



MONOLIX INSTALLATION GUIDE

Version 4.3.1

MARCH 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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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 Installation

2.1 Prerequisites

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

2.1.1 Linux specifics

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

2.1.2 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 About Installer

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

```
#> sh Monolix-4.3.1-matlab2010a-linux32.bin
or
#> sh Monolix-4.3.1-matlab2010bSP1-linux32.bin
or
#> sh Monolix-4.3.1-standalone2008b-linux32.bin
or
#> sh Monolix-4.3.1-matlab2010a-linux64.bin
or
#> sh Monolix-4.3.1-matlab2010bSP1-linux64.bin
or
#> sh Monolix-4.3.1-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.

2.3 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)

2.3.1 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

```

2.3.2 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
```

2.4 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`.

2.5 Installation use cases

2.5.1 Desktop

MONOLIX is installed on the computer of the user and the user has a personal activation key (see [Section 2.6.1 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.

2.5.2 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 2.6.1 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.

2.5.3 Application server with a shared MONOLIX installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.6.2 '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.

2.5.4 Application server with a remote connection

With a floating license MONOLIX is installed on a remote server using the procedure described in [Section 2.6.2 '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 2.6.1 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.

2.5.5 Application server with a desktop installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.6.2](#) '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.

2.5.6 Cluster installation with a shared MONOLIX installation

MONOLIX is installed on a master server using the procedure described in [Section 2.6.2](#) '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.

2.5.7 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 2.6.2](#) '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.

2.6 License

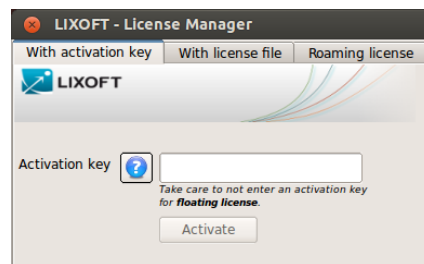
MONOLIX licenses can be of the following types:

- 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.

2.6.1 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.



2.6.2 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.

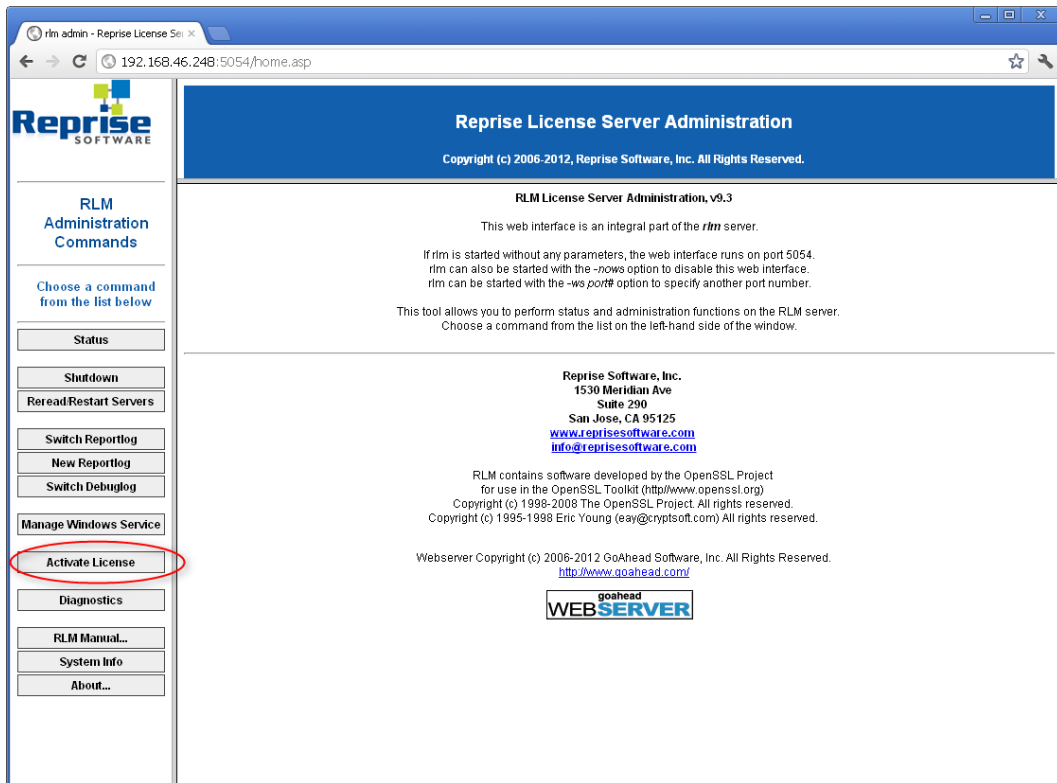
- If the web server port (5054) is not available you can launch RLM server with a new port by using the program option `-ws` (e.g: `rlm -ws 5055`) in this case, the access to RLM configuration through a web browser is done using the address `<IP>:<NEW PORT>` (e.g. `192.168.46.248:5055`).

- 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:

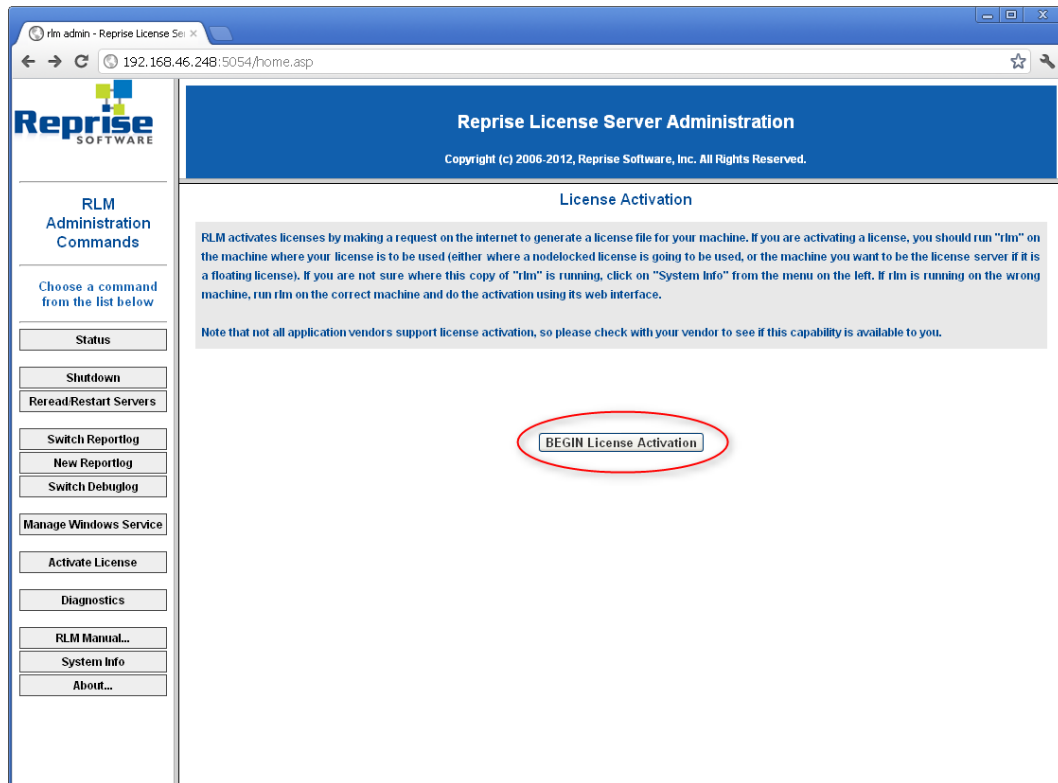
```
HOST <IP> <MAC ADDRESS> <NEW PORT>
```

e.g.

