



MONOLIX INSTALLATION GUIDE

Version 4.3.3

SEPTEMBER 2014

A software for the analysis of nonlinear mixed effects models

Maximum likelihood estimation

Model selection

Hypothesis testing

Graphical analysis

Data simulation

...

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

Contents

1	Downloading packages	4
2	Installation	5
2.1	Prerequisites	5
2.1.1	Linux specifics	5
2.1.2	Mac OS X 10.6 or higher specifics	5
2.1.3	Windows 64bits specifics	5
2.2	About Installer	5
2.3	Directory structure	7
2.3.1	Installation directory	7
2.3.2	User directory	8
2.4	Running MONOLIX	8
2.5	Installation use cases	9
2.5.1	Desktop	9
2.5.2	Desktop with a shared MONOLIX installation	9
2.5.3	Application server with a shared MONOLIX installation	9
2.5.4	Application server with a remote connection	9
2.5.5	Application server with a desktop installation	10
2.5.6	Cluster installation with a shared MONOLIX installation	10
2.5.7	Cluster installation with MONOLIX installed on each node	10
2.6	License	12
2.6.1	Desktop license	12
2.6.2	Floating license	12
2.6.3	Roaming license	22
3	Troubleshooting	23

3.1	Downloading MONOLIX	23
3.2	Running MONOLIX	24
4	ChangeLog	25

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, Mac OS X 10.6 or higher.

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.
 - Mac OS X 10.6 or higher / Matlab R2010bSP1 to R2011b
- Standalone versions:
 - Linux (32 bits)
 - Linux (64 bits)
 - Windows (32 bits)
 - Windows (64 bits)
 - Mac OS X 10.6 or higher

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 Mac OS X 10.6 or higher specifics

- You need `uudecode` to uncompress, and you need `install_name_tool` to configure the MONOLIX package (these are generally provided within the system).
- Make sure you have `gcc/g++/make` installed or install them by installing the command-line tools of Xcode.

2.1.3 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-4.3.3-matlab2010a-linux32.bin
```

or

```
#> sh Monolix-4.3.3-matlab2010bSP1-linux32.bin
```

or

```
#> sh Monolix-4.3.3-standalone2008b-linux32.bin
or
#> sh Monolix-4.3.3-matlab2010a-linux64.bin
or
#> sh Monolix-4.3.3-matlab2010bSP1-linux64.bin
or
#> sh Monolix-4.3.3-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.

- Mac OS X 10.6 or higher

- Matlab inter-active mode: the installer is a self-extractable archive. Run the following command:

```
#> sh Monolix-4.3.3-R2010b.bin
```
- Standalone mode: Double click on Monolix-4.3.3s.pkg and follow installer 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
├─ monolix433.....	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
│ ├─ libraries.....	LIBRARIES OF MODELS
│ ├─ 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
│ ├─ mlxeditor.....	DOCUMENTATION AND DEMOS FOR MLXTRAN EDITOR
│ └─ monolix.....	DOCUMENTATION AND DEMOS FOR MONOLIX
│ │ ├─ config.....	REFERENCE FOR CONFIGURATION FILES
│ │ ├─ 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
│   ├── config..... CONFIGURATION FILES
│   ├── license..... LICENSES
│   └─ monolix433..... MONOLIX VERSION DIRECTORY
│       ├── demos..... MODIFIABLE DEMOS
│       ├── log..... LOG FILES
│       ├── modules..... COMPILED MLXTRAN MODULES
│       ├── perlScripts..... PERL SCRIPTS
│       └─ tmp..... TEMPORARY 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`.
- Mac OS X 10.6 or higher
 - MATLAB version
 - * start MATLAB
 - * go to directory '`<install path>/matlab`' and type `monolix`.
 - Standalone version: go to the Applications folder of your computer (or where you have placed the executable), double click on `Monolix-4.3.3s.app`

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

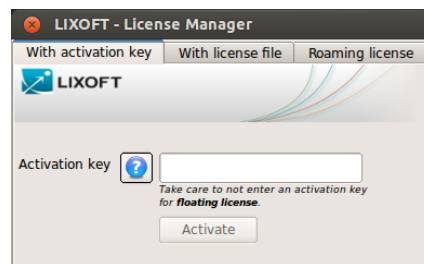
MONOLIX licenses can be of the following types:

- 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 .

