



MONOLIX INSTALLATION GUIDE

Version 4.2.1

FEBRUARY 2012

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. On Windows XP/Vista/Seven 64 bits, MONOLIX standalone version can run in 32 bits mode.

Choice of MONOLIX versions

- MATLAB versions:
 - Linux matlab-r2010b-r2011a-r2011b-r2012a (64 bits)
 - Linux matlab-r2009a-r2010a (32 bits)
 - Linux matlab-r2010b-r2011a-r2011b-r2012a (32 bits)
 - Linux matlab-r2009a-r2010a (64 bits)
 - Windows (seven and vista) matlab-r2009a-r2010a (32 bits)
 - Windows (seven and vista) matlab-r2010b (32 bits). Due to bugs in MATLAB 2010b, it is strongly recommended to use MATLAB 2010b-SP1.
- Standalone versions:
 - Linux (32 bits)
 - Linux (64 bits)
 - Windows (32 bits)
 - Windows (64 bits)¹

¹MONOLIX will run in 32 bits mode

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

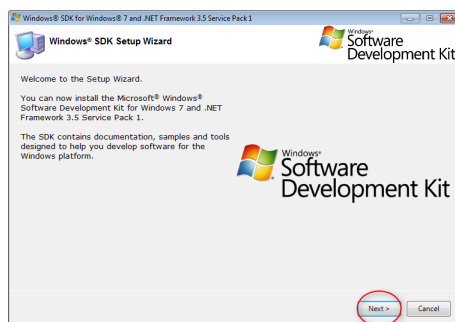
- install `sharutils` : `uudecode` is required to uncompress the MONOLIX package;
- make sure you have `gcc/g++/make` installed or install them.

2.1.2 Windows 64bits specifics

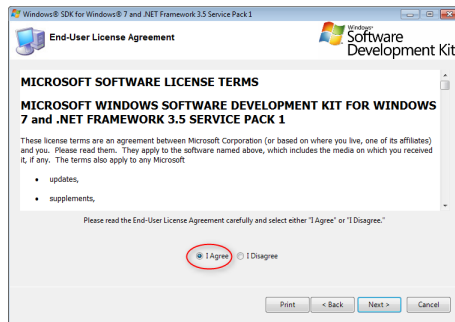
The 32 bits *standalone* version of MONOLIX runs fine on Windows 7 64bits. You will need to install the 64 bits Windows version of MONOLIX in any of these situations:

- On other 64 bits versions of Windows (non Windows 7);
- 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.

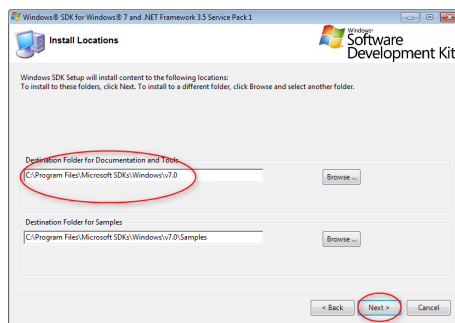
The installer of the 64 bits Windows version of MONOLIX executes the Windows SDK installer. This SDK embeds the C++ compiler required to generate MLXTRAN modules. The installation process is as follows:



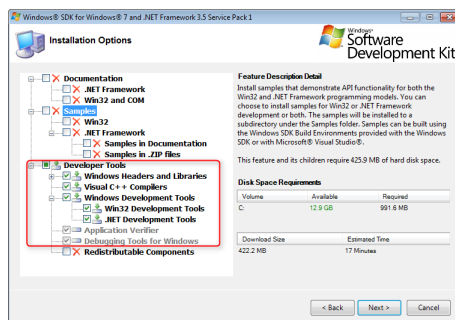
Welcome page of the SDK installer: click on 'next' button to continue;



