICS CONFIGURATIONS
│        └─ listOfGraphics.....GRAPHICS PREDEFINED CONFIGURATIONS
│        └─ project.....GRAPHICS DEFAULT CONFIGURATIONS FOR MLXTRAN
│        └─ settings.....GRAPHICS DEFAULT CONFIGURATIONS
│     └─ scenario.....PREDEFINED SCENARI
│     └─ system.....MONOLIX SYSTEM CONFIGURATION
│  └─ factory.....MLXTRAN C++ API
│  └─ jar.....JAVA LIBRARY
│  └─ lib.....C++ LIBRARY
│  └─ matlab.....MONOLIX MAIN PROGRAM
│     └─ libraires.....MODELS LIBRAIRES
│     └─ mlxCore.....MONOLIX CORE : ALL ALGORITHMS (SAEM, FIM, ...)
│     └─ mlxDelegate.....GLUE TO PRESENT MONOLIX PROJECT (HMI, BATCH, ...)
│     └─ mlxIO.....INPUT / OUTPUT COMPONENTS (READ .MAT, .XMLX, ...)
│     └─ mlxMath.....MISC MATHEMATICAL FUNCTIONS
│     └─ mlxTools.....SOME TOOLS (MAT TO XMLX)
│     └─ mlxUseful.....GENERIC COMPONENTS
│  └─ perlScripts.....PERL SCRIPTS
│  └─ resources.....DOCUMENTATION AND DEMOS
│     └─ demos.....DEMOS
│     └─ doc.....DOCUMENTATION

```

User directory

The user directory is created after the first launch of MONOLIX. This directory contains the basic configuration of MONOLIX, documentation, demos, log files, license file,

```
lixoft..... LIXOFT TOOLS DIRECTORY
├─ monolix..... MONOLIX ROOT DIRECTORY
│   └─ monolix430..... MONOLIX VERSION DIRECTORY
│       ├── log..... LOG FILES
│       ├── modules..... COMPILED MLXTRAN MODULES
│       ├── perlScripts ..... PERL SCRIPTS
│       ├── work..... USER WORKING DIRECTORY
│       ├── demos..... MODIFIABLE DEMOS
│       ├── tmp..... SET OF DEMOS (COPIED IN MONOLIX USER DIRECTORY)
│       ├── license..... TOOLS DIRECTORY
│       └─ config..... CONFIGURATION FILES
```

2.2.4 Running MONOLIX

- Linux
 - MATLAB version
 - * start MATLAB
 - * go to directory '`<install path>/matlab`' and type `monolix`.
 - Standalone version: go to '`<install path>/bin`' and type `./Monolix.sh`.
- Windows
 - MATLAB version
 - * start MATLAB
 - * go to directory `<install path>\matlab`' and type `monolix`.
 - Standalone version: go to '`<install path>\bin`' and type `Monolix.bat`.

2.2.5 Installation use cases

Desktop

MONOLIX is installed on the computer of the user and the user has a personal activation key (see [Section 2.2.6 Desktop license](#)). After the installation or during the first startup of MONOLIX a popup titled 'Lixoft Activate' appears and asks the activation key. When the activation procedure is finished, MONOLIX will be configured (typically a directory '`/Path/To/.../lixot/monolix`' is created in the user home directory) and launched.

Desktop with a shared MONOLIX installation

MONOLIX is installed on a remote server and the user accesses to MONOLIX through a shared directory (via CIFS, Network drive, NFS, ...) and the user has a personal activation key (see [Section 2.2.6 Desktop license](#)).

During the first startup of MONOLIX a popup title 'Lixoft Activate' appears and asks the activation key. When the activation procedure is finished, MONOLIX will be configured (typically a directory '`/Path/To/.../lixot/monolix`' is created in the user home directory) and launched.

Application server with a shared MONOLIX installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.2.6 'Floating license'](#). The license file (obtained during activation procedure) is copied in the directory

- `<monolix user install path>/config/system/access` for the MATLAB version of MONOLIX
- or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX .

The user accesses to MONOLIX through a shared directory (via CIFS, Network drive, NFS, ...). The user runs MONOLIX directly, no activation is required. Nevertheless, when a user runs MONOLIX a license token is taken.

If all license tokens are used (too many users run MONOLIX in the same time), a popup titled 'Lixoft activate' appears and the user is supposed to wait until at least one token is released.

Application server with a remote connection

With a floating license MONOLIX is installed on a remote server using the procedure described in [Section 2.2.6 'Floating license'](#). The license file (obtained during activation procedure) is copied in the directory

- `<monolix user install path>/config/system/access` for the MATLAB version of MONOLIX
- or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX .

The user accesses to MONOLIX using a remote desktop application.

The user runs MONOLIX directly, no activation is required. Nevertheless, when a user runs MONOLIX a license token is taken.

If all license tokens are used (too many users run MONOLIX in the same time), a popup titled 'Lixoft activate' appears and the user is supposed to wait until at least one token is released.

With desktop licenses MONOLIX is installed on a remote server, the user accesses to MONOLIX using a remote desktop application and has a personal activation key (see [Section 2.2.6 Desktop license](#)).

During the first startup of MONOLIX a popup title 'Lixoft Activate' appears and asks the activation key. When the activation procedure is finished, MONOLIX will be configured (typically a directory '/Path/To/.../lixot/monolix' is created in the user home directory) and launched.

Application server with a desktop installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.2.6 'Floating license'](#). Each MONOLIX user is supposed to have a copy of the license file obtained during the activation procedure. After the installation or during the first startup of MONOLIX, a popup titled 'Lixoft Activate' appears. The tab 'With License file' has to be selected. The user is supposed to browse to the copy of the license file to activate MONOLIX. When a user runs MONOLIX a license token is taken.

If all license tokens are used (too many users run MONOLIX in the same time), a popup titled 'Lixoft activate' appears and the user is supposed to wait until at least one token is released.

Cluster installation with a shared MONOLIX installation

MONOLIX is installed on a master server using the procedure described in [Section 2.2.6 'Floating license'](#). The license file (obtained during activation procedure) is copied in the directory

- `<monolix user install path>/config/system/access` for the MATLAB version of MONOLIX
- or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX.

Each cluster node accesses to MONOLIX through a shared directory (via CIFS, Network drive, NFS, ...).

The user runs MONOLIX directly, no activation is required. Nevertheless, when a user runs MONOLIX a license token is taken (there is no limit of runs on cluster nodes).

If all license tokens are used (too many users run MONOLIX in the same time), a popup titled 'Lixoft activate' appears and the user is supposed to wait until at least one token is released.

Cluster installation with MONOLIX installed on each node

License server (RLM) has to be installed on a master server and the license file is download using the procedure described in [Section 2.2.6 'Floating license'](#). MONOLIX is installed on each cluster.

During this installation it is not necessary to activate MONOLIX when the popup titled 'Lixoft activate' appears (just close the popup). The license file (obtained previously) is supposed copied in the directory

- `<monolix user install path>/config/system/access` for the MATLAB version of MONOLIX
- or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX

of each node.

2.2.6 License

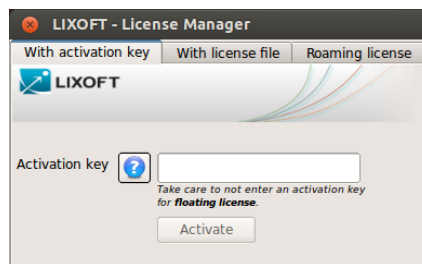
MONOLIX licenses can be of the following types:

- Individual license - named user. The named user can install and run MONOLIX on a predetermined number of different computers.
- Floating license - concurrent access. The license is hosted by a license server, and MONOLIX can either run on a server or individual workstations.

Remark: the former license management tool uses a license file (`license.ini`); this type of license is deprecated since MONOLIX version 4.1.3.

Desktop license

The activation key (provided by LIXOFT) must be entered in the dialog box titled 'LIXOFT license activation' ('With activation key' tab). This dialog box only appears when no license is available on the user's computer or when the license expires.



Floating license

The use of a floating license requires to set up a license server. In this case there are two installation strategies for MONOLIX users:

- install MONOLIX on a directory shared by all MONOLIX users,
- install MONOLIX on each user's computer and copy the license file obtained as described below into the directory:
 - `<monolix user install path>/config/system/access` for the MATLAB version of MONOLIX ,
 - or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX .

After the installation process, when the 'Lixoft activate window' appears just close the window (do not enter the activation key of the floating license). Then, start the RLM server, located at:

- `<monolix install path>/tools/rlm/rlm{.exe}` for the MATLAB version of MONOLIX ,
- or `<monolix install path>/bin/Monolix_mcr/runtime/tools/rlm/rlm{.exe}` for the standalone version of MONOLIX .

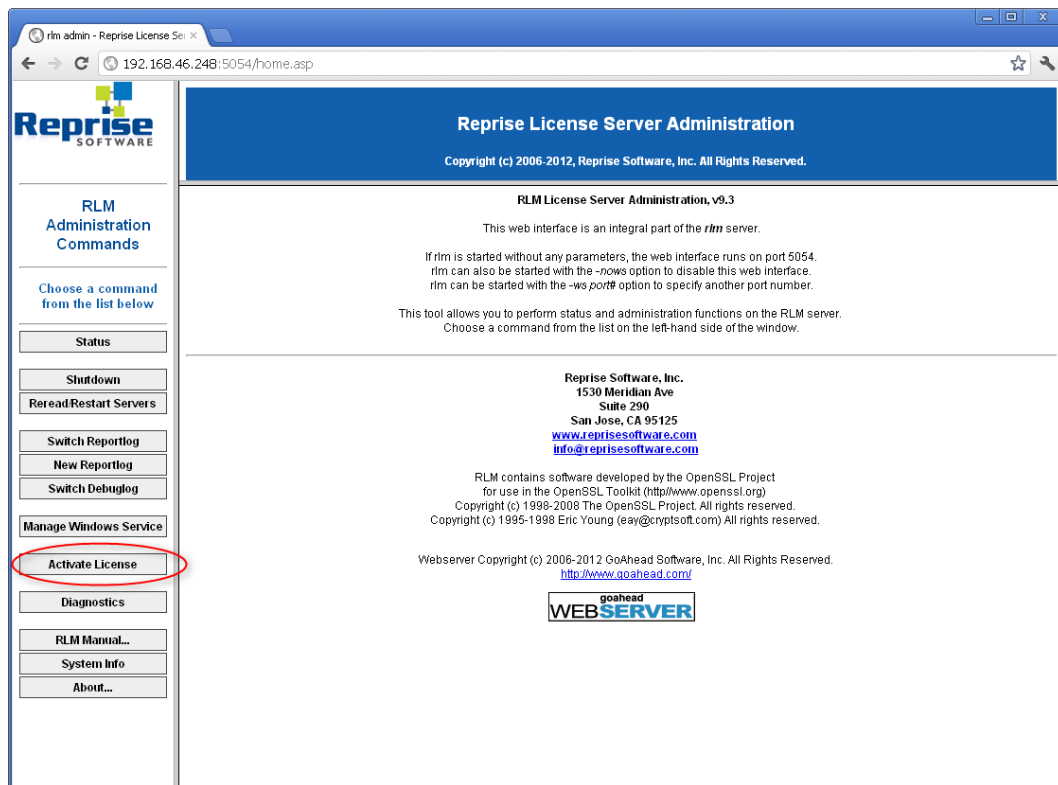
At this step there is no license available yet; the IT manager should use the RLM web server to download the license by following the procedure below:

1. In the web browser, type `<IP>:5054`, where `<IP>` is the IP address of the computer hosting the RLM server (e.g. `192.168.46.248:5054`).

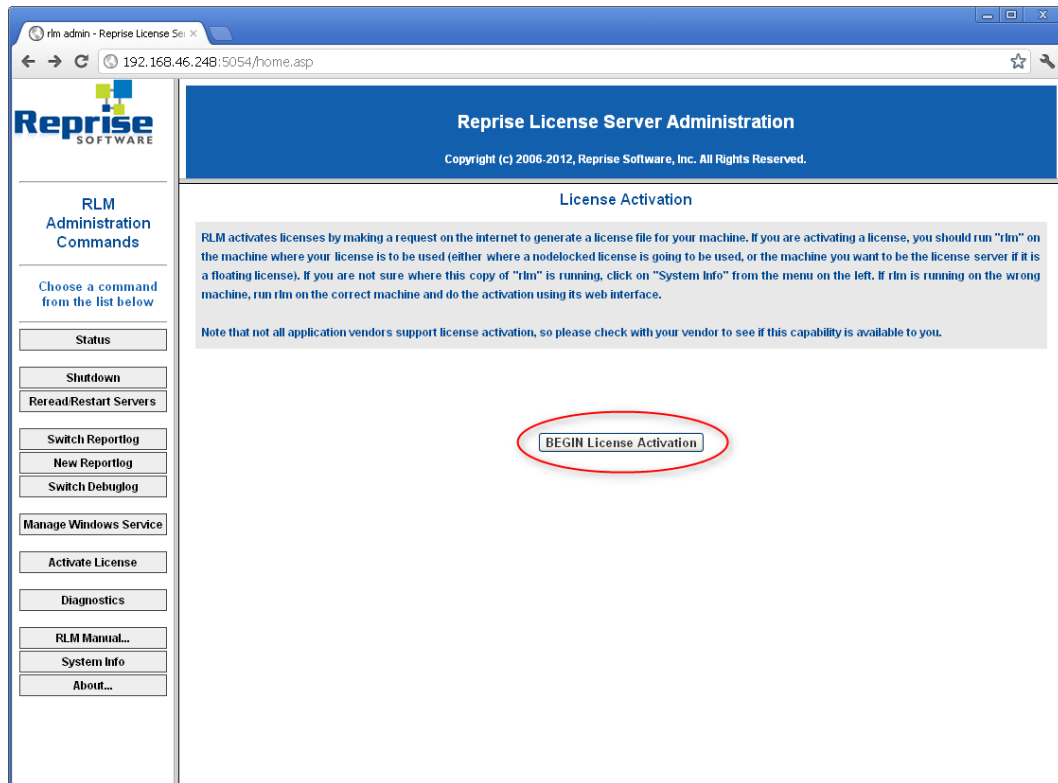
Notice that the RLM server opens two ports : 5053 and 5054. The first port (5053) is a service port used for the transactions of licenses. The second port (5054) is the RLM web server port used to access to the RLM configuration through a web browser.

It is possible that one or both ports may have been used by another application.

- If the web server port (5054) is not available you can launch RLM server with a new port by using the program option `-ws` (e.g: `rlm -ws 5055`) in this case, the access to RLM configuration through a web browser is done using the address `<IP>:<NEW PORT>` (e.g. `192.168.46.248:5055`).
- If the server port (5053) is not available, a file `config.conf` has to be created in the `rlm` directory and has to contain the following information:
`HOST <IP> <MAC ADDRESS> <NEW PORT>`
e.g.
`HOST 192.168.46.245 a8c0f82e 5060`



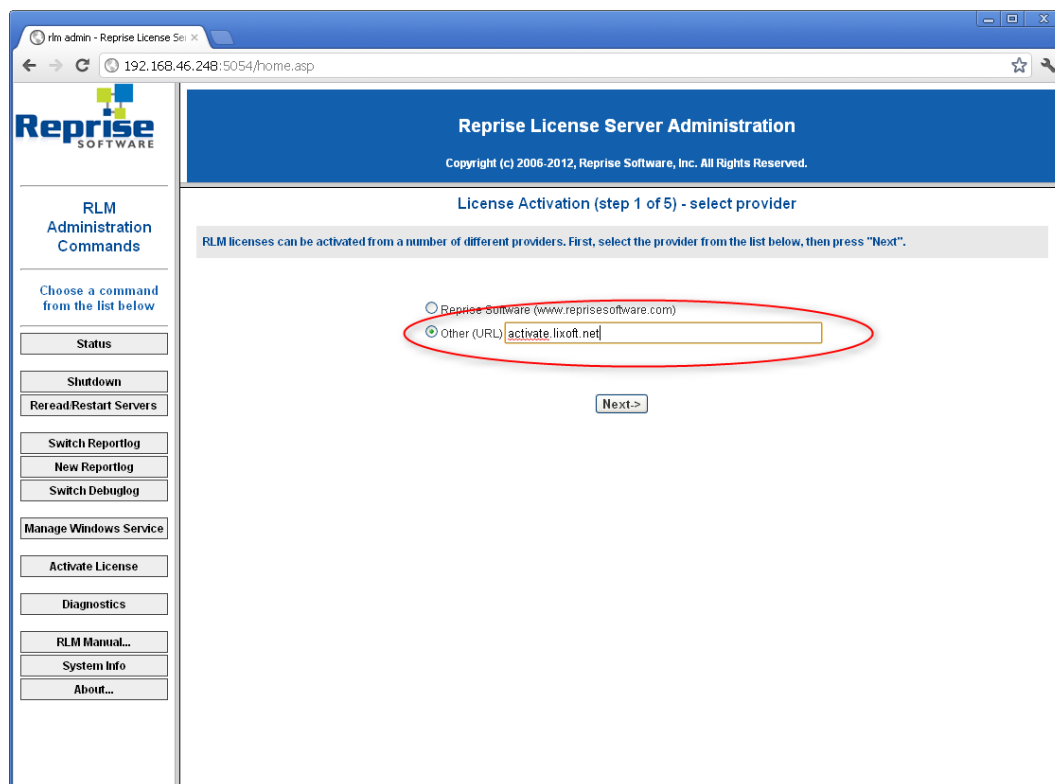
2. Begin license activation:



3. Enter the RLM activation url : `activate.lixoft.net`. And click on Next button.

If the rlm server does not have Internet access, the license has to be created by LIXOFT . Send a mail to support@lixoft.com with the following informations:

- Mac address of the computer hosting the RLM server
- IP address of the computer hosting the RLM server



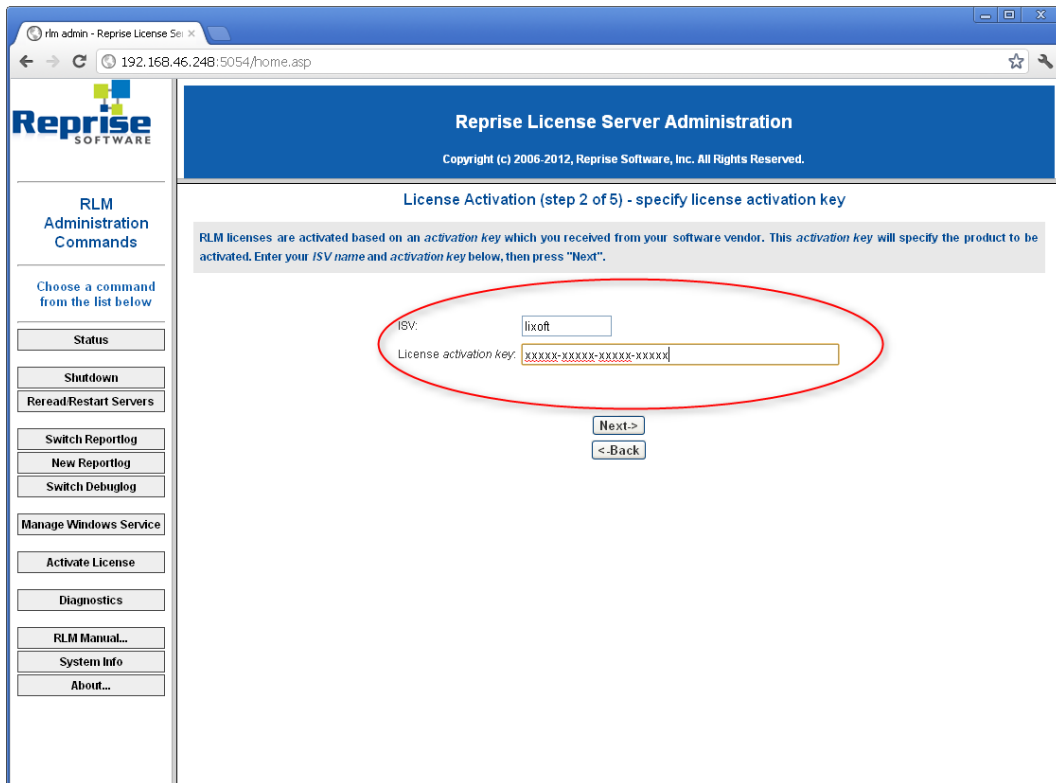
LIXOFT will send in return a '.lic' file which has to be copied in the directory

- <monolix install path>/config/system/access (MATLAB version of MONOLIX)
- <monolix install path>/bin/Monolix_mcr/runtime/config/system/access (standalone version of MONOLIX).

At this step, the installation of MONOLIX is complete.

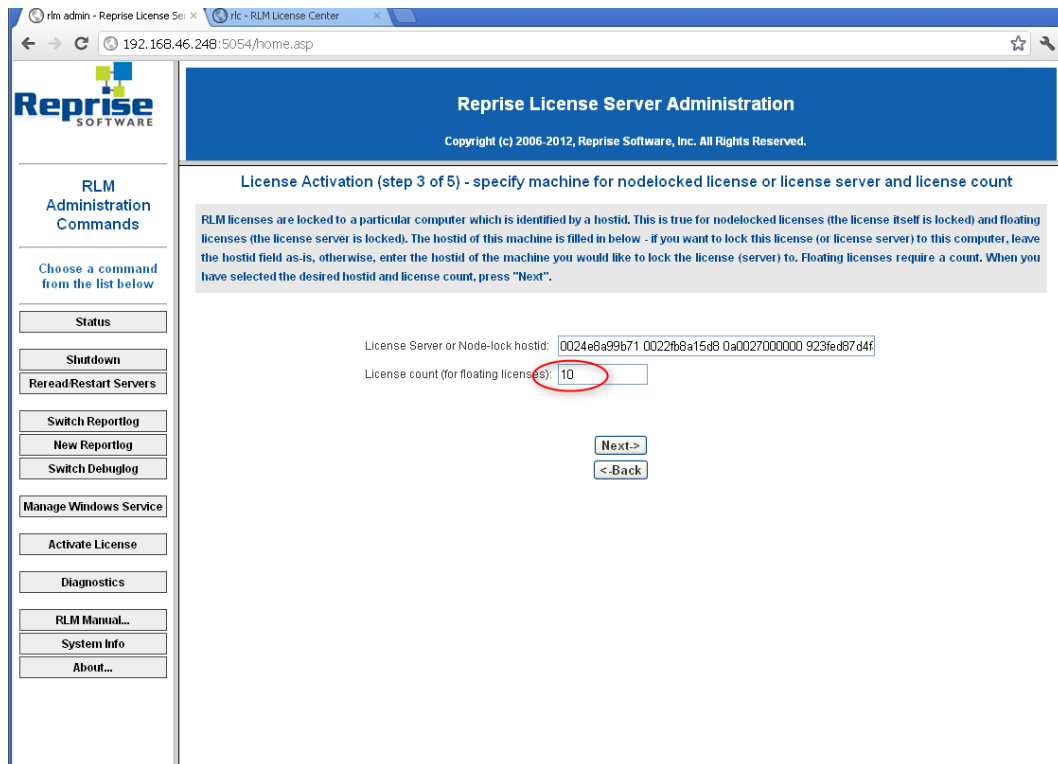
4. Activate the license.

Fill the ISV input with the string 'lixoft' (without the quotes) and the License activation key with the activation key provided by LIXOFT (key format is xxxx-xxxx-xxxx-xxxx)



5. Enter (at maximum) the number of bought licenses, then click on **Next** button

Notice, the number of licenses cannot exceed the number of bought licenses.



6. Select the license directory and file.

In the field named **License file to create** write the full path to license file
`<monolix install path>/config/system/access/myfloat.lic` for the MATLAB version of MONOLIX

or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version.

e.g: if the MONOLIX (matlab version) installation directory is `/media/share/monolix` the input field name **License file to create** should contain
`/media/share/monolix/config/access/myfloat.lic`

This license file has to be copied on each installation of MONOLIX :

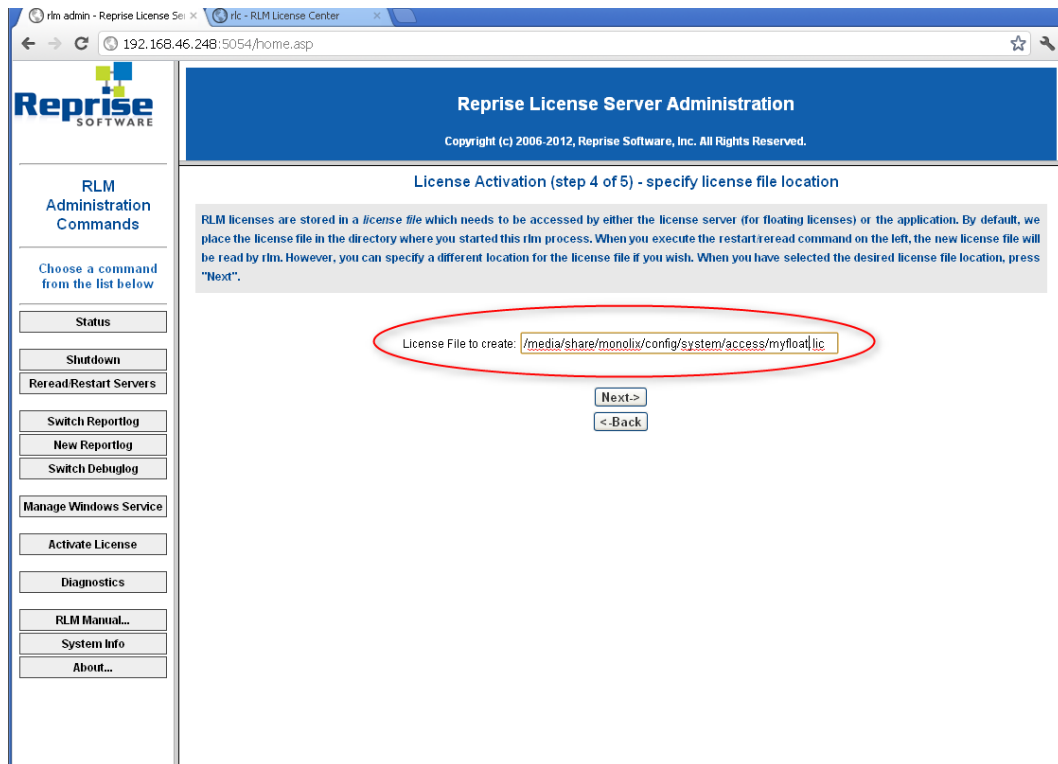
- If Monolix is installed on a shared space (i.e. each node of the cluster has an access to this directory), copy the license file into the directory
`<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version.
Make sure that the MONOLIX directory is accessible from each cluster node.

Example (with a MATLAB version of MONOLIX)

- MONOLIX is installed on the computer **master-computer** in the directory:
/usr/local/monolix/.
The license is in the directory :
/usr/local/monolix/config/access/
- The RLM server is run on the computer **master-computer**.
- Cluster computers mount the directory /usr/local/monolix/.
- Each monolix user runs MONOLIX from the previously mounted directory.
- If Monolix is installed on each node of the cluster, copy the license file on each computer in the directory <monolix install path>/config/system/access for the MATLAB version of MONOLIX or
<monolix install path>/bin/Monolix_mcr/runtime/config/system/access for the standalone version.

Example

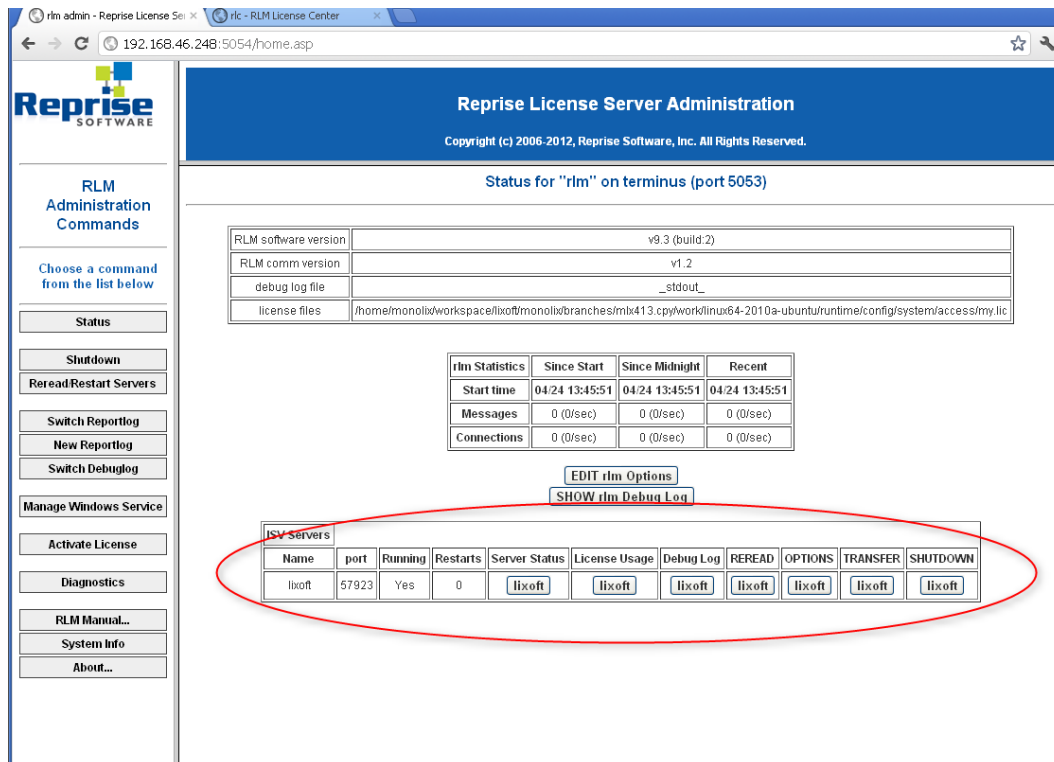
- The RLM server is executed on the computer **master-server**.
- MONOLIX is installed on each cluster node of the cluster.
- The license file is copied on **each cluster node** in the directory <monolix install path>/config/system/access/ for the MATLAB version of MONOLIX or <monolix install path>/bin/Monolix_mcr/runtime/config/system/access for the standalone version.
- Each monolix user runs MONOLIX from the cluster node.



7. Stop the server manually and restart it from the directory (or use option -c)

- `<monolix install path>/config/system/access/` for the MATLAB version
- `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX .

Now RLM is running with the provided license. This is verified in the web interface by clicking on **status** button.



8. RLM Server : server hostname and port considerations.

If for any reason, the server port or the server hostname is not registered in a DNS, it is possible to change these informations directly on licence file.

The line `HOST <hostname> <mac> <port>` can be changed by `HOST <rlm server ip> <mac> <new port>`.

9. RLM Server : firewall considerations.

If the RLM server is behind a firewall, the port 5053, 5054 and the ISV port have to be opened.

The ISV port can be set directly in license file by changing the ISV line as follow:

```
...
ISV lixoft port=<your ISV port>
...
```

10. Managing RLM server :

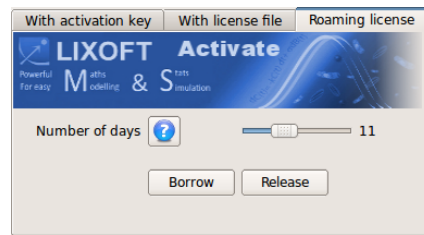
The documentation of the management of the RLM server provided by Reprise Software is available at

http://www.reprisesoftware.com/RLM_Enduser.html

Roaming license

RLM has the ability to allow a floating license to roam to a system which will subsequently be disconnected from the network for a short period of time. The resulting license can be used for the number of days specified when the license was set to roam, and is checked back in automatically at the end of this. In addition the user can return the roamed license back to license pool early if this is desired.

See **License activate tools** (which can be launched from the MONOLIX interface, in **tools** menu)



This feature is enabled on demand. An extra activation key will be provided by LIXOFT and the procedure to get the roaming license feature is identical to the installation of a floating license. To enable this feature, the file `system.xmlx` (stored in directory `<monolix install path>/config/-MATLAB version-` or `<monolix install path>/bin/Monolix_mcr/runtime/config/-standalone` version of MONOLIX - must be modified by setting to "on" the roaming option:

```
<?xml version="1.0" encoding="utf-8"?>
<monolix>
  <preference>
    <session>
      <userPath windows="%USERPROFILE%" linux="$HOME"/>
      <license activation="http://activate.lixoft.net" roaming="on"/>
    </session>
  </preference>
</monolix>
```

2.3 ChangeLog

```
1 Monolix 4.3
2 Bugs Fixes:
3 - bug fix: when using estimators uncertainty, the correlations were
  only simulated in 0,1 (instead of -1,1) .
4 - bug fix: predictions calculations could take too much time (even
  hang) in presence of RTTE data
5 - bug fix: error when removing covariates from the project
6 - bug fix: error when all the observations of one subject are null in
  combined2 (Fisher information matrix estimation)
7
8 Enhancements:
9   - GUI
10      -addition: monolix remembers now the last options selected in
      simulation interface
11      -addition: included a checkbox in order the user can choose
      among saving all the paths in relative or in absolute
12   - Algo
13      - Tables of population parameters and fisher after storing of
      results
14   - Graphics
15      - new setting in RTTE graphic : accuracy of grid
16      - stratify saved in graphics with projects
17      - settings (axes, labels) saved in projects, and stored while
      using of graphics
18      - export of graphics data
19   - MLXTran
20      - analytical solutions: ODE replaced by analytical solution when
      keywords (as pkmodel, compartment, ...) are used. This
      improves the processing time.
21      - DDE solver
22      - distribution functions (Student, Log-Normal...)
23      - ODE initial values can depend on time
24
25 Monolix 4.2.1 (2013-02-15)
26 Bugs Fixes:
27   - MLXTRAN Project : in STRUCTURAL_MODEL section resolved problem
      with path relative to %MLXPROJECT%
28   - mlxEditor, mlxPerlScript : under Suse Linux OS, conflict with
      libstdc++ and Qt librairies installed on the OS.
29   - Graphics : Kaplan Meier
30      - mean normalization
31      - survival curve: case of censured data
32   - simulations where wrong in presence of correlation between
      individual parameters
33   - MLXTRAN Model :
```

```
34      - Events could be close at a numerical epsilon for the solver
      , but not for the solver driver
35      Rarely, it resulted into an explicit integration failure,
      returning "NaN"
36      - For the simulation of RTTE models, the ordering of the
      output names had to be alphabetical
37      - Not declaring all regression variables that where selected
      from the data set crashed the application.
38      - Declaring some PK without actual doses within the data set
      raised an error.
39      - Using the deprecated syntax with several lagged
      compartments returned "NaN"
40      - Algorithms
41      - Error when some subjects had no doses in conditinal mode
      computation
42      - GUI
43      - "Display the data" button did not update the information
      when the dataset was changed after running algorithms
44      - Convergence assessment GUI failed when there where only one
      individual parameter
45      - structural models with several dots (.) were not compiled
      when clicking in the compile button in the Model
      selection GUI
46      - projects with more outputs in structural model than
      observations in dataset caused an error when it is loaded
47      - the editor was not saved in the preference file
48      - Convergence assessment graphics did not handled
      correctly when there were not variances on some
      parameters or their covariate dependence
49
50      Enhancements:
51      - add possibility to configure the compiler (used to create
      Structural Model plugins) through the file 'system.xmlx'
52      - user API:
53      - it is possible now to use matlab function "ver" to know
      Monolix version and Monolix API version
54      - mlxEditor:
55      - allow multiple files selection on open file dialog box
56      - add 'Find and replace'
57      - set tabs movable
58      - MLXTRAN Model :
59      - Continuous observations can be declared within the model.
60      - Macro for a depot absorption, with a target ODE component.
61      - Permutation kernel for mcmc included
62
63      Other:
64      - Licensing system : '.ini' files desactivated (only the '.lic'
      files are allowed)
```

```
65     - residual error models in main interface are shown now with
        their full name (those used in MLXTRAN project and model)
66 -----
67
68     Monolix 4.2.0 (2012-11-26)
69
70     Bugs Fixes:
71     - MLXTRAN Project : in OBSERVATION section when a prediction has
        the same name as an individual parameter the project parses
        fail
72     - PerlScript : bug with parameter '--use-matlab=false' was taken
        as 'true'
73     - Identity line works in observations vs predictions graphic
74     - Prediction distribution : percentiles are correctly displayed
75     - Color when stratify in covariables graphic
76     - Problem with prior (by default prior is Variance and not
        Standard Deviation, this implies a syntax error (
        standardDeviation <-> variance)
77     - Wrong data file for the demonstration project
        rtteWeibullCount_project.mlxtran
78     - "Display the data" button did not work
79     - bug when unchecking and checking "random effects" variability
        in simulation interface
80
81     Enhancements:
82     - Interval censoring for continuous data
83     - Extended priors on fixed effects
84     - Mlxtran model and Mlxtran project editor
85     - Perl script HMI
86     - Autosave
87     - Multiple covariate definitions
88     - Add batch-mode demo
89     - Add a doc package and a rlm server package (floating license
        server)
90     - Graphic
91     - BLQ graphic : possibility to choose his own interval of
        censored data
92     - Reorganisation of panel for list of graphics
93     - Background color for each graphic in preferences
94     - When split, limits are the same for all axes
95     - Obs. vs Pred., observations can be relied by individual
96     - Optimal bandwidth setting for parameter distribution
97     - CvSaem graphic : choice of axes number
98     - Interval-censored data and maximum number of events for time-to
        -event and drop-out data models
99     - Markov chain for categorical data
100    - Continuous-time Markov process for categorical data
101    - probit and normal cdf for Mlxtran model
```