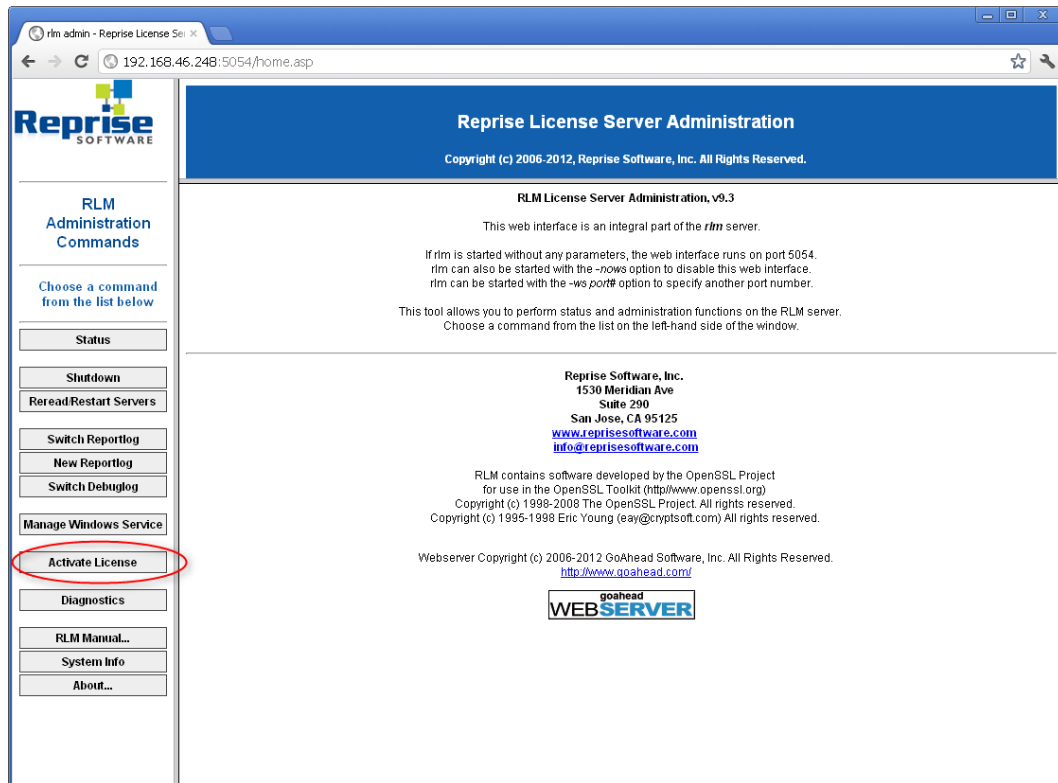
At this step there is no license available yet; the IT manager should use the RLM web server to download the license by following the procedure below:

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`).

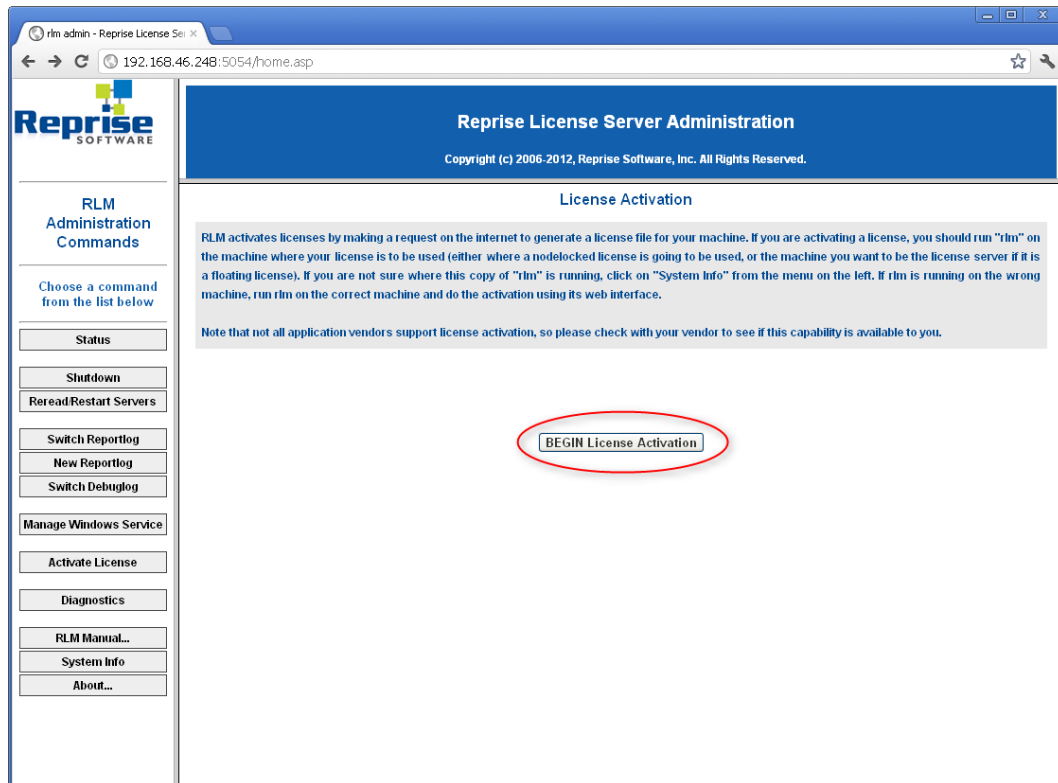
Notice that the RLM server opens two ports : 5053 and 5054. The first port (5053) is a service port used for the transactions of licenses. The second port (5054) is the RLM web server port used to access to the RLM configuration through a web browser.