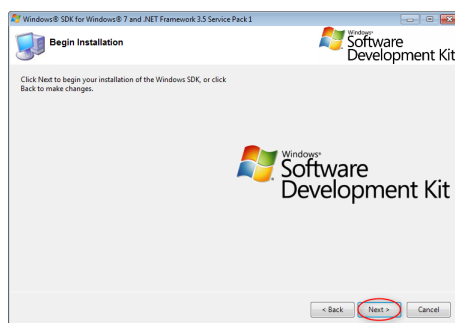
License agreement page: accept the agreement by selecting 'I agree', then click on 'next' button to continue;



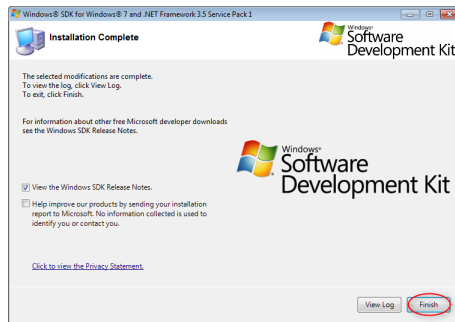
Choose the installation path. The proposed directories are required by MONOLIX ;



The component used by MONOLIX are the compiler only, therefore it is not necessary to install documentation and samples.



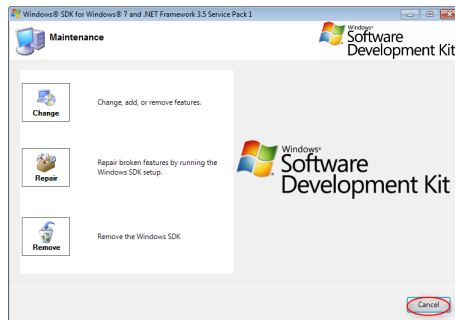
On 'Begin installation' page, click on 'next' button to continue;



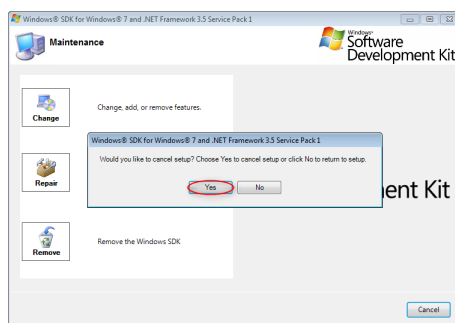
On 'Installation complete' page click on 'finish' button to continue;

After completion of the SDK installation procedure, the MONOLIX installer resumes the MONOLIX installation procedure.

If the SDK was already installed on the computer, the SDK installer will propose a list of actions:



No action is necessary, click on 'Cancel';



Confirm the 'Cancel' choice by clicking on 'Yes' button.

2.2 About Installer

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


```
#> sh Monolix-4.2.1-matlab2010a-linux32.bin
```

 or


```
#> sh Monolix-4.2.1-matlab2010bSP1-linux32.bin
```

```

or
#> sh Monolix-4.2.1-standalone2008b-linux32.bin
or
#> sh Monolix-4.2.1-matlab2010a-linux64.bin
or
#> sh Monolix-4.2.1-matlab2010bSP1-linux64.bin
or
#> sh Monolix-4.2.1-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,
- the personal user directory containing the MONOLIX workspace and documentation

2.3.1 Installation directory

```

Monolix.....MONOLIX ROOT DIRECTORY
├── monolix413.....MONOLIX VERSION DIRECTORY
│   ├── bin.....TOOLS DIRECTORY
│   ├── config.....CONFIGURATION FILES
│   ├── Demos.....SET OF DEMOS (COPIED IN MONOLIX USER DIRECTORY)
│   ├── graphics.....GRAPHICS CONFIGURATIONS
│   │   ├── listOfGraphics.....GRAPHICS PREDEFINED CONFIGURATIONS
│   │   ├── project.....GRAPHICS DEFAULT CONFIGURATIONS FOR MLXTRAN
│   │   └── settings.....GRAPHICS DEFAULT CONFIGURATIONS
│   ├── scenario.....PREDEFINED SCENARI
│   └── session.....MONOLIX SESSION 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
—	reference	REFERENCE PROJECT FOR THE VALIDATION SUITE
—	tools	EXTERNAL TOOL USED BY MONOLIX (CMAKE)