```
102     - New user API including simulation-estimation, convergence
103       assessment and simulations tools
104
105     - Possibility to define new covariates as transformation of
106       already defined ones
107
108   New graphics:
109     - Posterior and prior functions for bayesian
110     - Individual contribution for the LL
111     - Transition probabilities
112     - Kaplan-Meier survival function
113
114   New tables:
115     - Individual contribution to log-likelihood
116     - Covariates summary
117   -----
118   Monolix 4.1.4 (2012-07-16)
119
120   Bugs Fixes:
121     - Saving preferences from tools menu failed.
122     - Display remaining time (license) correctly.
123     - Problem with license activation file path.
124     - Add license agreement into Linux installer.
125     - The horizontal slider in "Check initial fixed effects"
126       interface did not appear for some number of individual
127       parameters.
128
129   Enhancements:
130     - Windows 64 RC.
131     - Management of the maximum number of threads for MLXTran models
132       (can be set from the preference tools: MonolixGUI->Tools->
133       Preference)
134     - License activate: inform user to not set activation key
135       if the license is a floating license.
136     - Documentation :
137       * Installation guide : Windows 64 bits.
138       * User Guide : Cluster section revised.
139       * Model MLxTRAN : list of keywords of the language.
140
141   -----
142   Monolix 4.1.3-sp2 (2012-05-29)
143
144   Enhancements:
145     - system.xmlx : possibility to not display Lixoft Activate.
146     - Lixoft Activate : add the possibility to send an email with
147       encoded computer information to create license @Lixoft.
```

```
143     - Lixoft Activate : manage "cannot connect to url" error by
      asking user to go on a web site or send an email.
144
145 Bugs Fixes:
146     - IOV Problem with R2010bSP1
147     - perlScripts : bug in the management of the configuration file
      for [program-execute-options] and run on a cluster.
148     - add 'rlmutil.exe' for windows packages (forgotten in previous
      packages).
149     - problem floating license.
150     - warnings for occasions without dose were removed.
151     - when the last Individual/Occasion had no dose, Monolix crashed.
152     - When there were syntax errors in the structural model, monolix
      said that it could not find the file instead giving the
      MLXTRAN message
153     - NaN observations are now mentionned as error when algorithms
      are launched.
154     - Update documentation : in batch mode section, there is a bad
      path.
155
156
157 -----
158
159 Monolix 4.1.3-sp1 (2012-05-21)
160
161 Bug Fixes:
162     - GUI:
163         * Check Initial Fixed Effects interface crashed when creating
          covariate and parameter s sliders for some sizes
164
165 -----
166
167 Monolix 4.1.3 (2012-05-02)
168
169 New Features:
170     - MLXTran model: allows negative categories
171     - License management: uses RLM as license provider
172     - Compiler manager: adds the possibility to choose the embedded
      compiler
173     - The Monolix and Matlab versions are now stored in the algorithm
      result files
174
175 Bug Fixes:
176     - MLXTRAN project:
177         - continuous transformation can take a mathematical
          expression
178         - problem with structural model path
179     - MLXTRAN model:
```

```
180         - Under Linux 64 bits, due to library conflicts with Matlab
181           R2010b and better, the multi-threaded
182           loading of the model description for the project
183             occasionally fails
184         - Only the last table variable is recorded, overwriting the
185           first one
186     - Graphics:
187       - log / linear works on all graphics
188       - when log-log scale is set for "observed versus predicted",
189         the diagonal line is not displayed anymore
190     - GUI:
191       - editor call did not work
192     - Algorithms:
193       * bug for individuals without some type of observations and
194         with IOV computing conditional mode
195       * bug when there were continuous outputs after discrete
196         outputs
197       * Fisher Information Matrix by Stochastic Appoximation does
198         now handle better the case when there are
199         no parameters to estimate in the residual error
200     - Session:
201       * when the directory monolixData/monolix<version> is renamed
202         during an active Monolix session, stopping
203         Monolix caused an exit of Matlab.
204
205 -----
206 Monolix 4.1.2: (2012-03-05)
207 -----
208
209 New Features:
210   - PerlScripts : possibility to save the results in the project
211     directory instead of the output directory
212   - In system.xmlx : automatically creates a directory hierarchy
213     for "monolixData" path
214
215 Enhancements:
216   - MLXTran (structural model) multi-threading processing
217     enhancement
218
219 Bug Fixes:
220   - Batch Processing failed when a very large number of projects
221     were launched
222   - MDV column: when MDV=2 only the regression variables were taken
223     into account
224   - Fixed a bug in graphics saving
```

```
215     - Fixed error when an empty result folder was timestamped
216     - Simulation of categorical data, whenever no category 0 is
      defined
217     - Fixed take into account UserPath defined in 'system.xmlx' for
      the preference file saving
218
219
220 -----
221
222     Monolix 4.1.1: (2012-02-13)
223
224 -----
225
226 New Features:
227     - timestamped backup
228     - preferences interface
229     - tools menu for activating license and preferences
230     - option for locking structural model modifications
231     - Project-MLXTRAN grammar modification : initialization of
      parameter is written now as beta_{pi,cov}, pop_{pi}, omega_{
      pi}, ...
232     - save graphics as png / ps / jpg / bmp or tiff
233     - selection of graphics/tables to be saved
234
235 Bug Fixes:
236     - Project-MLXTran: user can define the result folder
237     - LoQ difference between 3.2 and 4.1
238     - statistical test for error model and covariate model
239     - xmlx loading from 3.2 to 4.1
240     - correlation (levelName consistence with IOV) + parser error
241     - observation model (prediction = observation name)
242     - path for MONOLIX user profile can include special characters
243
244
245
246 -----
247
248     Monolix 4.1.0: (2012-01-23)
249
250 -----
251
252 psmlx:
253     - compatible with the mlxtran format of projects
254     - available on Windows OS
255
256 mlxtran:
257     - new syntax
258     - PK macros
```

```
259     - RTTE models
260
261 license:
262     - interface for installing the license file
263
264 Interface:
265     - setting for limits of axes
266     - information for the observation model
267     - shortcut for model libraries
268
269 File system:
270     - improved handling of special characters for filepaths
271
272 Demos:
273     - updated for the new mlxtran syntax
274     - dispatch of the model library for demos
275
276 Known Bugs:
277     - under Windows OS, user directory cannot contain special
      characters other than spaces
278
279
280
281 -----
282
283 Monolix 4.0.1: (2011-10-27)
284
285 -----
286
287 psmlx:
288     - use-matlab option did not work in command line mode
289     - multi-threading : multithreading did not work
290     - take account the p.coded files
291
292 mlxtran
293     - problem with FIM options : both linearization and
      stochasticApproximation appeared after a save with
      stochasticApproximation option set
294     - avoid the unloading of project when settings files does not
      exist : default settings are loaded
295 license:
296     - multi write database did not work well in multi-threading mode
297
298 Interface:
299     - save lists
300     - configuration panel
301     - launching some graphics alone is now possible
302     - the graphics were closed when "Use last estimates" were used
```

303 - when monolix was launched twice without loading or creating a
 project, two toolbars were created

304

305 Algorithm and simulations:

306 - simulation works now with dataset without EVID column and with
 MDV column

307

308 Results:

309 - the graphics fit now to the paper in .ps files

310 - xLabels were wrong for some graphics when several regression
 variables were present

311 - some graphics crashed when launched after some hypotheses
 tests were done

312 - Visual studio redistribuable problem

2.4 Troubleshooting

2.4.1 Downloading MONOLIX

Problem: *My web browser claims that the MONOLIX download website has insufficient reputation and suggests to stop the download.*

Solution: Some browsers like *Google Chrome* and *Internet Explorer* may ask whether to keep or remove the MONOLIX archive just after download because of the insufficient reputation of the MONOLIX download website, simply because it is not referenced, as opposed to the LIXOFT website. Please ignore the warning and choose to keep the file. You can use a MD5 tool to verify that the downloaded file is not corrupted.

Problem: *The MONOLIX archive is removed just after being downloaded.*

Solution: Some antivirus may consider the MONOLIX archive as risky and put it in *quarantine* or remove it. This is due to the fact that MONOLIX embeds a compiler for the MLXTRAN language. Two solutions are available:

1. Deactivate your antivirus auto-protection process during download and installation, or
2. Restore the file from the quarantine.

To restore the file from quarantine, please refer to the documentation of your antivirus software. For the most common examples:

- *Norton Antivirus 2012:*
 - Start *Norton Antivirus*
 - Choose **Advanced**, then **Quarantine**
- *Avast Antivirus 7:*
 - Open *Avast*
 - Choose **Maintenance**, then **Virus Chest**

You should see the downloaded file among the quarantined files. Execute the **Restore** action; the archive will be restored into the directory used for downloading. Click on the archive (ignore a possible “malware” warning, again related to the fact that MONOLIX embeds a compiler.), and installation will start.

2.4.2 Running MONOLIX

Problem: When launching the standalone version, my antivirus tells me that the file *mlxinitializer.exe* is risky.

Solution: If your antivirus apparently removed the file *mlxinitializer.exe*, check if it was actually put on *Quarantine*, or removed. If it is in *Quarantine*, please restore it by following the same instructions as provided above. If the file was removed you will need to reinstall MONOLIX.

You should be able to add this file to your antivirus *Trusted Zone* or *Trusted files*.

- *Norton Antivirus 2012:*
 - go to folder *Monolix/monolix430s/bin* in installation directory: for instance
c:/ProgramData/Monolix/monolix430s/bin
 - right click on *mlxinitializer.exe*, click on *Norton Antivirus*, then *Norton File Insight* then look for 'Unproven', and click 'Trust Now'.
- *Avast 7:* This software may start MONOLIX in a *SandBox*, i.e in a zone where the antivirus avoids any modification of the system or the files. He will ask you what to do at each run. Select *Run normally*.

You can also add *mlxinitializer.exe* to the exclusions in its *Auto-Sandbox* settings: option *Additional Protection/AutoSandbox* and then click on *Settings* button.

Chapter 3

Using MONOLIX

3.1 Introduction

In order to use MONOLIX, your problem must be described as a MONOLIX project. A project specifies

- the dataset to use
- the structural model
- the statistical model, which includes
 - covariate model for individual parameters
 - covariance model for random effects
 - observation model
- the tasks to run, their settings and initial values

The dataset is an ASCII file containing all the data for your study (see [Section 3.3.1](#) for a brief description) and the structural model is a function explaining the theoretical model behind your data. It can be easily described using the MLXTRAN language (see the document `modelMLXTRANtutorial.pdf` in MONOLIX documentation folder), or as a MATLAB function for a MATLAB version of MONOLIX.

A mathematical description of the statistical models handled by the software can be found in [Appendix A](#).

All these informations can be set in the MONOLIX main window.

In this chapter, we will describe the main window and its different sections, using a simple example.

3.1.1 The theophylline example

We will consider the theophylline data (see [\[6, 21\]](#)) as an example to illustrate how to use MONOLIX.

In this case subject i receives a dose D_i per kilo at time 0 and serum concentrations (y_{ij}) are measured at times (t_{ij}). Serum concentration is modeled by a first-order one compartment model. Then,

$$y_{ij} = \frac{D_i ka_i}{V_i ka_i - Cl_i} \left(e^{-\frac{Cl_i}{V_i} t_{ij}} - e^{-ka_i t_{ij}} \right) + a\varepsilon_{ij} \quad (3.1)$$

where ka_i is the absorption rate constants of subject i , V_i is the volume per kilo of subject i and Cl_i is the clearance per kilo of subject i . These three parameters are nonnegative real numbers and are assumed to be log-normally distributed. Here,

- the vector of regression (or design) variables is $x_{ij} = (D_i, t_{ij})$.
- the vector of individual parameters is $\psi_i = (ka_i, V_i, Cl_i)$,
- the model is assumed to be homoscedastic and $g \equiv a$.

The only available covariate is the weight (w_i) of the subjects.

The data file `theophylline_data.txt` is in the directory `<demos folder>/theophylline`. This file is in the so-called “NONMEM format” and contains the ID numbers of the subjects, the doses per kilo (D_i/w_i), the times (t_{ij}), the observed concentrations (y_{ij}), the weights (w_i) and the genders (s_i) (this additional covariate is not in the original dataset: it was added for the demo).

ID	AMT	T	DV	WEIGHT	SEX
1	4.02	0	.	79.6	M
1	.	0.25	2.84	79.6	M
1	.	0.57	6.57	79.6	M
⋮	⋮	⋮	⋮	⋮	
2	4.4	0	.	72.4	M
2	.	0.27	1.72	72.4	M
⋮	⋮	⋮	⋮	⋮	
12	5.3	24.15	1.17	60.5	F

Here, “AMT” (amount per kilo) holds for “ D/w ”, “T” is the time and “DV” (dependant variable) holds for “ y ”.

3.2 The main window

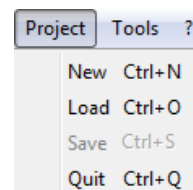
After starting MONOLIX, the main window appears empty. Only the “Project” and “?” (help) menus are available, there you need to choose or create a project to continue.
















The project can be created from scratch by clicking on **Project->New** in menu or modifying a previously loaded one (**Project->Load**).



It is then possible to save it with the menu **Project->Save** in any of three formats: as a MLXTRAN project (ASCII file with extension **.mlxtran**, recommended and default for new projects), as a binary MATLAB (**.mat**) file or as a XML (**.xmlx**) file.

Once the project is chosen, the different sections of the interface become visible. Those sections facilitate the project definition.



All the menu options also appear and the toolbar buttons become enabled.



-  create a new project
-  load an existing project
-  save the current project (**mlxtran**, **mat**, and/or XML file)
-  see the last results for the current project
-  display the data
-  estimate the population parameters,
-  estimate the Fisher information Matrix and the standard errors,
-  estimate the individual parameters,
-  estimate the log-likelihood,
-  display a set of graphics
-  $H_0 H_1$ β test the covariate model
-  $H_0 H_1$ η test the covariance model
-  $H_0 H_1$ e test the residual error model
-  simulate a new dataset
-  publish the results (not available with the standalone version)

-  about MONOLIX
-  quit MONOLIX

In our example, the project file `theophylline_project.mlxtran` is included in the Demos so you can load it or create a new one from scratch.

- To load the project, use the  button and select `theophylline_project` in the `<demos folder>/theophylline` folder (go to [Section 3.7](#) to see how to run the algorithms).
- To create a new project to analyze the theophylline data, use the  button and follow the instructions below.

3.3 The “Data and Model” frame

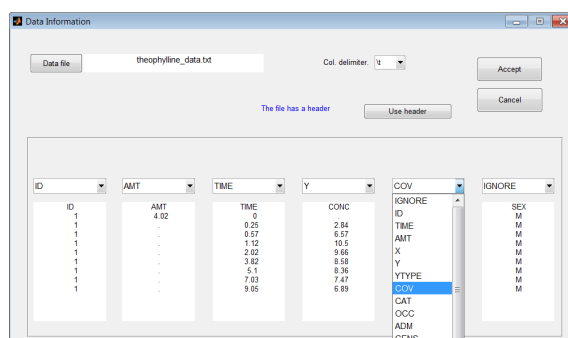
3.3.1 The data

The data file should contain a matrix in an ASCII format with or without header for each column. The columns of this matrix contain (in any order)

1. the ID of the subjects (can be any string or number, not necessarily ordered),
2. the regression variables (x_{ij}),
3. the observations (y_{ij}),
4. the covariates,
5. additional information (censoring, rate, tau ...).

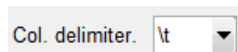
▷ *theophylline example:*

To select the theophylline dataset use the button **The data**. A new window is opened



- Select the data file `theophylline_data.txt`. The dialog box to select the dataset can be opened with the button **Data file**.

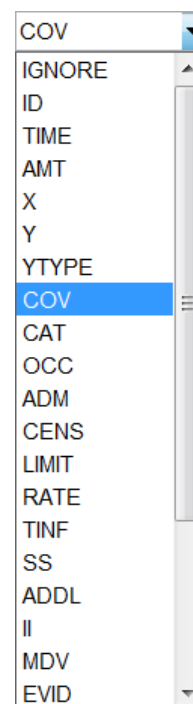
- If MONOLIX does not recognize the different columns you can choose one of the column delimiters from comma (“,”), semicolon (“;”), space (“ ”), tab (“\t”):



- Since the file has a header in the first line (ID AMT T DV WEIGHT SEX), MONOLIX will use the recognized columns by default. You can choose other headers for each column by yourself. Use **Use header** button whenever it is desired that MONOLIX uses the header from the file, instead of the current one.
- Check that MONOLIX has recognized the keywords (ID, AMT, T, DV) and translated them to (ID, AMT, TIME, Y).
- The headers WEIGHT and SEX are not recognized and set to IGNORE. Nevertheless, you can consider the weight as a **continuous covariate** by selecting the label COV for this column and the gender as a **categorical covariate** by selecting the label CAT for this column.
- Accept the data information with the **Accept** button

A list of the main headers identified by MONOLIX is

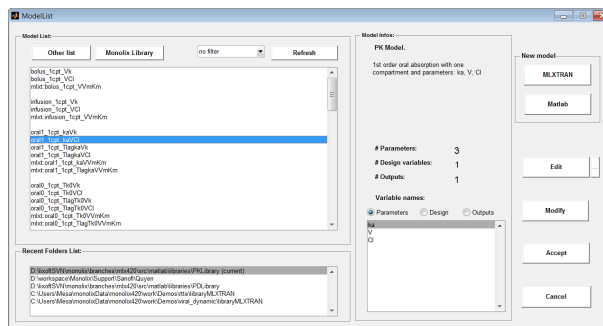
- ID (or #ID, I) to identify subjects
- TIME (or T) for the time
- AMT (or DOSE, D) for the dose
- X (or REG, XX) for any regression variable
- Y (or DV, CONC) for the observations
- YTYPE (or ITYPE, TYPE, DVID) for the type of observations when there are several types of observations (1 for the first type, 2 for the second type, ...). YTYPE is not necessary in the case of a single output.
- COV for the continuous covariates
- CAT for the categorical covariates
- OCCASION (or OCC) for the occasion
- ADM for the type of administration
- CENS for censored data. Can be -1 to represent right-censored data



- LIMIT for interval-censored data. It gives the lower limit while Y gives the upper limit
- RATE (or R) for the infusion rate
- TINF for the infusion duration
- SS for steady-state (requires column II)
- ADDL for the number of additional doses (requires column II)
- II (or TAU) for the inter-dose interval
- MDV (Missing Dependent Variable) MDV= 0 if the row contains an observation and MDV=1 otherwise. MDV is not necessary if a dot is used to say when a row does not contain any measurement (Y='.'). You can use MDV=2 to include times for regression variables updates and for prediction evaluation (see [Section 4.11](#)).
- EVID for Dose events. EVID is not necessary if DOSE='.' is used when a row does not contain any dose information. EVID=4 resets the system to the initial state.

3.3.2 The model function

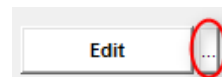
Use **The model** button to define the model function. In the **Model List** window, it is possible to select a model from the model library included in the software (PK library, PD library, VK library, discrete data library) by using the **Monolix Library** button; or from a personal list by using the **Other list** button.



Refer to `modelMLXTRANtutorial.pdf` for more details of how to implement your own model using MLXTRAN.

When a model is selected from one of these lists, the model information is summed up in the **Model Info** window: name of the function, number and names of the parameters, of design variables and of outputs.

Edit the model with the **Edit** button. If you use the MATLAB version of MONOLIX, then the MATLAB editor will be used by default. If you use the standalone version of MONOLIX (or if you want to use another editor with the MATLAB version), select your own editor with the **...** button. In standalone version, only the MLXTRAN models can be edited, and the only .m models that can be used are the built-in models.



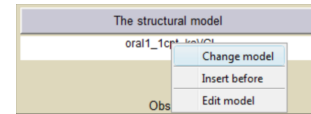
Note: MONOLIX includes now its own editor for MLXTRAN projects and models. Set the editor to ‘mlxEditor’ if you want to use it.

▷ *theophylline example:*

We use the first order oral absorption with one compartment model function (oral1_1cpt_kaVC1) from the PK library which has 1 design variable (time), 3 parameters (k_a , V , Cl) and 1 output (concentration).

Important: When a project is created (or loaded), there are two ways to change the structural model:

- by clicking on the button **The structural model**.
- by right-clicking on the name of the model.



3.3.3 The covariate model

Here, m is the number of covariates and d is the number of individual parameters. Then, **The covariate model** is a $m \times d$ matrix A containing only 0 and 1. For any $1 \leq k \leq m$ and any $1 \leq \ell \leq d$, $A_{k,\ell} = 1$ if the ℓ -component $\phi_{i,\ell}$ of the individual parameter ϕ_i is function of the k th covariate, and 0 otherwise.

▷ *theophylline example:*

Let us assume that no covariates are used in the model:

$$\begin{aligned}\log(ka_i) &= \mu_1 + \eta_{ka,i} \\ \log(V_i) &= \mu_2 + \eta_{V,i} \\ \log(Cl_i) &= \mu_3 + \eta_{Cl,i}\end{aligned}$$

The covariate model				
WEIGHT	0	0	0	0
SEX	0	0	0	0

Consider now that the log-volume is a linear function of the weight and that the log-clearance depends on the gender.

$$\begin{aligned}\log(ka_i) &= \mu_1 + \eta_{ka,i} \\ \log(V_i) &= \mu_2 + \beta_{W,V} w_i + \eta_{V,i} \\ \log(Cl_i) &= \mu_3 + \beta_{S,Cl} \mathbb{1}_{s_i=M} + \eta_{Cl,i}\end{aligned}$$

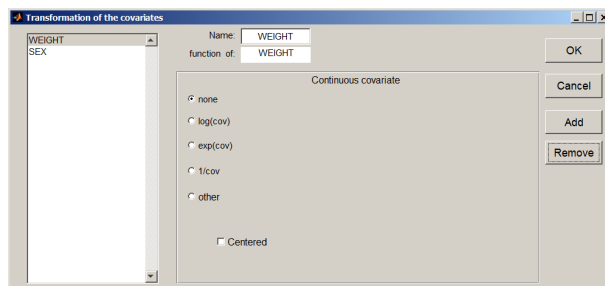
The covariate model				
WEIGHT	0	1	0	0
SEX	0	0	0	1

Here, the reference group are the female and the population parameters are

$$\begin{aligned}\log(Cl_{\text{pop,F}}) &= \mu_3 \\ \log(Cl_{\text{pop,M}}) &= \mu_3 + \beta_{S,Cl}\end{aligned}$$

3.3.4 Creating and transforming covariates

Some times, it is needed to use some transformed version of the original covariates. It can be done in the window opened when clicking on the button **transform**:



1.- transforming continuous covariates

It is possible to consider non-linear functions of the continuous covariates. Logarithmic, exponential or fractional polynomials are available and personal functions can be considered. This is also possible to center the covariates.

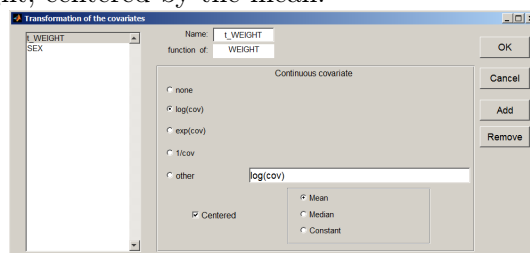
▷ *theophylline example*:

Consider for example, a log-transformation of the weight, centered by the mean:

$$w_i^* = \log(w_i) - \log(\bar{w})$$

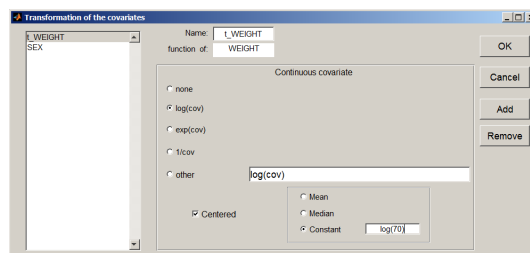
Then, the covariate model used for the volume is

$$V_i = V \left(\frac{w_i}{\bar{w}} \right)^{\beta_{w,v}} e^{\eta_{v,i}}$$



Instead of using the mean to center the log-transformation of weights, you can normalize the weight by some constant value a ($a = 70$ for example) by centering the transformed weight by $\log(70)$:

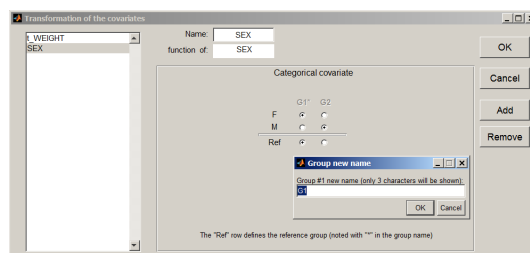
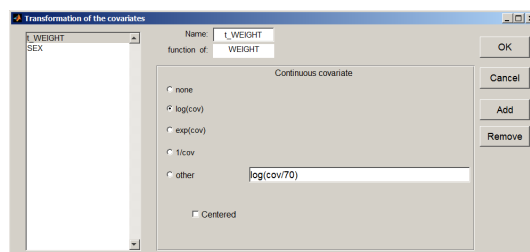
$$V_i = V \left(\frac{w_i}{70} \right)^{\beta_{w,v}} e^{\eta_{v,i}}$$



Remark: The pre-defined transformations will be removed in a future version of MONOLIX. We strongly recommend to write your own transformation using the “other” option. For example, the allometric transformation of the weight proposed above just reduces to:

2.- transforming categorical covariates

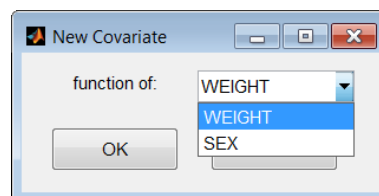
You can easily modify the groups defined by a categorical covariate. You can also select the reference group and modify the names of the groups (just click on G_k to change the name of the k -th group).



3.- creating new covariates

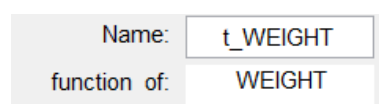
In some cases, it is needed to use different transforms of the same covariate, for instance to use **WEIGHT** for some parameter and **log(WEIGHT)** for other. It is possible by creating a new dependent covariates.

To create new covariates, click on **Add** button and select from which covariate, among the originals and already created ones, the new one will depend. Then click on **OK**.



The new covariate is added to the list at the left so you can use them like the original ones and define their transformations.

The new or transformed covariates receive a name by default that can be modified by the user at the top of the window.



It is also possible to remove the new covariates or the transformations from the original covariates with the button **Remove**.

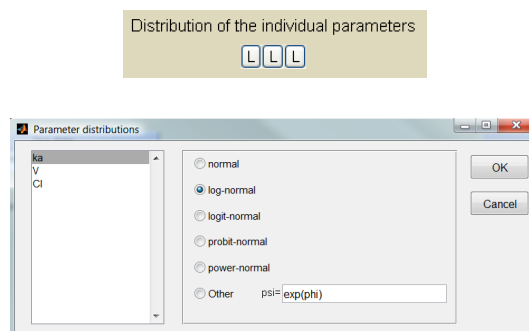
It is important to note that, the new covariates will be of the same type (continuous or categorical) than those from which they are function of, and that new categorical covariates can only be function of original (not transformed) categorical covariates.

Note: It is recommended to set the name of the modified or newly created covariates before creating new ones.

3.3.5 Distribution of the individual parameters

The default distribution of the individual parameters are defined by the structural model, but it is possible to change it in the MONOLIX window by clicking on the buttons below **Distribution of the individual parameters** to

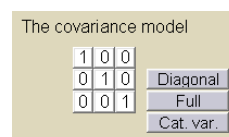
- **N** for a normal distribution $\psi = \varphi$
- **L** for a log-normal distribution
 $\psi = e^\varphi$
- **G** for a logit-normal distribution
 $\psi = (1 + e^{-\varphi})^{-1}$
- **P** for a probit-normal distribution
 $\psi = \mathbb{P}(\mathcal{N}(0, 1) \leq \varphi)$
- **B** for a power-normal (Box&Cox) distribution
 $\psi = (A\varphi + 1)^{\frac{1}{A}}$
- **C** for a custom (user defined) distribution



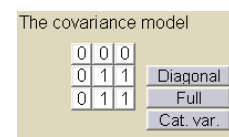
3.3.6 The covariance model of the random effects

The covariance model of the random effect is a $d \times d$ matrix Δ formed by 0 and 1. For any $1 \leq j \leq d$ and any $1 \leq l \leq d$, $\delta_{jl} = 1$ if there is a correlation between η_{ij} and η_{il} , and $\delta_{jl} = 0$ elsewhere. $\delta_{jj} = 0$ means that the variance of the j th random effect is 0.

A diagonal covariance matrix is obtained by setting the matrix Δ to



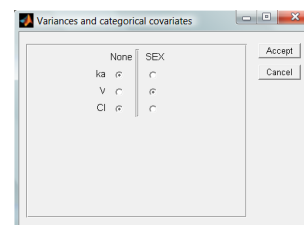
Assume now that the absorption rate does not vary between subjects and that clearance and volume are correlated. Then, Δ should be set to



You can also assume different variances in the groups defined by a categorical covariate (click on the button **Cat.var.**).

Assume for example that the variance of the volume depends on the gender

Remark: In the different groups, the random effects have different variances but the same correlations. In this example, the correlation between Volume and Clearance is the same for male and female.



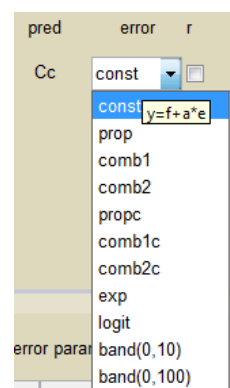
3.3.7 The observations model

The **observations model** can be defined in the structural model function (for discrete data: count, categorical, RTTE, etc) or it can be a residual error model (for continuous data).

The observation model section shows, for each observation, the variables name and their type following the structural model definition. If the observation name is not set in the structural model (for continuous observations, it can be given the prediction name instead, see MLXTRAN models description) then it can be defined by the user using the interface. For the continuous observations, we consider the general form $y = f + g e$ where e is a sequence of independent random variables normally distributed with mean 0 and variance 1. Some extensions assume that there is a transformation t such that $t(y) = t(f) + g e$. It is also possible to assume that the residual errors are correlated. Here are some examples of error models:

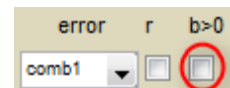
- const: constant error model $y = f + a e$
- prop: proportional error model $y = f + b f e$
- comb1: combined error model $y = f + (a + b f) e$
- comb2: combined error model $y = f + a e_1 + b f e_2$
- propc: proportional error model + power $y = f + b f^c e$
- comb1c: combined error model + power $y = f + (a + b f^c) e$
- comb2c: combined error model + power $y = f + a e_1 + b f^c e_2$
- exp: exponential error model $t(y) = \log(y)$ and $y = f e^{a e}$
- logit: logit error model $t(y) = \log(y/(1 - y))$
- band(A,B): extended logit error model $t(y) = \log((y - A)/(B - y))$

name	type
concentration	continuous



Select the checkbox **r** if you want to consider autocorrelation on the residual errors.

You can also constrain the second parameter **b** in **comb1** and **comb1c** error models to be positive by checking **b>0**



3.4 The “Initialization” frame

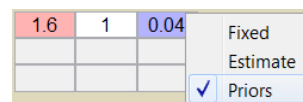
Initial values are specified for the **Fixed effects**, for the **Variances of the random effects** and for the **Residual error parameters**. It is usually recommended to run SAEM with different initializations and to compare the results (see *convergence assessment tool* in [Section 3.7.7](#)).

A right click on an initial value displays a list with three options.

The default choice is **Estimate** for maximum likelihood estimation.

The choice of the “**Fixed**” option (initial values in pink), means that this parameter must be kept to its initial value and so, it will not be estimated. Use the **Priors** option (initial values in blue) to specify a prior distribution for this parameter.

Only the two options **Estimate** and **Fixed** are available for the variances and residual error model parameters

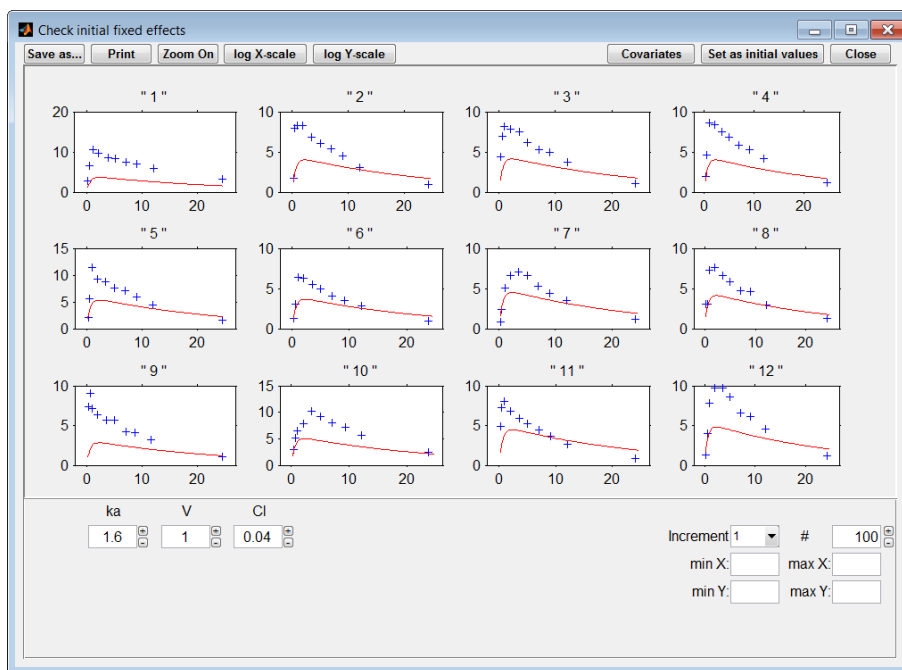


You can also switch between to estimate standard deviations or variances

Stand. dev. of the random effects

111

3.4.1 Check initial fixed effects



The fits obtained with the initial fixed effects are displayed for continuous observations. It can be useful in case of complex models (e.g. defined with differential equations), in order to find some “good” initial values. You can change the values of the parameters with the buttons + and - and see how the fits change.

3.4.2 Use the last estimates

If you have already estimated the population parameters for this project, then you can use the **Use the last estimates** button to use the previous estimates as initial values.

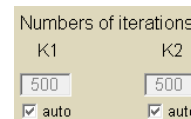
3.5 The “Algorithm” frame

There are several settings that control the behavior of the algorithms and the results graphics and tables generation (see [Section 3.13](#)). The main interface gives access directly to some of them:

- **Seed**: The default value of the seed used for the random numbers generator is 123456. This seed can be randomly generated with the **New seed** button.

- **Number of iterations:** There are two stages in the population parameters estimation algorithm. Use K_1 and K_2 to define the number of iterations for each one.

If **auto** is selected, then algorithm will determine automatically if it can jump from one stage to the other or if it can finish the estimation process. In this case, the numbers K_1 and K_2 will represent the maximum number of iterations for each stage. Here, these numbers will not exceed 500 and 200.

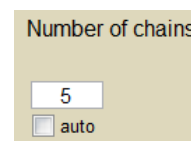


Numbers of iterations

K1	K2
500	500
<input checked="" type="checkbox"/> auto	<input checked="" type="checkbox"/> auto

- **Number of chains:** When the dataset is small, just a few of subjects for instance, replicating the dataset can improve the precision of the estimation. The number of (Markov) chains specifies how many times the dataset need to be replicated.

You can specify this number yourself,

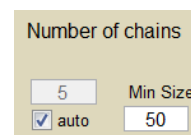


Number of chains

5

☐ auto

or you can let MONOLIX to compute how many replicates are needed to ensure a minimum number of subjects. In this case, you should specify this minimum size and any time you change the dataset, the number of chains will be updated according to the number of subjects present in the new dataset.



Number of chains

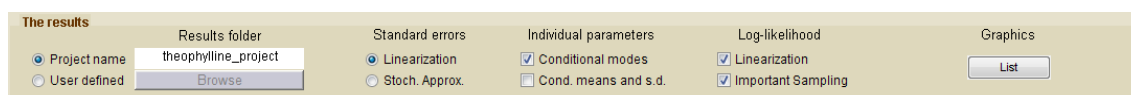
5 Min Size

☒ auto 50

For instance, in the *theophylline example* there are only 12 subjects in the dataset. Setting to 50 the minimum number of subjects, MONOLIX choose to use 5 Markov chains.

- **Simulated annealing:** A Simulated Annealing version of SAEM is used to estimate the population parameters (the variances are constrained to decrease or increase slowly during the first iterations of SAEM, see [Section 3.13.1](#))
- **Monte-Carlo Sizes:** It can be specified the number of simulated samples used to compute *Prediction distribution* graphic, the *NPDEs* (Normalized Prediction Distribution Errors) and the *VPCs* (Visual Predictive Checks), the log-likelihood estimation when the *Importance Sampling* algorithm is used (see [Section 3.7.4](#))
- **Display:** The number of iterations between two updates of the convergence graphics produced by the algorithm (e.g. SAEM convergence window when estimating population parameters).

3.6 The “Results” frame



The results

Results folder		Standard errors	Individual parameters	Log-likelihood	Graphics
<input checked="" type="radio"/> Project name	theophylline_project	<input checked="" type="radio"/> Linearization	<input checked="" type="checkbox"/> Conditional modes	<input checked="" type="checkbox"/> Linearization	<input type="button" value="List"/>
<input type="radio"/> User defined	<input type="button" value="Browse"/>	<input type="radio"/> Stoch. Approx.	<input type="checkbox"/> Cond. means and s.d.	<input checked="" type="checkbox"/> Important Sampling	

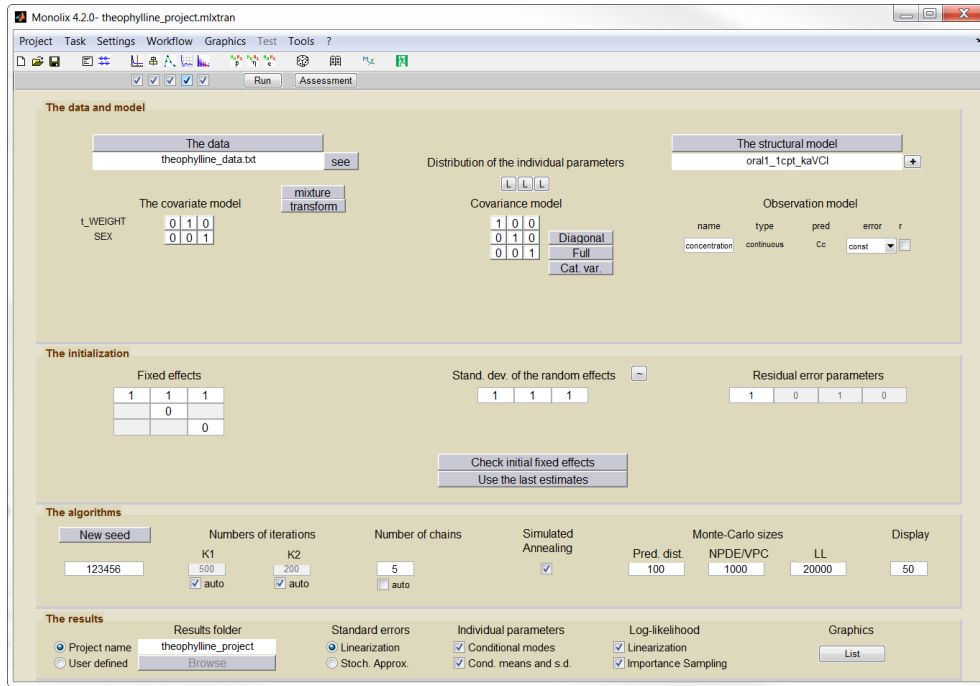
- The **Results** folder is the folder where all the results are stored.

- **Project name:** the result folder is determined automatically from the name of the project as “<project folder>/<project name>/”.
- **User defined name:** the name and the directory of the results folder are defined by the user.
- **Standard errors:** Which algorithm to use when computing Fisher Information Matrix and standard errors. Can be by **Linearization** (using a linear approximation of the model) or by **Stochastic Approximation** (the observed Fisher Information Matrix of the exact model is estimated by stochastic approximation).
- **Individual parameters:** says if the **Conditional modes** and/or **Conditional means and standard deviations** should be computed when estimating the individual parameters
- **Log-likelihood:** says which algorithms to use when estimating the log-likelihood. Can be by **Linearization** (using a linear approximation of the model) and/or by **Importance Sampling** (the log-likelihood of the exact model is estimated by Monte-Carlo).
- **Graphics:** Use List button to choose the list of graphics to produce when the results are computed.


3.7 Executing tasks

MONOLIX includes several estimation algorithms: estimation of the population parameters, the Fisher information matrix and standard errors, the individual parameters, and log-likelihood. Also, different types of results are available in the form of graphics and tables.

We will consider the following project with the theophylline data for illustration. Here, the log-weight centered by the mean is used as a continuous covariate and the gender as categorical.



3.7.1 Estimation of the population parameters

Maximum likelihood estimation of the population parameters is performed with the  button. The sequence of estimated parameters (θ_k) is displayed in a figure which is automatically saved as **saem.png** in the results folder at the end of the estimation. Also, the final estimations are displayed in the MATLAB command window.

This algorithm produces the file **pop_parameters.txt** in the result folder, with all the estimated parameters: population parameters, variances (or standard deviations), correlations, error model parameters, etc. It also includes the project filename, the date and hour of the run, and the version of MONOLIX. The estimation of the population parameters by groups defined by the categorical covariates used in the model are also given.

The same information is printed in the screen (MATLAB command window for MATLAB version and DOS or linux terminal for standalone version). The algorithm convergence graph (**saem.png**), as well as a copy of the used project in **.mat** and **.xmlx** formats are also saved. Also, if the structural model is coded using MLXTRAN, a copy of this file is included.

▷ *theophylline example:*

The final estimations for our example, and the convergence graphics for this exemple are:

We clearly see on these graphics that the trajectory of (θ_k) is much more random during the first stage than during the second stage. The number of iterations used for the SAEM algorithm were $K_1 = 173$ and $K_2 = 120$.

Remark 1: This figure shows that, despite a very poor initial guess, SAEM algorithm converges