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`



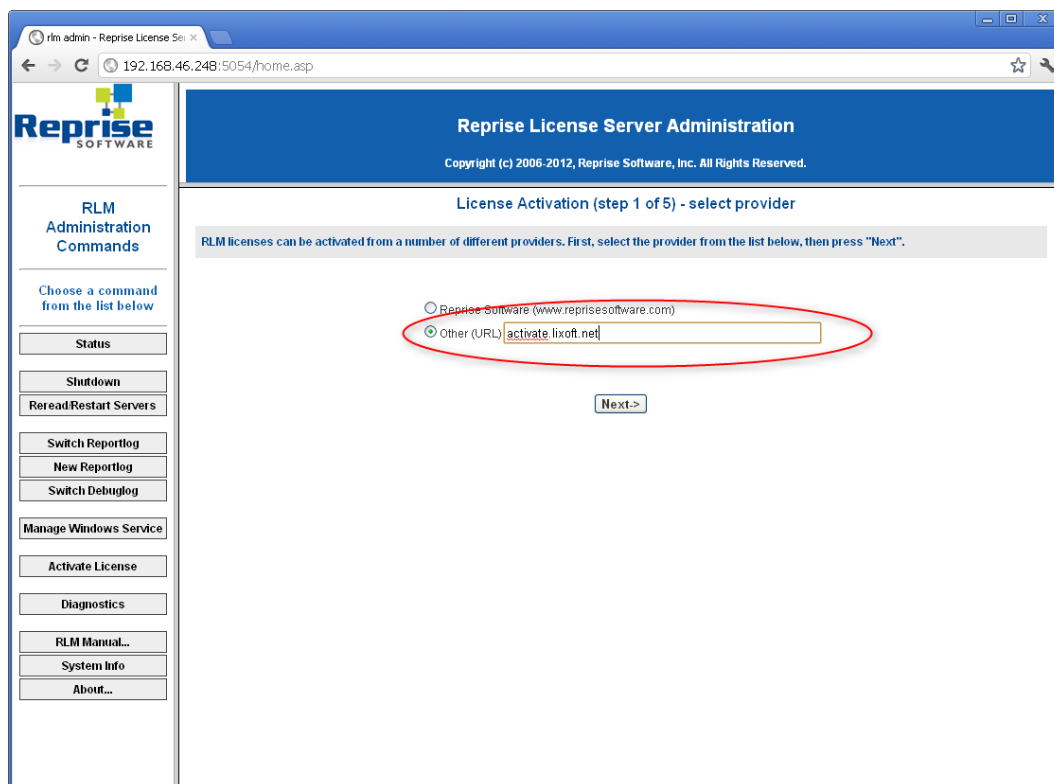
2. Begin license activation:



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



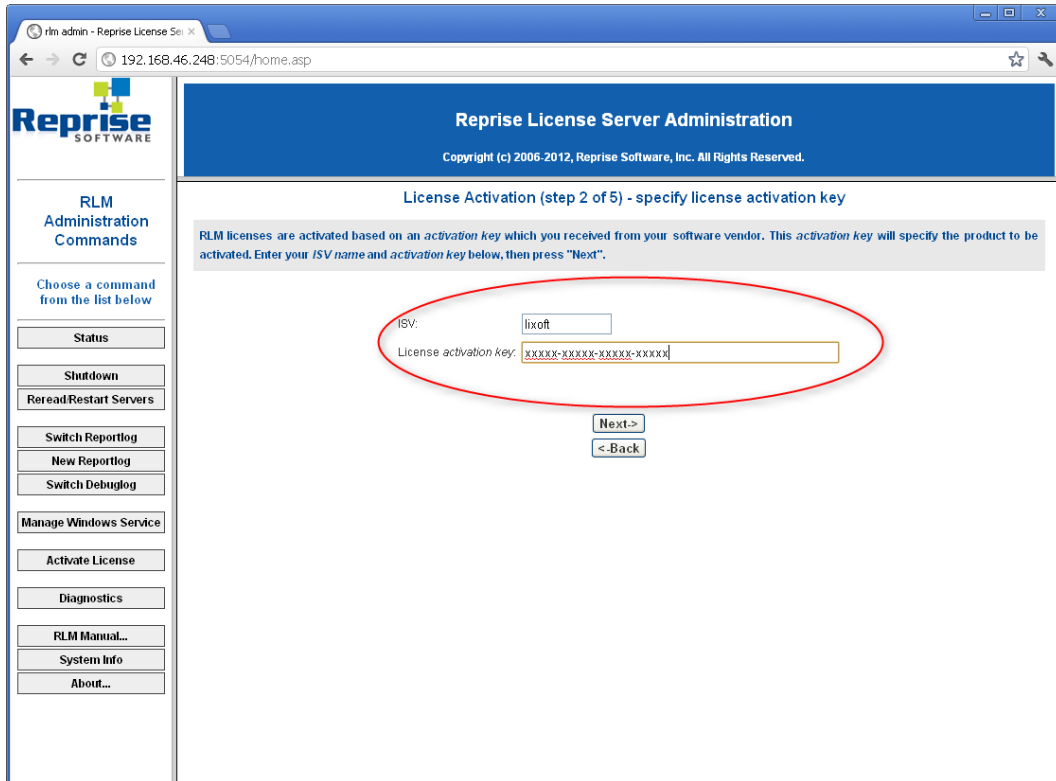
LIXOFT will send in return a '.lic' file which has to be copied in the directory

- <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.