```
HOST 192.168.46.245 a8c0f82e 5060
```



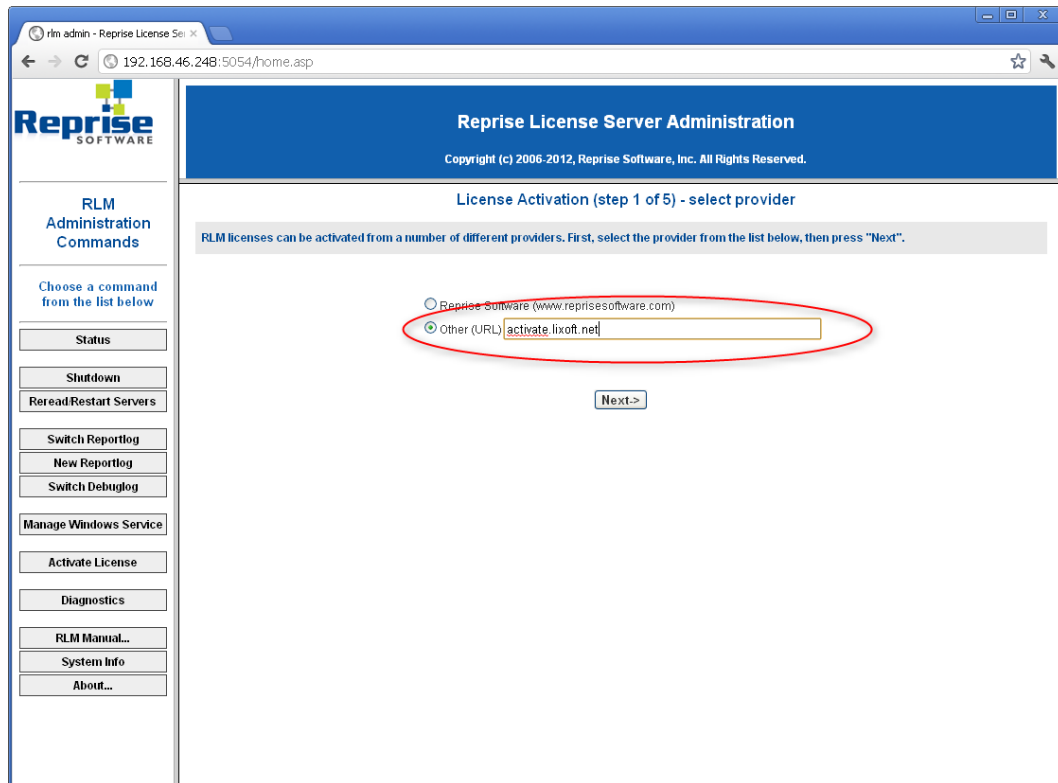
2. Begin license activation:



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



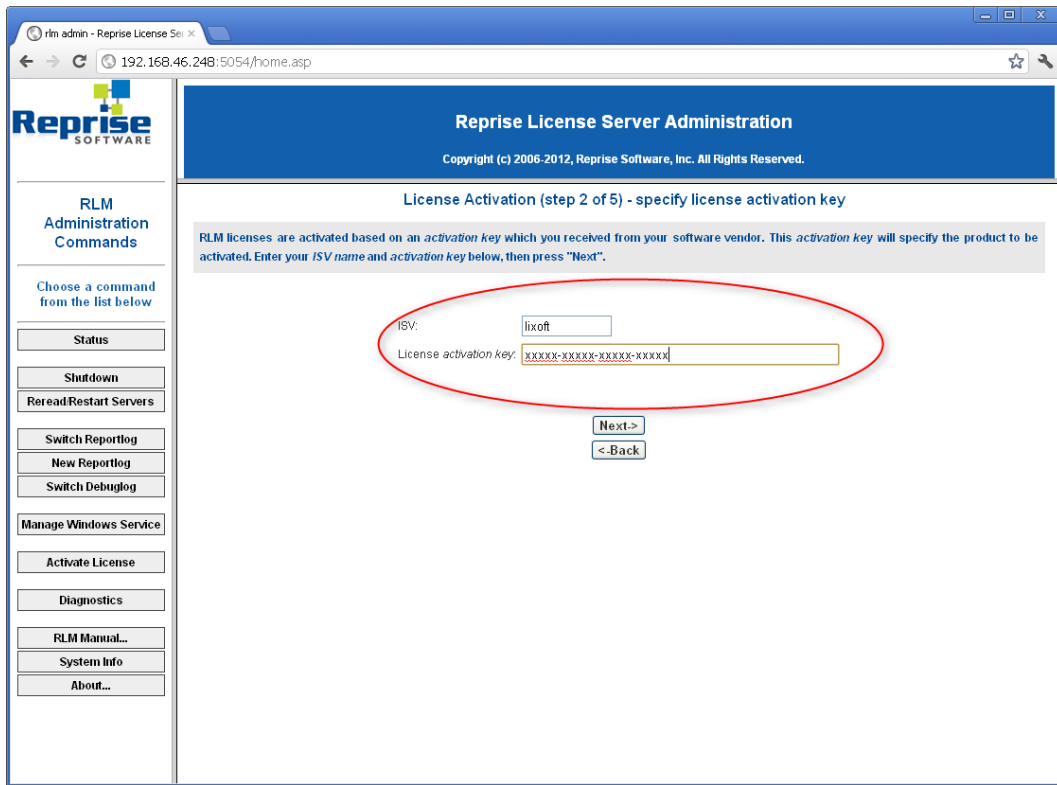
LIXOFT will send in return a '.lic' file which has to be copied in the directory

- `<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.

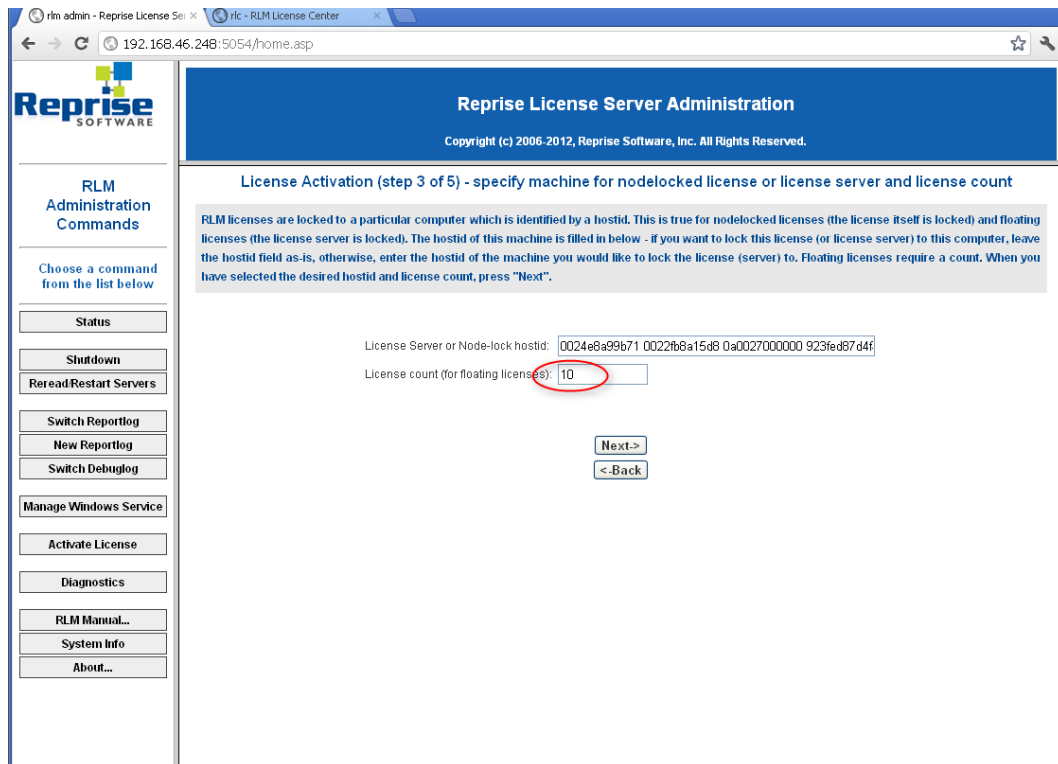
4. Activate the license.

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 :

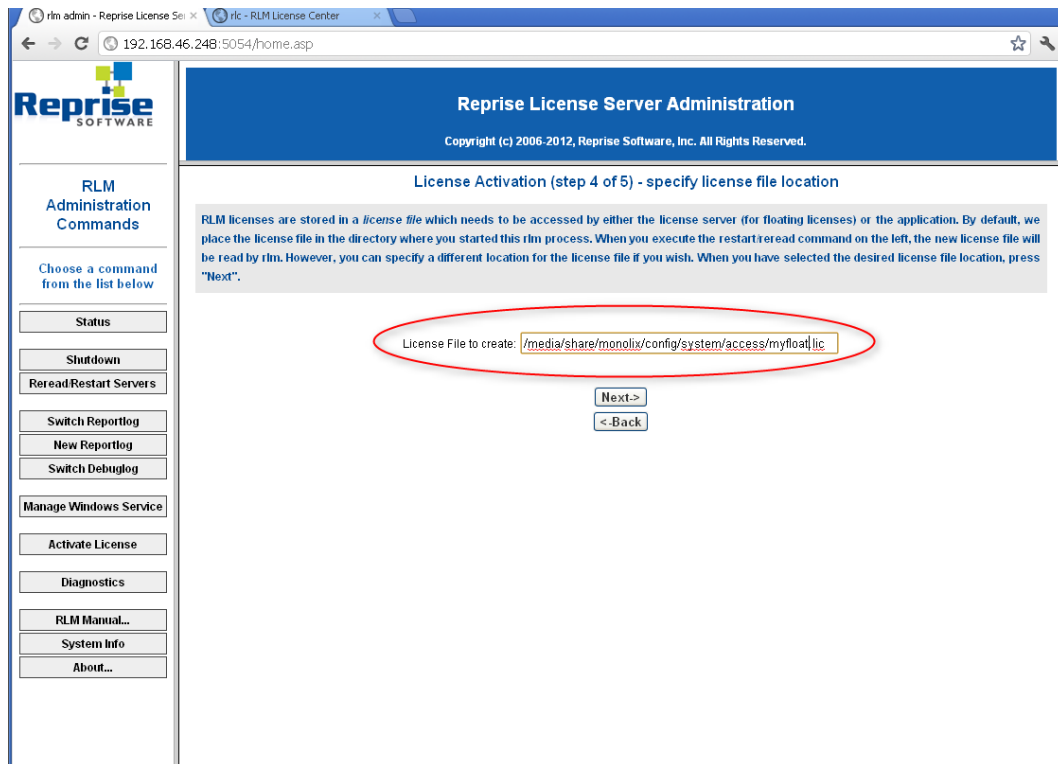
- If Monolix is installed on a shared space (i.e. each node of the cluster has an access to this directory), copy the license file into the directory
`<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