```

Estimation of the population parameters

      parameter
ka      :      1.58
V       :      0.455
beta_V(t_WEIGHT) : -0.423
Cl      :      0.0438
beta_Cl(SEX_M)   : -0.157

omega_ka      :      0.651
omega_V      :      0.12
omega_Cl     :      0.253

a           :      0.731

-----
Estimation of the population parameters by groups

      parameter
Cl_(SEX=F*) :      0.0438
Cl_(SEX=M ) :      0.0374

Numerical covariates
  t_WEIGHT = log(WEIGHT)      Centered by the mean ( log(mean(WEIGHT)) = 4.2425 )
Categorical covariates
  SEX
    Reference group: F
    Other groups:  M

```

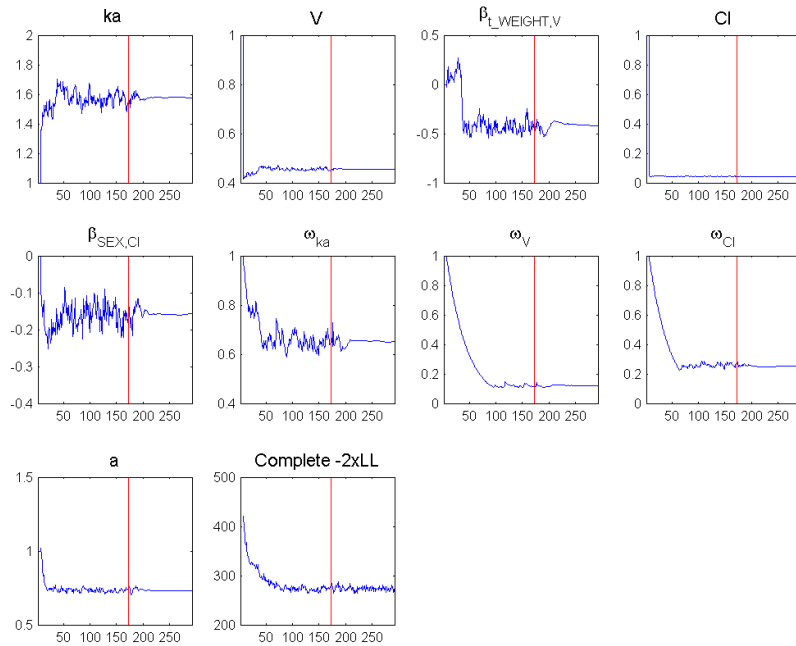
in very few iterations to the neighborhood of the solution. Thus, in this example, a good estimation of the parameters can be obtained with very few iterations of SAEM (try for instance with $K_1 = K_2 = 20$ and any initial guess...). Also simulated annealing is not necessary for this project.

However it is not always the case. One can see in the figure below that the choice of the first number K_1 of iterations is crucial. In this example, the total number of iterations is $K_1 + K_2 = 100$, with $K_1 = 50$ on the left and $K_1 = 1$ on the right. The second example shows that $K_1 = 1$ iterations is not enough to reach the neighborhood of the solution. Then, because of the averaging during the K_2 next iterations, SAEM will require many more iterations to converge than in the first example.

Remark 2: The individual parameters of each subject are “roughly” estimated during the last iterations of SAEM (by estimating the conditional means $E(\phi_i|y; \hat{\theta})$). These “rough” estimates are used for the results if the individual parameters are not better estimated later.

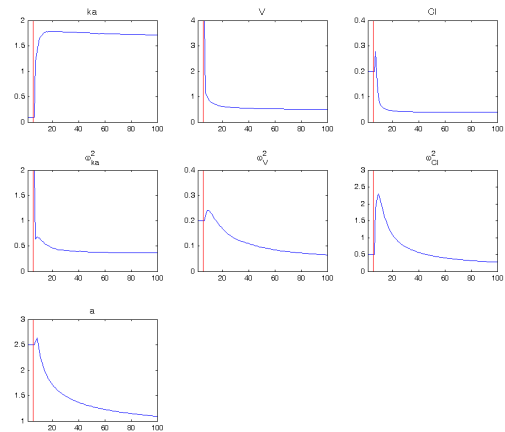
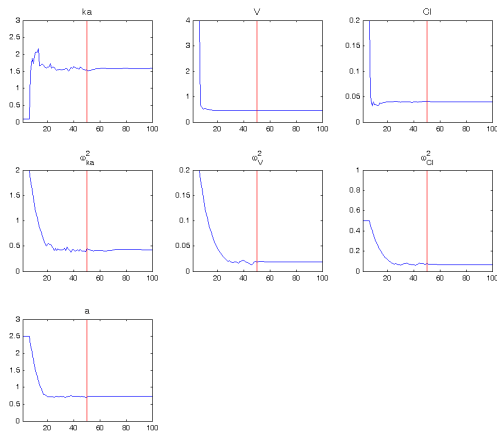
3.7.2 Estimation of the standard errors

Computes Fisher information matrix and so the standard errors of the different estimators and their correlation. There are two different algorithms: **by linearization** where the structural model is linearized, and so the full statistical model is approximated by a gaussian model, or **by**



A "nice convergence" of SAEM

A "poor convergence" of SAEM



Stochastic approximation where the exact model is used, and the Fisher information matrix (F.I.M) is approximated stochastically (slower but more precise).

The final estimations are displayed in the command MATLAB window together with the popula-

tion parameters:

1. the estimated fixed effects, their standard-errors, the absolute and relative p -values obtained from the Wald test (only for the coefficients of the covariates),
2. the estimated variances (or standard deviations) and their standard-errors,
3. the estimated residual error parameters and their standard-errors,
4. the estimated correlation matrix of the random effects if the covariance matrix is not diagonal,
5. the correlation matrix of the fixed effect estimates, with the smallest and largest eigenvalues,
6. the correlation matrix of the variance components estimates, with the smallest and largest eigenvalues,

All that information is appended to the file `pop_parameters.txt`.

▷ *theophylline example:*

```

Estimation of the population parameters

      parameter      s.e. (lin)    r.s.e.(%)    p-value
ka          :      1.58         0.31         20
V            :      0.455        0.02          4
beta_V(t_WEIGHT) :    -0.423        0.31         74      0.18
Cl           :      0.0438       0.0055         12
beta_Cl(SEX_M) :    -0.157        0.16        104      0.34

omega_ka     :      0.651        0.15         22
omega_V      :      0.12         0.036         30
omega_Cl     :      0.253        0.063         25

a            :      0.731        0.056          8

-----
correlation matrix of the estimates(linearization)

ka          1
V           0.14      1
beta_V(t_WEIGHT)  0    0.04      1
Cl          -0.04    -0.1    0.09      1
beta_Cl(SEX_M)  -0     0    -0.12   -0.76      1

Eigenvalues (min, max, max/min): 0.24  1.8  7.6

omega_ka     1
omega_V     -0.02      1
omega_Cl     -0    -0.02      1
a           -0.03   -0.1   -0.06      1

Eigenvalues (min, max, max/min): 0.87  1.1  1.3


-----
Estimation of the population parameters by groups|

      parameter      s.e. (lin)    r.s.e.(%)
Cl_(SEX=F*) :      0.0438       0.0055         12
Cl_(SEX=M ) :      0.0374       0.004          11

```

Remark: The Wald test indicates here that $\beta_{W,V}$ and $\beta_{S,Cl}$ are not significantly different from 0: we can consider that the log-volume is not a linear function of the log-weight, and that the clearance of the males and females are not significantly different (of course any statistical inference with only 12 subjects can be dubious...).

3.7.3 Estimation of the individual parameters

Although the population parameter estimation algorithm gives a rough estimation of the individual parameters, it can be estimated two more precise estimators: the conditional mode and the conditional means. Those estimators can be computed with the  button.

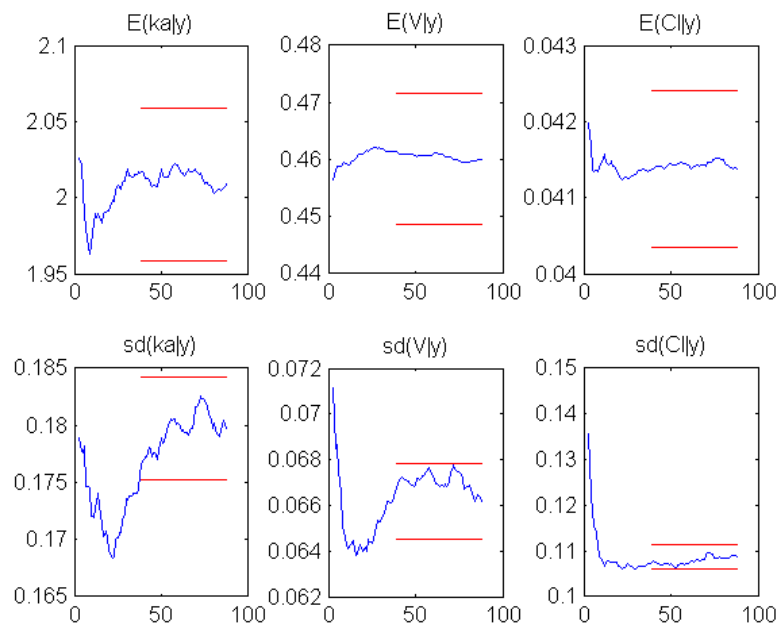
If the option **Estimate the conditional modes** is selected, the individual parameters are estimated by maximizing the conditional probabilities $p(\phi_i|y_i; \hat{\theta})$.

If the option **Estimate the cond. means and s.d.** is selected, the conditional means and standard deviations are estimated by MCMC. For each parameter, the mean of these quantities over all the subjects is displayed together with a r_{mcmc} interval.


Two files **indiv_parameters.txt** and **indiv_eta.txt** are created with the estimated individual parameters and random effects in table format. Also, if there were defined priors on some fixed effects, and it was selected prior distribution method for some of them, a new file called **simulatedPopParams.txt** is created simulations using their posterior distribution laws.

▷ *theophylline example*:

Here, $r_{mcmc} = 5\%$ and $L_{mcmc} = 50$



3.7.4 Estimation of the log-likelihood

The estimation of the log-likelihood is performed with the  button. Two different algorithms are proposed to estimate the log-likelihood: by **linearization** and by **Importance sampling**.

▷ *theophylline example*:

In our example, the two different estimates of the log-likelihood are computed.

The value of the two estimated $-2 \times$ log-likelihoods, the standard error of the Monte-Carlo estimate, The AIC and the BIC are displayed in the command MATLAB window:

```

Log-likelihood Estimation by linearization

-2 x log-likelihood:           340.41
Akaike Information Criteria   (AIC):  358.41
Bayesian Information Criteria (BIC):  362.78

```

```

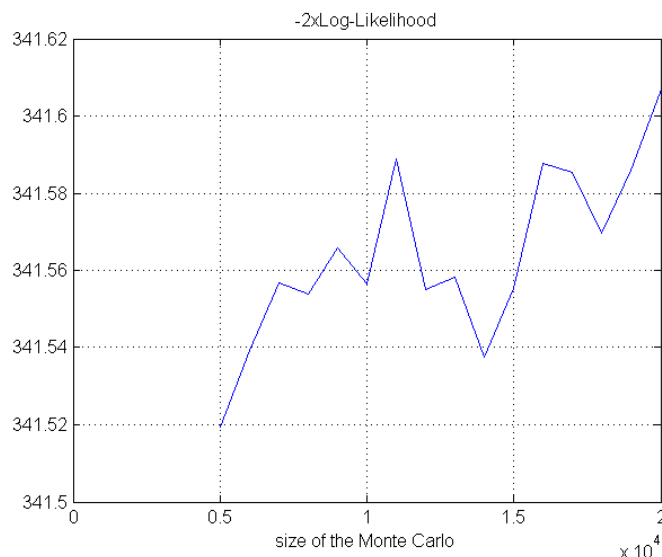
Log-likelihood Estimation by important sampling
Sampling distribution for the random effects: t with 5 d.f

-2 x log-likelihood:           341.61 (0.064)
Akaike Information Criteria   (AIC):  359.61 (0.064)
Bayesian Information Criteria (BIC):  363.97 (0.064)