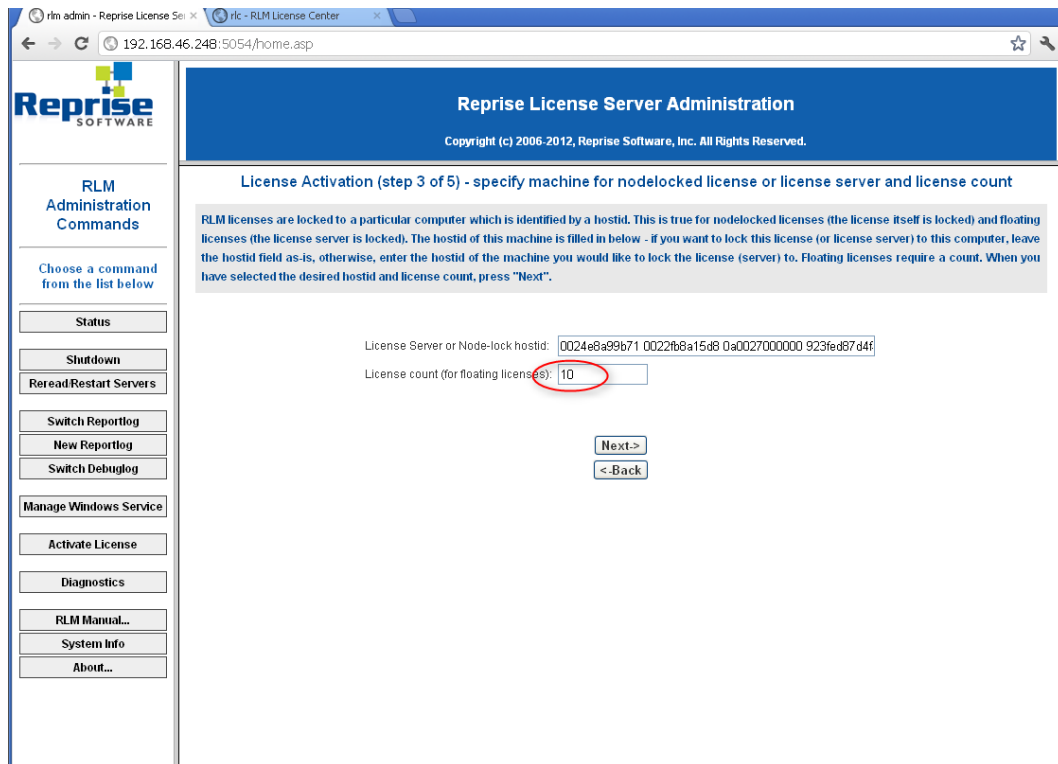
4. Activate the license.

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 :

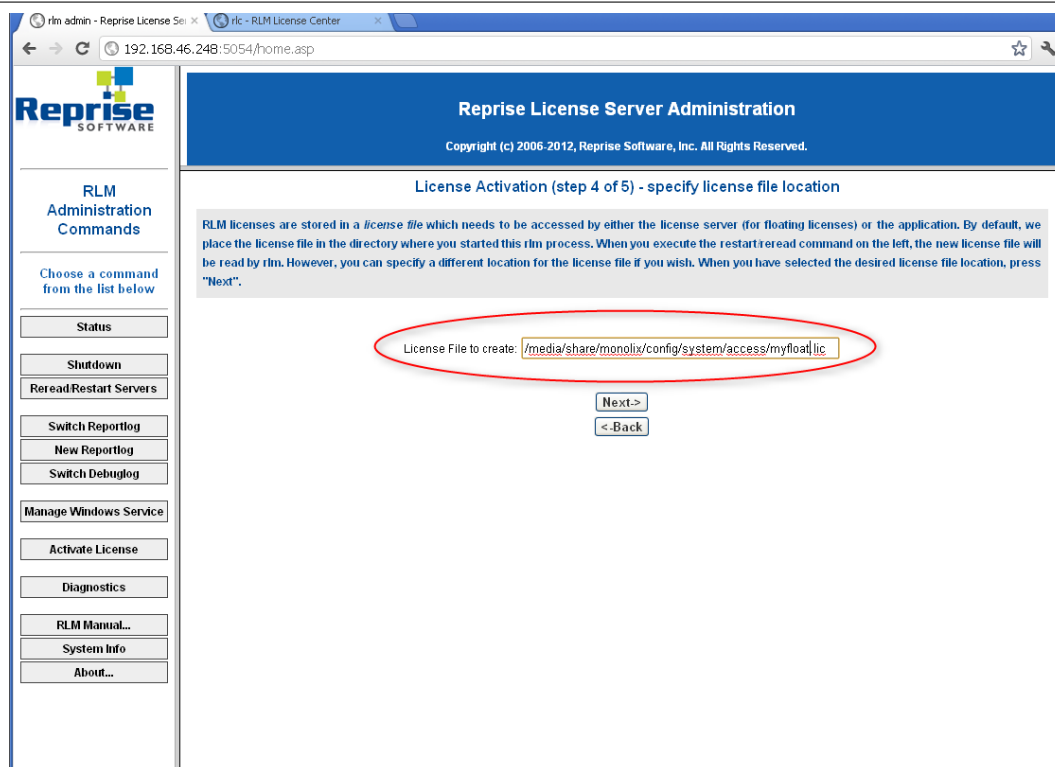
- If Monolix is installed on a shared space (i.e. each node of the cluster has an access to this directory), copy the license file into the directory
`<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