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,

monolixData.....	MONOLIX ROOT DIRECTORY
— monolix413.....	MONOLIX VERSION DIRECTORY
— doc	MONOLIX DOCUMENTATION
— log.....	LOG FILES
— script_modules.....	COMPILED MLXTRAN MODULES
— perlScripts	PERL SCRIPTS
— work.....	USER WORKING DIRECTORY
— Demos.....	MODIFIABLE DEMOS
— license.....	TOOLS DIRECTORY
— config.....	CONFIGURATION FILES
— tmp.....	SET OF DEMOS (COPIED IN MONOLIX USER DIRECTORY)

2.4 About Plugins

MONOLIX can embed the BiM plugin, a faster and more accurate ODE solver, not included by default due to its license restrictions. The plugin must therefore be downloaded and installed separately:

- Linux
 - libBim.tgz (using the command: `tar xzf libBim.tgz` or your graphical archiver)
 - copy the files stored in the directory libBim into the library directory of MONOLIX :
 - * for the MATLAB version : `<install path>/lib`
 - * for the standalone version : `<install path>/bin/Monolix_mcr/runtime/lib`
- Windows : copy libBim.dll into the library directory of MONOLIX :
 - for the matlab version : `<install path>\lib`

- for the standalone version : `<install path>\bin\Monolix_mcr\runtime\lib`
With the standalone version of MONOLIX the directory `<install path>` is located at:
 - * under Window XP or Windows Server 2003:
`c:\Documents And Settings\All Users\Application Data`
 - * under Window Vista, Windows 7 or Windows Server 2008:
`c:\ProgramData`
- Important notice:** these directories may be hidden by the operating system, thus you have to configure your file browser for access.

2.5 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`.

2.6 Installation use cases

2.6.1 Desktop

MONOLIX is installed on the computer of the user and the user has a personal activation key (see [Section 2.7.1 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 `monolixData` is created in the user home directory) and launched.

2.6.2 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 2.7.1 Desktop license](#)).

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 `monolixData` is created in the user home directory) and launched.

2.6.3 Application server with a shared MONOLIX installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.7.2](#) '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.

2.6.4 Application server with a remote connection

With a floating license MONOLIX is installed on a remote server using the procedure described in [Section 2.7.2](#) '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 2.7.1 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 `monolixData` is created in the user home directory) and launched.

2.6.5 Application server with a desktop installation

MONOLIX is installed on a remote server using the procedure described in [Section 2.7.2](#) '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.

2.6.6 Cluster installation with a shared MONOLIX installation

MONOLIX is installed on a master server using the procedure described in [Section 2.7.2](#) '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.

2.6.7 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 2.7.2](#) '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.

2.7 License

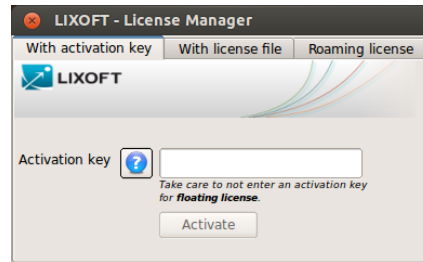
MONOLIX licenses can be of the following types:

- 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.

2.7.1 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.



2.7.2 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 .