Elapsed time is 3.51 seconds.
CPU time is 9.73 seconds.

```


The Monte-Carlo estimator converges to the observed log-likelihood when the size of the Monte-Carlo increases. The sequence of estimates, as a function of the Monte-Carlo size, is displayed as a Figure:



The estimated log-likelihoods are appended to `pop_parameters.txt`.

Remark: The log-likelihood can not be computed by **linearization** for discrete outputs (categorical, count, etc.) nor for mixture models or when the posterior distribution have been estimated for some parameters with priors.

3.7.5 Computing results

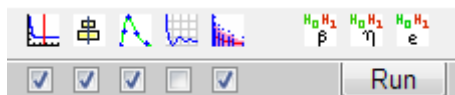
Use the button  to compute produce some graphics and tables.

It is possible to specify the list of graphics (with button `List` at the bottom of the main interface), which of them should be saved and which tables should be produced (menu **Graphics->Outputs to save**). For more details see [Section 3.8](#).

3.7.6 Running several algorithms

With the button **Run**, you can execute successively several tasks. The list of tasks to run is called “scenario” or “workflow”. You can define your own scenario by checking the corresponding checkboxes at the left of the **Run** button.

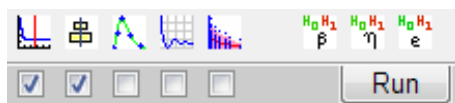
For example, define the following workflow



in order to:

1. estimate the population parameters,
2. estimate the standard errors,
3. estimate the individual parameters,
4. display graphical results using the individual parameters estimated previously.

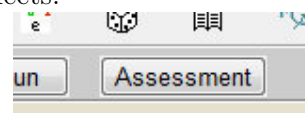
If you just want to compute the population parameters with their standard errors, define the workflow:



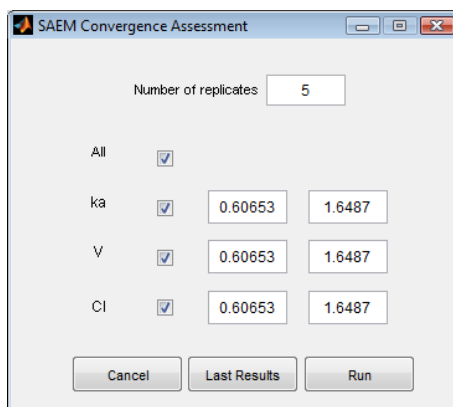
3.7.7 Algorithms convergence assessment

MONOLIX includes a convergence assessment tool. It is possible to execute a workflow as defined above but for different, randomly generated, initial values of fixed effects.

Click in the **Assessment** button on the workflow bar to open the **Assessment** graphical interface.



You can enter the number of runs, or replicates, the parameters to generate initial values and the intervals where those values should be (uniformly) simulated. Click on **Run** to execute the tool.

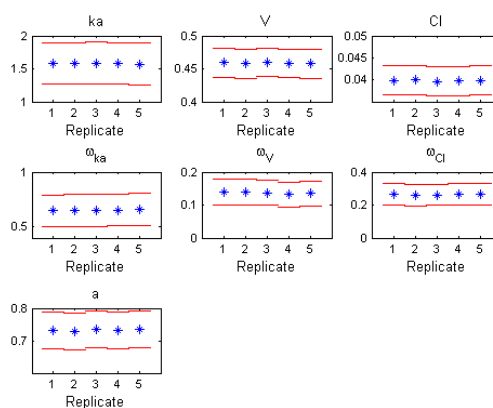


Remarks:

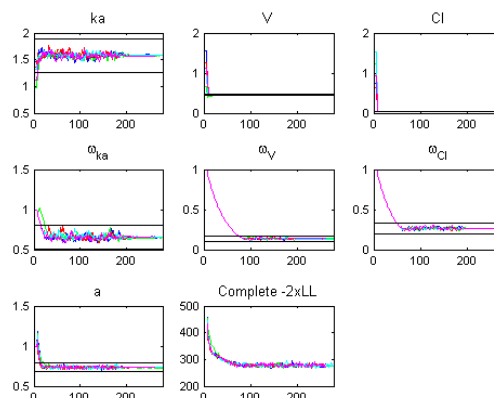
- The project workflow is used (see [Section 3.7.6](#)).
- Population parameters estimation must be selected.
- A result folder is generated for each set of initial parameters.

Two kinds of graphics are given as a summary of the results,

one showing the estimated values (blue) with the estimated standard errors (red bars) for each replicate (if the Fisher information matrix estimation was included in the scenario)





and the superimposed convergence graphics for each parameter. In case of F.I.M estimation is included, then the black lines represents the mean of the estimated s.e.



Also, a `.mat` file is produced with all the results used for those graphics. Press **Last Results** button to reproduce the last result graphics if you already have ran the tool for the current project, and **Cancel** to close the interface.

3.8 Plots and results

From the main interface toolbar, you can

- display the observed data y as a function of the regression variable (e.g. `time` for a PK applications): .
- Produce several graphics and tables from the results of the algorithms: .

You can select which figures to show in menu **Graphics->List** or button **List** in the interface (see [Section 3.8.4](#)) and which figures and/or tables to save ([Section 3.8.6](#))

You can also produce one specific graphic.

Note: By default the new projects do not save the graphics and do not produce the tables. If you want MONOLIX to create some table, you must select it in menu **Graphics->Output to save**.

MONOLIX allows to change some visual preferences determining the way the graphics are shown (set of line colors and styles, markers, etc). It is also possible to specify the format where the graphics should be saved. [Section 4.14](#) shows how you can set some preferences with an interface and [Appendix C](#) gives an overview of all the parameters that can be set and how.

3.8.1 The graphics

The proposed figures are separated in three groups:

- **Reduced:** Graphics rapid to create, good to have a first view of the goodness of the fits.

- **Simulation:** Graphics requiring simulations, so they can take some time to be produced. Includes some Visual Predictive Checks (VPC) graphics.
- **Others:** other graphics proposed.

Reduced :

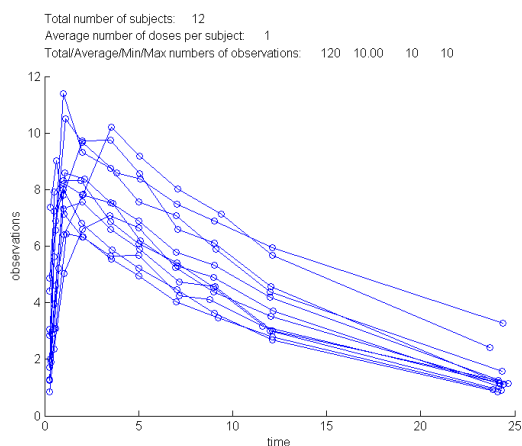
Project Summary: displays some information about the project (date, datafile,...)

15-Oct-2012 09:52:15

Output : concentration
Data file : theophylline_data.txt
Structural model : oral1_1cpt_kaVCI
Results folder : theophylline_project

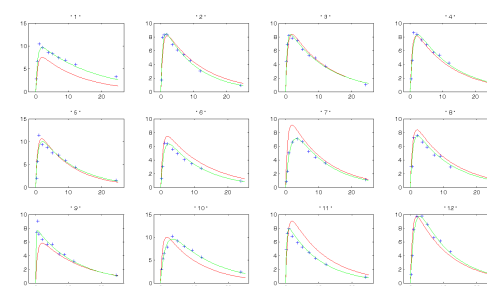
Project path : C:\monolixData\monolix420\work\Demos\theophylline
Data path : C:\monolixData\monolix420\work\Demos\theophylline
Model path : D:\matlab\libraries\FKLlibrary
Results path : C:\Desktop

Spaghetti plot: displays the original data as a “spaghetti plot”.

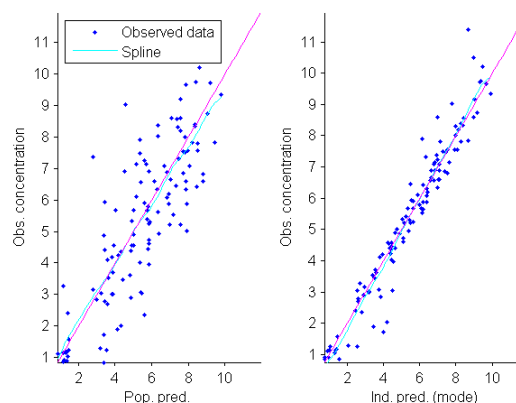


Individual fits: displays the individual fits, using the population parameters with the individual covariates (red) and the individual parameters (green) on a continuous grid.

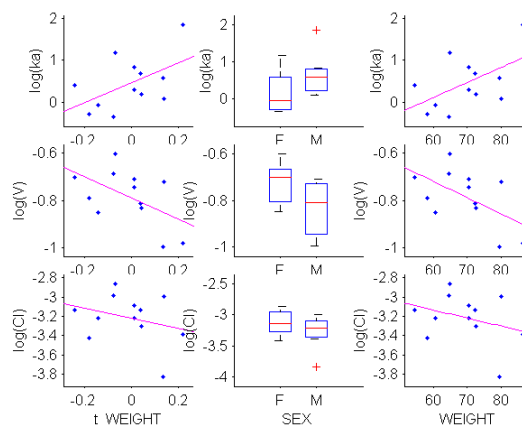
It is also possible to display the median and a confidence interval for (y_{ij}) estimated with a Monte Carlo procedure. The design and the covariates of each subject are used for the simulation.



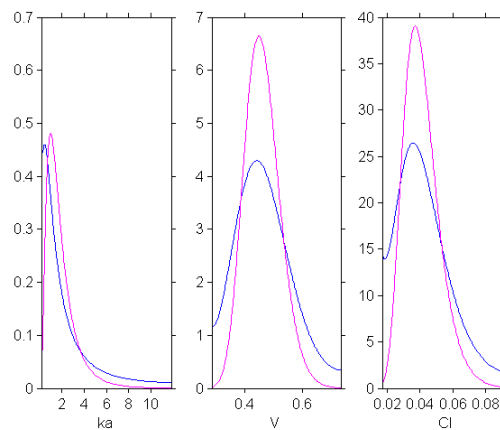
Obs. vs Pred.: displays observations versus the predictions (\hat{y}_{ij}) computed using the population parameters (on the left), and with the individual parameters (on the right)



Covariates: displays the estimators of the individual parameters in the gaussian space, and those for random effects, (e.g. the conditional expectations $\mathbb{E}(\varphi_{i\ell}|y;\hat{\theta})$ and $\mathbb{E}(\eta_{i\ell}|y;\hat{\theta})$, $1 \leq i \leq N$ and the conditional modes) *v.s.* the covariates.



Parameter Distributions: displays the estimated population distributions of the individual parameters. Settings allows you to show a summary of the theoretical distributions (mean, median, mode, quartiles, percentiles, standard-deviation), histograms, and a non-parametric estimation of the distribution

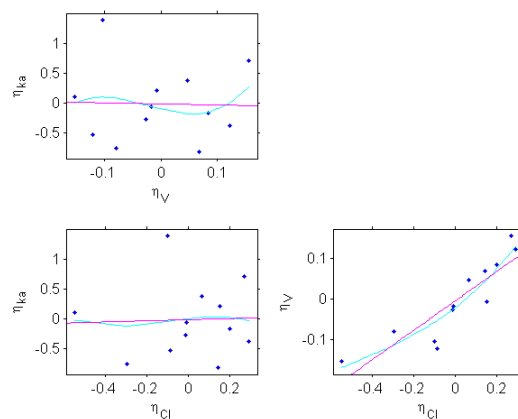
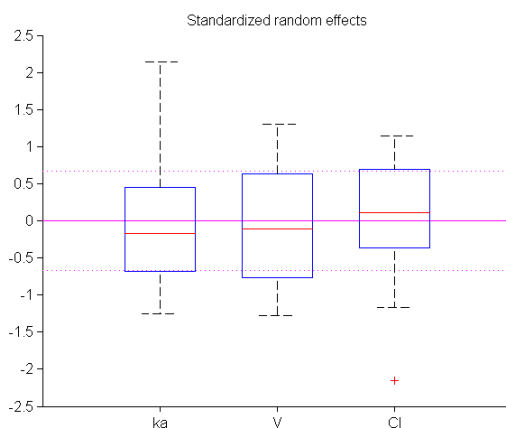
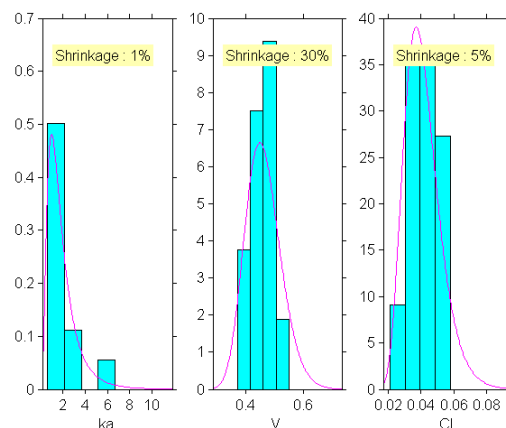


It is also possible to display the empirical distribution of the individual parameters and the shrinkages computed as follows for each random effect:

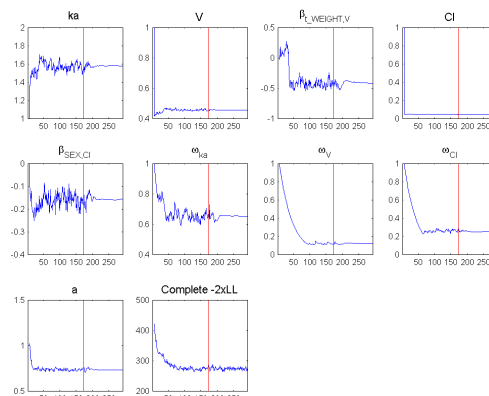
$$\text{Shrinkage} = 1 - \frac{\text{Var}(\hat{\eta})}{\hat{\omega}^2}$$

Random Effects(boxplot): displays the distribution of the random effects with boxplots. The horizontal dotted lines show the interquartile interval of a standard Gaussian distribution.

Random Effects(joint dist.): generates scatter plots for each pairs of random effects.



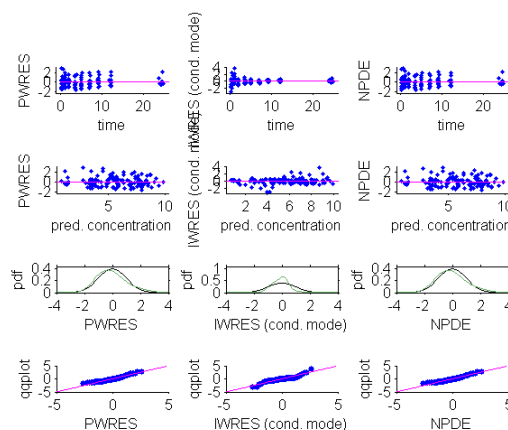
Convergence SAEM: displays the sequence of the estimated parameters (θ_k).



Simulations :

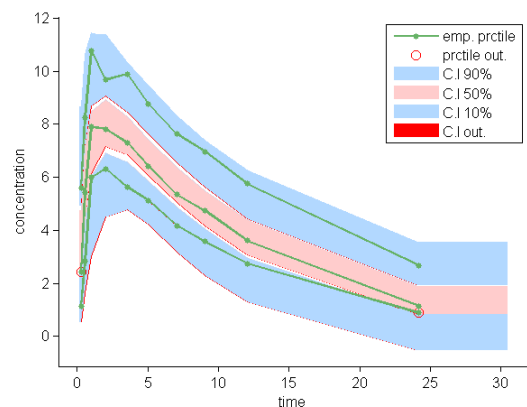
Residuals: displays the PWRES (population weighted residuals), the IWRES (individual weighted residuals) and the NPDE (Normalized Prediction Distribution Errors) v.s. x (top) and v.s. the predictions (bottom).

The PWRES are computed using the population parameters and the IWRES are computed using the individual parameters. For discrete outputs, only NPDE and individual NPDE are used.

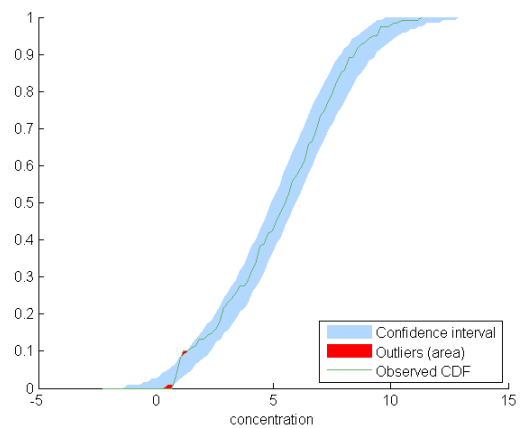


For continuous outputs, this figure shows the empirical distributions of the weighted residuals and the NPDE together with the standard Gaussian pdf and qqplots to check if the residuals are Gaussian.

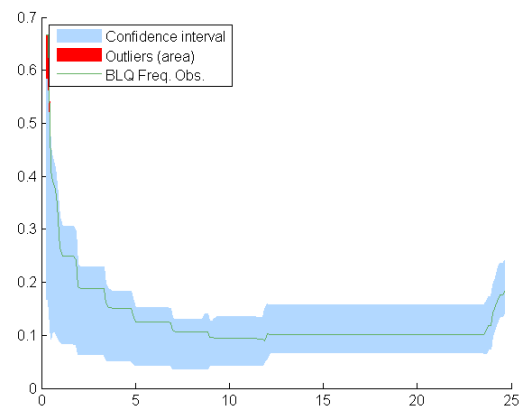
Diagnostic VPC: Allows to compare the empirical distribution of the observations and theoretical distribution (computed from simulations in observation times) inside some parameterizable bins.



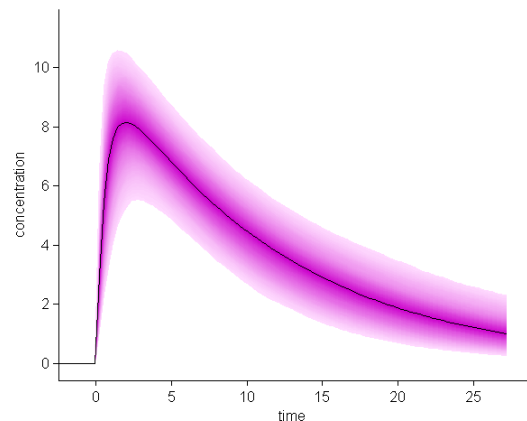
NPC: Allows to compare empirical cumulative distribution function (CDF) of the observations with theoretical's (computed from simulations).



BLQ: Shows the proportion of censored data on time. It is possible to chose the censoring interval. This graphic is only available for projects with censored data.

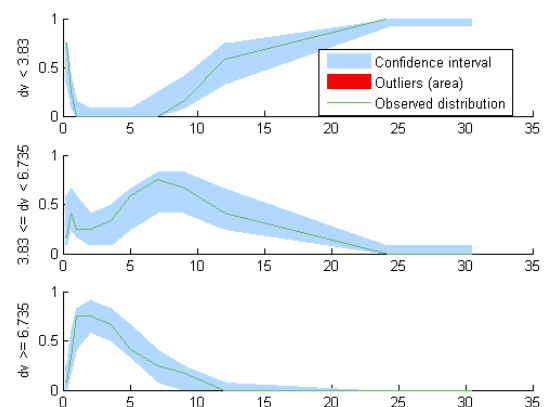


Prediction distribution: Allows to compare the observations with the theoretical distribution of the predictions.

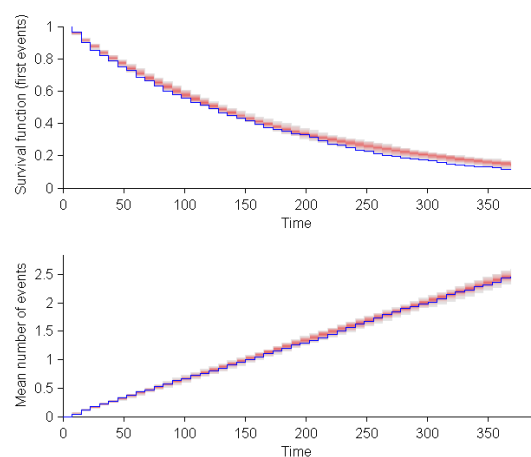


Others :

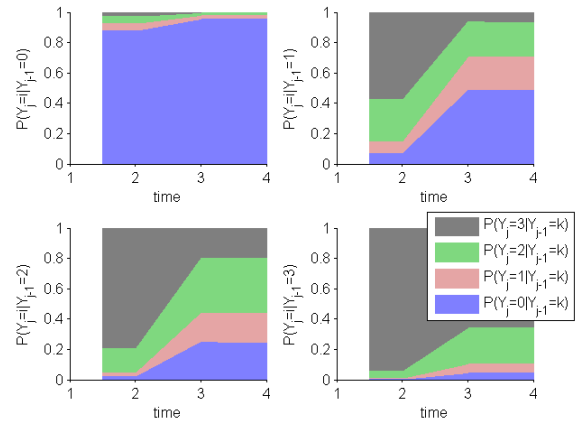
Categorized data: Allows to check the distribution of the observations in categories that can be parameterized by the user.



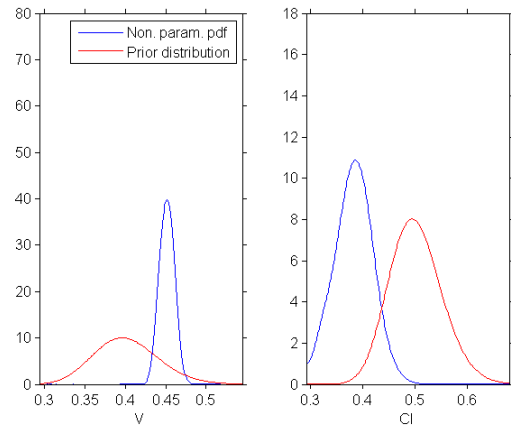
Time to Event data: Shows empiric (from observations) and theoretical (from simulations) survival function and average number of events for *Time to event* data. Only available for outputs of type **event**.



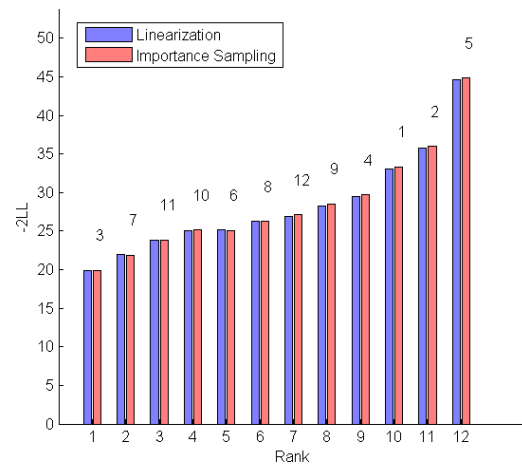
Transition Probabilities: For discrete observations, shows the proportion of each category knowing the previous one. Can be used on any discrete model.



Posterior Distribution: Shows the priors (theoretical) and the posterior (simulations) distributions for each parameter estimated by “posterior distribution”. Requires the estimation of the conditional means of the individual parameters.



Contribution to log-likelihood: Displays the contribution of each subject observations to the total log-likelihood. Requires the estimation of the log-likelihood, and both estimators are shown if they have been computed.



3.8.2 The tables

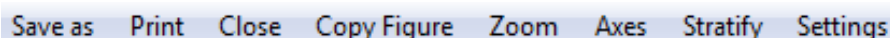
MONOLIX can produce five kinds of ASCII table files:

- **Observation times** contains the regression variables, the individual predictions, the population predictions, the weighted population residuals, the weighted individual residuals and the NPDE, for all the observation times in the dataset.
- **Fine-grid times** contains the regression variables, the individual predictions, the population predictions in a fine (regular) grid.
- **All times** contains the regression variables, the individual predictions, the population predictions for a possibly larger set of times in the dataset, including observation times, lines where MDV column is set to 2.
- **LL individuals contribution** contains subject contribution to the total log-likelihood.
- **Covariates summary** contains a summary of all the covariates defined in the project.

The first three tables can include new columns according to the **table** definition in the structural model as described in [Section 4.11](#).

3.8.3 The graphics menu bar

The graphics menu bar proposes different options



- It is possible to save, close or print the figure and, in Windows, to copy and paste it to any other document.
- Zoom menu activates or de-activates the zoom
- The Axes menu proposes to use semi-log or log-log scale plots. Settings option gives the opportunity to choose labels and to change the scale of graphics. It is also possible to use the same axis limits for the different plots of the same graphic.
- The Stratify menu opens the stratify window, see [Section 3.8.5](#) below.
- The Settings menu opens a new window with the settings of the current graphic.

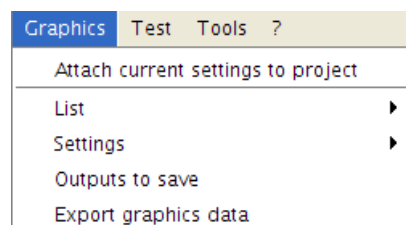
3.8.4 Main interface Graphics Menu

This menu options allows to handle the graphics configurations of the project, which are used each time the results figures and tables are launched. Those configurations have three parts: the list of result graphics to produce, each graphic settings and the list of graphics to save and tables

to produce.

There are 5 options in MONOLIX **Graphics** menu.

- Attach the current settings to project
- List
- Settings
- Outputs to save
- Export graphics data



Attach the current settings to project

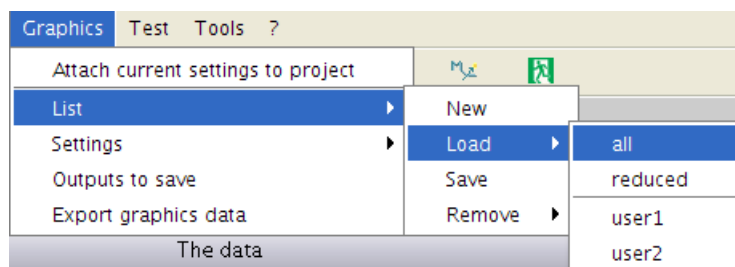
When this option is chosen, the current settings of the opened figures are used as current project defaults.


List

This menu allows to manage the list of graphics to display.

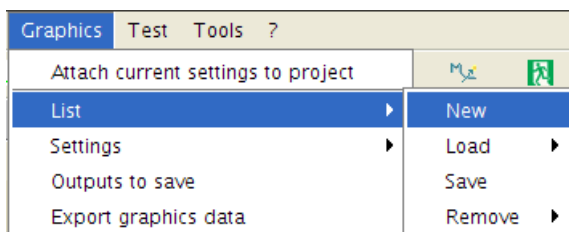
Three options are available :

- **Load**
Allows to load already defined lists. Those lists are divided in two section: MONOLIX predefined lists and user defined lists.

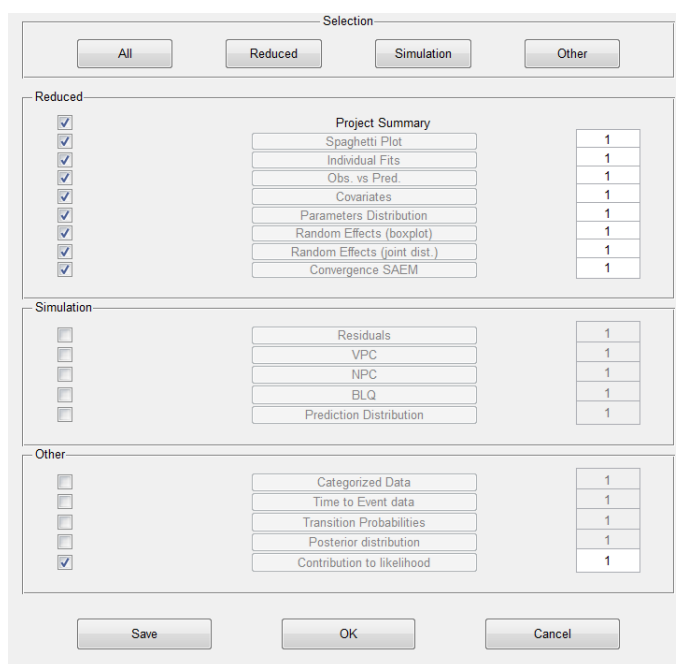


The chosen list determines the figures that will be opened next time the results graphics are launched (button ).

- **New**
Allows to define and save a list.



This option opens a window that allows to create a list and then either to export to a .xmlx file or to use in the current project.



MONOLIX proposes four predefined lists: **Reduced**, **Simulation**, **Others** as explained in [Section 3.8.1](#), and **All**. The default list is **reduced**.



To define the list, it should be selected which graphics to show for each output (checkboxes at the left, each column represents an output) and how many times (at the right).

It is possible to launch a single graphic by clicking on the corresponding button.

Reduced		
<input checked="" type="checkbox"/>	Project Summary	
<input checked="" type="checkbox"/>	Spaghetti Plot	1
<input checked="" type="checkbox"/>	Individual Fits	1
<input checked="" type="checkbox"/>	Obs. vs Pred.	1
<input checked="" type="checkbox"/>	Covariates	1
<input checked="" type="checkbox"/>	Parameters Distribution	1
<input checked="" type="checkbox"/>	Random Effects (boxplot)	1
<input checked="" type="checkbox"/>	Random Effects (joint dist.)	1
<input checked="" type="checkbox"/>	Convergence SAEM	1
Simulation		
<input type="checkbox"/>	Residuals	1
<input type="checkbox"/>	VPC	1
<input type="checkbox"/>	NPC	1
<input type="checkbox"/>	BLQ	1
<input type="checkbox"/>	Prediction Distribution	1
Other		
<input type="checkbox"/>	Categorized Data	1
<input type="checkbox"/>	Time to Event data	1
<input type="checkbox"/>	Transition Probabilities	1
<input type="checkbox"/>	Posterior distribution	1
<input checked="" type="checkbox"/>	Contribution to likelihood	1

To export the defined list, use the *Save* button. The list should be saved in the proposed folder to be used by MONOLIX.

In order to use the defined list in the current project, click on the button *OK*.

Save	OK	Cancel
-------------	-----------	---------------

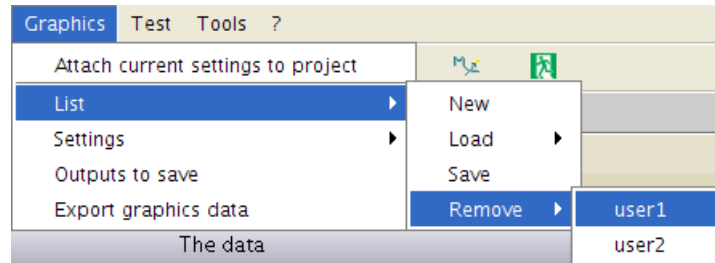
Remark : This window is available in MONOLIX main interface.

The algorithms							
New seed	Numbers of iterations		Number of chains	Simulated Annealing	Monte-Carlo sizes		Display
123456	K1 500 <input checked="" type="checkbox"/> auto	K2 200 <input checked="" type="checkbox"/> auto	1 <input type="checkbox"/> auto	<input checked="" type="checkbox"/>	Pred. dist. 100	NPDE/VPC 500	LL 10000
The results							
Results folder		Standard errors	Individual parameters	Log-likelihood	Graphics		
<input checked="" type="radio"/> Project name	theophylline_cens1_project	<input type="radio"/> Linearization	<input checked="" type="checkbox"/> Conditional modes	<input checked="" type="checkbox"/> Linearization	<div style="border: 2px solid red; border-radius: 10px; padding: 5px; display: inline-block;">List</div>		
<input type="radio"/> User defined	Browse	<input checked="" type="radio"/> Stoch. Approx.	<input type="checkbox"/> Cond. means and s.d.	<input checked="" type="checkbox"/> Important Sampling			

- **Save**
Saves project's graphic list

Graphics	Test	Tools	?
Attach current settings to project			
List			
Settings			
Outputs to save			
Export graphics data			
		<div style="border: 1px solid black; padding: 2px;"> New Load Save Remove </div>	

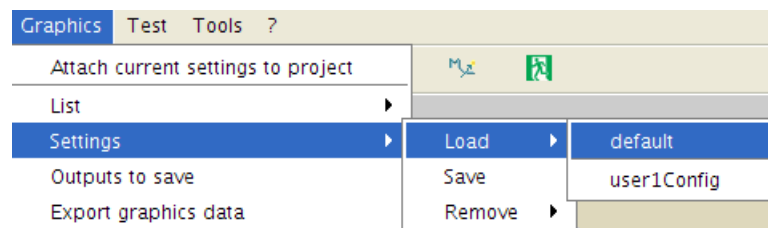
- **Remove**
Remove an user defined list.



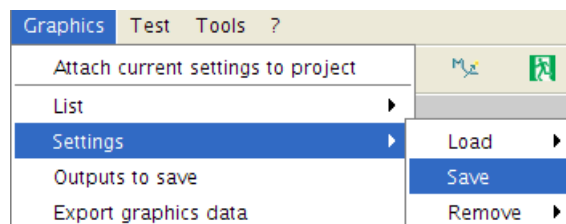
Settings

Allows to handle predefined graphic configurations : load, save and remove.

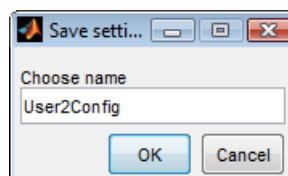
- **Load**
Allows to load already defined configurations. Those configurations are divided in two section: MONOLIX predefined configurations and user defined configurations.
The opened graphics are automatically updated when a configuration is loaded.



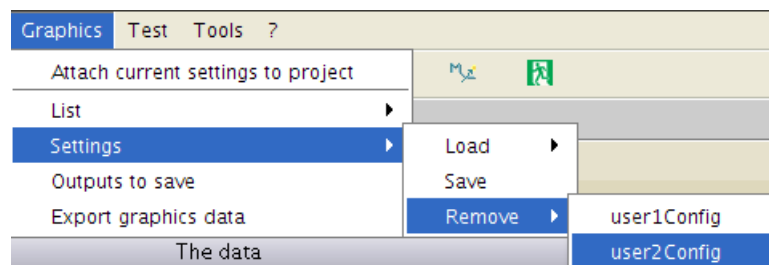
- **Save**
Allows to save a current configuration. The saved file will be included to the Load list.



Enter a name to save the configuration.



- Remove
Remove an user defined configuration.

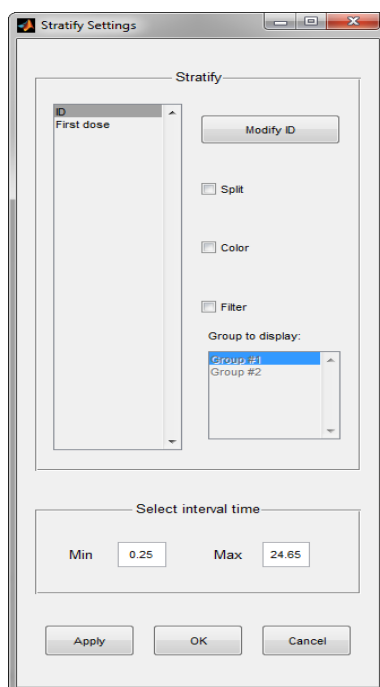


Export graphics data

This feature is used to export graphics data in the aim to reproduce his own graphics. For each generated graphic, one (or severals) table(s)goresse passssssssss will be created in the results folder.

3.8.5 Stratify

The **Stratify** menu allows to create and use covariates for stratification purposes. It is possible to select a categorical covariate for splitting, filtering or coloring the dataset. Also, in the bottom section, it can be defined a time filter



3.8.6 Settings

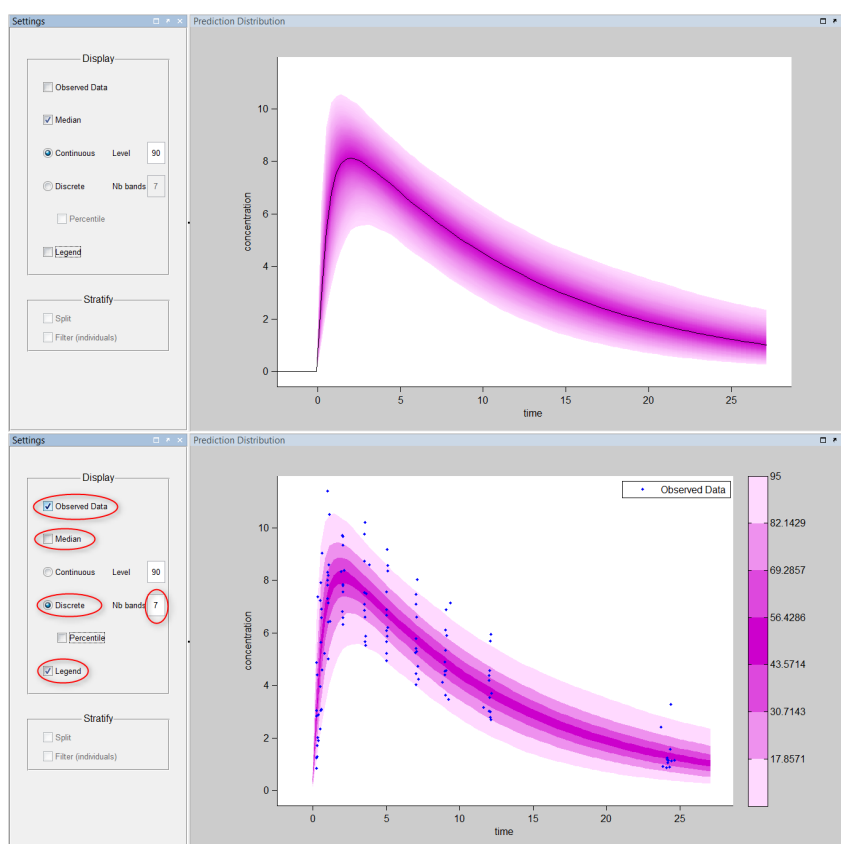
Each graphic has its own settings, which can be accessed by **Settings** menu. The most common types of options are described below.

Display options

Most of the graphical components can be made visible or hidden, allowing the user to focus on the desired information.

For some graphics, it is possible to select which plots to show.

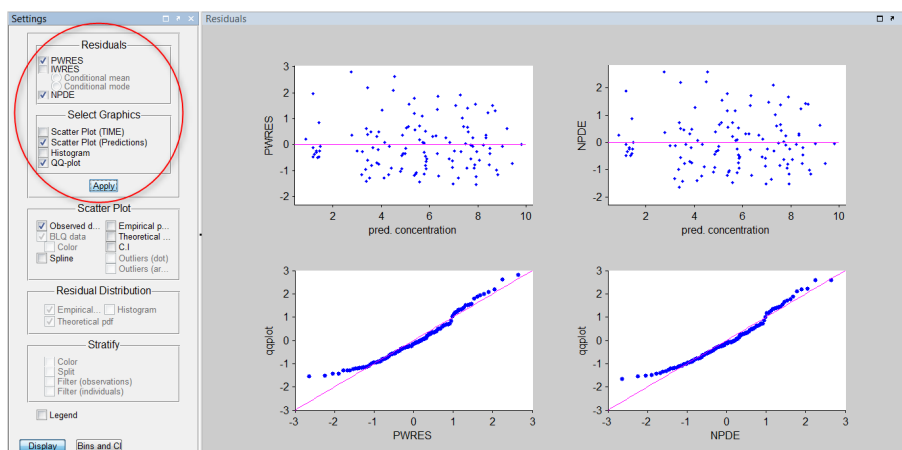
Prediction Distribution with two different configurations



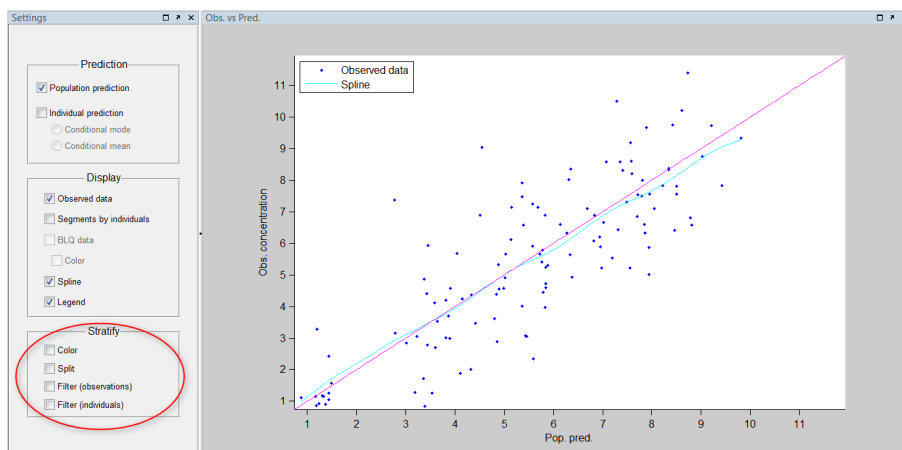
Stratify options

Some graphics can be stratified using the filters issued from the **Stratify** interface mentioned in [Section 3.8.5](#). It is possible to activate the splits, filters, and/or colors for groups of individuals and also to filter observations for some time interval (the first regression variable is used if no time column exists).

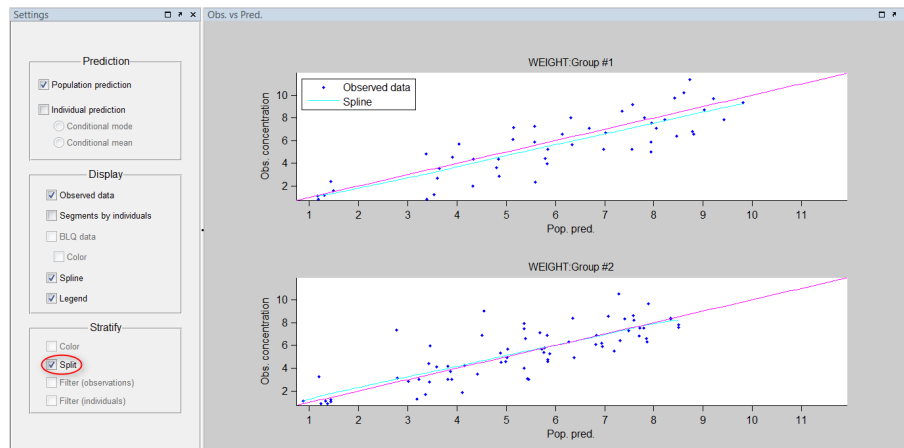
Residuals with 2 kinds of residuals with scatter plots (predictions) and QQ-plot chosen



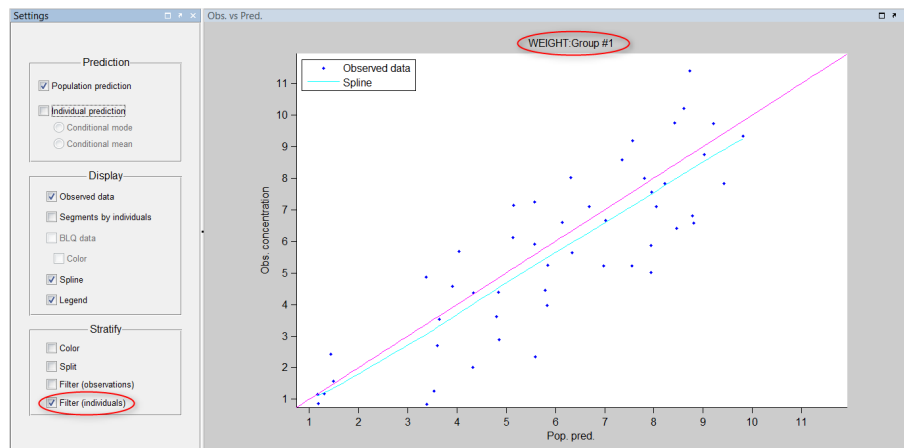
Predictions Vs Observations without applying stratify



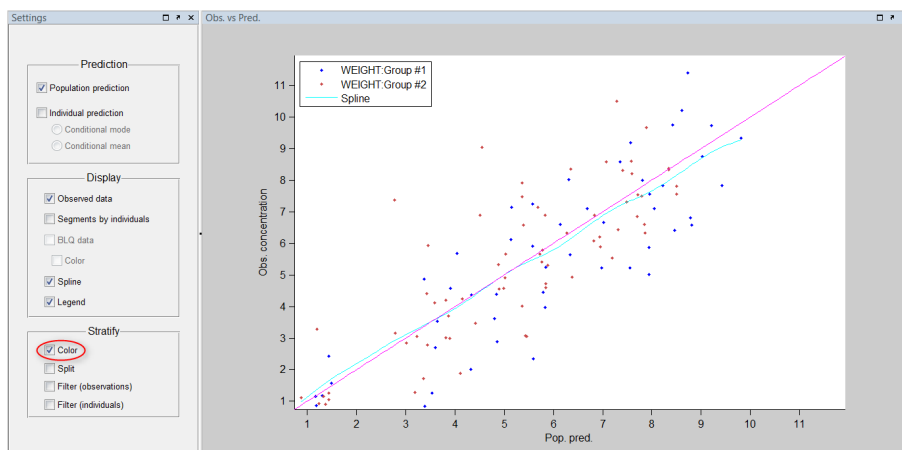
Split: Predictions Vs Observations with Split option set



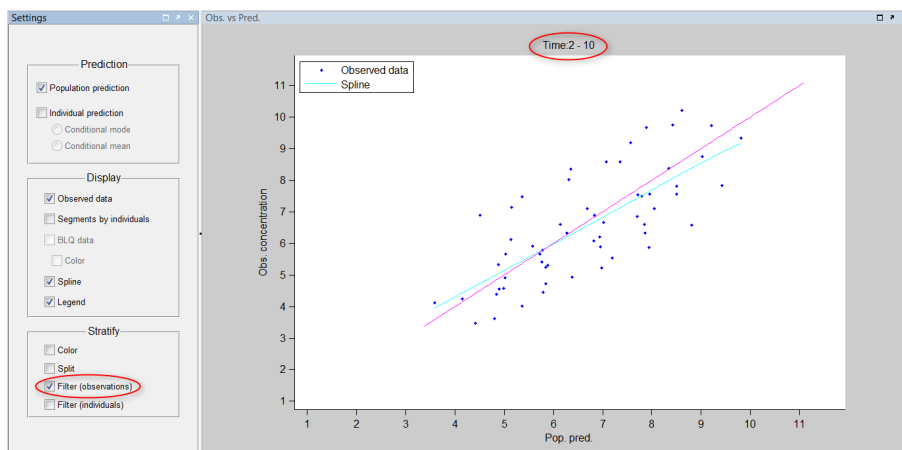
Individuals filter: Predictions Vs Observations with Filter (individuals) option set



Color: *Predictions Vs Observations* with Color option set

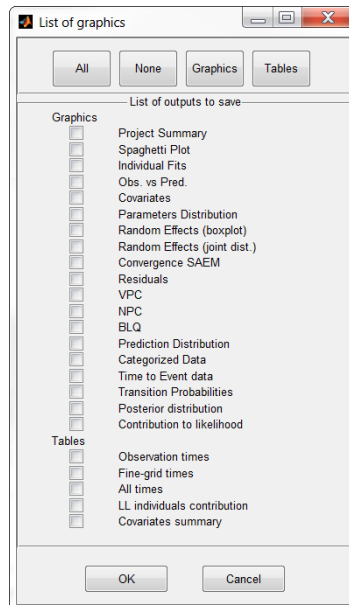


Observations filter: *Predictions Vs Observations* with Filter (observations) option set



Saving graphics

It is possible to choose which graphics to save. Clicking on **Outputs to save** in **Graphics** menu, a window is opened :



The save starts after the display of the graphics.

Computations options

The user can modify some parameters required to compute the information to be represented. This allows him to tune the graphics.

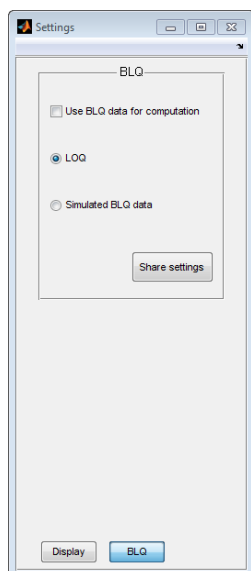


Figure 3.1: BLQ settings

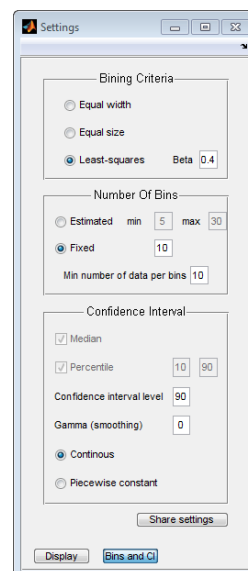
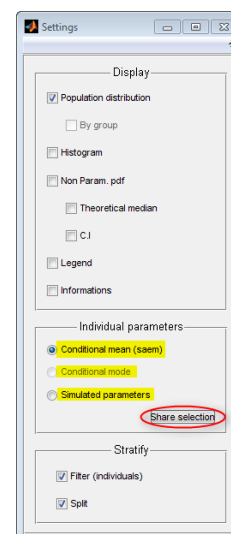


Figure 3.2: Bins settings

Share

Some options are identical for several graphics and can be set independently from one graphic to the other. The button *Share* allows to set the current values to all the graphics sharing those options. The following table describes links between the different graphics. The three columns contain respectively the shared options, the *Share* button name, and the concerned graphics.

Option	Button name	Graphics
BLQ	Share settings	Predictions Vs Observations Residuals VPC NPC
BINS	Share settings	Residuals VPC Categorized data
Estimators	Share selection	Parameter distribution Random effects (boxplot) Joint distribution



3.9 Testing hypotheses

Three kind of tests can be performed:

- β tests the covariate model for the fixed effects,
- η tests the covariance model for the random effects,
- ϵ tests the residual variance model.

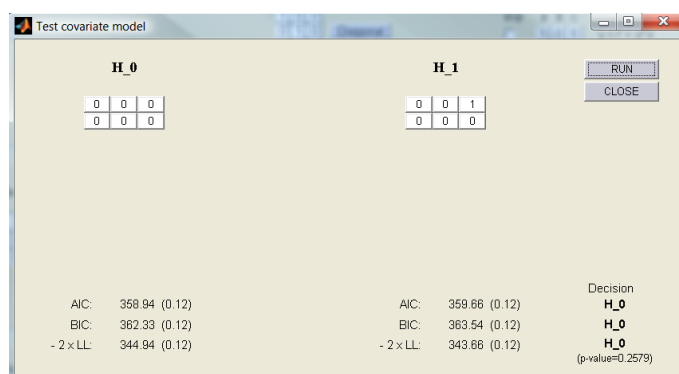
The β button allows to define the matrix A_0 and A_1 that define the covariate model under hypotheses H_0 and H_1 . Consider as an example that we want to test whether the clearance of a subject is function of his weight. Thus, assuming that the absorption rate and the volume are not function of any covariate under both hypotheses, we want to test model H_1 against model H_0 defined as follows:

H_0			H_1		
0	0	0	0	0	1
0	0	0	0	0	0

The other parameters used for the model and the algorithm are those defined in the main MONOLIX window.

The maximum likelihood estimate and the likelihood are computed under both hypotheses. For both hypotheses, the AIC and BIC criteria are displayed, together with the *deviance* ($-2 \times \log \ell(y; \hat{\theta})$). The brackets contain the s.e. of these statistics. The Likelihood Ratio Test (LRT) is performed and the level of significance (*p-value*) is displayed. Here, the log-likelihood is estimated using a Monte-Carlo Importance Sampling algorithm. The Monte-Carlo size is defined as the “LL” size in the MONOLIX window.

▷ *theophylline example*:



H_0			H_1				
0	0	0	0	0	1		
0	0	0	0	0	0		
AIC: 358.94 (0.12)			AIC: 359.86 (0.12)			Decision	
BIC: 362.33 (0.12)			BIC: 363.54 (0.12)			H_0	
- 2 x LL: 344.94 (0.12)			- 2 x LL: 343.86 (0.12)			H_0	
						H_0	
						(p-value=0.2579)	

Here, AIC, BIC and the LRT agree with the Wald test to conclude that $\beta_{(WEIGHT,CL)}$ is not significant (then, there is no significant effect of the weight on the clearance).

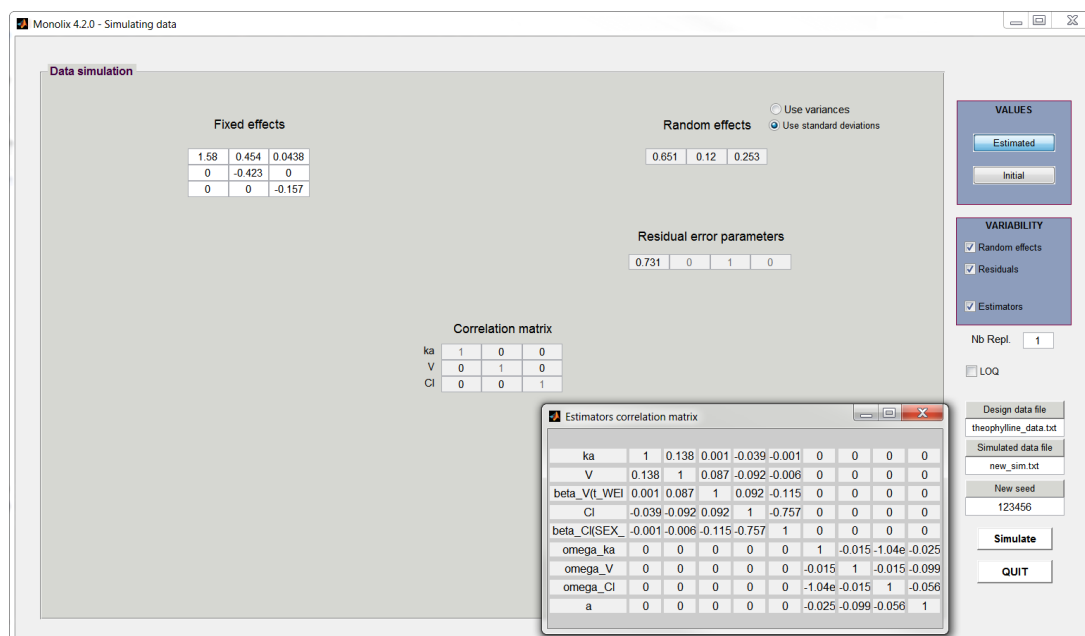
The η button allows to define the structure of the covariance matrix Ω_0 and Ω_1 of the random effects under hypothesis H_0 and H_1 .

The ϵ button allows to define the residual variance models under hypothesis H_0 and H_1 .

A file is generated for each test with the estimations for each hypothesis test and the comparison results.

3.10 Simulation

Use the  button to open the simulation interface in order to create one or several simulated datasets.



From this interface you can simulate new datasets.

A set of (\tilde{y}_{ij}) is simulated using the regression variables (x_{ij}) and the covariates of the original dataset. The simulated data has exactly the same format than in the original data. The only difference is that the observed (y_{ij}) are replaced with the simulated ones (\tilde{y}_{ij}) .

You are free to set the population parameters yourself or you can use the estimated values, or the initial values given in the main interface.

By clicking on the button **Design data file**, you can also change the design (number of subjects, observation times, covariate values, etc) used for simulations by selecting a new dataset from this interface. However, the chosen dataset must contain exactly the same covariates that were used in the main interface (same name and type among categorical or continuous).


It is also possible to simulate several replicates with the same parameters. All the replicates are stored in the same file and a column **REPL** (for replicate) is added.


You can specify different sources of variability for simulating this dataset: random effects, residual error, uncertainty of the estimates (only if the parameters were estimated).

If you want to simulate with censored data, select **LOQ**. The opened dialog allows to select the censoring intervals. For each output, you can enter one number to specify the LOQ so the observations are censored if $Ysim \leq LOQ$, or an interval $[A, B]$ to censor if $A \leq Ysim \leq B$.

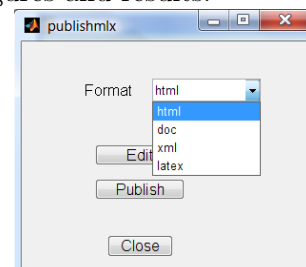
3.11 Publishing the outputs

Beware: this feature is not available with the stand-alone version of MONOLIX.

Use the  button to generate a report on your project, including figures and results.

Use the  button to modify the MATLAB script which selects the different procedures that will be executed.



You can generate your report as a `html`, `doc`, `xml` or `latex` file and all the files will be saved in the results folder.



3.12 The results folder

As explained before, several output files are generated by the different tasks. All of them are saved in the result folder chosen by the user (see [Section 3.7.5](#)). Here we make a summary of some of those files and when are they generated.

1. With the population parameters estimation (button):

- `results.mat` is a binary "MAT-file" file that contains all the results
- `project.mat` and `project.xmlx` contain the project respectively in `.mat` and `.xmlx`. Thus, this project can be reloaded with the  button and running the SAEM algorithm with the  button will reproduce the same results.
- `pop_parameters.txt` contains the estimated population parameters.
- `saem.png` is a PNG file where the sequence of estimates (θ_k) is plotted.

Some of the variables stored in this `results.mat` are:

`fixed_effects` : the estimated fixed effects
(for the log-parameters in the case of log-normal distributions)
`cov_random` : the estimated covariance matrix of the random effects
`g_abc` : the estimated parameters of the error model

2. With the Fisher information matrix estimation (button):

- The results of population parameters estimations are completed with the estimated squared errors (s.e), the relative s.e and the p-value for covariates coefficients as shown in [Section 3.7.2](#) and appended to the file `pop_parameters.txt`.

3. With the individual parameters estimation (button):

- A file `indiv_parameters.txt` which contains the estimated individual parameters is generated: the conditional modes ($m(\phi_i|y;\hat{\theta}), 1 \leq i \leq N$) and/or the conditional expectation

$(\mathbb{E}(\phi_i|y; \hat{\theta}), 1 \leq i \leq N)$ with the conditional standard deviations $(\sqrt{\text{Var}(\phi_i|y; \hat{\theta})}, 1 \leq i \leq N)$ and the covariates.

- A new file `indiv_eta.txt` that contains the estimated random effects is generated: the conditional modes $(m(\eta_i|y; \hat{\theta}), 1 \leq i \leq N)$ and/or the conditional expectation $(\mathbb{E}(\eta_i|y; \hat{\theta}), 1 \leq i \leq N)$ with the conditional standard deviations $(\sqrt{\text{Var}(\eta_i|y; \hat{\theta})}, 1 \leq i \leq N)$ and the covariates.
- The file `simulatedPriors.txt` is created whenever it is estimated the posterior distribution of parameters with priors and the conditional distributions (means and s.d) are estimated. It contains some samples of those parameters simulated following the posterior distribution

4. With the log-likelihood estimation (button

- the value of the $(-2)\log$ -likelihood together with AIC, BIC are added at the bottom of the file `pop_parameters.txt`.

The last three algorithms complete the `results.mat` file with their own results, adding fields like

<code>se_fixed</code>	: the standard-errors of the estimated fixed effects
<code>pv_fixed</code>	: the p-values for the estimated fixed effects (for the log-parameters in the case of log-normal distributions)
<code>se_random</code>	: the standard-errors of the diagonal elements of this estimated covariance matrix
<code>se_g_abc</code>	: the standard-errors of the estimated parameters of the error model
<code>logl</code>	: the estimated log-likelihood
<code>condmode_param</code>	: the individual conditional mode of the parameters $\arg \max_{\psi} \mathbb{P}(\psi y)$
<code>condexp_param</code>	: the individual conditional expectation of the parameters $\mathbb{E}(\psi y)$
<code>condsd_param</code>	: the individual conditional standard errors of the parameters

5. With the results (button:

Produced ASCII table files if the corresponding tables were selected (see [Section 3.8.2](#)):

- `predictions.txt` contains `Observation times` table.
- `finegrid.txt` contains `Fine-grid times` table.
- `fulltimes.txt` contains `Fine-grid times` table.
- `individualContributionToLL.txt` contains `LL individuals contribution` table.
- `covariatesSummary.txt` contains `Covariates summary` table.

Produced graphic files:

Depending on the chosen figure format (see [Section 4.14](#)) you will have

- for Postscript (ps format):

- `results.ps` includes a selection of graphics: spaghetti-plots, residuals, observation vs. predictions, etc.
- `individual_fits.ps` includes the individual fits for all subjects, plotted in several pages.
- Any other format:
 - One file for each graphic and several files for `individual fits` graphic, according to the number of subjects in the dataset.

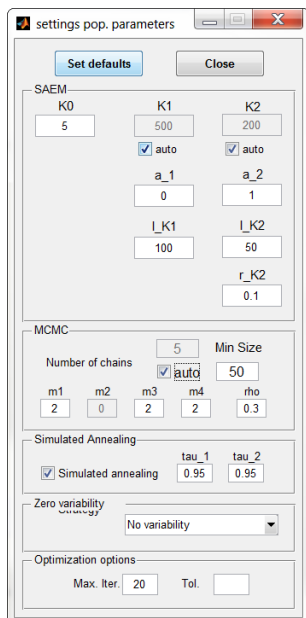
5. Other files:

- The hypothesis tests (buttons $H_0 H_1$, $H_0 H_1$, $H_0 H_1$) generate files with each test results.
- Publish report files
- Simulated files
- One .zip file for each run containing the corresponding results if timestamping has been activated (see [Section 4.14](#)).

Note: The graphics are saved like they are produced, i.e using current graphics settings (see [Section 3.8.4](#)) and window size. You can change the settings and set the figure container size before re-run the **Results**. Or you can modify the graphic window itself and save it with the menu **Save As**.

3.13 Settings

3.13.1 The population parameters estimation



The 'settings pop. parameters' dialog box includes the following settings:

- SAEM:**
 - K0:** 5
 - K1:** 500, ☒ auto
 - K2:** 200, ☒ auto
 - a_1:** 0, **a_2:** 1
 - l_K1:** 100, **l_K2:** 50
 - r_K2:** 0.1
- MCMC:**
 - Number of chains:** 5, ☒ auto
 - Min Size:** 50
 - m1:** 2, **m2:** 0, **m3:** 2, **m4:** 2, **rho:** 0.3
- Simulated Annealing:**
 - ☒ Simulated annealing
 - tau_1:** 0.95, **tau_2:** 0.95
- Zero variability:**
 - Zero variability: No variability
- Optimization options:**
 - Max. Iter:** 20, **Tol.:**

K_0 is the number of burning iterations, K_1 and K_2 the numbers of SAEM iterations. If **auto** is checked, K_1 and K_2 are automatically adjusted.

The sequence of stepsizes (γ_k) decreases as $1/k^{a_j}$, $j = 1, 2$. If $a_1 = 0$ and $a_2 = 1$, then $\gamma_k = 1$ during the first K_1 iterations and $\gamma_k = 1/(k - K_1 - 1)$ during the next K_2 iterations.

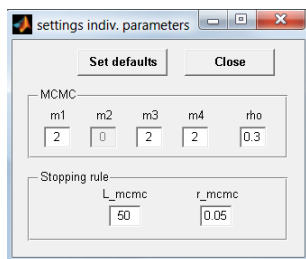
l_{K_1} , l_{K_2} and r_{K_2} define the stopping rules when **auto** is checked. The number of iterations K_1 increases with l_{K_1} ; K_2 increases with l_{K_2} and decreases with r_{K_2} .

The default number of Markov chains is $L = 1$.

m_1 , m_2 , m_3 and m_4 are the numbers of transitions of the four different kernels used in the MCMC algorithm. The default value of m_2 is 0. Indeed this transition is recommended only in some specific cases, when the observed kinetics are very different (i.e. viral kinetics of responders, non responders, rebounders, ...).

When Simulated Annealing is checked, the temperature decreases as τ_1^k and τ_2^k . Note that you can use $\tau_j > 1$ to force the estimated variance(s) to increase from a small initial value to the estimated value. Then, $\tau_2^k > 1$ can be used if you want to obtain fits as good as possible and $\tau_1^k > 1$ if you want to obtain inter-subject variability as small as possible.

3.13.2 The individual parameters estimation



The 'settings indiv. parameters' dialog box includes the following settings:

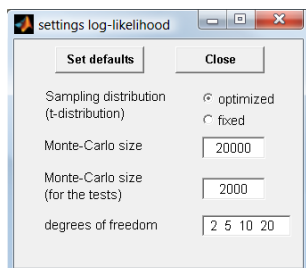
- MCMC:**
 - m1:** 2, **m2:** 0, **m3:** 2, **m4:** 2, **rho:** 0.3
- Stopping rule:**
 - L_mcmc:** 50, **r_mcmc:** 0.05

MCMC is used to estimate the conditional distributions of the individual parameters when **Estimate the cond. means and s.d.** is checked.

m_1 , m_2 , m_3 and m_4 are the numbers of transitions of the four different kernels used in the MCMC algorithm.

L_{mcmc} and r_{mcmc} define the stopping rule of the MCMC algorithm. The number of iterations of MCMC increases with L_{mcmc} and decreases with r_{mcmc} .

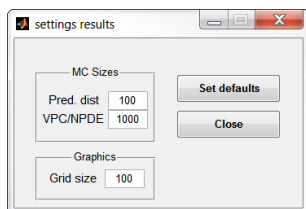
3.13.3 The log-likelihood



A t -distribution is used as proposal. The degrees of freedom number of this distribution can be either fixed or optimized. In such a case, the default possible values are 2, 5, 10 and 20 $d.f.$.

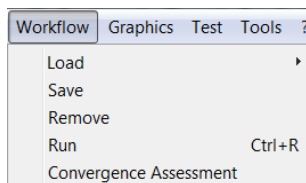
A distribution with a small number of $d.f.$ (i.e. heavy tails) should be avoided in case of stiff ODE's defined models. We recommend to set $d.f. \geq 5$.

3.13.4 The results



You can set the Monte-Carlo sizes used for the VPC and NPDE (default value is 500) and for Prediction distribution (default is 100). You can also set the grid size used for graphics and tables using continuous grids (like individual fits and prediction distribution).

3.13.5 Predefined scenarios



MONOLIX proposes the possibility to create, load and save predefined sets of settings called workflows. Each workflow include the scenario, the algorithms and results settings. Four of them are proposed but users can define new ones by selecting all the settings for the current project, and then saving it as workflow.

Chapter 4

Advanced features

The different features of MONOLIX 4.3.0 are illustrated with several examples available in the Demos folder.

4.1 Libraries of models

Several libraries with a large collection of pharmacokinetic and pharmacodynamic models are included in the MONOLIX software (in the folder `libraries`):

- **PK library:** 1cpt, 2cpt and 3cpts PK models; linear and nonlinear eliminations; single dose, multiple dose or steady-state designs.
- **PKe0 library:** PK models (1cpt and 2cpt) with an effect compartment (to be used with a PD model).
- **PD library:** immediate response and turnover PD models.
- **VK library:** some basic viral kinetic models (HIV and HCV).
- **Discrete library:** some basic models for count data, ordered categorical data, and repeated time to event (RTTE) models.



To use one of these models, click on the button `structural model`, or right-click on the list of currently selected models to open the `Model List` window. Select the library with the button `Monolix Library` and select one model from the list.

Of course, you can create your own libraries. If you use the MATLAB version of MONOLIX, you can write new models with MATLAB or MLXTRAN. If you use the standalone version, you should write your models with MLXTRAN. See `modelMLXTRANtutorial.pdf` for more details.

4.2 Pharmacokinetic and pharmacodynamic data

warfarin: warfarin_PKPD1_project, warfarin_PKPD2a_project,
warfarin_PKPD2b_project, warfarin_PKPD3_project, warfarin_PKPD4_project



It is possible to simultaneously analyze pharmacokinetic and pharmacodynamic data, with a pharmacokinetic function f_{PK} and a pharmacodynamic function f_{PD} . In this context,

- The observation column of the dataset contains both pharmacokinetic and pharmacodynamic observations. The YTYPE column indicates the type of each observation (1=PK and 2=PD),
- If you are using .m models of the library, the output of the f_{PK} function is an input of the function f_{PD} :
 1. Choose first the f_{PK} function and choose the corresponding error model g_{PK} .
 2. Then use the  button to add the second model f_{PD} and choose the corresponding error model g_{PD} . It is possible to remove the selected model from the MONOLIX window using the  button. A right click on the list, after selecting the name of the model, allows to change this model,

Examples: warfarin_PKPD1_project, warfarin_PKPD2a_project

- If you write your own model using MLXTRAN, you need to define two outputs (one to fit the data defined with YTYPE=1 and one to fit the data defined with YTYPE=2).

Examples: warfarin_PKPD2b_project, warfarin_PKPD3_project,
warfarin_PKPD4_project

- The individual parameter vector φ is the union of the PK and PD parameters,
- Set the initial values for the fixed effects and the variance of random effects as usual, Set the initial values of the two error models,
- Run the estimation algorithm,
- The button  displays the spaghetti plots for both types of observations in two figures.
- The button  displays the chosen result figures and tables (see [Section 3.8.4](#)) for each output.

4.3 Using priors on a fixed effect

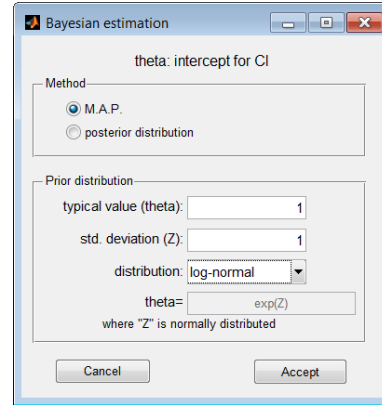
When you select to define a prior distribution on a fixed effect, a new window will open to define its law. As for individual parameters, you can choose from some given distributions (normal, log-normal, logit-normal and probit-normal) or you can define your own as a transform T of a gaussian distributed variable:

Assuming θ to be the chosen fixed effect

$$\theta = t(Z)$$

where $Z \sim \mathcal{N}(\mu_Z, \sigma_Z^2)$ is a gaussian distributed variable.

You must specify m_θ the typical value of θ ($\mu_Z = t^{-1}(m_\theta)$) and the the variance or standard deviation of Z . By default, the current initial value will be used as typical value. Also, selecting a different typical value will set it automatically as initial value for the corresponding parameter.



You can also choose between two estimation methods: M.A.P. and posterior distribution.

Note: MONOLIX can estimate the M.A.P only for

- gaussian priors if θ is a covariate coefficient (β)
- priors with same distribution than the corresponding individual parameter if θ is an intercept. For instance, if V is set as **log-normal** distributed, then the M.A.P of

$$\theta = \text{intercept of } V$$

can only be computed for **log-normal** priors on θ .

4.4 Categorical covariate model

EXAMPLES

Categorical covariates: PDsim1_project, PDsim2_project, PDsim3_project, phenorbabital2_project

Mixed effects models categorical covariates are described in [Section A.2.3](#).

PDsim1_project, PDsim2_project, PDsim3_project are three pharmacodynamic examples. PDsim1_data, PDsim2_data, PDsim3_data contain simulated data obtained using an Emax model.

SEX is used as a categorical covariate: SEX= 0 for males and SEX= 1 for females.

Different models are used C50:

- PDsim1_data and PDsim2_data:

$$\log(C50_i) = \log(C50_{pop}) + \beta \mathbb{1}_{SEX_i=1} + \eta_{C50,i}$$

PDsim1_data was generated using $\beta = 0$ while PDsim2_data was generated using $\beta = 0.4$.

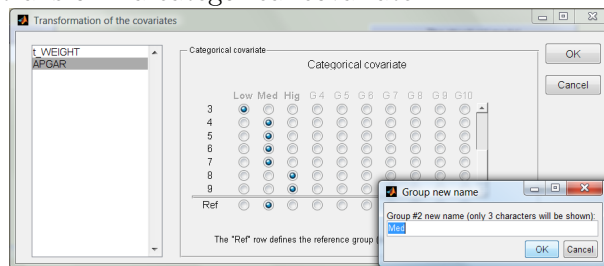
- PDsim3_data:

$$\log(C50_i) = \log(C50_{pop}) + \eta_{C50,i}$$

where $Var(C50_i) = (0.1)^2$ if $SEX_i = 0$ and $Var(C50_i) = (0.3)^2$ if $SEX_i = 1$.

phenobarbital2_project illustrates how to transform a categorical covariate.

Here, the *APGAR* score is classified into 3 groups: Low ($APGAR \leq 3$), Medium ($4 \leq APGAR \leq 7$), High ($APGAR \geq 8$). Just click on the name of the groups to rename them.



4.5 Model with censored data

4.5.1 Modeling BLQ data

EXAMPLES

theophylline: theophylline_cens1_project, theophylline_cens2_project


Mixed effects models with BLQ data are described [Section A.5](#).

As an illustration, we will consider a censored version of the theophylline data.

The data files `theophylline_cens1_data.txt` and `theophylline_cens2_data.txt` are the same as the original data file `theophylline_data.txt` used in the previous section but with several left-censored observations (y_{ij}). The limit of quantification (LOQ_{ij}) can be the same for all the patients (see `theophylline_cens1_data.txt`) or it can vary from one patient to another, and even from one observation time to another (see `theophylline_cens2_data.txt`). In the data set which includes BLQ data, the censored observations are replaced with the *LOQ* values and a new column **CENS** is added with a binary variable equal to 1 if the observation is censored and 0 otherwise.

ID	DOSE	TIME	Y	WEIGHT	CENS
1	4.02	0	.	79.6	0
1	.	0.25	3.00	79.6	1
1	.	0.57	6.57	79.6	0
⋮	⋮	⋮	⋮	⋮	⋮
2	4.4	0	.	72.4	0
2	.	0.27	2.5	72.4	1
2	.	0.52	7.91	72.4	0
⋮	⋮	⋮	⋮	⋮	⋮
12	5.3	24.15	3.00	60.5	1

In the **Data Information** window, this new column is referenced with the **CENS** header.

Then, MONOLIX can be used as usual. The button  displays the same figures as the usual MCMC-SAEM with points associated to a censored observation displayed differently.

4.5.2 Modeling interval censored data

EXAMPLES

censored_data: censored_project

In order to handle right-censored data, the column **CENS** can take -1 as value to tell that $y_{ij}^{(cens)} \geq LOQ_{ij}$ where LOQ_{ij} is the value given in the dataset on the corresponding line of column **Y**.

To give both limits of interval censored data, a new column **LIMIT** is needed to specify the lower limit while the **Y** value gives the upper limit. For this, the **CENS** column must be 1.

For instance, assume that we have the following dataset

(1)	ID	TIME	AMT	Y	YTYPE	LIMIT	CENS
(2)	1	0	50.00
(3)	1	0	.	90	2	.	-1
(4)	1	0.5	.	2	1	.	1
(5)	1	1	.	2	1	1	1
	\vdots	\vdots	\vdots	\vdots	\vdots	\vdots	\vdots

Line (3) says that the observation of type $YTYPE = 2$ at time 0 is right-censored ($y_{11}^{(2)} \geq 90$), line (4) says that the first observation of type $YTYPE = 1$ is left-censored ($y_{11}^{(1)} \leq 2$), and line (5) says that the observation is interval censored ($y_{12}^{(1)} \in (1, 2)$) because of the existence of a numerical value in column **Limit**

4.6 Model with inter-occasion variability

EXAMPLES

IOV: iov1_project, iov2_project, iov3_project, iov4_project

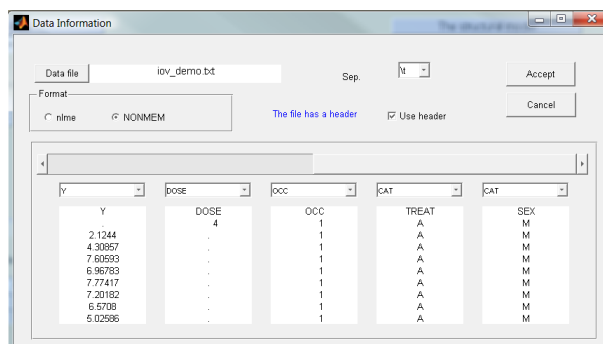
Mixed effects models with IOV are described [Section A.6](#).

Occasions are defined in the datafile, using a column **OCC** or a column **EVID**.

Then inter-occasion variability (IOV) can be introduced in the model with the **IOV** button. The covariate model and the covariance structure of the IOV are defined in a new window. According to the model described in [Section A.6](#), we consider two kinds of covariates. The covariates that do not change with the occasion are displayed in the main MONOLIX window and the covariates that change with the occasion are displayed in the IOV window.

Example 1: iov1_project

A cross-over study was simulated. The data set **iov1a_data.txt** contains the column **OCC** and two categorical covariates, **TREAT** for treatment and **SEX**. Since the first time for each occasion is 0, MONOLIX guesses that there is no “overlapping” between the occasions.



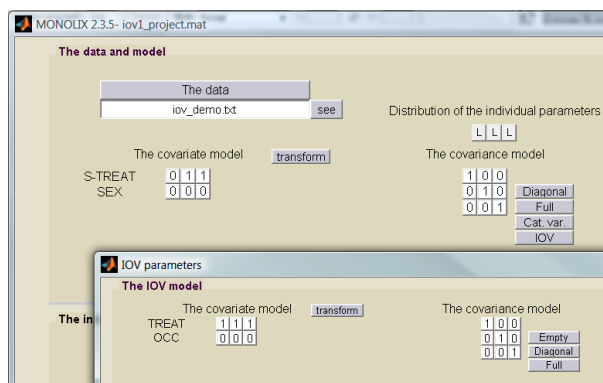
Data file: Sep:

Format: ☐ nlme ☒ NONMEM The file has a header ☒ Use header

Y	DOSE	OCC	TREAT	SEX
2.1244	4	1	A	M
4.30957	.	1	A	M
7.60593	.	1	A	M
6.96783	.	1	A	M
7.77417	.	1	A	M
7.20182	.	1	A	M
6.5708	.	1	A	M
5.02595	.	1	A	M

Here, the treatment (A or B) changes with the occasion. Thus, **TREAT** is a covariate that will appear in the IOV window as well as **OCC**. Furthermore, the sequence of treatments is not the same for all the subjects (A-B for some patients and B-A for the other ones). Thus, the treatment sequence (denoted **S-TREAT**) can be considered as a new covariate (this does not change with the occasion). MONOLIX automatically creates this new categorical covariate and displays it in the main MONOLIX window.

On the other hand, **S-OCC** is not created as a new categorical covariate because all the subjects have the same sequence 1-2 in this example.



The data and model

The data:

Distribution of the individual parameters:

The covariate model:

S-TREAT	0	1	1
SEX	0	0	0

The covariance model:

1	0	0
0	1	0
0	0	1

IOV parameters

The IOV model

The covariate model:

TREAT	1	1	1
OCC	0	0	0

The covariance model:

1	0	0
0	1	0
0	0	1

SAEM estimates the two covariance matrices and the coefficient of the different covariates:

Estimation of the population parameters

	parameter	s.e.	r.s.e.(%)	p-value	Categorical covariates
ka	: 1.51	0.083	5		TREAT
beta_ka(TREAT_B)	: 0.0225	0.042	186	0.59	Reference group: A
V	: 0.469	0.014	3		Other groups: B
beta_V(TREAT_B)	: -0.196	0.02	10	0	S-TREAT
beta_V(S-TREAT_B-A)	: 0.0388	0.038	98	0.31	Reference group: A-B
Cl	: 0.0377	0.0017	4		Other groups: B-A
beta_Cl(TREAT_B)	: -0.195	0.031	16	3.1e-010	SEX
beta_Cl(S-TREAT_B-A)	: 0.136	0.059	44	0.022	Reference group: F
					Other groups: M
omega_ka	: 0.277	0.039	14		OCC
omega_V	: 0.0971	0.016	17		Reference group: 1
omega_Cl	: 0.152	0.026	17		Other groups: 2
gamma_ka	: 0.0794	0.035	43		
gamma_V	: 0.041	0.016	39		
gamma_Cl	: 0.118	0.017	14		
a	: 0	-	-		Elapsed time is 9.05 seconds.
b	: 0.132	0.0041	3		CPU time is 8.95 seconds.
c	: 1	-	-		>>

Example 2: iov2_project

We use the same simulated data as in the previous example (`iov1_data.txt`). Here, the occasions are defined with `EVID=4` and the initial times for each occasion are arbitrary.

Example 3: iov3_project

Data with several occasions without wash-out was simulated. Here, the occasions are defined with the column `OCC`. Without `EVID=4` and with increasing times, MONOLIX guesses that there is some “overlapping” between the occasions

Important: Overlapping between occasions can only be handled with a model defined by a system of differential equations using `MLXTRAN`. Analytic solution of the PK model (*i.e.* MATLAB models of the PK library) cannot be used in this situations.

Example 4: iov4_project

There is an additional level of inter-occasion variability. Data was simulated with the following covariance structure:

$$IIV = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad IOV^{(1)} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad IOV^{(2)} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Running population parameter estimations, you will see that, for each variability level, the estimated variances are closed to 0 for those parameters that were simulated without variability at that levels.

Note: When there is `OCC` column or `EVID=4`, it is not possible to use the simulation interface, nor hypothesis tests on covariance models.

4.7 Discrete data models

EXAMPLES

discrete data: categorical1_project, categorical2_project, count1_project, count2_project, markov1a_project, markov1b_project, markov2_project, hmm0_project, hmm1_project, rtteExpo_project,
warfarin: warfarin_cat1_project, warfarin_cat2_project

Mixed effects models for discrete data are described in [Section A.7](#).

All the MLXTRAN models shown in this section are also stored in the `discreteLibrary` folder. Either MLXTRAN or MATLAB (if you are using the MATLAB version of MONOLIX) can be used to create models for discrete data. The output of the model should be the log-likelihood.

4.7.1 ordered categorical data models

In these examples, the outcome can take four possible values: 0, 1, 2, 3.

Example 1: categorical1_project

Its MLXTRAN model is `categorical1_mlxt.txt`:

DESCRIPTION: Ordered categorical model

INPUT:

```
parameter = {th1, th2, th3}
regresor   = {PER, DOSE}
```

OBSERVATION:

```
level = {
  type = categorical
  categories = {0, 1, 2, 3}
  logit(P(level<=0)) = th1
  logit(P(level<=1)) = th1 + th2
  logit(P(level<=2)) = th1 + th2 + th3
}
```

$$\begin{aligned} P(Y = 0) &= \frac{1}{1 + e^{-\theta_1}} \\ P(Y \leq 1) &= \frac{1}{1 + e^{-\theta_1 - \theta_2}} \\ P(Y \leq 2) &= \frac{1}{1 + e^{-\theta_1 - \theta_2 - \theta_3}} \end{aligned}$$

OUTPUT:

```
output = level
```

Example 2: categorical2_project

Its MLXTRAN model is `categorical2_mlxt.txt`:

DESCRIPTION: Ordered categorical model with regression variables

INPUT:

```
parameter = {th1, th2, th3, th4, th5}
regresor = {PER, DOSE}
```

OBSERVATION:

```
level = {
  type = categorical
  categories = {0, 1, 2, 3}
  logit(P(level<=0)) = th1 + th4*PER + th5*DOSE
  logit(P(level<=1)) = th1 + th4*PER + th5*DOSE + th2
  logit(P(level<=2)) = th1 + th4*PER + th5*DOSE + th2 + th3
}
```

$$P(Y = 0) = \frac{1}{1 + e^{-\theta_1 - \theta_4 PER - \theta_5 DOSE}}$$

$$P(Y \leq 1) = \frac{1}{1 + e^{-\theta_1 - \theta_4 PER - \theta_5 DOSE - \theta_2}}$$

$$P(Y \leq 2) = \frac{1}{1 + e^{-\theta_1 - \theta_4 PER - \theta_5 DOSE - \theta_2 - \theta_3}}$$

OUTPUT:

```
output = level
```

4.7.2 count data models

In these examples, the outcome can take any positive value: 0, 1, 2, 3,...

The MLXTRAN models are, respectively `count1_mlxt.txt` and `count2_mlxt.txt`.

Example 1: count1_project

DESCRIPTION: Basic Poisson model

INPUT:

```
parameter = lambda
```

OBSERVATION:

```
Y = { type = count,
      log(P(Y=k)) = -lambda + k*log(lambda) - factln(k) }
```

$$P(Y = k) = \frac{e^{-\lambda} \lambda^k}{k!}$$

OUTPUT:

```
output = Y
```

Example 2: count2_project

DESCRIPTION: Count data model, negative binomial distribution

INPUT:

```
parameter = {delta, lambda}
```

OBSERVATION:

```
Y = {
  type = count

  h1 = 1/(1+lambda*delta)
  llam = log(h1)/delta
  lh2 = log(1-h1)

  lg1 = gammaln(k+1/delta)
  lg2 = gammaln(1/delta)
```

$$P(Y = k) = \frac{\Gamma(k + 1/\delta)}{k! \Gamma(1/\delta)} (1 + \delta\lambda)^{-\frac{1}{\delta}} \left(\frac{\lambda}{\lambda + 1/\delta} \right)^k$$

```

if (k > 0)
  aux = llam + lg1 - lg2 + k*lh2 - factln(k)
else
  aux = llam
end

log(P(Y=k)) = aux
}

```

OUTPUT:
output = Y

4.7.3 discrete Markov models

For discrete Markov models, you must specify the transition probability matrix and, optionally the probability for the initial state.

Here we show two examples of models `markov1b_mlxt.txt` and `markov2_mlxt.txt` with 2 and three states respectively.

INPUT:
parameter = {p, p11, p21}

OBSERVATION:
State = {
 type = categorical
 categories = {1,2}
 dependence = Markov
 P(State=1)= p
 P(State=1|State_p=1) = p11
 P(State=1|State_p=2) = p21
}

OUTPUT:
output=State

INPUT:
parameter = {a11, a12, a21, a22, a31, a32}

OBSERVATION:
State = {
 type = categorical
 categories = {1,2,3}
 dependence = Markov
 logit(P(State<=1|State_p=1)) = a11
 logit(P(State<=2|State_p=1)) = a11+a12
 logit(P(State<=1|State_p=2)) = a21
 logit(P(State<=2|State_p=2)) = a21+a22
 logit(P(State<=1|State_p=3)) = a31
 logit(P(State<=2|State_p=3)) = a31+a32
}

OUTPUT:
output=State

4.7.4 hidden Markov models

- For $i = 1, 2, \dots, N$, let $z_i = (z_{ij}, j \geq 1)$ be a Markov Chain with memory 1 that takes its values in $\{1, 2, \dots, M\}$:

$$P(z_{ij} = m | z_{i,j-1}, z_{i,j-2}, \dots, z_{i,1}) = P(z_{ij} = m | z_{i,j-1})$$

- Let $p_{\ell mi} = P(z_{ij} = m | z_{i,j-1} = \ell)$ and $\Pi_i = (p_{\ell mi})$ be the transition matrix of the Markov Chain z_i .
- Assume that (y_{ij}) takes discrete values in $\{0, 1, 2, \dots\}$ and that

$$P(y_{ij} = k | z_{i1}, z_{i2}, \dots) = P_{\psi_i}(y_{ij} = k | z_{ij})$$

Objective: Estimate the population distributions of the transition matrices (Π_i) and the individual parameters (ψ_i).

In the following examples, mixtures of $M = 2$ Poisson distribution are used. The MATLAB models `hmm1_mlx.m` and `hmm0_mlx.m` are stored in the `discreteLibrary` folder.

Example 1: `hmm1_project`

The model `hmm1_mlx.m` assumes a HMM with $M = 2$ states

Here, $M = 2$,

$$\begin{aligned}\Pi &= \begin{pmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{pmatrix} \\ p_{11} &= \frac{1}{1 + e^{-\beta_1}} \quad ; \quad p_{12} = 1 - p_{11} \\ p_{21} &= \frac{1}{1 + e^{-\beta_1 + \beta_2}} \quad ; \quad p_{22} = 1 - p_{21}\end{aligned}$$

and 2 Poisson distributions

$$\begin{aligned}\text{if } z = 1, \quad y &\sim \text{Poisson}(\lambda_1) \\ \text{if } z = 2, \quad y &\sim \text{Poisson}(\lambda_2)\end{aligned}$$

Example 2: `hmm0_project`

Here, we use the same conditional distributions for (y_{ij}) but the (z_{ij}) are sequences of *independent* random variables (Markov chain with memory 0).

$$p_1 = \frac{1}{1 + e^{-\beta}} \quad ; \quad p_2 = 1 - p_1$$

4.7.5 repeated time to event models (RTTE)

Examples: `rtteExpo_project`, `rtteWeibull_project`

Repeated events are observed at random times between day 0 and day 365 for 500 patients. The first event which occurs after day 365 is not observed: the time of this event is censored. We consider here a very simple model with a constant hazard function

$$h(t) = H_{base}$$

In the data file `rtte_data.txt`, we use `EVENT=1,2,...` for the observed events and `EVENT=0` for the censored event:

ID	TIME	Y
1	0	0
1	153	1
1	262	2
1	365	0
2	0	0
2	34	1
2	109	2
2	365	0

The MLXTRAN model is then

DESCRIPTION: RTTE with constant hazard function

INPUT:

parameter = Te

OBSERVATION:

Event = {type=event, hazard=1/Te}

OUTPUT:

output = Event

Other hazard functions can be defined as shown in `rtteWeibull_project` demo.

Note: It is not possible to use the simulation interface for RTTE data.

4.7.6 joint modelling of continuous and discrete outputs

To illustrate the ability of MONOLIX to model jointly continuous and discrete outputs, we use the warfarin data assuming here that the PD of warfarin is an ordered categorical data with 3 possible scores: 1 if $PCA < 30$, 2 if $30 \leq PCA \leq 50$, 3 if $PCA > 50$. This new data is stored in `warfarin_cat_data.txt`.

The MLXTRAN models `oral1_categorical_mlxt.txt` and `oral1_ke0_categorical_mlxt.txt` are stored in the `libraryMLXTRAN` folder next to the project file. Both models assume that the probability of a high (resp. low) PCA decreases (resp. increases) with the concentration.

Example 1: warfarin_cat1_project

An immediate response model is used in this example:

DESCRIPTION: First order oral absorption with a lag-time, and ordered categorical data

INPUT:

parameter = {Tlag, ka, V, Cl, th1, th2, th3}

PK:

Cc= pkmodel(Tlag,ka,V,Cl)

OBSERVATION:

Level = {
type=categorical

```
categories={1,2,3}
logit(P(Level<=1)) = -th1 + th2*Cc
logit(P(Level<=2)) = -th1 + th2*Cc + th3
}
```

OUTPUT:
output = {Cc, Level}

Example 2: warfarin_cat2_project

We use the same model as previously with an additional effect compartment

DESCRIPTION: First order oral absorption with a lag-time, effect compartment,
and ordered categorical data

INPUT:
parameter = {Tlag, ka, V, Cl, ke0, th1, th2, th3}

EQUATION:
{Cc,Ce}= pkmodel(Tlag,ka,V,Cl,ke0)

OBSERVATION:
Level = {
type=categorical
categories={1,2,3}
logit(P(Level<=1)) = -th1 + th2*Ce
logit(P(Level<=2)) = -th1 + th2*Ce + th3
}

OUTPUT:
output = {Cc, Level}

Demos `pkrtteExpo_project` and `pkrtteWeibull_project` are two examples where PK data is modeled at the same time than RTTE data.

4.8 Complex residual error models

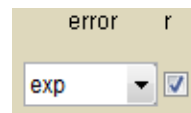
EXAMPLES

error model: `PKcorr1_project`, `PKcorr2_project`, `Emax_errorband_project`

Residual error models are described in [Section A.3](#) and their use with MONOLIX is described in [Section 3.3.7](#).

4.8.1 autocorrelated residual errors

Assuming autocorrelated residual errors is extremely easy with MONOLIX. Choose your error model as usual and just select the autocorrelation option with the checkbox:



`PKcorr1_project` and `PKcorr2_project` are two PK examples where an exponential residual error model with autocorrelated errors (ε_{ij}) is assumed:

$$\log(y_{ij}) = \log(f(t_{ij}; \psi_i)) + \varepsilon_{ij}$$

- Equally spaced sampling times are used in `PKcorr1_data`: $t_{i,j+1} - t_{ij} = 1$. Then,

$$\text{corr}(\varepsilon_{ij}, \varepsilon_{ij'}) = \rho^{|j'-j|}$$

- Irregular sampling times are used in `PKcorr2_data`. Then,

$$\text{corr}(\varepsilon_{ij}, \varepsilon_{ij'}) = \rho^{|t_{ij'} - t_{ij}|}$$

Data was simulated using $\rho = 0.5$ for both examples.

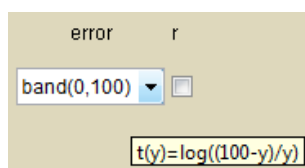
4.8.2 residual errors for bounded data

Example: `E_max_errorband_project`

We assume in this example that the data takes continuous values in $(0, 100)$. Then, we consider the following residual error model:

$$\log\left(\frac{y_{ij}}{100 - y_{ij}}\right) = \log\left(\frac{f(t_{ij}; \psi_i)}{100 - f(t_{ij}; \psi_i)}\right) + \varepsilon_{ij}$$

The error model `band(0,100)` is predefined in MONOLIX and can be selected:



4.9 Complex PK models

EXAMPLES

PK models: `admin1_project`, `admin2_project`, `infusion_2cpt_project`, `ss1_project`, `admin2_project`, `oral0_1cpt_MD_project`, `oral0_2cpt_SS_project`, `bolus_1cptMM_project`, `phenobarbital_project`

4.9.1 Complex administrations

Example 1: `admin1_project`

The data file `admin1_data.txt` contains real PK data. This example is a combination of oral and IV bolus administrations. Then the model takes into account the bioavailability.

The MLXTRAN model `admin1_mlxt.txt` is stored in the folder `libraryMLXTRAN`.

DESCRIPTION: Combination of oral and IV bolus administrations.

INPUT:

`parameter = {F, ka, V, CL}`