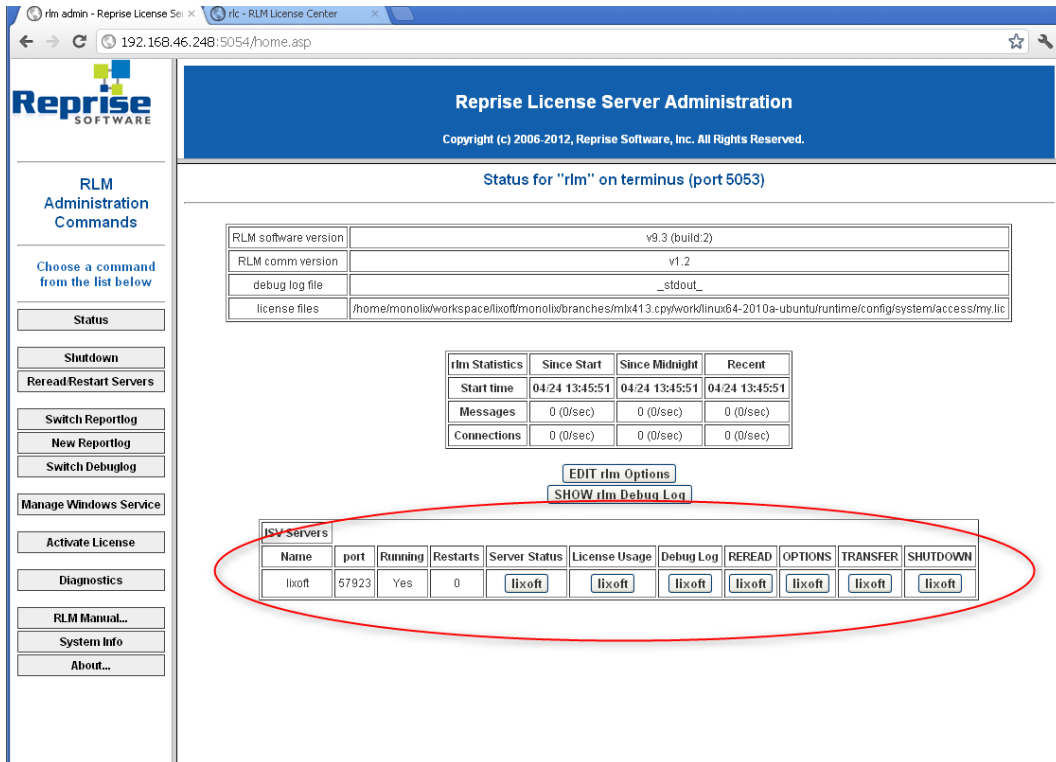
- The RLM server is executed on the computer **master-server**.
- MONOLIX is installed on each cluster node of the cluster.
- The license file is copied on **each cluster node** in the directory <monolix install path>/config/system/access/ for the MATLAB version of MONOLIX or <monolix install path>/bin/Monolix_mcr/runtime/config/system/access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

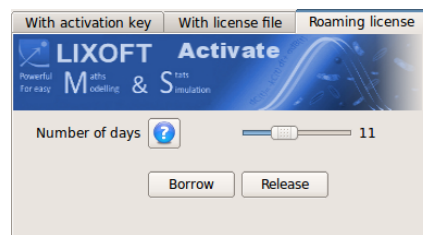
The documentation of the management of the RLM server provided by Reprise Software is available at