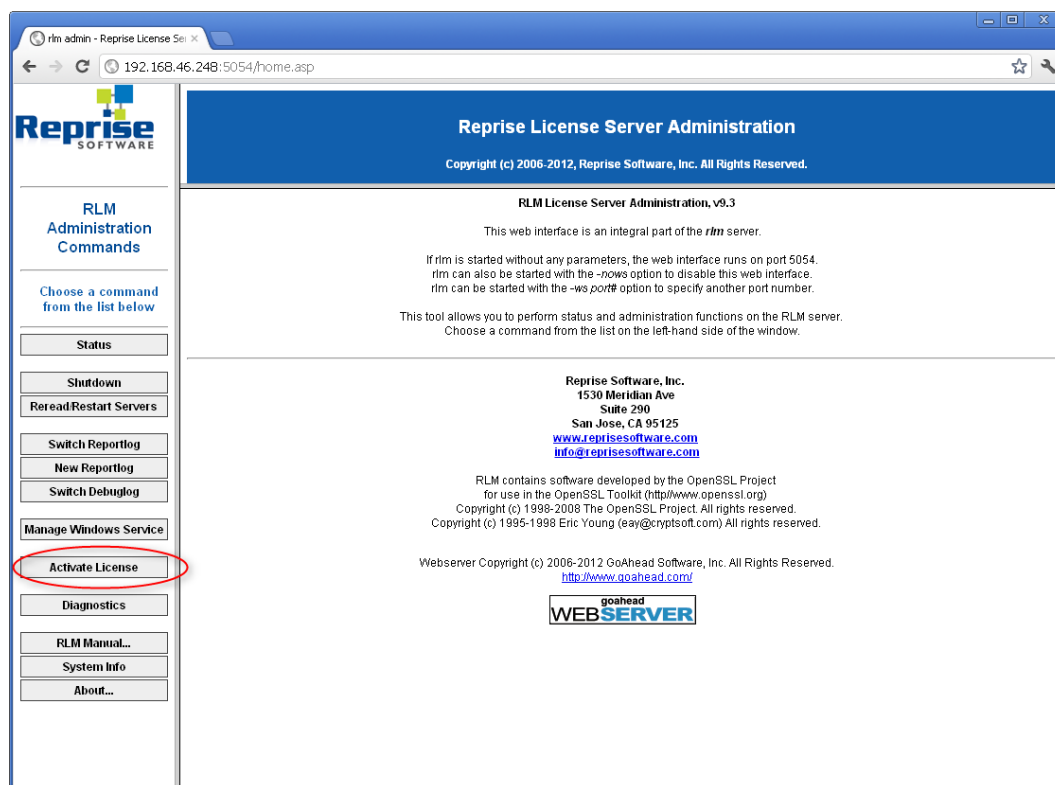
At this step there is no license available yet; the IT manager should use the RLM web server to download the license by following the procedure below:

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`).

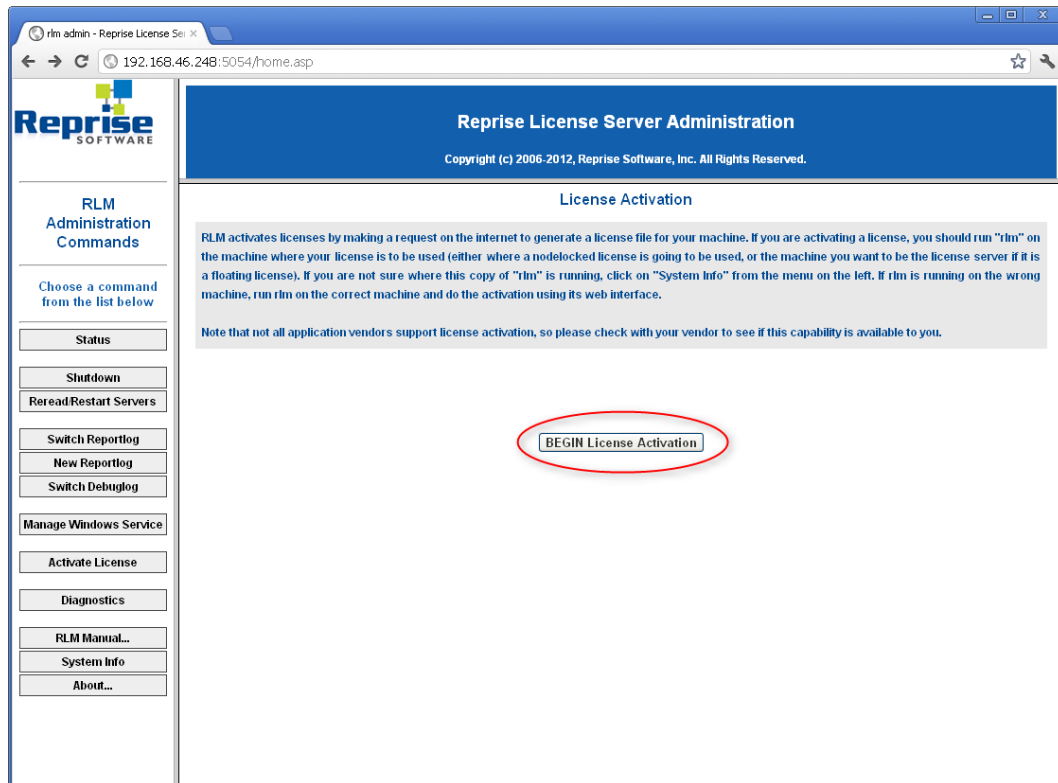
Notice that the RLM server opens two ports : 5053 and 5054. The first port (5053) is a service port used for the transactions of licenses. The second port (5054) is the RLM web server port used to access to the RLM configuration through a web browser.