```

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;
; Version 1 using PK macros

PK:
compartment(amount=Ac)
absorption(adm=1, ka, p=F)
iv(adm=2)
elimination(k=CL/V)
Cc=Ac/V

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;
; Version 2 using PK macros and ODEs

;PK:
;compartment(cmt=1, amount=Ad)
;compartment(cmt=2, amount=Ac)
;iv(adm=1, cmt=1, p=F)
;iv(adm=2, cmt=2)

;EQUATION:
;k=CL/V
;ddt_Ad = -ka*Ad
;ddt_Ac = ka*Ad - k*Ac
;Cc=Ac/V

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;

OUTPUT:
output = Cc

```

Example 2: admin2_project

The data file `admin2_data.txt` contains real PK data. This example is a combination of 3 oral and 1 infusion administrations. Then the model takes into account the 3 bioavailabilities. The MLXTRAN model is `admin2_mlxt.txt`.

4.9.2 Steady-state

Example: ss1_project

The data file `ss1_data.txt` contains real PK data. This example is a combination of single dose and steady-state.

MLXTRAN models do not handle steady state administrations, and PK library models only handles this kind of doses, when all the subjects have exactly one steady doses. That is why, MONOLIX adds some doses artificially as an approximation of the steady state, converting the doses to the multiple doses case, but ensuring that no doses are added before a previous dose, event or observation of each subject. You can define the maximum number of doses that should be added in the preferences file (see [Appendix C](#)).

Note: Steady-state doses are treated like if there were a new occasion with `EVID= 4`. That means that it is possible to add inter-occasion variability and that it will not be possible to use the simulation interface nor the hypothesis test on covariance model.

4.10 Mixture models and model mixtures

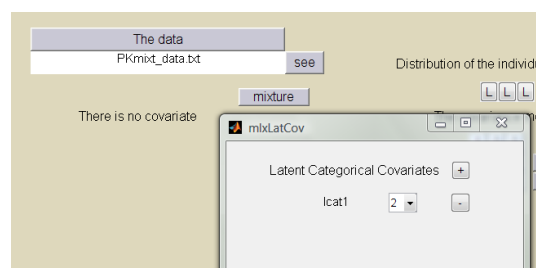
EXAMPLES

mixtures: PKmixture_project, bsmm_project, wsmm_project

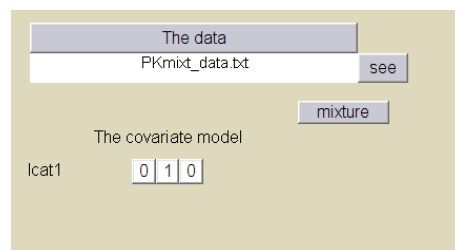
Mixture models and mixture of models are described in [Section A.8](#).

4.10.1 Mixture models

Click on the **mixture** button to create latent covariates and define the number of categories for each latent covariate.



Then consider these latent covariates that you have created as a categorical covariate and define your covariate model as usual.



See PKmixture_project as an illustrative example: PK data were simulated using a one compartment model and assuming two categories for the volume ($\beta = 0.5$). In this simulated example, the column **GROUP** contains the labels (*i.e.* the groups), but the column **GROUP** is set to **IGNORE**. Project PKgroup_project uses the same data file and the same model, but using the known categorical covariate (setting **GROUP** to **CAT**). Then, a comparison of the results provided with these two projects can be used to validate the proposed methodology for mixtures.

Similar exercises can easily be done with the examples provided for categorical covariates in [Section 4.4](#).

4.10.2 Model mixtures

Between subjects model mixtures (BSMM) and within subjects model mixture (WSMM) must be defined in the MLXTRAN file using the reserved key-words **BSMM** or **WSMM** (see the examples below).

On the other hand, the statistical models (defined with the Graphical User Interface) are slightly different:

- BSMM assumes no inter-individual variabilities for the proportions of each group (*i.e.* the probabilities to belong to the different groups)

- WSMM assumes inter-individual variabilities for the proportions of each model.

bsmm_project is an example of BSMM.

Probabilities p and $1 - p$ are associated to models f_1 and f_2 . Here, p is an unknown population parameter (i.e. with no inter-individual variability).

The MLXTRAN file **bsmm_mlxt.txt** uses the reserved key-word BSMM.

DESCRIPTION: Between subject model mixture

INPUT:
parameter = {a, b, c, p}

EQUATION:
f1 = a
f2 = b*exp(-c*t)
f=bsmm(f1, p, f2, 1-p)

OUTPUT:
output = f

wsmm_project is an example of WSMM.

Proportions p and $1 - p$ are associated to models f_1 and f_2 . Here, p is an individual parameter logit-normally distributed with some inter-individual variability (to be estimated).

The MLXTRAN file **wsmm_mlxt.txt** uses the reserved key-word WSMM.

DESCRIPTION: Within subject model mixture

INPUT:
parameter = {a, b, c, p}

EQUATION:
f1 = a
f2 = b*exp(-c*t)
f=wsmm(f1, p, f2, 1-p)

OUTPUT:
output = f

4.11 Tables

The  button can generate some tables (see [Section 3.8.2](#)) containing several informations: predictions, residuals,...

It is possible to include several additional columns in those tables by appending a **table** keyword in section **OUTPUT**: at the end of the MLXTRAN script file as explained in MLXTRAN models documentation.

For each variable set in **table**, a column will be created with the values of those variables for each estimator of the individual parameters.

For instance, if you want to include the volume and the clearance used to compute the predictions, append the line

```
table={V,C1}
```

to the section **OUTPUT**: of the MLXTRAN model.

4.12 Using MONOLIX in MATLAB command line or scripts

It is provided some MATLAB commands in order to access to the functionalities of MONOLIX from MATLAB command line. It is useful when it is not desired or possible to use the software interface. It allows also to write some MATLAB scripts to, for instance, estimate population parameters for several projects.

Important: There are two important things to know when using MONOLIX in command line

- The command line functions should not be used at the same time that the main interface (in particular methods that generate graphics). It is recommended also to close all the figures obtained for one project before creating new ones.
- Users under floating licenses must be aware that a token is reserved from first use of MONOLIX commands, and it must be freed manually. For that, you can close MATLAB or call
» `clear classes;`

As explained in [Chapter 3](#), MONOLIX requires a project and for that we provide the class `MonolixProject`.

You can create one from any MONOLIX project file

```
» aMonolixProject = MonolixProject('Path/to/myProject.mlxtran');
```

or you can load a new one if the object is already created

```
» aMonolixProject = MonolixProject('Path/to/myProject1.mlxtran');
```

```
» ...
```

```
» aMonolixProject.load('Path/to/myProject2.mlxtran');
```

Once the project created, the class `MonolixProject` proposes methods to:

- 1) define a scenario / workflow:
 - » `aMonolixProject.setSaem()`: to include or not population parameters estimation on the scenario. Computes also a first, rough, estimation of the conditional mean and conditional variance of the individual parameters.
 - » `aMonolixProject.setFisher()`: to define if Fisher information matrix estimation (and so standard error of estimates) should be included in the scenario and which algorithm (linearization or stochastic approximation) must be used.
 - » `aMonolixProject.setIndiv()`: to include or not individual parameter estimators and says which estimator to compute among *conditional mode* and *conditional mean* (both can be estimated at the same time). In the second case, it estimates also the conditional standard deviation and variance.
 - » `aMonolixProject.setLogLikelihood()`: to include or not the log-likelihood estimation and specify the algorithms to use between linearization and importance sampling. Both can be estimated at the same time.
 - » `aMonolixProject.setGraphics()`: to include or not the graphics and tables generation on the scenario. Allows also to say which graphic to create and/or save and which tables should be created. You can also choose the graphic format to be used for saved figures.
- 2) execute a scenario / workflow:

- » `aMonolixProject.run()`: runs the project scenario as explained in [Section 3.7.6](#).
- 3) execute individual tasks:
 - » `aMonolixProject.runSaem()`: executes only the population parameters estimation
 - » `aMonolixProject.runFisher()`: executes only the Fisher information matrix estimation
 - » `aMonolixProject.runIndiv()`: executes only the individual parameters estimation.
 - » `aMonolixProject.runLogLikelihood()`: executes only the log-likelihood estimation.
 - » `aMonolixProject.runGraphics()`: produce graphics and results tables.
 - » `aMonolixProject.convergenceAssessment()`: executes the convergence assessment tool of the algorithms as described in [Section 3.7.7](#) with default arguments. It can be specified the number of replicates, the parameters to simulate the initial values, and the intervals for simulation. It returns the `.mat` file holding the results.
 - » `aMonolixProject.simulationEstimation()`: executes a project scenario on the original dataset and on several new datasets simulated using the previously estimated parameters. It returns a structure with all estimations so the users can make their own analysis. This tool can not be used with *Event* observations type, and do not simulate censored data. It allows to specify the number of replicates, the sources of variability (estimator uncertainty, individual parameter model, etc), among others. In order to reproduce the same simulated datasets, you can specify also the `seed` and/or random number generator stream (see `RandStream` help in matlab).
 - » `aMonolixProject.runSimulation()`: allows to simulate a dataset. Several options are possible in order to choose the variability sources, the design, the population parameters, etc.
- 4) control the display:
 - » `aMonolixProject.toggleFigures();` sets the display configuration when individual task or complete scenario is ran.
Note: if you are working in a no-desktop environment, you should enter
» `aMonolixProject.toggleFigures('OFF');`
- 5) manage objects:
 - » `aMonolixProject.load()`: see hereabove
 - to save the project in a new directory / file enter:
» `aMonolixProject.save('Path/to/myNewProject.mlxtran');`
 - to overwrite the original project file:
» `aMonolixProject.save();`

- 6) miscellaneous:

- » `folder=aMonolixProject.getResultsFolder();` returns the folder in which all the result files are saved (see description in [Chapter 3](#))
- » `aMonolixProject.setResultsFolder('Directory',newfolder);` to define the folder where the result files will be saved.

For further details on the `MonolixProject` class, or to see the list of available methods, type
» `doc MonolixProject`

or,
» `help MonolixProject`

In order to have more information about a given method and its arguments, type

» `help MonolixProject/method`

Important: The old functions proposed to user to create its own scripts are deprecated and they will be removed in a future version. In order to adapt their scripts to MONOLIX evolution, the function `ver` should be used to know the MONOLIX version from MATLAB command line:

» `v=ver('monolix');`

» `v.Version`

For older versions of MONOLIX, MATLAB function `ver` will return empty (`[]`).

Is it also possible to know if MATLAB version is compatible with the MONOLIX package that has been installed. For instance

» `if mlxIsMatlabCompatible();error('Wrong Matlab version');end`

4.13 Full script projects

As said before, there are several formats to save your projects. Besides the binary `.mat` format, MONOLIX proposes a human readable ASCII file with `.mlxtran` extension, and an XML-like format with `.xmlx` extension.

Saving a project in the MLXTRAN format will create two `.xmlx` files with the advanced algorithm and graphics settings and the `.mlxtran` file with the description of the project (statistical model, dataset definition, structural model, etc):

```
; this script is generated automatically
```

```
DESCRIPTION:
```

```
warfarin_PK_project.mlxtran
```

```
DATA:
```

```
path = "%MLXPROJECT%/",  
file = "warfarin_data.txt",  
headers = {ID,TIME,DOSE,Y,YTYPE,COV,COV,CAT},  
columnDelimiter = "\t"
```

```
VARIABLES:
```

```
age [use=cov],  
sex [use=cov, type=cat],  
wt,  
t_wt = log(wt/70) [use=cov]
```

```
INDIVIDUAL:
  Cl = {distribution=logNormal, covariate=t_wt, iiv=yes},
  V = {distribution=logNormal, covariate=t_wt, iiv=yes},
  ka = {distribution=logNormal, iiv=yes},
  tlag = {distribution=logNormal, iiv=yes}

STRUCTURAL_MODEL:
  file = "oral1_1cpt_TlagkaVC1",
  path = "%MLXPATH%/libraries/PKLibrary",
  output = {Cc}

OBSERVATIONS:
  concentration = {type=continuous, prediction=Cc, error=combined1}
  .
  .
  .
```

In the case that the two configuration files are missing, a warning will appear when loading the project and MONOLIX will use the defaults settings. For description on how to write your own MLXTRAN projects, see [ProjectMLXTRAN.pdf](#).

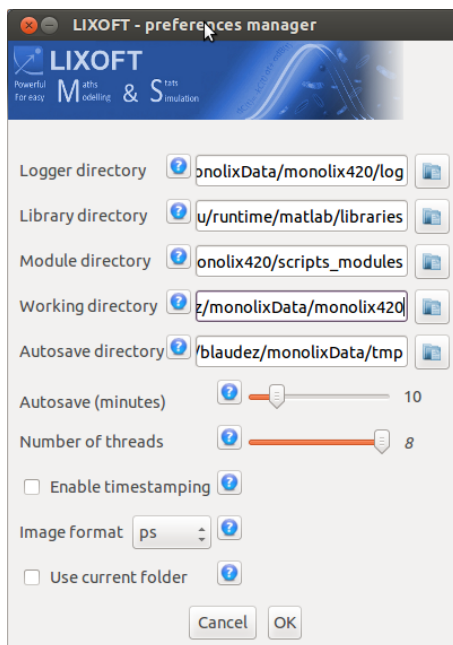
The XML-like format (.xmlx extension) is composed by only one file containing all the project information

```
<monolix>
  <project name="warfarin_PK_project.xml">
    <covariateDefinitionList>
      <covariateDefinition columnName="wt" name="t_wt" transformation="log(cov/70)" type="continuous"/>
      <covariateDefinition columnName="age" type="continuous"/>
      <covariateDefinition columnName="sex" type="categorical">
        <groupList>
          <group name="0" reference="true" values="0"/>
          <group name="1" values="1"/>
        </groupList>
      </covariateDefinition>
    </covariateDefinitionList>
    <settings>
      <tasks>
        <scenario computeResults="reduced" estimateFisherInformationMatrix="true"
          estimateIndividualParameters="true" estimateLogLikelihood="false" estimatePopulationParameters="true"/>
        <individualParameterAlgorithms conditionalDistribution="false" conditionalMode="true"/>
        <logLikelihoodAlgorithms importantSampling="true" linearization="true"/>
        <fisherInformationMatrixAlgorithms linearization="true"/>
      </tasks>
      <options>
        <estimateVariances value="true"/>
        <showStandardErrorsInPercents value="true"/>
        <resultFolder uri="%MLXPROJECT%/warfarin_PK_project" value="automatic"/>
      </options>
    </settings>
  </project>
</monolix>
```

4.14 Preferences

There are several preferences that can be customized by each user. They are stored in `'/Path/To/.../lixoft/monolix/config/preference.xmlx'` and are loaded at the start of MONOLIX. Some of them can be set from a dialog box. It can be opened from the 'Tools' menu: It allows to personalize some user directories:

- log files
- structural model libraries
- module directory (i.e. the directory containing the structural built from MLXTRAN script files)
- working directory : generally the directory containing the projects



and also:

- to limit the number of threads used by MLXTRAN (structural model) - by default this maximum is the number of logical processors.
- to enable timestamping: backup of the current state of the project results folder saved in results directory as a zip file.
- to configure the saved graphics format (png, ps, jpg, bmp, tiff). Notice the 'ps' file allows to create a single file for several graphics, unlike the other formats which create one file for each graphic.
- to tell MONOLIX to use the current folder as the default folder for all the directory related dialog boxes.

Several other options are available but they must be modified directly on the file. They are divided in two categories: graphic and session related preferences. You will find more details about the content of this file in [Appendix C](#).

For fast reference we mention here some of the session related settings that can not be modified with that dialog box.

- **historic_size:** size of the historic list for project files, and structural models.
- **editor:** text editor used to edit MLXTRAN models. It could be set also with `[...]` button in ModelList interface (see [Section 3.3.2](#)).

- **lockModels**: set to 1 to hide all the options related to structural model modification: options **Compile** and **Edit** on context menu on the main interface, and buttons **New**, **Modify**, **Edit**, **Compile** on the model selection interface.
- **modelFilter**: select the default filter for the structural model: use **m**, **mlxtran** or **none** to filter on **.m** files, **MLXTRAN** files or to not filter at all.

Others settings allows to define installation preferences and are stored in the file **system.xmlx** which is located in **config** on the MONOLIX installation folder (**'/Path/To/runtime/config'**). This file is shared by all the users and administration rights may be needed to modify it.

They include:

- **userPath** : select the default path of the **'monolixData'** directory. The path is set by default to **'%USERPROFILE%'** under Windows or **'\$HOME'** under Linux. If this setting is changed, make sure to keep a user-specific path.
- **compiler** : under Linux OS, it is possible to choose the embedded compiler of MONOLIX (this setting is located in the file **'system.xmlx'**). Set the argument **embed** to true, if the embedded compiler has been chosen.
- **compiler.build-linux** : under Linux OS, it is possible to configure the compiler options by using **compilation-options** tag. It is also possible to force the compiler by using **force-compiler** tag (e.g. use **icpc**, the INTEL compiler). These options have to be used carefully and may lead some problems.
- **display-license-activate** : this setting, located in the file **'system.xmlx'** allows to disable the popup windows **'Lixoft Activate'**

Note: Both preference files are read when MONOLIX is open, so in order to MONOLIX to take the changes into account, it must be reopened. If you use MONOLIX from MATLAB command line, then you should do

```
» clear classes
```

Chapter 5

PERLMLX and the batch mode

5.1 Introduction

PERLMLX is a helper tool that can be used to run

- one or several projects
- an user defined list of project files

defined through MLXTRAN or via XMLX project files.

PERLMLX can be executed on Windows and Linux platforms (MATLAB and standalone version of MONOLIX are supported) and it can launch multiple runs simultaneously (which can reduce drastically processing time).

All these features make PERLMLX a very efficient tool for mass processing.

PERLMLX is provided with a simple HMI but some users may prefer the command-line interface (users working on clusters will have to use this command-line interface since clusters are not managed by the HMI).

Note: PERLMLX relies on Perl scripts (hence its name !) which supposes of course that Perl has been installed on the platform.

This chapter is organized as follows:

- **Section 5.2** lists the environment variables that shall be set for PERLMLX to run (nothing mandatory in fact but the definition of environment variables can me the scripts easier to write)
- **Section 5.3** describes PERLMLX "HMI mode"
- **Section 5.4** describes PERLMLX "standalone mode"

- [Section 5.5](#) describes how to launch MONOLIX without PERLMLX (the so called "Batch mode")
- [Section 5.6](#) describes how to use PERLMLX on cluster installations.

5.2 Environment variables

When PERLMLX is used in `command-line mode`, it is recommended to setup environment variables (nothing mandatory but as will be seen later these variables will make the scripts easier to write):

- 'MONOLIX' to: `'/My/Path/To/Monolix.4.3.0-standalone-linux32'`
- 'MONOLIXDATA' to: `'/MyPath/To/runtime/resources'`

These environment variables can be set with the shell commands below:

- Linux:
 - type the command lines:
`gandalf#> export MONOLIX=/My/Path/To/Monolix.4.3.0-standalone-linux32`
 - or add the following lines in your `'.bashrc'` config file
`gandalf#> gedit /.bashrc`
add the following line at the end of the file `'.bashrc'`:
`export MONOLIX=/My/Path/To/Monolix.4.3.0-standalone-linux32`
- Under Windows (XP, Vista or 7)
 - type the command lines:
`c:\set MONOLIX=c:\My\Path\To\Monolix.4.3.0-standalone-win32`
 - or use the graphical environment to set up the path and the variable MONOLIX to
`c:\My\Path\To\Monolix.4.3.0-standalone-win32`

Note: by default MONOLIX is installed beneath `c:\Document And Settings\All Users\ApplicationData` which is a hidden directory (so please refer to your operating system's documentation if MONOLIX directory does not show in your explorer)

5.3 HMI mode

HMI version of PERLMLX is an executable named `mlxPerlScript`.

The HMI is divided in eight sections:

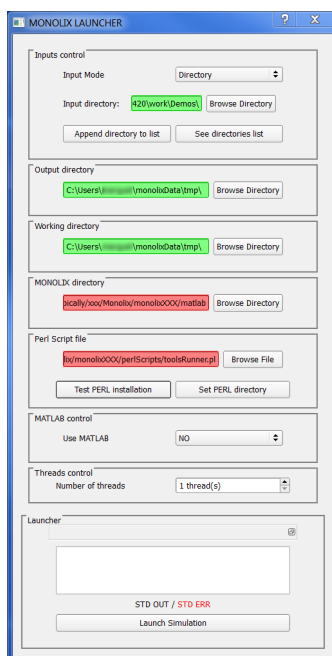
- **Inputs control:** used to define either the project files or the directories (containing the project files) on which MONOLIX shall be run.
 - If **Directory** is selected the user can enter via the **text edit** (or with the help of the **Browse Directory** button) the directory(ies) which shall be processed. All the project files contained in the selected directory(ies) and its sub-directories will be processed.
 - If **File** is selected user can enter via the **text edit** (or with the help of the **Browse File** button) the MLXTRAN or XMLX projects that shall be processed.

Whatever is the input selection mode, only the directories / files appended to the list (through button **Append directory / file to list**) will be processed. Press button **See directories / files list** to control this list (items can be discarded from the list via **Delete element** button).

- **Output directory:** directory where the results will be stored.
- **Working directory:** directory where all intermediate and temporary files are stored.
- **MONOLIX directory:** directory where MONOLIX is installed
Something like `'/My/Path/To/Monolix/matlab'` for MATLAB version and `'/My/Path/To/Monolix'` (where `'Monolix.bat/.sh'` can be found) on stand-alone installations.
- **Perl Script file:** directory where the Perl script `toolsRunner.pl` can be found.
Note: Button **Test PERL installation** can be used to verify that perl command can be accessed through the HMI. When this button is pressed a call to `'perl -v'` (perl version) is done. If this call is unsuccessful the **STD OUT / STD ERR** will be painted in yellow (perl version will be displayed in a white background otherwise). User can then use the **Set PERL directory** button to select the directory where Perl is installed.
- **MATLAB control:** combo **Use MATLAB** shall be set to **NO** on standalone versions and **YE** on MATLAB versions (path to MATLAB installation shall then be entered)
Note: path to MATLAB installation is something like `'Path/To/MATLAB/R2012a'`. What is important is that a subdirectory `'bin'` where `'matlab.exe'` can be found exists under this path.
- **Threads control:** enter the number of threads that can be opened. On multiprocessor machines this control can be used to force PERLMLX to use the maximum processing power (or on the contrary limited resources!).

- **Launcher:** see below.

Note: it is recommended to try the `perl` installation before pressing this button (see `Perl Script` file item hereabove).



Note: it is possible to save and restore configuration via `File` menu, actions `Export` / `import mlxPerlScript Cfg`

Note: light green and light red are used to distinguish between valid and invalid directories / files names.

User shall press the **Launch Simulation** button (in the **Launcher** group box at the bottom of the HMI) to start the simulation. This group box can be docked and will show in the text edit:

- exact transcript of the launched `Perl` process
- standard output and error from the launched `Perl` process

5.4 Standalone mode

To launch PERLMLX in standalone mode, user shall use script ‘toolsRunner.pl’. Several options are made available to control this script (these options are introduced in the following sub section). It is also possible to control these options via a reusable configuration file (which is introduced in the second subsection).

5.4.1 Options

Here are the different options available for script ‘toolsRunner.pl’:

argument	value	description
-tool	execute	name of tools to execute (required parameter)
-toolhelp		display help documentation
-output-directory	<directory>	output directory path, where the results are stored
-thread	<number of thread>	number of simultaneous projects to run
-input-directories	<dir1,..dirN>	list of input directories containing project files
-input-project-list	<project1, ...,projectN>	input list of projects separated by comma
-input-project-file-list	<project file list>	input file containing list of project files
-use-matlab		MATLAB version of MONOLIX instead of standalone
-matlab-path	<matlab path>	MATLAB path (if use-matlab is set)
-monolix-path	<path of monolix>	MONOLIX path
-working-directory	<directory>	directory where all intermediate and temporary files are stored
-config	<path of configuration file>	config file path

Some examples of correct instruction sets are givent in the following paragraphs:

Running MONOLIX on a demo file

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl \
--tool=execute \
--input-project-list=$MONOLIXDATA/demos/categorical_covariate/PDsim1_project.mlxtran \
--output-directory=$MONOLIXDATA/work/output \
--monolix-path=$MONOLIX/bin \
--working-directory=/home/gandalf/tmp
```

In this example a standalone version of MONOLIX is launched (with the parameter ‘-monolix-path’) using the MLXTRAN project ‘PDsim1_script.mlxtran’. The output directory has been set to ‘/MyPath/To/runtime/resources/work/output’

Running MONOLIX on the Demos directory

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl \  
--tool=execute \  
--input-directories=$MONOLIXDATA/demos \  
--monolix-path=$MONOLIX/bin \  
--output-directory=$MONOLIXDATA/work/output \  
--working-directory=/home/gandalf/tmp
```

This illustrates an execution of MONOLIX on all XMLX and MLXTRAN projects present in the directory ‘\$MONOLIXDATA/work/Demos’

Running MONOLIX on a project file list

First edit a file list using a simple text editor (gedit, emacs, vim, kwrite, ...) :

gandalf#> gedit myslst.lst then execute ‘toolsRunner.pl’ :

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl \  
--tool=execute \  
--input-project-file-list=./myslst.lst \  
--output-directory=$MONOLIXDATA/work/output \  
--monolix-path=$MONOLIX/bin \  
--working-directory=/home/gandalf/tmp
```

5.4.2 Setting up the configuration file

Script 'toolsRunner.pl' can also be used with 'config' option and a '.ini' configuration file (the file can be created using a simple text editor). Here is the information that this configuration file shall contain:

subsection	parameters	description
[path]	MATLAB	MATLAB path (required for a MATLAB version of MONOLIX)
	MONOLIX	MONOLIX path
[monolix]	standalone	standalone version?
[program-generic-options]	thread	number of threads: it is recommended that the number of threads is smaller or equal to the number of processor cores available on the computer
[program-execute-options]	workingDirectory	directory used by PERLMLX to store intermediate results
	command prefix	add a command prefix to a MONOLIX command, this parameter is useful in cluster mode (ex: use of 'qsub' before the MONOLIX command)
	script-embed	MONOLIX generates a script containing a command line; this parameter is used in the cluster mode: the qsub command is run on a script without any command line argument, with the command line embedded into a script
	useProjectDirectoryToSaveResult	the default directory of results is stored in same directory as project directory

In the following paragraphs examples of correct configuration files are given:

- **example using the MATLAB version under Linux OS**

```

\[path\]
; MATLAB version of MONOLIX
; MATLAB path
matlab=/opt/matlab/
; directory of MONOLIX

```



```
monolix=/opt/Monolix-4.3.0-matlab-linux32
[monolix]
; standalone version? No
standalone=false
[program-generic-options]
; execution on the nodes
thread=2
[program-execute-options]
; PERLMLX need a temporary directory to store intermediate files
workingDirectory=/tmp
```

- **example using the standalone version under Linux OS**

```
[path]
; MONOLIX directory
monolix=/opt/Monolix-4.3.0-standalone-linux32/bin
[monolix]
; use of the standalone version
standalone=true
[program-generic-options]
; execution on the nodes
thread=2
[program-execute-options]
; PERLMLX need a temporary directory to store intermediate files
workingDirectory=/tmp
```

- **example using the MATLAB version on a Linux cluster**

```
[path]
; MATLAB version of MONOLIX
; MATLAB path
matlab=/opt/matlab/
; directory of MONOLIX
monolix=/opt/Monolix-4.3.0-standalone-linux32
[monolix]
; not the standalone version
standalone=false
[program-generic-options]
; on a cluster multi-threading is not necessary:
; the cluster uses a queue to dispatch program
; execution on the nodes
thread=1
[program-execute-options]
; PERLMLX need a temporary directory to store intermediate files
```

```
workingDirectory=/tmp
```

```
; Specific options to run MONOLIX on a cluster
; qsub is generally the program to submit a process on a cluster
; qsub is typically applied to a script, script-embed option
; allows to create a shell script containing the MONOLIX command
command-prefix=qsub -V -u gandalf
script-embed=true
```

Then, a user working on a cluster can run MONOLIX as usual:

```
gandalf#> perl /opt/Monolix-matlab/perlScripts/toolsRunner.pl \
--tool=execute \
--config=$MONOLIXDATA/work/myconfig.ini \
--input-directories=$MONOLIXDATA/demos \
--output-directory=$MONOLIXDATA/work/output
```

Running MONOLIX on a demo file

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl \
--tool=execute \
--input-project-list=$MONOLIXDATA/demos/categorical_covariate/PDsim1_project.mlxtran \
--output-directory=$MONOLIXDATA/work/output \
--config=$MONOLIXDATA/work/myconfig.ini
```

Running MONOLIX on the Demos directory

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl \
--tool=execute \
--input-directories=$MONOLIXDATA/demos \
--output-directory=$MONOLIXDATA/work/output \
--config=$MONOLIXDATA/work/myconfig.ini
```

Running MONOLIX on a project file list

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl --tool=execute \
--input-project-file-list=./mylist.lst \
--output-directory=$MONOLIXDATA/work/output \
--config=$MONOLIXDATA/work/myconfig.ini
```

5.5 Batch mode in depth

5.5.1 Running MONOLIX without PERLMLX

It is possible to run MONOLIX using a simple command line:

- with the standalone version of MONOLIX

```
$MONOLIX/bin/Monolix.sh [-nowin] \  
                        -p <project> \  
                        -f [run|saem|fim|ll|graphics]
```

- with the MATLAB version of MONOLIX (the command has to be launched from the `matlab` directory of the installation of MONOLIX, i.e. `<monolix install path>/matlab`)

```
matlab -wait \  
      -nosplash \  
      -nodesktop \  
      -r "monolix('-nowin', \  
                '-p','<project>', \  
                '-f','[run|saem|fim|ll|graphics]', \  
                '-destroy' \  
                ),exit"
```

5.5.2 MONOLIX Program options

- **-nowin** : without opening a window, mandatory in no-desktop environments.
- **-p <project>** : project to run
- **-f run|saem|fim|ll|graphics**
 - **run**: run a workflow
 - **saem**: estimate population parameters
 - **fim**: estimate the standard errors of the estimates and Fisher information matrix
 - **ll**: estimate the log-likelihood
 - **graphics**: generate the result graphics

5.5.3 Example

Run the standalone version of MONOLIX on the project `PDsim1_project.mlxtran`:

```
$MONOLIX/bin/Monolix.sh \  
-nowin \  
-p $MONOLIXDATA/demos/categorical_covariates/PDsim1_script.mlxtran -f run
```

Here MONOLIX is executed without displaying a window (option -nowin).

Example: shell script to run MONOLIX on all MLXTRAN files on a directory:

```
1 if [ -d $1 ]; then
2 for mlxtran\_i in `find $1 -type f | grep mlxtran$`; do
3     echo "Run Monolix in $mlxtran_i";
4     $MONOLIX/bin/Monolix.sh -nowin -p $mlxtran_i -f run
5 end
6 else
7 echo "$1 is not a directory"
8 fi
```

5.6 MONOLIX on cluster

5.6.1 Cluster filesystem

To run MONOLIX on a cluster, each cluster node must have access to the MONOLIX directory and to the user home directory.

Each node shares a common file system containing the user directories. The common filesystem may also contain MATLAB and MONOLIX . However, in the case of the standalone version of MONOLIX , it is recommended to have MONOLIX installed on a local drive for each node, since the standalone binary is large: if installed on the network, the startup time on a cluster may take too long.

5.6.2 Task submission mechanism

Generally, a task is submitted to the cluster using a specific command, e.g. `qsub` in the case of *Torque*, *PBS* or *GridEngine* (former *SGE*). This command runs a script, provided as parameter, on a cluster node chosen by the cluster scheduler.

The MONOLIX batch tool allows to run this command through the configuration file. To enable the cluster functionality, the options `command-prefix` and `script-embed` must be set in the configuration file, where `command-prefix` is the command used to submit a task (generally `qsub`) and `script-embed` allows to encapsulate the low level MONOLIX command (see [Section 5.5.1](#)).

At this point, when the command `toolsRunner.pl` is executed, each instance of MONOLIX takes place on a cluster node chosen by the cluster scheduler.

5.6.3 Example

Setting up a configuration file

The following configuration file enables a cluster mode (e.g. *Torque*, *PBS*, *GridEngine*). A task is submitted to the cluster using the command '`qsub`' which runs a script on a cluster mode.

```
[path]
; use a MATLAB version of MONOLIX
; MATLAB path
matlab=/opt/matlab/
; MONOLIX directory
monolix=/opt/Monolix-4.3.0-standalone-linux32
[monolix]
;do not use standalone version
standalone=false
[program-generic-options]
; one thread: on a cluster multi-threading is not necessary:
; the cluster uses a queue to dispatch program
; execution on the nodes
thread=1
[program-execute-options]
; PERLMLX needs a temporary directory to store intermediate files
workingDirectory=/tmp
; Specifics options to run MONOLIX on a cluster
; qsub is generally the program to submit a process on a cluster
; Typically qsub uses a script as the process to run; the script-embed option
; allows to create a shell script containing the MONOLIX command
command-prefix=qsub -V -u gandalf
script-embed=true
```

Submit tasks on a cluster

Here each project stored in the directory `$MONOLIXDATA/monolix430/work/Demos` is run on the cluster nodes. This directory has to be shared by all nodes (typically, under Linux OS, with NFS), with exactly the same path.