 or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

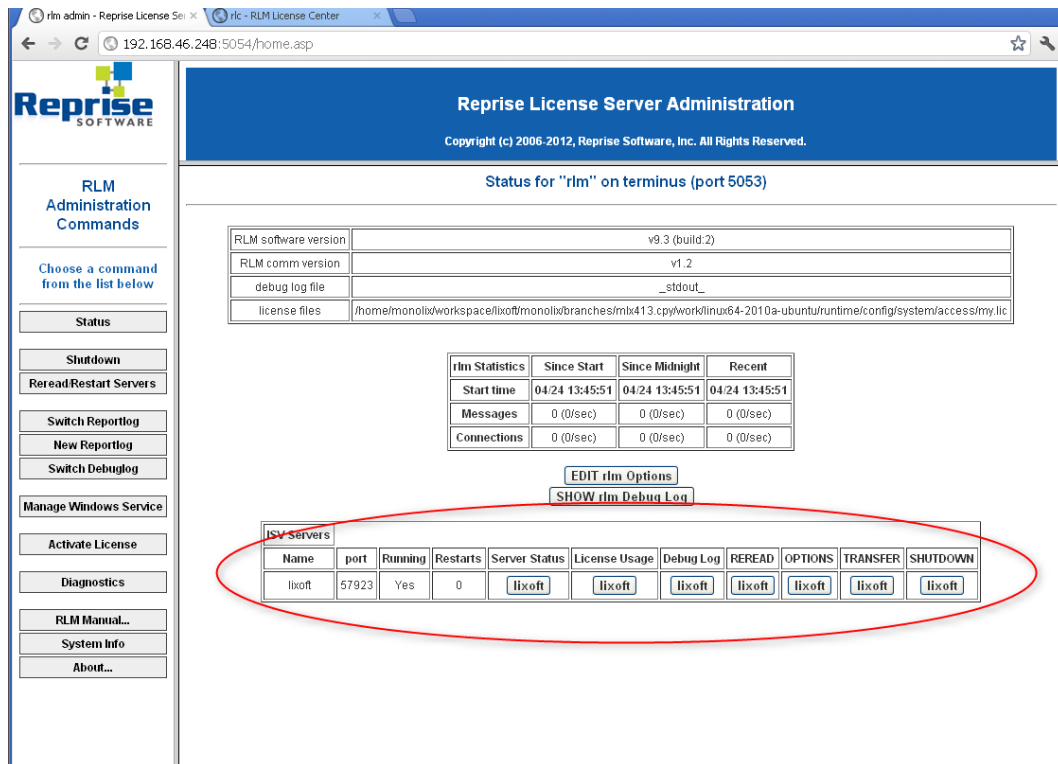
- The RLM server is executed on the computer **master-server**.
- MONOLIX is installed on each cluster node of the cluster.
- The license file is copied on **each cluster node** in the directory `<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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



Reprise License Server Administration
Copyright (c) 2006-2012, Reprise Software, Inc. All Rights Reserved.

Status for "rlm" on terminus (port 5053)

RLM software version	v9.3 (build:2)
RLM comm version	v1.2
debug log file	_stdout_
license files	/home/monolix/workspace/lixoft/monolix/branches/mlx413.cpy/work/linux64-2010a-ubuntu/runtime/config/system/access/my.lic

rlm Statistics	Since Start	Since Midnight	Recent
Start time	04/24 13:45:51	04/24 13:45:51	04/24 13:45:51
Messages	0 (0/sec)	0 (0/sec)	0 (0/sec)
Connections	0 (0/sec)	0 (0/sec)	0 (0/sec)

EDIT rlm Options
SHOW rlm Debug Log

ISV Servers										
Name	port	Running	Restarts	Server Status	License Usage	Debug Log	REREAD	OPTIONS	TRANSFER	SHUTDOWN
lixoft	57923	Yes	0	lixoft	lixoft	lixoft	lixoft	lixoft	lixoft	lixoft

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 :

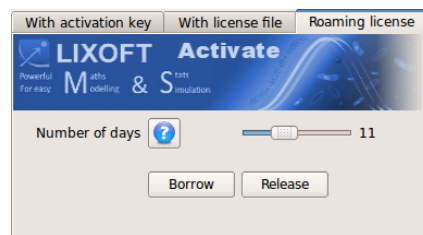
The documentation of the management of the RLM server provided by Reprise Software is available at

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

2.6.3 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>
```