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/monolix433s/bin* in installation directory: for instance
`c:/ProgramData/Monolix/monolix433s/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 4.3.3 (2014-09)
- 2 Bug fixes:
- 3 - bug fix: fixed effects where not correctly initialized when they
were not simulated
 - 4 - bug fix: problems estimating autocorrelation (SAEM) and the
corresponding Fisher information matrix
 - 5 - bug fix: limits of the confidence intervals in VPC
 - 6 - bug fix: performance loss on Windows
 - 7 - bug fix: multiple runs of the Stand Alone version in a Windows ".
bat" script lengthened its "PATH" variable. It could get commands
ignored for being too long.
 - 8 - bug fix: On Windows 64 bits, spaces in user account's name
prevented the compilation for Mlxtran
 - 9 - minor bug fix: Display of the version of Monolix in Matlab help
 - 10 - bug fix: overlooked eliminations in secondary compartments for
analytical solutions
- 11 Enhancements:
- 12 - add configuration option for sysadmin to enforce number of
structural model threads and maximum computational matlab threads
 - 13 - change of the coefficient of simulated annealing
 - 14 - compatibility with Matlab 2014a
 - 15 - default naming convention changed to avoid extra use of '_':
 - 16 - covcategory instead of cov_category in parameter names
 - 17 - transformed covariates are called as tCov instead of t_Cov
 - 18 - latent covariate by default are now called lcat, lcat1, etc
 - 19 - Mlxtran compilation is shielded against system-wide configurations
set by compiler g95
 - 20 - warning for macro "elimination(C1)" if the volume isn't defined in
the base compartment "cmt". The default volume is still "volume
=1".
- 21
- 22 Monolix 4.3.2 (2014-05)
- 23 Bug Fixes:
- 24 - bug fix: several latent covariates made algorithms crash
 - 25 - bug fix: Fixed parameters are no longer modified in convergence
assessment
 - 26 - bug fix: in presence of several regresors, the x-label were not
correct set in some graphics
 - 27 - bug fix: datasets with EVID=2 or 3 were not correctly filtered when
some subjects did not have observations causing an error
 - 28 - bug fix: Covariates graphics represented simulated individual
parameters untransformed instead of the transformed ones when the
simulated ones were chosen
 - 29 - bug fix: autocorrelations were not correctly bounded when all the
subjects had only one observation
 - 30 - bug fix: license activate with combo

```
31 - bug fix: License Manager : when a license already existed (and was
    not expired), the licence Manager Interface did not download a
    new license file
32 - bug fix: License Manager : when a license file from <USERPATH>/
    lixoft/monolix/license was copied on itself the content of the
    file was erased
33 - bug fix: Matlab 2013 compatibility produced a loss of performances
34
35 Monolix 4.3.1 (2014-03)
36 Bugs Fixes:
37 - bug fix: Matlab 2013 compatibility
38 - bug fix: the 'TASKS' section of the Monolix project was not
    correctly parsed when graphicSetting or algorithmSetting
    contained '_a', '_b', '_c' which are tokens for the error model
39 - bug fix: Analytical Solution : pkmodel(ka,V,C1) failed when ka=1,C1
    =1 and V=1
40 - bug fix: tte graphics better grid ajustement
41 - bug fix: cond.mode estimation in presence of mixtures and other
    covariates were biased
42 - bug fix: fisher information matrix estimation could fail when only
    one parameter were estimated
43 - bug fix: SAEM failed when using variances set as "fixed" and
    covariate dependent variances.
44 - bug fix: problem preparing results in presence of priors with MAP
45 - bug fix: simulation with estimator uncertainty failed in presence
    of correlations between individual parameters
46
47
48 Enhancements:
49 - add an option '--log-file' to specify the location of the log file
50 -results
51 -population parameter names where changed to be more consistent
    with other Lixoft tools like mlXplore
52 -tables with estimations are now separated in:
53 - estimations.txt population parameters, standard errors (s.e)
    and relative standard errors (r.s.e)
54 - fim_lin.txt Fisher information matrix estimated by
    linearisation
55 - fim_sa.txt Fisher information matrix estimated by stochastic
    approximation
56 - tables with estimations includes now also the effects for
    reference categories (fixed to zero).
57
58
59 Monolix 4.3 (2014-02)
60 Bugs Fixes:
61 - bug fix: when using estimators uncertainty, the correlations were
    only simulated in 0,1 (instead of -1,1) .
```

```
62 - bug fix: predictions calculations can take too much time (even hang
    ) in presence of RTTE data
63 - bug fix: error when removing covariates from the project
64 - bug fix: error when all the observations of one subject are null in
    combined2 (Fisher information matrix estimation)
65
66 Enhancements:
67   - GUI
68     - addition: monolix remembers now the last options selected in
        simulation interface
69     - addition: checkbox for the user to choose among saving the
        paths as relative or absolute addresses
70   - Algo
71     - Tables of population parameters and fisher after storing of
        results
72   - Graphics
73     - new setting in RTTE graphic : accuracy of grid
74     - stratify saved in graphics with projects
75     - settings (axes, labels) saved in projects, and stored while
        using the graphics
76     - export of graphics data
77   - MLXTran
78     - analytical solutions: ODE replaced by analytical solution when
        keywords (as pkmodel, compartment, ...) are used. This
        improves the processing time.
79     - DDE solver
80     - distribution functions (Student, Log-Normal...)
81     - ODE initial values can depend on time
82
83 Monolix 4.2.1 (2013-02-15)
84 Bugs Fixes:
85   - MLXTRAN Project : in STRUCTURAL_MODEL section resolved problem
        with path relative to %MLXPROJECT%
86   - mlxEditor, mlxPerlScript : under Suse Linux OS, conflict with
        libstdc++ and Qt librairies installed on the OS.
87   - Graphics : Kaplan Meier
88     - mean normalization
89     - survival curve: case of censored data
90   - simulations where wrong in presence of correlation between
        individual parameters
91   - MLXTRAN Model :
92     - Events could be close at a numerical epsilon for the solver
        , but not for the solver driver
93     Rarely, it resulted into an explicit integration failure,
        returning "NaN"
94   - For the simulation of RTTE models, the ordering of the
        output names had to be alphabetical
```

```

95         - Not declaring all regression variables that where selected
          from the data set crashed the application.
96         - Declaring some PK without actual doses within the data set
          raised an error.
97         - Using the deprecated syntax with several lagged
          compartments returned "NaN"
98     - Algorithms
99     - Error when some subjects had no doses in conditinal mode
      computation
100    - GUI
101        - "Display the data" button did not update the information
          when the dataset was changed after running algorithms
102        - Convergence assessment GUI failed when there was only one
          individual parameter
103        - structural models with several dots (.) were not compiled
          when clicking in the compile button in the Model
          selection GUI
104        - projects with more outputs in structural model than
          observations in dataset caused an error when it was
          loaded
105        - the editor was not saved in the preference file
106            - Convergence assessment graphics did not handled
              correctly when there was not variance on some
              parameters or their covariate dependence
107
108    Enhancements:
109        - add possibility to configure the compiler (used to create
          Structural Model plugins) through the file 'system.xmlx'
110        - user API:
111            - it is now possible to use matlab function "ver" to know
              Monolix version and Monolix API version
112        - mlxEditor:
113            - allow multiple files selection on open file dialog box
114            - add 'Find and replace'
115            - set tabs movable
116        - MLXTRAN Model :
117            - Continuous observations can be declared within the model.
118            - Macro for a depot absorption, with a target ODE component.
119        - Permutation kernel for mcmc included
120
121    Other:
122        - Licensing system : '.ini' files desactivated (only the '.lic'
          files are allowed)
123        - residual error models in main interface are now displayed with
          their full name (those used in MLXTRAN project and model)
124    -----
125
126    Monolix 4.2.0 (2012-11-26)