```
gandalf#> perl $MONOLIX/perlScripts/toolsRunner.pl -tool=execute \
-input-directories=$MONOLIXDATA/work/Demos \
-output-directory=$MONOLIXDATA/work/output \
-config=$MONOLIXDATA/work/myconfig.ini
```

where MONOLIX and MONOLIXDATA are environment variables defined as explained in [Section 5.2](#).

Chapter 6

Validation suite

6.1 Introduction

The validation suite is the highest level of the tests, and is provided on request. It consists in a set of project runs, whose results are compared with references results. A customer can also add his own projects in the suite. A more detailed documentation on the testing strategy and the development processes is also available on request.

The process of the validation suite consists in taking a set of projects with predefined scenarii and to launch them with MONOLIX . The result files are then compared with the reference files. Due to the Matlab kernel, slight numerical differences can appear between two Matlab versions for a same project. This is why the validation suite is launched for each operating system and each Matlab version with different references. It must be executed in batch mode, i.e. via a command line, without a graphical interface.

6.2 Prerequisites

The informations below are required to run the validation suite in batch mode:

- directory path of MONOLIX,
- directory path of MATLAB (does not apply to standalone MONOLIX)
- directory path of references files

A Perl installation is also required to run the validation suite.

6.3 Combinations

As described above, several sets of references results are required to cover platform variabilities. The combinations are listed as follows.

MONOLIX version	Matlab version	Operating system
Install.exe	2008b	Windows 32 bits
R2010a-Install.exe	2010a	Windows 32 bits
R2010b-Install.exe	2010bSP1	Windows 32 bits
R2010b-Install.exe	2011a	Windows 32 bits
R2010b-Install.exe	2011b	Windows 32 bits
R2010b-Install.exe	2012a	Windows 32 bits
standalone2008b-linux32.sh	2008b	Linux 32 bits
matlab2010a-linux32.sh	2010a	Linux 32 bits
matlab2010bSP1-linux32.sh	2010bSP1	Linux 32 bits
matlab2010bSP1-linux32.sh	2011a	Linux 32 bits
matlab2010bSP1-linux32.sh	2011b	Linux 32 bits
matlab2010bSP1-linux32.sh	2012a	Linux 32 bits
standalone2008b-linux64.sh	2008b	Linux 64 bits
matlab2010a-linux64.sh	2010a	Linux 64 bits
matlab2010bSP1-linux64.sh	2010bSP1	Linux 64 bits
matlab2010bSP1-linux64.sh	2011a	Linux 64 bits
matlab2010bSP1-linux64.sh	2011b	Linux 64 bits
matlab2010bSP1-linux64.sh	2012a	Linux 64 bits

6.4 Extensive coverage through the demo projects

The projects from the validation suite are designed to provide maximum coverage of the set of functionalities of MONOLIX. The two types of structural models, Matlab and MLXTRAN, are included in these projects. Currently, the suite includes 17 projects:

- **Emax_errorband_project** : transformed error model,
- **iov3_project**, **ss2_project** : inter occasion variability (IOV) with several levels,
- **theophylline2_project**, **warfarin_PKPD1_project**, **warfarin_PKPD4_project**, **warfarin_PK_project** : methodologic cases with classical database,
- **categorical1_project**, **count1_project** : discrete observed variables,
- **pkrtteExpo_project**, **rtteWeibullCount_project** : repeated time to event,
- **PKmixt_project** : model of mixtures and mixture models,
- **PDsim1_project**, **phenobarbital2_project** : categorical covariates,
- **bolus_1cptMM_project**, **demo_project**, **sequential_oral0_oral1_project** : advanced and complex administrations.

6.5 Execution

Program parameters

argument	value	description
-help		display help documentation
-output-directory	<directory>	output directory path, where the results are stored
-thread	<number of thread>	number of simultaneous projects to run
-reference-directory	<directory>	reference directory containing project files
-use-matlab	true ou false	MATLAB version of MONOLIX instead of standalone
-matlab-path	<matlab path>	MATLAB path (if use-matlab is set)
-monolix-path	<path of monolix>	MONOLIX path
-keep-output	true ou false	saves output directory

Examples

Here we set the environment variable

- 'MONOLIXSTD' to '/opt/Monolix.4.3.0-standalone-linux32',
- 'MONOLIX' to '/opt/Monolix.4.3.0-matlab2010bSP1-linux32',
- 'MATLAB' to '/opt/MATLAB/R2010b' and
- 'VALIDATIONSUITE' to '/home/gandalf/validationSuite'

To set environment variables, see [Section 5.2](#).

Running the validation suite with standalone version

Go to the validation suite directory (here /home/gandalf/validationSuite/scripts).
Then,

```
gandalf#> perl validationSuite.pl \
--reference-directory=$VALIDATIONSUITE/reference/lin32/2008b \
--monolix-path=$MONOLIXSTD/bin \
--output-directory=/home/gandalf/output
```

This illustrates an execution of MONOLIX on all XMLX and MLXTRAN projects present in the directory '\$VALIDATIONSUITE/reference/lin32/2008b'. If the validation is successful, the user should get

```
[2012/04/27 16:53:00] [INFO]: Comparison results
Check ss2_project project :
OK

Check pkrtteExpo_project project :
OK

Check rtteWeibullCount_project project :
OK

Check warfarin_PKPD4_project project :
OK

Check sequential_oral0_oral1_project project :
OK

Check theophylline2_project project :
OK

Check warfarin_PKPD1_project project :
OK

Check warfarin_PK_project project :
OK

Check Emax_errorband_project project :
OK

Check PKmixt_project project :
OK

Check PDSim1_project project :
OK

Check categorical1_project project :
OK

Check demo_project project :
OK
```

Running the validation suite with matlab version

Go to the validation suite directory (here /home/gandalf/validationSuite/scripts).
Then,

```
gandalf#> perl validationSuite.pl --use-matlab=true \
--reference-directory=$VALIDATIONSUITE/reference/lin32/2010b \
--monolix-path=$MONOLIX/matlab \
--output-directory=/home/gandalf/output
--matlab-path=$MATLAB
```

Running the validation suite with matlab version and saving output directory

In the validation fails, it can be useful to store the output directory using the option 'keep-output':

```
gandalf#> perl validationSuite.pl --use-matlab=true --keep-output=true \  
--reference-directory=$VALIDATIONSUITE/reference/lin32/2010b \  
--monolix-path=$MONOLIX/matlab \  
--output-directory=/home/gandalf/output \  
--matlab-path=$MATLAB
```

```
[2012/04/27 18:20:10] [INFO]: Comparison results  
Check ss2_project project :  
OK  
  
Check pkrtteExpo_project project :  
KO  
Fields with differences:  
IF_sa  
se_fixed_sa (error: 0.01)  
pv_fixed_sa (rel error: 0.01)  
se_random_sa (error: 0.01)  
se_gabc_sa (rel error: 0.01)  
C0_sa (error: 0.001)  
Cth_sa (error: 0.001)  
  
Check rtteWeibullCount_project project :  
KO  
Fields with differences:  
IF_sa  
se_fixed_sa (error: 1)  
pv_fixed_sa (error: 0.1)  
se_random_sa (error: 0.1)  
C0_sa (error: 0.01)  
Cth_sa (error: 10)  
  
Check warfarin_PKPD4_project project :  
OK  
  
Check sequential_oral0_oral1_project project :  
OK  
  
Check theophylline2_project project :  
OK  
  
Check warfarin_PKPD1_project project :  
OK
```

The display shows the fields in the results which are not equal to reference results, and indicates the order of errors.

It exists two kinds of error:

- absolute error