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`



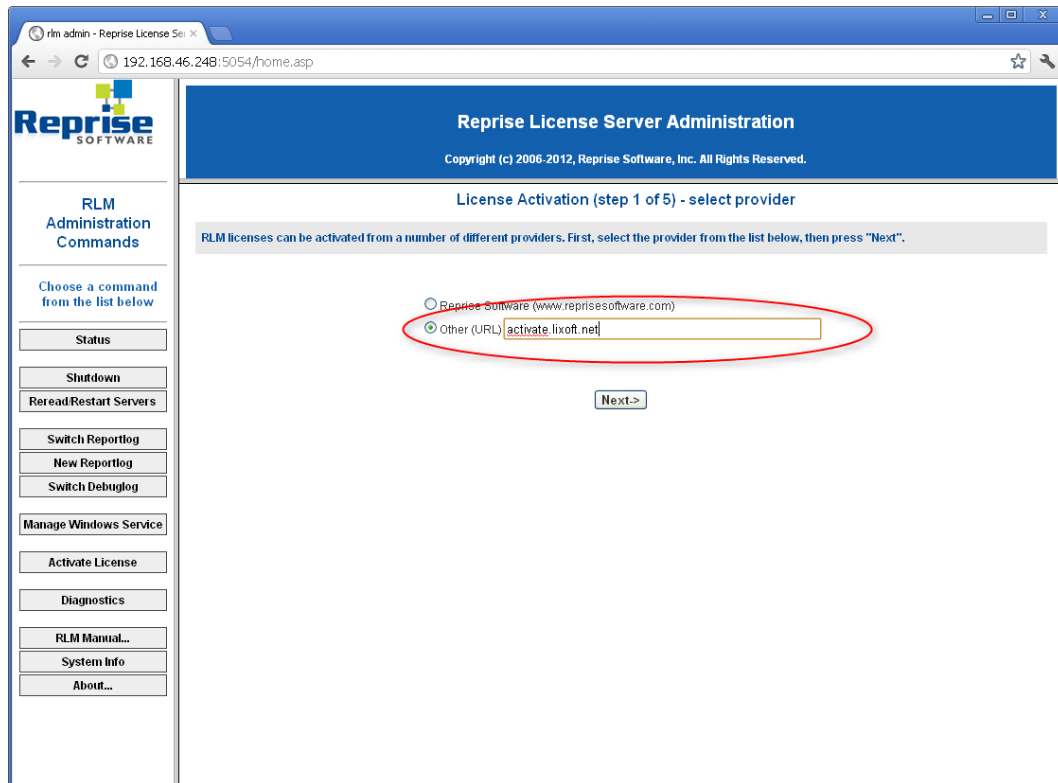
2. Begin license activation:



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



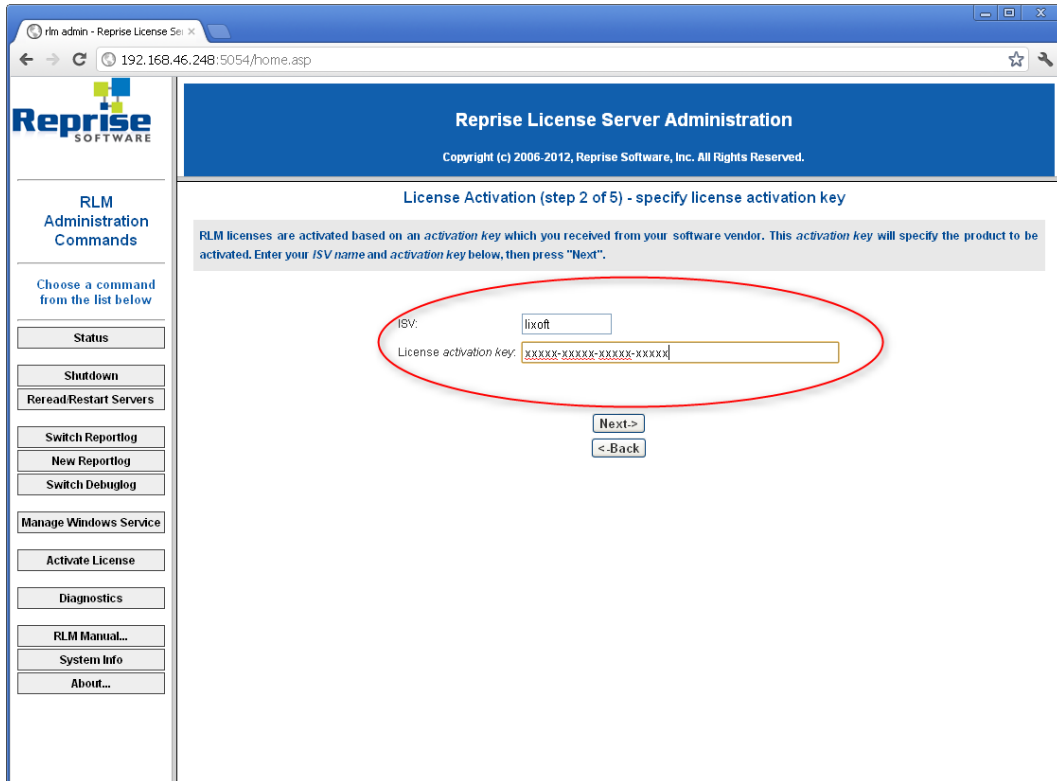
LIXOFT will send in return a '.lic' file which has to be copied in the directory

- <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.

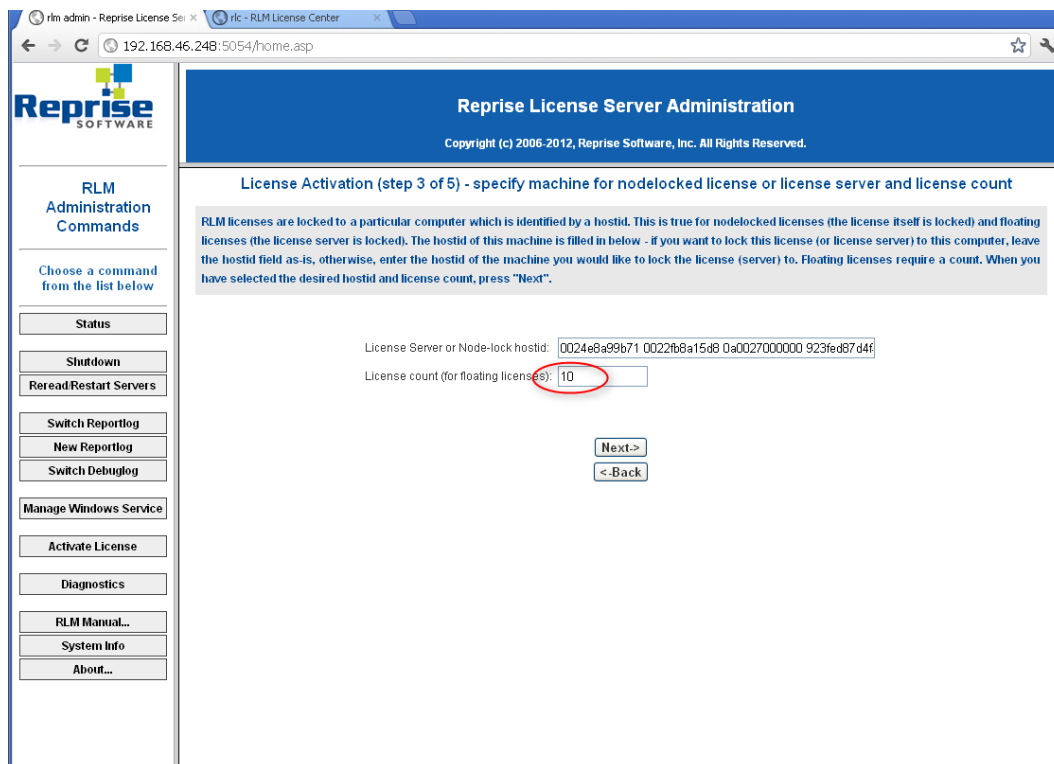
4. Activate the license.