```

```
127
128 Bugs Fixes:
129   - MLXTRAN Project : in OBSERVATION section when a prediction has
      the same name as an individual parameter the project parses
      fail
130   - PerlScript : bug with parameter '--use-matlab=false' was taken
      as 'true'
131   - Identity line works in observations vs predictions graphic
132   - Prediction distribution : percentiles are correctly displayed
133   - Color when stratify in covariables graphic
134   - Problem with prior (by default prior is Variance and not
      Standard Deviation, this implies a syntax error (
      standardDeviation <-> variance)
135   - Wrong data file for the demonstration project
      rtteWeibullCount_project.mlxtran
136   - "Display the data" button did not work
137   - bug when unchecking and checking "random effects" variability
      in simulation interface
138
139 Enhancements:
140   - Interval censoring for continuous data
141   - Extended priors on fixed effects
142   - Mlxtran model and Mlxtran project editor
143   - Perl script HMI
144   - Autosave
145   - Multiple covariate definitions
146   - Add batch-mode demo
147   - Add a doc package and a rlm server package (floating license
      server)
148   - Graphic
149     - BLQ graphic : possibility to choose its own interval of
      censored data
150     - Reorganisation of panel for the list of graphics
151     - Background color for each graphic in preferences
152     - When split, limits are the same for all axes
153     - Obs. vs Pred., observations can be relied by individual
154     - Optimal bandwidth setting for parameter distribution
155     - CvSaem graphic : choice of axes number
156   - Interval-censored data and maximum number of events for time-to-
      event and drop-out data models
157   - Markov chain for categorical data
158   - Continuous-time Markov process for categorical data
159   - probit and normal cdf for Mlxtran model
160   - New user API including simulation-estimation, convergence
      assessment and simulations tools
161   - Possibility to define new covariates as transformation of
      already defined ones
162
```

```
163 New graphics:
164     - Posterior and prior functions for bayesian
165     - Individual contribution for the LL
166     - Transition probabilities
167     - Kaplan-Meier survival function
168
169 New tables:
170     - Individual contribution to log-likelihood
171     - Covariates summary
172 -----
173
174 Monolix 4.1.4 (2012-07-16)
175
176 Bugs Fixes:
177     - Saving preferences from tools menu failed.
178     - Display remaining time (license) correctly.
179     - Problem with license activation file path.
180     - Add license agreement into Linux installer.
181     - The horizontal slider in "Check initial fixed effects"
      interface did not appear for some number of individual
      parameters.
182
183 Enhancements:
184     - Windows 64 RC.
185     - Management of the maximum number of threads for MLXTran models
      (can be set from the preference tools: MonolixGUI->Tools->
      Preference)
186     - License activate: inform user to not set activation key
187       if the license is a floating license.
188     - Documentation :
189       * Installation guide : Windows 64 bits.
190       * User Guide : Cluster section revised.
191       * Model MLxTRAN : list of keywords of the language.
192
193 -----
194
195 Monolix 4.1.3-sp2 (2012-05-29)
196
197 Enhancements:
198     - system.xmlx : possibility to hide Lixoft Activate display.
199     - Lixoft Activate : add the possibility to send an email with
200       encoded computer information to create license @Lixoft.
201     - Lixoft Activate : manage "cannot connect to url" error by
      asking user to go on a web site or to send an email.
202
203 Bugs Fixes:
204     - IOV Problem with R2010bSP1
```

```
205     - perlScripts : bug in the management of the configuration file
206       for [program-execute-options] and run on a cluster.
207     - add 'rlmutil.exe' for windows packages (forgotten in previous
208       packages).
209     - problem floating license.
210     - warnings for occasions without dose were removed.
211     - when the last Individual/Occasion had no dose, Monolix crashed.
212     - When there were syntax errors in the structural model, monolix
213       said that it could not find the file instead of giving the
214       MLXTRAN message
215     - NaN observations are now mentionned as error when algorithms
216       are launched.
217     - Update documentation : in batch mode section, there is a bad
218       path.
219
220 -----
221
222 Monolix 4.1.3-sp1 (2012-05-21)
223
224 Bug Fixes:
225     - GUI:
226         * Check Initial Fixed Effects interface crashed when creating
227           covariate and parameter s sliders for some sizes
228
229 -----
230
231 Monolix 4.1.3 (2012-05-02)
232
233 New Features:
234     - MLXTran model: allows negative categories
235     - License management: uses RLM as license provider
236     - Compiler manager: adds the possibility to choose the embedded
237       compiler
238     - The Monolix and Matlab versions are now stored in the algorithm
239       result files
240
241 Bug Fixes:
242     - MLXTRAN project:
243         - continuous transformation can take a mathematical
244           expression
245         - problem with structural model path