3 Troubleshooting

3.1 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.

3.2 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/monolix431s/bin` in installation directory: for instance
`c:/ProgramData/Monolix/monolix431s/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.

4 ChangeLog

```
1 Monolix 4.3
2 Bugs Fixes:
3 - bug fix: when using estimators uncertainty, the correlations were
4   only simulated in 0,1 (instead of -1,1) .
5 - bug fix: predictions calculations could take too much time (even
6   hang) in presence of RTTE data
7 - bug fix: error when removing covariates from the project
8 - bug fix: error when all the observations of one subject are null in
9   combined2 (Fisher information matrix estimation)
10
11 Enhancements:
12 - GUI
13   -addition: monolix remembers now the last options selected in
14     simulation interface
15   -addition: included a checkbox in order the user can choose
16     among saving all the paths in relative or in absolute
17 - Algo
18   - Tables of population parameters and fisher after storing of
19     results
20 - Graphics
21   - new setting in RTTE graphic : accuracy of grid
22   - stratify saved in graphics with projects
23   - settings (axes, labels) saved in projects, and stored while
24     using of graphics
25   - export of graphics data
26 - MLXTran
27   - analytical solutions: ODE replaced by analytical solution when
28     keywords (as pkmodel, compartment, ...) are used. This
29     improves the processing time.
30   - DDE solver
31   - distribution functions (Student, Log-Normal...)
32   - ODE initial values can depend on time
33
34 Monolix 4.2.1 (2013-02-15)
35 Bugs Fixes:
36 - MLXTRAN Project : in STRUCTURAL_MODEL section resolved problem
37   with path relative to %MLXPROJECT%
38 - mlxEditor, mlxPerlScript : under Suse Linux OS, conflict with
39   libstdc++ and Qt librairies installed on the OS.
40 - Graphics : Kaplan Meier
41   - mean normalization
42   - survival curve: case of censured data
43 - simulations where wrong in presence of correlation between
44   individual parameters
45 - 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 Monolix 4.1.3-sp1 (2012-05-21)
159
160 Bug Fixes:
161     - GUI:
162         * Check Initial Fixed Effects interface crashed when creating
      covariate and parameter s sliders for some sizes
163
164 -----
165
166 Monolix 4.1.3 (2012-05-02)
167
168 New Features:
169     - MLXTran model: allows negative categories
170     - License management: uses RLM as license provider
171     - Compiler manager: adds the possibility to choose the embedded
      compiler
172     - The Monolix and Matlab versions are now stored in the algorithm
      result files
173
174 Bug Fixes:
175     - MLXTRAN project:
176         - continuous transformation can take a mathematical
      expression
177     - problem with structural model path
178     - 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