```
se_fixed_sa (error: 0.01)
```

- relative error

```
pv_fixed_sa (rel error: 0.01)
```

During the comparison, the absolute error is used. In the case where this error is too large ($> 10^{-3}$), the relative error is used.

Chapter 7

Software plugins

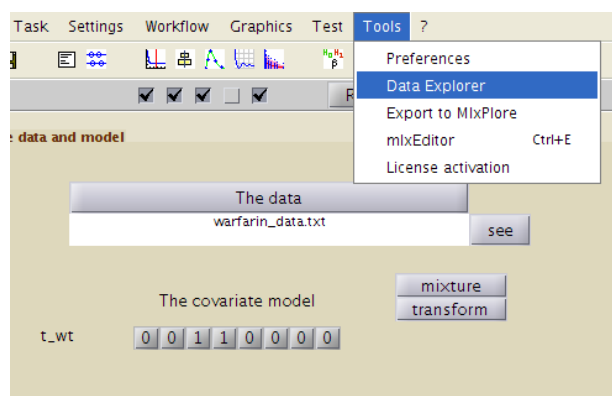
7.1 Introduction

MONOLIX can be extended with the following plug-ins:

- DATXPLORE is a graphical and interactive software for the exploration and visualization of data.
- MLXPLORE is a graphical and interactive software for the exploration and visualization of complex pharmacometric models. It also includes the ability to study the statistical variability of the models, and to model and study complex administrations designs.

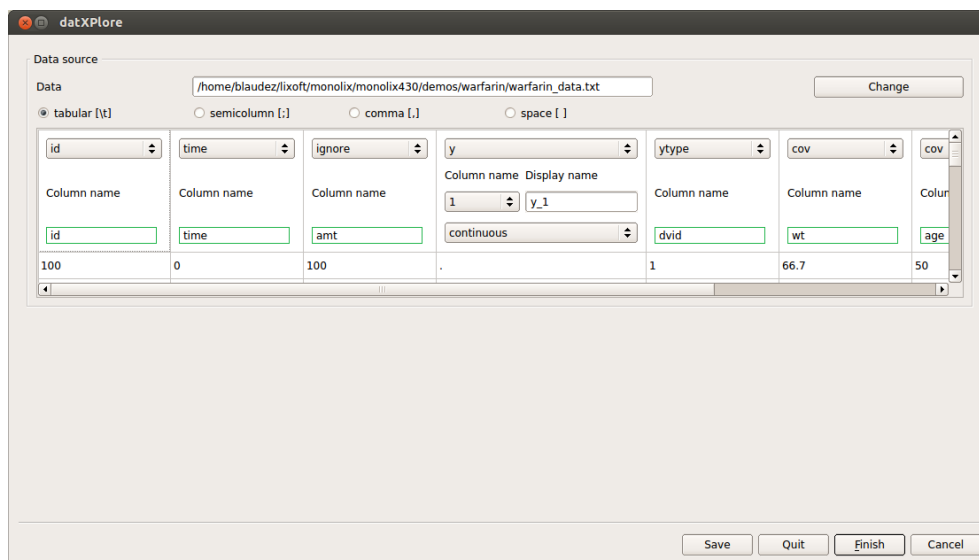
Both DATXPLORE and MLXPLORE are available as standalone software, however they make a powerful combination with MONOLIX , sharing data and models.

7.2 DATXPLORE

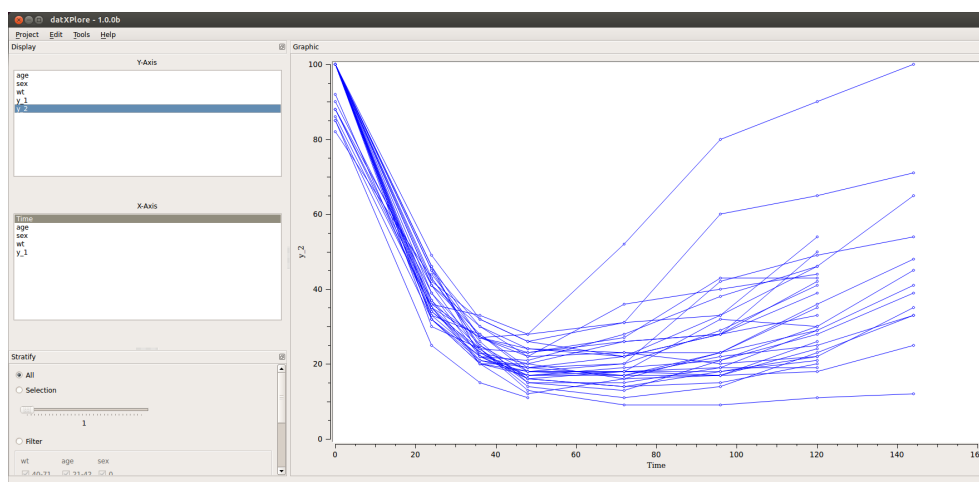


DATXPLORE can be launched from the MONOLIX graphical user interface via the entry Tools → Data Explorer

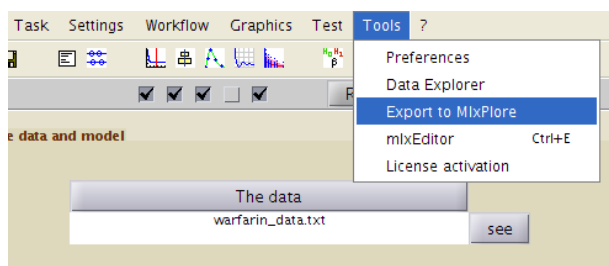
DATXPLORE opens an interface to choose and set the type of the dataset columns



The DATXPLORE graphical user interface then allows to view and manipulate data. Please refer to the DATXPLORE documentation to learn about its features.



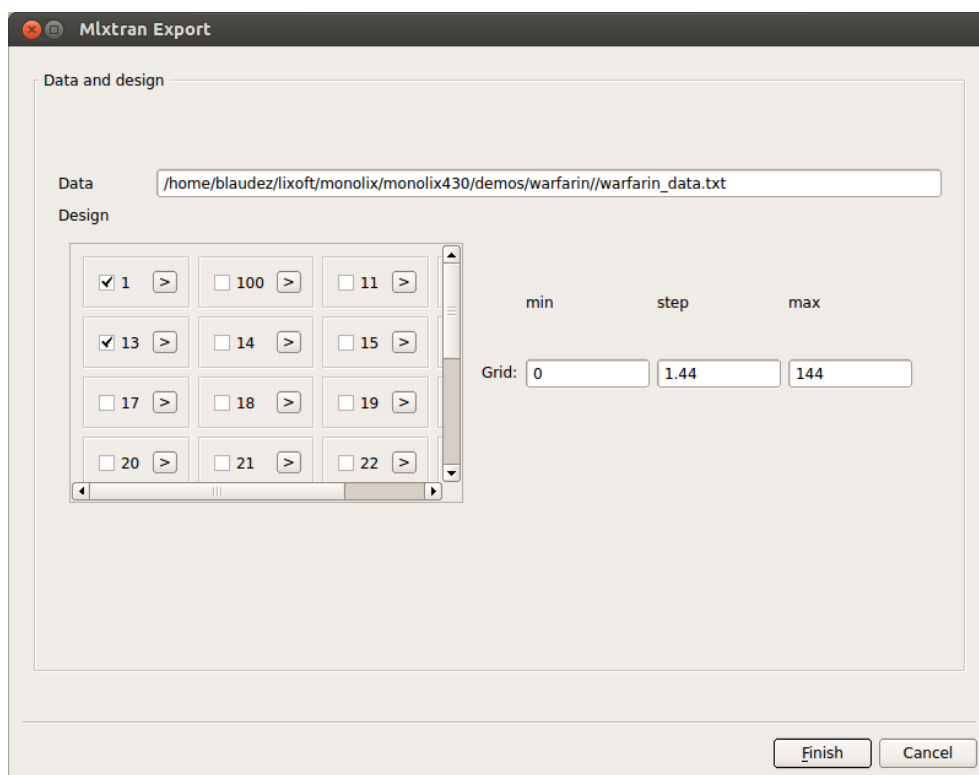
7.3 MLXPLORE



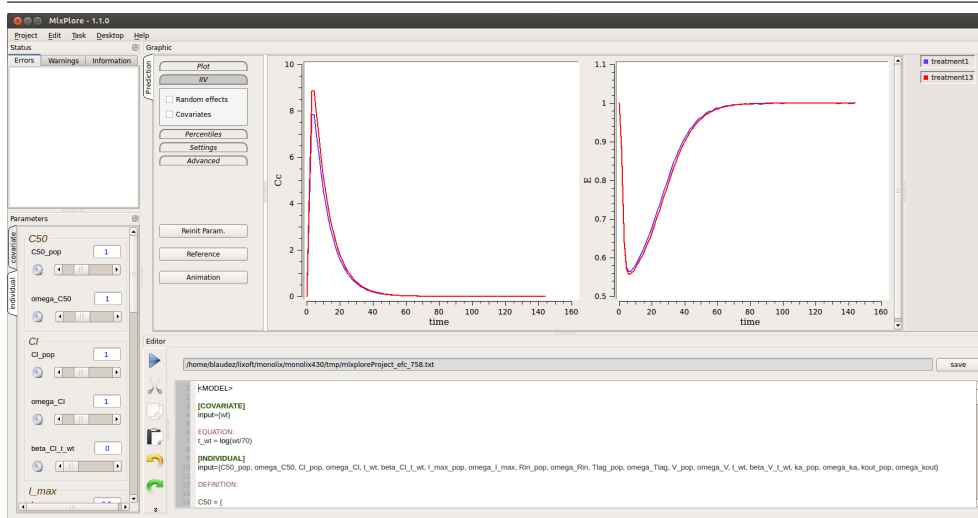
MLXPLORE (version 1.1 and higher) can be launched from the MONOLIX graphical user interface via the entry **Tools** → **Export to MlxPlore**

The model export requires to define a design:

- set the time grid (by default the grid is set by using the values of the data set)
- select the subjects which will be used to set the administration design



MLXPLORE is then executed. Please refer to the MLXPLORE documentation to learn about its features.



Appendix A

The statistical models

A.1 The nonlinear mixed effects model

Detailed and complete presentations of the nonlinear mixed effects model can be found in [5, 6, 21]. See also the many references therein.

We consider the following general nonlinear mixed effects model for continuous outputs:

$$y_{ij} = f(x_{ij}, \psi_i) + g(x_{ij}, \psi_i, \xi) \varepsilon_{ij} \quad , \quad 1 \leq i \leq N \quad , \quad 1 \leq j \leq n_i \quad (\text{A.1})$$

Here,

- $y_{ij} \in \mathbb{R}$ is the j th observation of subject i ,
- N is the number of subjects,
- n_i is the number of observations of subject i ,
- the regression variables, or design variables, (x_{ij}) are assumed to be known, $x_{ij} \in \mathbb{R}^{n_x}$,
- for subject i , the vector $\psi_i = (\psi_{i,\ell}; 1 \leq \ell \leq n_\psi) \in \mathbb{R}^{n_\psi}$ is a vector of n_ψ individual parameters:

$$\psi_i = H(\mu, c_i, \eta_i) \quad (\text{A.2})$$

where

- $c_i = (c_{im}; 1 \leq m \leq M)$ is a known vector of M covariates,
- μ is an unknown vector of fixed effects of size n_μ ,
- η_i is an unknown vector of normally distributed random effects of size n_η :

$$\eta_i \sim_{i.i.d.} \mathcal{N}(0, \Omega)$$

- the residual errors (ε_{ij}) are random variables with mean zero and variance 1,
- the residual error model is defined by the function g and some parameters ξ .

Here, the parameters of the model are $\theta = (\mu, \Omega, \xi)$. We will denote $\ell(y; \theta)$ the likelihood of the observations $y = (y_{ij}; 1 \leq i \leq n, 1 \leq j \leq n_i)$ and $p(y, \psi; \theta)$ the likelihood of the complete data $(y, \psi) = (y_{ij}, \psi_i; 1 \leq i \leq n, 1 \leq j \leq n_i)$. Thus,

$$\ell(y; \theta) = \int p(y, \psi; \theta) d\psi.$$

Let us see now the statistical model used in MONOLIX 4.3.0 more in details.

A.2 The statistical model for the individual parameters

In MONOLIX 4.3.0, we assume that ψ_i is a transformation of a Gaussian random vector φ_i :

$$\psi_i = h(\varphi_i) \quad (\text{A.3})$$

where, by rearranging the covariates (c_{im}) into a matrix C_i , φ_i can be written as

$$\varphi_i = C_i \mu + \eta_i \quad (\text{A.4})$$

A.2.1 Examples of transformations

Here, different transformations (h_ℓ) can be used for the different components of $\psi_i = (\psi_{i,\ell})$ where $\psi_{i,\ell} = h_\ell(\varphi_{i,\ell})$ for $\ell = 1, 2, \dots, \ell$. Let us denote by $\Phi(u)$ the cumulative distribution function of a Gaussian distributed random variable.

- $\psi_{i,\ell}$ has a log-normal distribution if $h_\ell(u) = e^u$,
- assuming that $\psi_{i,\ell}$ takes its values in $(0, 1)$, we can use a logit transformation $h_\ell(u) = 1/(1 + e^{-u})$, or a probit transformation $h_\ell(u) = \Phi(u)$.
- assuming that $\psi_{i,\ell}$ takes its values in (A, B) , we can define $h_\ell(u) = A + (B - A)/(1 + e^{-u})$, or $h_\ell(u) = A + (B - A)\Phi(u)$.

In the following, we will use either the parameters ψ_i or the Gaussian transformed parameters $\varphi_i = h^{-1}(\psi_i)$.

The model can address continuous and/or categorical covariates.

A.2.2 Example of continuous covariate model

Consider a PK model that depends on volume and clearance and consider the following covariate model for these two parameters:

$$\begin{aligned} CL_i &= CL_{\text{pop}} \left(\frac{W_i}{W_{\text{pop}}} \right)^{\beta_{CL,W}} \left(\frac{A_i}{A_{\text{pop}}} \right)^{\beta_{CL,A}} e^{\eta_{i,1}} \\ V_i &= V_{\text{pop}} \left(\frac{W_i}{W_{\text{pop}}} \right)^{\beta_{V,W}} e^{\eta_{i,2}} \end{aligned}$$

Where W_i and A_i are the weight and the age of subject i and where W_{pop} and A_{pop} are some “typical” values of these two covariates in the population. Here, ψ_i will denote the PK parameters (clearance and volume) of subject i and φ_i its log-clearance and log-volume. Let

$$W_i^* = \log\left(\frac{W_i}{W_{\text{pop}}}\right) \quad ; \quad A_i^* = \log\left(\frac{A_i}{A_{\text{pop}}}\right)$$

Then,

$$\begin{aligned} \varphi_i &= \begin{pmatrix} \log(CL_i) \\ \log(V_i) \end{pmatrix} \\ &= \begin{pmatrix} 1 & 0 & W_i^* & A_i^* & 0 \\ 0 & 1 & 0 & 0 & W_i^* \end{pmatrix} \begin{pmatrix} \log(CL_{\text{pop}}) \\ \log(V_{\text{pop}}) \\ \beta_{CL,W} \\ \beta_{CL,A} \\ \beta_{V,W} \end{pmatrix} + \begin{pmatrix} \eta_{i,1} \\ \eta_{i,2} \end{pmatrix} \\ &= C_i \mu + \eta_i \end{aligned}$$

A.2.3 Example of categorical covariate model

Assume that some categorical covariate G_i takes the values $1, 2, \dots, K$. Assume that if patient i belongs to group k , *i.e.* $G_i = k$, then

$$\log(CL_i) = \log(CL_{\text{pop},k}) + \eta_i$$

where $CL_{\text{pop},k}$ is the population clearance in group k .

Let k^* be the reference group. Then, for any group k , we will decompose the population clearance $CL_{\text{pop},k}$ as

$$\log(CL_{\text{pop},k}) = \log(CL_{\text{pop},k^*}) + \beta_k$$

where $\beta_{k^*} = 0$.

The variance of the random effects can also depend on this categorical covariate:

$$\eta_i \sim \mathcal{N}(0, \Omega_k) \quad \text{if } G_i = k$$

Remark: It is assumed in MONOLIX 4.3.0 that the correlation matrix of the random effect is the same for all the groups. In other words, only the variances of the random effects can differ from one group to another.

MONOLIX

Choice of the transformation is described in [Section 3.3.5](#).

Selection of the covariate model is described in [Section 3.3.3](#).

Examples with categorical covariates are given in [Section 4.4](#).

A.3 The residual error model

The within-group errors (ε_{ij}) are supposed to be Gaussian random variables with mean zero and variance 1. Furthermore, we suppose that the ε_{ij} and the η_i are mutually independent.

Different error models can be used in MONOLIX 4.3.0 :

- the constant error model assumes that $g = a$ and $\xi = a$,
- the proportional error model assumes that $g = b f$ and $\xi = b$,
- a combined error model assumes that $g = a + b f$ and $\xi = (a, b)$,
- an alternative combined error model assumes that $g = \sqrt{a^2 + b^2 f^2}$ and $\xi = (a, b)$,
- a combined error model with power assumes that $g = a + b f^c$ and $\xi = (a, b, c)$,
- ...

Furthermore, all these error models can be applied to some transformation of the data:

$$t(y_{ij}) = t(f(x_{ij}, \psi_i)) + g(x_{ij}, \psi_i, \xi) \varepsilon_{ij} \quad (\text{A.5})$$

For example:

- the exponential error model assumes that $y > 0$:

$$\begin{aligned} t(y) &= \log(y) \\ y &= f e^{g\varepsilon} \end{aligned}$$

- the logit error model assumes that $0 < y < 1$:

$$\begin{aligned} t(y) &= \log(y/(1-y)) \\ y &= \frac{f}{f + (1-f)e^{-g\varepsilon}} \end{aligned}$$

- the logit error model can be extended if we assume that $A < y < B$:

$$\begin{aligned} t(y) &= \log((y-A)/(B-y)) \\ y &= A + (B-A) \frac{f-A}{f-A + (B-f)e^{-g\varepsilon}} \end{aligned}$$

It is possible with MONOLIX to assume that the residual errors (ε_{ij}) are correlated:

$$\text{corr}(\varepsilon_{i,j}, \varepsilon_{i,j+1}) = \rho^{(x_{i,j+1} - x_{i,j})} \quad (\text{A.6})$$

Here, we assume that $0 \leq \rho < 1$ and that for any i , $(x_{i,j}, 1 \leq j \leq n_i)$ is an increasing sequence of regression scalar variables.

Selection of the residual error model is described [Section 3.3.7](#).

Several examples of residual error models are provided with the demos:

- combined error model: `warfarin/warfarin_PK_project`
 - exponential error model: `PK/Bolus1cptMM_project`
 - extended logit error model: `error model/Imax_errorband_project`
 - autocorrelated residual errors: `error model/infusion_correrror_project`
-

A.4 Multi-responses model

The basic model can be extended to multi-responses:

$$\begin{aligned} y_{ij}^{(1)} &= f_1(x_{ij}^{(1)}, \psi_i) + g_1(x_{ij}^{(1)}, \psi_i; \xi_1) \varepsilon_{ij}^{(1)}, \quad 1 \leq i \leq N, \quad 1 \leq j \leq n_{i1} \\ &\vdots \\ y_{ij}^{(L)} &= f_L(x_{ij}^{(L)}, \psi_i) + g_L(x_{ij}^{(L)}, \psi_i; \xi_L) \varepsilon_{ij}^{(L)}, \quad 1 \leq i \leq N, \quad 1 \leq j \leq n_{iL} \end{aligned}$$

This is useful, for example, for PKPD models in which the input of the PD model $x_{ij}^{(2)}$ is the concentration, that is the output of the PK model $f_1(x_{ij}^{(1)}, \psi_i)$.

How to handle models with multiple outputs is described in [Section 4.2](#).

Several examples are provided using the warfarin data:

`warfarin_PKPD1_project`, `warfarin_PKPD2_project`, `warfarin_PKPD3_project`,
`warfarin_PKPD4_project`.

A.5 Model with censored data

A.5.1 BLQ data

In some context, because of assay limitation, when data y_{ij} are inferior to a limit of quantification (LOQ), we do not observe y_{ij} but only the censored value LOQ . These data are usually named BLQ (Below the Limit of Quantification) data or left-censored data.

Let denote $I_{obs} = \{(i, j) | y_{ij} \geq LOQ\}$ and $I_{cens} = \{(i, j) | y_{ij} \leq LOQ\}$ the index sets of the uncensored and censored observations respectively. For $(i, j) \in I_{cens}$, let $y_{ij}^{cens} = y_{ij}$ denote the unknown value of the censored observation j of subject i . Let denote y_i^{cens} the vector of censored observations of subject i . Finally, we observe

$$y_{ij}^{obs} = \begin{cases} y_{ij} & \text{if } (i, j) \in I_{obs}, \\ LOQ & \text{if } (i, j) \in I_{cens}. \end{cases}$$

We denote $y_i^{obs} = (y_{i1}^{obs}, \dots, y_{in_i}^{obs})$ as the observations of subject i and $y^{obs} = (y_1^{obs}, \dots, y_N^{obs})$ the total observations dataset.

A.5.2 Interval censored data

It is possible now also to model interval censored data, i.e data where it is only known that y_{ij} is above a limit of detection LOD_{ij} but below the limit of quantification $y_{ij}^{cens} \in [LOD_{ij}, LOQ_{ij})$. The intervals could be $(-\infty, LOQ_{ij})$ (left censored data, as above) and $[LOQ_{ij}, +\infty)$ (right censored data).

MONOLIX

How MONOLIX handles BLQ data is described in [Section 4.5](#).

A.6 Modeling the inter-occasion variability

We will denote y_{ikj} the j th observation for subject i during occasion k :

$$y_{ikj} = f(\psi_{ik}, t_{ikj}) + g(\psi_{ik}, t_{ikj}, \xi)\varepsilon_{ikj} \quad (\text{A.7})$$

Here, $\psi_{ik} = h(\varphi_{ik})$ is the individual parameter of subject i at occasion k :

$$\varphi_{ik} = C_{ik} \mu + \eta_i + \kappa_{ik} \quad (\text{A.8})$$

- C_{ik} is the matrix of covariates of subject i at occasion k ,
- η_i random effect of subject i (inter-subject variability): $\eta_i \sim \mathcal{N}(0, \Omega)$,
- κ_{ik} random effect of subject i at occasion k (inter-occasion variability): $\kappa_{ik} \sim \mathcal{N}(0, \Gamma)$,
- η_i and κ_{ik} are assumed to be independent,
- Ω inter-subject variability covariance matrix,
- Γ inter-occasion variability covariance matrix.

A.7 Discrete data models

The basic model proposed in [\(A.1\)](#) is a regression model used for fitting continuous data that can be extended for categorical data or count data models. Assume that (y_{ij}) takes its values in $\{0, 1, 2, \dots\}$. We define the conditional likelihood of the observations using a mixed effects model:

$$\mathbb{P}(y_{ij} = k | \psi_i) = f(k, x_{ij}, \psi_i) \quad , \quad 1 \leq i \leq N \quad , \quad 1 \leq j \leq n_i \quad (\text{A.9})$$

In other words, for any i , the probability that y_{ij} takes the value k depends on some (unknown) individual parameter ψ_i and possibly on some (known) design variable x_{ij} .

A mixed hidden Markov models (mixed HMM, or MHMM) assumes that there exists some non observed sequences (z_{ij}) (the states) that take their values in $1, 2, \dots, L$ such that, for any i ,

- $(z_{ij}, j \geq 1)$ is a Markov Chain,
- conditionally to the sequence of states (z_{ij}) , the (y_{ij}) are independent random variables
- the transition probabilities $\mathbb{P}(z_{i,j+1} = v | z_{ij} = u)$ and the emission probabilities (*i.e.* conditional probabilities) $\mathbb{P}(y_{ij} = k | z_{ij} = u)$ depend on some individual parameters ψ_i .

MONOLIX

How to model categorical data, count data and HMM is described respectively in Sections [Section 4.7.1](#), [Section 4.7.2](#) and [Section 4.7.4](#).

A.8 Mixture models and model mixtures

A.8.1 Mixture models

In MONOLIX, a mixture model assume that there exist some “latent” categorical covariate G that takes K values. Then, the mixture model reduces to the categorical covariate model described [Section A.2](#) but here, the categorical covariates are unknown: they are treated as random variables and the probabilities

$$\pi_k = \mathbb{P}(G_i = k)$$

are part of the statistical model and should be estimated as well.

A.8.2 Model mixtures

Let f_1, f_2, \dots, f_K be K different structural models,

- **Between Subject Model Mixture (BSMM)**

We assume that some categorical covariate G takes K values and that

$$y_{ij} = f_k(x_{ij}, \psi_i) + \varepsilon_{ij} \quad , \quad \text{if } G_i = k$$

In a BSMM model, the “latent” categorical covariates are unknown: they are treated as random variables and the probabilities

$$\pi_k = \mathbb{P}(G_i = k)$$

are part of the statistical model and should be estimated as well.

- **Within Subject Model Mixture (WSMM)**

For any patient i , let $p_{i,1}, p_{i,2}, \dots, p_{i,K}$ be K proportions such that

$$\begin{aligned} y_{ij} &= f_i(x_{ij}, \psi_i) + \varepsilon_{ij} \\ f_i &= p_{i,1}f_1 + p_{i,2}f_2 + \dots + p_{i,K}f_K \end{aligned}$$

In a WSMM model, the proportions $(p_{i,k})$ are additional individual parameters that should be modeled as well (under the constraint that the sum is 1).

How to use mixture models is described in [Section 4.10.1](#).

Examples of BSMM and WSMM with MONOLIX are presented in [Section 4.10.2](#).

A.9 Prior models on fixed effects parameters

It is possible to define prior distribution models on the fixed effects. The allowed distributions:

- log-normal
- logit-normal
- probit-normal
- user-defined: transformation of a gaussian distribution:

$$h^{-1}(\mu) \sim \mathcal{N}(\mu_0, \sigma_\mu^2)$$

where h is any increasing function defined for all real numbers.

How to use priors on fixed effects is described in [Section 4.3](#).

Appendix B

The data-set

B.1 General description

The **data-set** structure contains for each subject measurements, dose regimen, covariates etc ... i.e. all the information collected during the trial.

This information is organized by line (i.e. each line contains a piece of information) and each column shall be associated to a **column-type** (there are fifteen different **column-types** which will be described in this annex) for the software to read the **data-set**. It is very similar and compatible with the structure used by the *Nonmem* software.

ID	AMT	TIME	CONC	WEIGHT	SEX
1	4.02	0	.	79.6	M
1	.	0.25	2.84	79.6	M
1	.	0.57	6.57	79.6	M
1	.	1.12	10.5	79.6	M
...

One of the first thing that the software does is to define the *line type*. Indeed, a line can be:

- a **dose-line**: a line that contains information about the dose's regimen
- a **response-line**: a line that contains a measure
- a **regression-line**: a line that contains regression value(s) (since it is possible to have several regression variables)
- a **covariate-line**: a line that contains covariate values(s) (since it is possible to have several covariates)
- a **comment-line**: any line containing character '#'
- a **title-line**: it is the first line of the **data-set** which can be used to define **column-names** (see following paragraph)

Combinations are possible and a line can be both a **dose-line** and a **regression-line** (in other words it is possible to define in a same line a dose regimen and the regression values). But a line **cannot be both a dose-line and a response-line**. In other words two lines will be necessary to define a dose-regimen and a measure at the same time-stamp.

The **title-line** is the first line of the **data-set**. It is free and can be used to specify **column-names**. It is important to understand the difference between **column-names** and a **column-types**: as already stated the **column-names** are totally free but the **column-types** shall belong to a list of pre-defined keywords. They are used to identify the column's role.

For instance, fourth column of the sample **data-set** contains measurement information and will then have **column-type** Y. A name (CONC) has been entered to indicate that the measurement corresponds to a concentration.

It is possible to group the **column-types** based on their functionality:

- **subject identification headers**: **column-types** ID and OCC are used to identify subjects.
- **time headers**: **column-types** TIME and DATE (or DAT1, DAT2, DAT3) are used to time stamp data.
- **dose headers**: **column-types** AMT (alias: DOSE), ADM, RATE, TINF, SS and II (alias: TAU) are used to define doses (respectively dose amount, dose administration, dose rate, dose infusion time, dose **steady-state** and **inter-dose interval**).
Note: ADM is in fact a **super column-type** which groups three different **column-types**: ADM_TYPE, ADM_TARGET, ADM_CMT. They are grouped because all of them are relative to administration type.
- **response headers**: **column-types** Y (alias: DV, CONC) , YTYPE, CENS, LIMIT are used to define responses (respectively response value, response type, censored response flag and response limit).
- **covariate headers**: **column-types** COV and CAT are used to define continuous and categorical covariates.
- **regression headers**: **column-type** X (alias: REG, XX) is used to define regression variables.
- **control and event headers**: **column-types** MDV and EVID can be used
 - either to control data by tagging lines as **dose-lines**, **response-lines** or **regression-lines** (i.e. line containing information to define regression variables)
 - or to mark unusual events.

Note: for several **column-types**, alias have been defined because they have been used in the present document as synonyms of the headers' types. For instance DV or CONC are sometimes used instead of Y.

After this introduction it is time for a more in-depth description of **column-types**.

B.2 In-depth description of column-types

B.2.1 Description of column-types used to identify subject-occasions

ID: subject identifier

A **data-set** shall contain one column with the **column-type** ID (an exception is thrown if there is no column with **column-type** ID or several columns with **column-type** ID).

The column is used to identify the different subjects.

The content of the column is totally free: numbers / strings ...

Note: string ‘.’ will not be interpreted as a repetition of the previous line. As a consequence the **data-set** [B.1](#) generates two **subject-occasions**:

- first **subject-occasions** is ‘John’
- second **subject-occasions** is ‘.’
- Note: there is no occasion defined.

John
John
John
.

Table B.1: A **data-set** that defines two **subject-occasions**: subject ‘John’ and subject ‘.’

OCC: occasion identifiers

It is possible to have in a **data-set** one or several columns with the **column-type** OCC.

The content of the column is totally free: numbers / strings ...

Note: string ‘.’ will not be interpreted as a repetition of the previous line. As a consequence the **data-set** B.2 generates three **subject-occasions**:

- subject-occasion #1: ‘John’ occasion ‘Occ₁’
- subject-occasion #2: ‘John’ occasion ‘Occ₂’
- subject-occasion #3: ‘John’ occasion ‘.’

ID	OCC	...
John	Occ ₁	...
John	Occ ₂	...
John

Table B.2: A **data-set** that defines three **subject-occasions**

IMPORTANT NOTE: Occasions are ordered lexicographically. For instance the **data-set** B.3 defines subject ‘John’ with four occasions:

- first occasion is ‘1’
- second occasion is ‘10’
- third occasion is ‘11’
- fourth occasion is ‘2’
- fifth occasion is ‘3’

ID	OCC	...
John	1	...
John	2	...
John	3	...
John	10	...
John	11	...

Table B.3: Ordering of occasions within a subject

B.2.2 Description of column-types used to time-stamp data

TIME: data time stamp

A **data-set** shall not contain more than one column with the **column-type** **TIME** (an exception will be thrown otherwise).

Time can be defined as :

- a double: **xx.yy**
- using hours, minutes format with optional AM/PM tag: **hh:mm** [AM/PM]
- using hours, minutes seconds format with optional AM/PM tag: **hh:mm:ss** [AM/PM]

Note: String ‘.’ will not be interpreted as a repetition of the previous line. It will throw an exception as any non-compliance with formats listed here-above.

Note: When there is no **column-type** **TIME**, the **column-type** **DATE** is used to time-stamp data (see next section).

If there is neither **TIME** nor **DATE** **column-type**, first **regression-column** (i.e. first column with **column-type** **X**) will be used to time-stamp data.

If there is neither **TIME**, nor **DATE/REGRESSION** **column-type**, an exception is thrown since it is then impossible to time-stamp data.

DATE/DAT1/DAT2/DAT3: date information

A **data-set** shall not contain more than one **column-type** DATE / DAT1-3 (an exception will be thrown otherwise).

DATE can be defined as:

- any double value
- using month, day format: `mm-dd`
- using month, day, year format (two or four digits): `mm-dd-yy` / `mm-dd-yyyy`

DAT1 can be defined as:

- using day, month format: `dd-mm`
- using day, month, year format (two or four digits): `dd-mm-yy` / `dd-mm-yyyy`

DAT2 can be defined as:

- using month, day format: `mm-dd`
- using month, day, year format (two or four digits): `mm-dd-yy` / `mm-dd-yyyy`

DAT3 can be defined as:

- using day, month format: `dd-mm`
- using year, day, month format (two or four digits): `yy-dd-mm` / `yyyy-dd-mm`

Note: day month year separator shall be either string ‘/’ or string ‘-’. It is possible to mix separators between lines but the use of another separator will raise an exception.

Note: year, day month shall be integers (an exception is thrown if it is impossible to convert to int string between two separators).

Note: string ‘.’ will not be interpreted as a repetition of the previous line but will throw an exception as any non-compliance with formats listed here-above.

Note: when year is coded with two digits then it is interpreted as 20xx. For instance, using format DAT2, 12/07/41 is interpreted as december the 7th 2041.

Note: when there is no year information PC clock is used.

Note: It is possible to mix dates with and without year information across subjects. Within a subject if year information is present on one line it shall be present for all lines regarding the subject (otherwise an exception will be thrown).

ID	OCC	DATE	...	Comments
John	Occ1	7/6	...	
John	Occ1	1/12	...	
John	Occ2	1/1/1986	...	Exception thrown: year was not specified in preceding lines
Mike	Occ1	07/6	...	No year specification for Mike
Mike	Occ1	1/1	...	
Melinda	Occ1	12/12/2004	...	Year information for Melinda
Melinda	Occ1	1-12-2002	...	Delimiters can be mixed within a subject
Melinda	Occ2	12/2/2003	...	
Melinda	Occ2	12/12/2003	...	

Table B.4: Using column-type DATE to define a date

B.2.3 Description of column-types used to define the dose regimen

AMT:dose amount

A data-set shall not contain more than one column-type AMT (an exception will be thrown otherwise). The content of column AMT will be called the **dose-column**.

Column AMT shall either contain a double value or string ‘.’.

When a **dose-column** contains a double value d_{Amount} with $d_{\text{Amount}} \neq 0$ then it will be considered as a **dose-line** (i.e. a line containing dose information). If $d_{\text{Amount}} = 0$ then it will be interpreted as a **dose-line** if the **response-column** (i.e. the content of column with column-type Y, see section B.2.6) contains either 0 or string ‘.’.

Note: when a line contains both dose and response information (see section B.2.6) dose information is not taken into account. For instance if the line content is

TIME	ID	AMT	Y
12.1	Tom	1.1	12.6

then response Y is set to 12.6 at time 12.1 but no dose is added ! Of course it is possible to specify a response and a dose at same time but lines shall be duplicated. With:

TIME	ID	AMT	Y
12.1	Tom	.	12.6
12.1	Tom	1.1	.

a response Y is set to 12.6 at time 12.1 and a dose amount 1.1 is also set at time 12.1.

ADM_TYPE: dose administration type

A **data-set** shall not contain more than one column with **column-type** ADM_TYPE (an exception will be thrown otherwise).

An exception will also be thrown if a **data-set** contains a column with **column-type** ADM_TYPE and a column with **column-type** ADM_CMT or ADM_TARGET.

For **dose-lines**, this column shall contain only strings that can be converted to int (an exception will be thrown otherwise).

They are used to associate a compartment to the dose.

ADM_CMT: dose compartment

A **data-set** shall not contain more than one column with **column-type** ADM_CMT (an exception will be thrown otherwise). An exception will also be thrown if the **data-set** contains a column with **column-type** ADM_CMT and a column with **column-type** ADM_TYPE or ADM_TARGET.

For **dose-lines**, this column behaves exactly like column ADM_TYPE. For **reponse-lines**, this column behaves exactly as YTYPE.

ADM_TARGET: dose target

A **data-set** shall not contain more than one column with **column-type** ADM_TARGET (an exception will be thrown otherwise). An exception will also be thrown if the **data-set** contains a column with **column-type** ADM_TARGET and a column with **column-type** ADM_TYPE or ADM_CMT.

This column can contain any string to specify the administration's type.

Note: string '.' will not be interpreted as repetition of previous column but as a type of administration.

RATE, TINF: rate and infusion time

A **data-set** shall not contain more than one column with **column-type** RATE or TINF (an exception will be thrown otherwise).

The column's content is meaningful only for **dose-lines** and format shall be for such lines:

- '.': interpreted as 0
- any double value

An exception is thrown in case of non-compliance.

SS, II: steady-state and inter-dose interval

Steady-state is used to specify that any transitory effect is over and that the system response is now a periodic function of doses.

To realize this, a fixed (5 actually) number of doses is added (the period between doses is set to **interdose-interval**) before the dose entered with the SS flag set to true. Let's take an example:

ID	TIME	AMT	SS	II	EVID	Y	COMMENT
Tom	-25	5	0	0	4	.	<i>This dose is automatically added. Note that first dose has wash-out (EVID = 4)</i>
Tom	-20	5	0	0	1	.	<i>This dose is automatically added.</i>
Tom	-15	5	0	0	1	.	<i>This dose is automatically added.</i>
Tom	-10	5	0	0	1	.	<i>This dose is automatically added.</i>
Tom	-5	5	0	0	1	.	<i>This dose is automatically added.</i>
Tom	0	5	1	2	1	.	This line implies that the system shall have reached its steady-state at time 0. This is why 5 doses are added (at times -25, -20, ... , -5) before this dose

The first added dose will have **wash-out**, thus for clarity an **EVID** column has been included in the previous example. But of course it is possible to specify a **steady-state** even if there is no **EVID** column in the **data-set**.

However an **II** column is mandatory to specify the period between the five added doses to reach **steady-state**. The absence of this column will throw an exception (see hereunder for the complete list of exceptions).

It is possible to find in a **data-set** a mix of **steady-state** and **non steady-state** doses. To prevent doses from *colliding* it has been decided not to add doses before a user defined dose. Let's take an example:

ID	TIME	AMT	SS	II	EVID	Y	COMMENT
Tom	-10	4	0	0	1	.	User entered a dose at time (-10). This dose does not have steady-state and <i>collides</i> with dose at time (0) with steady-state since it normally implies addition of doses at times {-25, -20, ... , -5} These conflicting declarations are solved by the cancellation of doses at time {-25, -20, -15, -10}
Tom	-5	5	0	0	4	.	<i>This dose is automatically added.</i> <i>Note that the first dose has still wash-out (EVID = 4)</i>
Tom	0	5	1	2	1	.	This line implies that system shall have reached its steady-state at time 0. This is why 5 doses are added (at times -25, -20, ... , -5) before this dose.

Format restrictions:

- a **data-set** shall not contain more than one column with **column-type** SS (an exception will be thrown otherwise).
- a **data-set** shall not contain more than one column with **column-type** II (an exception will be thrown otherwise).
- when a **data-set** contains a column with **column-type** SS and no column with **column-type** II then an exception is thrown.
- when a **data-set** contains a column with **column-type** II and no column with **column-type** SS or ADDL then a SS column is created with:
 - SS = 1 when **inter-dose interval** is strictly positive
 - SS = 0 otherwise
- when a **data-set** contains a column with **column-type** II and no column with **column-type** SS but a column with **column-type** ADDL then a SS column is created with:
 - SS = 1 when **inter-dose interval** is strictly positive and ADDL = 0
 - SS = 0 otherwise
- the column is meaningful only for **dose-lines**. Its format shall be (for all lines including **reponse-lines** for which SS information is not applicable) :
 - SS shall be either 0 or 1 (‘.’ will be replaced by 0)
 - II shall contain a double value and

- `ii_value` shall be positive (or null).
- when `SS = 0` then `ii_value` shall be null.
- when `SS = 1`, `ii_value` shall be strictly positive.

An exception is thrown in case of non-compliance.

ADDL: Additional dose line

Additional dose lines is a useful shortcut to specify dose regimens with repetitive treatments. For instance to specify a dose of 10 every 12 hours during 3 days it is possible to write:

ID	TIME	AMT	Comment
Tom	0	10	Dose of 10 during 3 days.
Tom	12	10	
Tom	24	10	
Tom	36	10	
Tom	48	10	
Tom	60	10	
Tom	72	10	

but ADDL and II (*interdose-interval*) can also be used to specify the same information in a single line

ID	TIME	AMT	ADDL	II	Comment
Tom	0	10	6	12	Seven (6+1) doses of 10 every 12 hours \Leftrightarrow dose of 10 during 3 days.

More details on the ADDL column:

- ADDL shall only contain positive (or null) integers or ‘.’ (which will be replaced by 0). Non-compliance will throw an exception
- when there is an ADDL column there shall exist an II (*interdose interval*) column. Non-compliance will throw an exception
- for *dose-lines* with ADDL strictly positive, the *interdose-interval* shall be strictly positive (non-compliance will throw an exception).
ADDL is the number of times the dose shall be repeated and column II contains the dose repetition interval. With following notations:

ID	TIME	AMT	ADDL	II
1	t_{Dose}	d_{amount}	n_{ADDL}	i_{Dose}

there will be $(n_{ADDL}+1)$ doses of d_{amount} at times $t_{Dose}, t_{Dose}+i_{Dose}, t_{Dose}+2i_{Dose}, \dots, t_{Dose}+n_{ADDL} i_{Dose}$

Two important remarks concerning regression values:

- if there is a **regression-column** (i.e. a column with **column-type X**), its value will also be repeated for added doses.

Even though this value has not been specified but obtained via interpolation (see section [B.2.5](#)).

With following notations:

ID	TIME	AMT	ADDL	II	X(REG)
1	t_{Dose}	d_{amount}	n_{ADDL}	i_{Dose}	x_{Reg}

additional regressions (the regression is set to x_{Reg}) are added at times t_{Dose} , $t_{Dose}+i_{Dose}$, $t_{Dose}+2i_{Dose}$, \dots , $t_{Dose}+n_{ADDL} i_{Dose}$.

Reminder: x_{Reg} is either a numerical value or ‘.’ which means that its value will be set by interpolation (see section [B.2.5](#))

- when regression values are defined after the first added dose, warnings are generated. Indeed these values will not be repeated and can possibly interfere with automatically added regression values at dose time. So the warning is generated for the user to confirm that its data make sense.

For instance the following data-set will generate a warning:

ID	TIME	AMT	ADDL	II	X	Y	COMMENT
1	0	10	3	10	6	.	This line specifies a regimen of 4 doses of 10 every 6 hours. Regression value is set to 6.
1	2	.	.	.	4	5	Response-line. Regression value set to 4
1	4	3	Response-line. No regression value defined (a NaN will be generated for the regression at this time stamp since there is no interpolation for response-line - see section B.2.5)
1	5	.	.	.	4.5	1.5	Response-line. Regression value set to 4.5
1	7	.	.	.	1.8	0.12	A warning is generated for this line since it defines regression value after an automatically added dose. Indeed first line specified that doses shall be created at times 6, 12, 18.

Note: concerning **wash-outs** for repeated dose: if a dose has **wash-out** (EVID=4) and a repetition is required, duplicated doses will have **wash-out** set to false. Following table illustrates this point:

ID	TIME	AMT	ADDL	II	EVID	COMMENT
1	0	10	3	10	4	This line specifies a regimen of 4 doses of 10 every 6 hours. What's more first dose has wash-out
1	6	10	0	0	1	Three additional doses are generated as required.
1	12	10	0	.	1	There is no wash-out for these doses. EVID is set to 1 since additional lines are dose lines .
1	18	10	0	.	1	

B.2.4 Description of column-types used to define covariates

COV: Continuous Covariate

It is possible to have in a **data-set** one or several columns with **column-type** COV.

Continuous covariate columns shall contain either strings that can be converted to double or ‘.’ (an exception will be thrown otherwise).

There shall be one covariate defined per **subject-occasion** and an exception will be thrown

- if there are several values defined for the same **subject-occasion**
- if there is no value defined for a **subject-occasion**.

Note: String ‘.’ can be used to prevent multiple definitions of a covariate for a **subject-occasion** (it is interpreted as an absence of definition).

Several valid and problematic schemes are given in the following tables:

ID	OCC	COV	Comment
Tom	1	13	Continuous covariate set to 13 for id Tom, first occasion.
Tom	1	13	
Tom	1	13	
Tom	1	13	

ID	OCC	COV	Comment
Tom	1	.	Continuous covariate set to 12 for id Tom, first occasion.
Tom	1	.	
Tom	1	12	Note: covariate has not necessarily to be defined at first occurrence of subject-occasion in the data-set .
Tom	1	.	
Tom	1	.	

ID	OCC	COV	Comment
Tom	1	.	Exception thrown: continuous covariate undefined for subject Tim first occasion.
Tom	1	.	
Tom	1	.	

ID	OCC	COV	Comment
Tom	1	.	Exception thrown: two different continuous covariate values for subject Tom first occasion.
Tom	1	.	
Tom	1	12	
Tom	1	14	

CAT: categorical covariate.

It is possible to have in a **data-set** one or several columns with **column-type** CAT.

It is possible to enter in a **CAT** column any string and ‘.’ has no special meaning.

There shall be one categorical covariable defined per **subject-occasion** and an exception will be thrown:

- if there are several values defined for the same **subject-occasion**
- if there is no value defined for a **subject-occasion**.

Note: as string ‘.’ has no peculiar interpretation, following scheme will throw an exception:

ID	OCC	CAT	Comment
Tom	1	.	Exception thrown: two different categorical covariates (‘.’ and ‘F’) have been found for id Tom, first occasion.
Tom	1	.	
Tom	1	F	
Tom	1	.	

B.2.5 Description of column-types used to define regressions

X: regression value

It is possible to have in a **data-set** one or several columns with **column-type X**.

The **regression-columns** (i.e. columns with **column-type X**) shall contain either strings that can be converted to double or **'.'** (non-compliance will raise an exception).

Within a given **subject-occasion**, string **'.'** will be interpolated (nearest neighbor interpolation is used) for **dose-lines** only (N.B.: if there is an **EVID** column **dose-lines** correspond to **EVID = 1** or **EVID = 4**)

If a **subject-occasion** contains only **'.'** for a regression an exception is thrown (since it is then impossible to interpolate values).

NOTE: An exception is raised when within a **subject-occasion** there are two different values for a regression at the same time.

Let's take an example:

ID	OCC	TIME	X	AMT	Y	EVID	Comment
Tom	1	0	.	1	.	1	Regression X will be interpolated at times 0 and 25 and will remain undefined (i.e. set to NaN) at times 10, 20, 30.
Tom	1	5	1	.	12	0	
Tom	1	10	.	.	10	0	
Tom	1	15	12	1.5	.	1	
Tom	1	20	-6	.	8	0	
Tom	1	25	.	0.2	.	4	
Tom	1	30	.	.	0.1	0	
Tom	2	0	.	1	.	1	Exception thrown: No regression value defined for subject Tom second occasion.
Tom	2	5	1	.	12	0	
Tom	2	10	.	.	10	0	
Tom	3	0	0.1	1	.	1	Exception thrown: Regression is defined twice at time 5 with different values (X=1 first time and X=1.1 on following line).
Tom	3	5	1	.	12	0	
Tom	3	5	1.1	2	.	1	
Tom	3	10	10	.	14	0	

NOTE: For first occasion X is set to:

- $X(0) = 1$ (it is a **dose-line** so an interpolation is realized. Note: nearest interpolation is realized and here nearest sample corresponds to a **response-line**)
- $X(5) = 1$ (from direct reading of input file even if the line does not correspond to a dose)

- $X(10) = \text{NaN}$ (regression is undefined in the input file but since it is not a **dose-line**, no interpolation is realized)
- $X(15) = 12$ (from direct reading of input file)
- $X(20) = -6$ (from direct reading of input file even though the line does not correspond to a dose)
- $X(25) = -6$ (it is a **dose-line** so an interpolation is realized. Note: nearest interpolation is realized and here nearest sample corresponds to a **response-line**)
- $X(30) = \text{NaN}$ (regression is undefined in the input file but since it is not a **dose-line**, no interpolation is realized)

B.2.6 Description of column-types used to define responses

Y: Response

A **data-set** shall not contain more than one column with **column-type Y** (an exception will be thrown otherwise).

Response-column (i.e. column with **column-type Y**) shall contain double value or string `'.'`. Any other value will raise an exception.

When there is no **EVID** or **MDV** column (see hereunder), a line is considered as a **response-line** if it contains:

- in **response-column**: a string which can be converted to a double value `obsValue`
- no **dose-column** (i.e. content of the column with **dose-type AMT**) or in **dose-column**: either string `'.'` or a 0

Note: When `obsValue = 0`, the line is considered as a **response-line** if there is no **dose-column** or if string `'.'` is in **dose-column**. As a consequence, when there are null values in both **dose-column** and **response-column**, line is considered as a **dose-line**.

Note: when non null double value are both present in **dose-column** and **response-column**, an exception is thrown (as already state a line can not be a **dose-line** and a **response-line**).

Following table sums up the different situations

...	DOSE	Y	Comment
...	0	0	Two null values \Rightarrow line is considered as a dose-line
...	3.14	.	String <code>'.'</code> in response-column \Rightarrow dose-line
...	12	0	Null double in column observation and non null value in column dose \Rightarrow dose-line
...	.	0	String <code>'.'</code> in dose column \Rightarrow response-line
...	0	1.1	Null value in dose-column and non null value in response-column \Rightarrow response-line
...	14	8.8	Exception thrown: double non null values in both columns

YTYPE: reponse type

A **data-set** shall not contain more than one column with **column-type** YTYPE (an exception will be thrown otherwise). An exception is also thrown if the **data-set** contains a column ADM_CMT and a column YTYPE (see section B.2.3 for description of column CMT).

For **response-lines**, YTYPE identifies the response type or name with ‘.’ not interpreted as a repetition or previous line but as the name of a reponse. For instance with:

TIME	DOSE	Y	Y_TYPE
0	.	12	Cc
5	.	6	Cc
10	.	4	.
15	.	3	.
20	.	2.1	Cc2
25	.	2	Cc2

three different types of responses are created:

- Response ‘Cc’: $y_{Cc}(0) = 12$, $y_{Cc}(5) = 6$
- Response ‘.’: $y_{.}(10) = 4$, $y_{.}(15) = 3$
- Response ‘Cc2’: $y_{Cc2}(20) = 2.1$, $y_{Cc2}(25) = 2$

CENS: censored response

A **data-set** shall not contain more than one column with **column-type** CENS (an exception will be thrown otherwise).

Possible values are -1, 1, 0 (string ‘.’ will be interpreted as 0) and an exception will be thrown if any other value is used.

- CENS = 1 means that the value in **response-column** ($y_{observed}$, the content of the column with **column-type** Y) is an upper limit \Leftrightarrow true observation y verifies $y < y_{observed}$
- CENS = 0 means the the value in **response-column** corresponds to a valid observation (no interval associated)
- CENS = -1 means that the value in **response-column** ($y_{observed}$) is a lower bound \Leftrightarrow true observation y verifies $y > y_{observed}$

LIMIT: limit for censored values.

A **data-set** shall not contain more than one column with **column-type LIMIT** (an exception will be thrown otherwise).

If a **data-set** contains a column with **column-type LIMIT**, it shall contain a column with **column-type CENS** (an exception is thrown otherwise).

Column **LIMIT** shall contain either a string that can be converted to a double or ‘.’ (non compliance will raise an exception).

- when column **LIMIT** contains a string that can be converted to a double and **CENS = 1**, then value y_{limit} in column **LIMIT** is interpreted as the lower bound of the observation interval \Leftrightarrow with $y_{observed}$ the value in the **response-column** (the content of the column with **column-type Y**), true observation y verifies $y_{limit} < y < y_{observed}$
- when column **LIMIT** contains a string that can be converted to a double and **CENS = -1**, then value y_{limit} in column **LIMIT** is interpreted as the upper bound of the observation interval \Leftrightarrow with $y_{observed}$ the value in the **response-column**, true observation y verifies $y_{limit} > y > y_{observed}$

B.2.7 Description of column-types used to define controls and events

EVID: event identification data item.

A **data-set** shall not contain more than one column with **column-type** EVID (an exception will be thrown otherwise).

- EVID shall contain an integer belonging to interval $[0 ; 4]$:
- EVID = 0 or ‘.’: observation event \Leftrightarrow the line is a **response-line**
- EVID = 1: dose event \Leftrightarrow the line is a **dose-line**
- EVID = 2: other event. UNUSED (exception thrown)
- EVID = 3: reset event. UNUSED (exception thrown)
- EVID = 4: reset dose event \Leftrightarrow indicates **wash-out**

Non-compliance with above format will raise exception.

Note: when a line is tagged (EVID = 0 or ‘.’) and the observation contained in column Y cannot be converted to a double value, an exception is thrown. Indeed since EVID = 0 indicates that the line is a **response-line** there is a contradiction if the content of Y cannot be converted to a double.

Note: when a line is tagged (EVID = 1, EVID = 4) with a string in **dose-column** (i.e. content of the column with **column-type** AMT) which cannot be converted to a double an exception is thrown (same rationale that in preceding note).

MDV: Missing dependent values.

It is possible to have in a **data-set** one or several columns with **column-type** MDV.

MDV shall contain only integers belonging to interval $[0 ; 2]$. Non-compliance will raise an exception.

When there are multiple MDV columns, a *synthetic* value MDV_{synth} is computed as:

- if MDV = 0 in all columns \Rightarrow MDV_{synth} = 0
- if MDV = 1 in at least one column \Rightarrow MDV_{synth} = 1
- if MDV = 2 in at least one column (and no column with MDV = 1) \Rightarrow MDV_{synth} = 2

When a line is tagged MDV = 1 then the value in column Y will not be taken into account (the value in **dose-column** - if any valid value is present - will be taken into account).

When a line is tagged **MDV = 0** AND if it contains a string convertible to a double value in **response-column** (the column with **column-type Y**) then the value is taken into account. Otherwise an exception will be thrown. Values in **dose-column** (the column with **column-type AMT**) will not be taken into account.

When a line is tagged **MDV = 2** then the value in **response-column** is not taken into account (the value in **dose-column**, if present, will be taken into account). The values in **regressions-columns** are taken into account.

MDV and EVID cross checks.

An exception is thrown when **MDV = 1** and **EVID = 0** (it is considered as a conflicting instruction since **EVID** indicates that line shall be a **response-line** and the **MDV** that data in the **response-column** shall be discarded).

An exception is also thrown when **MDV = 0** and **EVID = 1** (same reason as previously).

Appendix C

Preferences

This appendix provides the details of MONOLIX preferences. The preferences are defined in the `preferences.xmlx` file. The file is loaded when MONOLIX is started.

C.1 General

The user can modify the data to customize his own preferences.

1. Go to directory `/Path/To/lixoft/monolix/config/` and open the `preference.xmlx` file.
2. Modify the chosen fields, then save and restart MONOLIX if the software is opened.

Note : To restore default settings, just delete the file and restart.

This chapter describes the correspondences between the file data and preferences in MONOLIX.

C.2 Graphic settings

Generally, data are visual settings of graphics.

There are 3 kinds of patterns:

1. matrix - *value* corresponds to the number of rows and *vector* contains all the elements of the matrix.
2. list of chars - `<charList>` tag contains a set of tags `<char>` which have chars as value.
3. numeric value - can be a string, an integer or a real.

C.2.1 Categorized Data

Data	Description	Type
fill_cat_color	Color of theoretical distribution line	matrix
fill_out_color	Outliers color	matrix
fill_CI	Color of confidence intervals	matrix
line_LineStyle	Lines style	value
line_LineWidth	Lines width	value
line_Color	Lines color	matrix
bins_Color	Color of bins limit lines	matrix
figure_background	Color of figure background	matrix

C.2.2 Covariates

Data	Description	Type
data_Color	Data colors	matrix
data_Marker	Data markers	List of characters
data_MarkerSize	Size of data markers	value
spline_LineStyle	Line style of spline	value
spline_LineWidth	Line width of spline	value
spline_Color	Line color of spline	matrix
regression_LineStyle	Style of regression line	value
regression_LineWidth	Width of regression line	value
regression_Color	Color of regression line	matrix
line_LineStyle	Lines style	value
line_LineWidth	Lines width	value
line_Color	Lines color	matrix
figure_background	Color of figure background	matrix

C.2.3 Parameters distribution

Data	Description	Type
histo_Color	Histogram color	matrix
paramEstimatedPDF_LineStyle	Style of non parametric pdf line	value
paramEstimatedPDF_LineWidth	Width of non parametric pdf line	value
paramEstimatedPDF_Color	Color of non parametric pdf line	matrix
predictedPdf_LineStyle	Style of population distribution line	value
predictedPdf_LineWidth	Width of population distribution line	value
predictedPdf_Color	Color of population distribution line	matrix
predictedEstimatedPDF_LineStyle	Style of theoretical median line	value
predictedEstimatedPDF_LineWidth	Width of theoretical median line	value
predictedEstimatedPDF_Color	Color of theoretical median line	matrix
confidence_LineStyle	Style of confidence intervals line	value
confidence_LineWidth	Width of confidence intervals line	value
confidence_Color	Color of confidence intervals line	matrix
figure_background	Color of figure background	matrix

C.2.4 Individual fits

Data	Description	Type
data_Color	Data colors	matrix
data_Marker	Data markers	List of characters
data_MarkerSize	Size of data markers	value
cens_Color	Censored data colors	matrix
cens_Marker	Censored data markers	List of characters
cens_MarkerSize	Size of censored data markers	value
populationFits_Color	Color of population fits line	matrix
populationFits_LineStyle	Style of population fits line	value
populationFits_LineWidth	Width of population fits line	value
IndividualFits_Color	Color of individual fits line	matrix
IndividualFits_LineStyle	Style of individual fits line	value
IndividualFits_LineWidth	Width of individual fits line	value
percentile	Percentile marker	value
confidence_pop_color	Color of prediction interval line	matrix
confidence_pop_linestyle	Style of prediction interval line	value
median_pop_linestyle	Style of median line	value
median_pop_color	Color of median line	matrix
figure_background	Color of figure background	matrix

C.2.5 Joint distribution

Data	Description	Type
data_Color	Data colors	matrix
data_Marker	Data markers	List of characters
data_MarkerSize	Size of data markers	value
spline_LineStyle	Line style of spline	value
spline_LineWidth	Line width of spline	value
spline_Color	Line color of spline	matrix
regression_LineStyle	Style of regression line	value
regression_LineWidth	Width of regression line	value
regression_Color	Color of regression line	matrix
figure_background	Color of figure background	matrix

C.2.6 Predictions vs observations

Data	Description	Type
data_Color	Data colors	matrix
data_Marker	Data markers	List of characters
data_MarkerSize	Size of data markers	value
cens_Color	Censored data colors	matrix
cens_Marker	Censored data markers	List of characters
cens_MarkerSize	Size of censored data markers	value
spline_LineStyle	Line style of spline	value
spline_LineWidth	Line width of spline	value
spline_Color	Line color of spline	matrix
regression_LineStyle	Style of regression line	value
regression_LineWidth	Width of regression line	value
regression_Color	Color of regression line	matrix
figure_background	Color of figure background	matrix
segments_LineStyle	Line style of segments	value
segments_LineWidth	Line width of segments	value
segments_Color	Line color of segments	matrix

C.2.7 Residuals

Data	Description	Type
<code>data_Color</code>	Data colors	matrix
<code>data_Marker</code>	Data markers	List of characters
<code>data_MarkerSize</code>	Size of data markers	value
<code>cens_Color</code>	Censored data colors	matrix
<code>cens_Marker</code>	Censored data markers	List of characters
<code>cens_MarkerSize</code>	Size of censored data markers	value
<code>spline_LineStyle</code>	Line style of spline	value
<code>spline_LineWidth</code>	Line width of spline	value
<code>spline_Color</code>	Line color of spline	matrix
<code>line_LineStyle</code>	Lines style	value
<code>line_LineWidth</code>	Lines width	value
<code>line_Color</code>	Lines color	matrix
<code>bins_Color</code>	Color of bins limit lines	matrix
<code>plot_emp_color</code>	Color of empirical percentile line	matrix
<code>plot_emp_linestyle</code>	Style of empirical percentile line	List of characters
<code>plot_emp_linewidth</code>	Width of empirical percentile line	value
<code>plot_emp_marker</code>	Marker of outlier dots	value
<code>plot_emp_markersize</code>	Size of outlier dots marker	value
<code>plot_out_color</code>	Color of outlier dots	matrix
<code>plot_sim_color</code>	Color of theoretical percentile line	matrix
<code>plot_sim_linewidth</code>	Width of theoretical percentile lines	value
<code>plot_sim_linestyle</code>	Style of theoretical percentile lines	List of characters
<code>fill_cat_color</code>	Color of confidence interval	matrix
<code>fill_out_color</code>	Color of outliers area	matrix
<code>regression_LineStyle</code>	Style of regression line	value
<code>regression_LineWidth</code>	Width of regression line	value
<code>regression_Color</code>	Color of regression line	matrix
<code>histo_Color</code>	Histogram color	matrix
<code>empdens_LineStyle</code>	Style of empirical pdf line	value
<code>empdens_LineWidth</code>	Width of empirical pdf line	value
<code>empdens_Color</code>	Color of empirical pdf line	matrix
<code>thdens_LineStyle</code>	Style of theoretical empirical pdf line	value
<code>thdens_LineWidth</code>	Width of theoretical empirical pdf line	value
<code>thdens_Color</code>	Color of theoretical empirical pdf line	matrix
<code>figure_background</code>	Color of figure background	matrix

C.2.8 Spaghetti

Data	Description	Type
<code>data_Color</code>	Data colors	matrix
<code>data_Marker</code>	Data markers	List of characters
<code>data_MarkerSize</code>	Size of data markers	value
<code>cens_Color</code>	Censored data colors	matrix
<code>cens_Marker</code>	Censored data markers	List of characters
<code>cens_MarkerSize</code>	Size of censored data markers	value
<code>line_LineStyle</code>	Lines style	value
<code>line_LineWidth</code>	Lines width	value
<code>figure_background</code>	Color of figure background	matrix

C.2.9 Prediction distribution

Data	Description	Type
<code>data_Color</code>	Data colors	matrix
<code>data_Marker</code>	Data markers	List of characters
<code>data_MarkerSize</code>	Size of data markers	value
<code>fill_shading</code>	Prediction distribution area	matrix
<code>fill_shading_discrete</code>	Prediction distribution area in discrete case	matrix
<code>line_LineStyle</code>	Lines style	value
<code>line_LineWidth</code>	Lines width	value
<code>bins_Color</code>	Color of bins limit lines	matrix
<code>plot_emp_color</code>	Color of empirical percentile line	matrix
<code>plot_emp_linestyle</code>	Style of empirical percentile line	List of characters
<code>plot_emp_linewidth</code>	Width of empirical percentile line	value
<code>median_color</code>	Color of median line	matrix
<code>figure_background</code>	Color of figure background	matrix

For `fill_shading` and `fill_shading_discrete` settings, a 2×3 matrix is necessary, that corresponds to the two limit colors used to fill the areas.

C.2.10 VPC

Data	Description	Type
data_Color	Data colors	matrix
data_Marker	Data markers	List of characters
data_MarkerSize	Size of data markers	value
cens_Color	Censored data colors	matrix
cens_Marker	Censored data markers	List of characters
cens_MarkerSize	Size of censored data markers	value
line_LineStyle	Lines style	value
line_LineWidth	Lines width	value
line_Color	Lines color	matrix
plot_emp_color	Color of empirical percentile line	matrix
plot_emp_linestyle	Style of empirical percentile line	List of characters
plot_emp_linewidth	Width of empirical percentile line	value
plot_emp_marker	Marker of outlier dots	value
plot_emp_markersize	Size of outlier dots marker	value
plot_out_color	Color of outlier dots	matrix
plot_sim_color	Color of theoretical percentile line	matrix
plot_sim_marker	Marker of theoretical percentile	matrix
plot_sim_markersize	Size of theoretical percentile marker	matrix
plot_sim_linewidth	Width of theoretical percentile lines	value
plot_sim_linestyle	Style of theoretical percentile lines	List of characters
fill_cat_color	Color of confidence interval	matrix
fill_out_color	Color of outliers area	matrix
figure_background	Color of figure background	matrix

C.2.11 NPC - BLQ

Data	Description	Type
fill_cat_color	Color of theoretical CDF	matrix
fill_out_color	Color of median line	matrix
fill_CI	Color of confidence intervals	matrix
line_LineStyle	Lines style	value
line_LineWidth	Lines width	value
line_Color	Lines color	matrix
figure_background	Color of figure background	matrix

C.2.12 Time to event (Kaplan-Meier)

Data	Description	Type
<code>figure_background</code>	Color of figure background	matrix
<code>fill_shading</code>	Confidence interval area	matrix
<code>fill_shading_average</code>	Confidence interval area for average	matrix
<code>median_color</code>	Color of median line	matrix
<code>median_lineStyle</code>	Line style of median	value
<code>median_lineWidth</code>	Line width of median	value
<code>median_average_color</code>	Color of average median	matrix
<code>median_average_lineStyle</code>	Line style of average median	value
<code>median_average_lineWidth</code>	Line width of average median	value
<code>cens_Color</code>	Censored data colors	matrix
<code>cens_Marker</code>	Censored data markers	List of characters
<code>cens_MarkerSize</code>	Size of censored data markers	value
<code>average_color</code>	Average line color	matrix
<code>average_lineStyle</code>	Line style of average	value
<code>average_lineWidth</code>	Line width of average	value
<code>survival_color</code>	Survival function line color	matrix
<code>survival_lineStyle</code>	Survival function line style	value
<code>survival_lineWidth</code>	Survival function line width	value

For `fill_shading` setting, a 2×3 matrix is necessary, that corresponds to the two limit colors used to fill the areas.

C.2.13 Transition probabilities

Data	Description	Type
<code>figure_background</code>	Color of figure background	matrix
<code>line_LineStyle</code>	Lines style	value
<code>line_LineWidth</code>	Lines width	value
<code>bins_Color</code>	Color of bins limit lines	matrix
<code>line_LineStyle</code>	Lines style	value
<code>line_LineWidth</code>	Lines width	value
<code>line_Color</code>	Lines color	matrix

C.2.14 Prior distribution

Data	Description	Type
<code>figure_background</code>	Color of figure background	matrix
<code>confidence_LineStyle</code>	Style of confidence intervals line	value
<code>confidence_LineWidth</code>	Width of confidence intervals line	value
<code>confidence_Color</code>	Color of confidence intervals line	matrix
<code>histo_Color</code>	Histogram color	matrix
<code>nonParamPDF_LineStyle</code>	Style of non parametric pdf line	value
<code>nonParamPDF_LineWidth</code>	Width of non parametric pdf line	value
<code>nonParamPDF_Color</code>	Color of non parametric pdf line	matrix
<code>priorPDF_LineStyle</code>	Style of prior distribution line	value
<code>priorPDF_LineWidth</code>	Width of prior distribution line	value
<code>priorPDF_Color</code>	Color of prior distribution line	matrix
<code>medianPDF_LineStyle</code>	Style of theoretical median line	value
<code>medianPDF_LineWidth</code>	Width of theoretical median line	value
<code>medianPDF_Color</code>	Color of theoretical median line	matrix

C.2.15 Individual contribution

Data	Description	Type
<code>figure_background</code>	Color of figure background	matrix
<code>bar_Color</code>	Color of bars	matrix

For `bar_Color` setting, a 2×3 matrix is necessary, that corresponds to the two likelihoods.

C.2.16 Convergence of SAEM

Data	Description	Type
<code>figure_background</code>	Color of figure background	matrix

C.3 Session related settings

C.3.1 session

Field	Description	Type
<code>timestamp_value</code>	Use timestamping	value
<code>historic_size</code>	Size of historic file (projects, models)	value
<code>nbDatasetRows</code>	(see <code>nbShownColumns</code> in <code>dataSelection</code> gui)	value
<code>save_graphics_format</code>	Printed graphics format	value
<code>lockModels</code>	Lock possibility to modify models	value
<code>modelFilter</code>	Filter of structural model	'none', 'm' or 'mlxtran'
<code>useCurrentFolderByDefault</code>	Use current folder by default	value
<code>editor</code>	Editor to use	editor path

C.3.2 project

Field	Description	Type
<code>dosesToAddForSteadyState</code>	number of doses to simulate Steady state	value

C.3.3 gui**datasetSelection**

Field	Description	Type
<code>nbShownColumns</code>	number of columns to show	value
<code>nbRows</code>	number of rows to show (maximum 10)	value

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