246     - MLXTRAN model:
247         - Under Linux 64 bits, due to library conflicts with Matlab
248           R2010b and following versions, the multi-threaded
249           loading of the model description for the project
250           occasionally fails
```

```
240         - The last table variable only is recorded, overwriting the
           first one
241     - Graphics:
242         - log / linear works on all graphics
243         - when log-log scale is set for "observed versus predicted",
           the diagonal line is not displayed anymore
244     - GUI:
245         - editor call did not work
246     - Algorithms:
247         * bug for individuals without some type of observations and
           with IOV computing conditional mode
248         * bug when there were continuous outputs after discrete
           outputs
249         * Fisher Information Matrix by Stochastic Approximation does
           now handle the case better when there is
250         no parameter to estimate in the residual error
251     - Session:
252         * when the directory monolixData/monolix<version> is renamed
           during an active Monolix session, stopping
253         Monolix caused an exit of Matlab.
254
255 -----
256
257     Monolix 4.1.2: (2012-03-05)
258
259 -----
260
261 New Features:
262     - PerlScripts : possibility to save the results in the project
           directory instead of the output directory
263     - In system.xmlx : automatically creates a directory hierarchy
           for "monolixData" path
264
265 Enhancements:
266     - MLXTran (structural model) multi-threading processing
           enhancement
267
268 Bug Fixes:
269     - Batch Processing failed when a very large number of projects
           were launched
270     - MDV column: when MDV=2 only the regression variables were taken
           into account
271     - Fixed a bug in graphics saving
272     - Fixed error when an empty result folder was timestamped
273     - Simulation of categorical data, whenever no category 0 is
           defined
```



```
275     - Fixed take into account UserPath defined in 'system.xmlx' for
      the preference file saving
276
277
278 -----
279
280     Monolix 4.1.1: (2012-02-13)
281
282 -----
283
284     New Features:
285     - timestamped backup
286     - preferences interface
287     - tools menu for activating license and preferences
288     - option for locking structural model modifications
289     - Project-MLXTRAN grammar modification : initialization of
      parameter is written now as beta_{pi,cov}, pop_{pi}, omega_{
      pi}, ...
290     - save graphics as png / ps / jpg / bmp or tiff
291     - selection of graphics/tables to be saved
292
293     Bug Fixes:
294     - Project-MLXTran: user can define the result folder
295     - LoQ difference between 3.2 and 4.1
296     - statistical test for error model and covariate model
297     - xmlx loading from 3.2 to 4.1
298     - correlation (levelName consistence with IOV) + parser error
299     - observation model (prediction = observation name)
300     - path for MONOLIX user profile can include special characters
301
302
303
304 -----
305
306     Monolix 4.1.0: (2012-01-23)
307
308 -----
309
310     psmlx:
311     - compatible with the mlxtran format of projects
312     - available on Windows OS
313
314     mlxtran:
315     - new syntax
316     - PK macros
317     - RTTE models
318
319     license:
```

```
320     - interface to install the license file
321
322 Interface:
323     - setting for axes' limits
324     - information for the observation model
325     - shortcut for model libraries
326
327 File system:
328     - improved handling of special characters for filepaths
329
330 Demos:
331     - updated for the new mlxtran syntax
332     - dispatch of the model library for demos
333
334 Known Bugs:
335     - under Windows OS, user directory cannot contain special
      characters other than spaces
336
337
338
339 -----
340
341 Monolix 4.0.1: (2011-10-27)
342
343 -----
344
345 psmlx:
346     - use-matlab option didn't work in command line mode
347     - multi-threading : multithreading didn't work
348     - take into account the p.coded files
349
350 mlxtran
351     - problem with FIM options : both linearization and
      stochasticApproximation appeared after a save with
      stochasticApproximation option set
352     - avoid the unloading of project when settings files does not
      exist : default settings are loaded
353 license:
354     - multi write database didn't work well in multi-threading mode
355
356 Interface:
357     - save lists
358     - configuration panel
359     - launching some graphics alone is now possible
360     - graphics were closed when "Use last estimates" were used
361     - when monolix was launched twice without loading or creating a
      project, two toolbars were created
362
```

```
363 Algorithm and simulations:
364     - simulation works now with dataset without EVID column and with
      MDV column
365
366 Results:
367     - the graphics fit now to the paper in .ps files
368     - xLabels were wrong for some graphics when several regression
      variables were present
369     - some graphics crashed when launched after some hypotheses
      tests were done
370     - Visual studio redistribuable problem
```