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 :

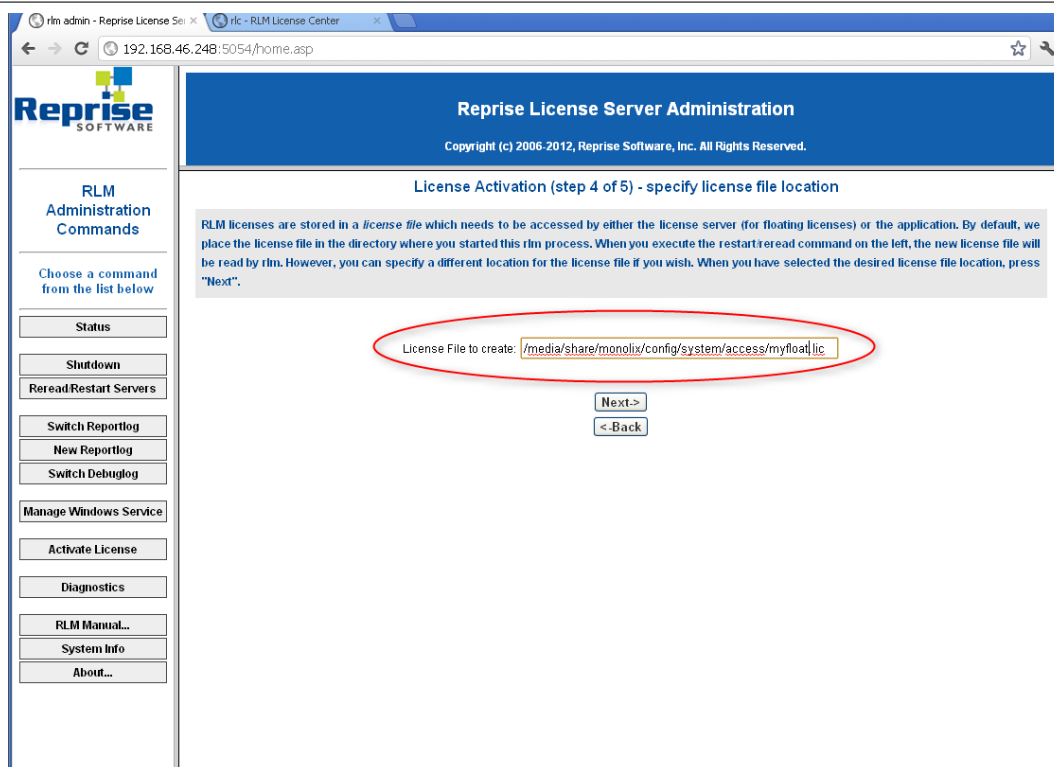
- If Monolix is installed on a shared space (i.e. each node of the cluster has an access to this directory), copy the license file into the directory
`<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

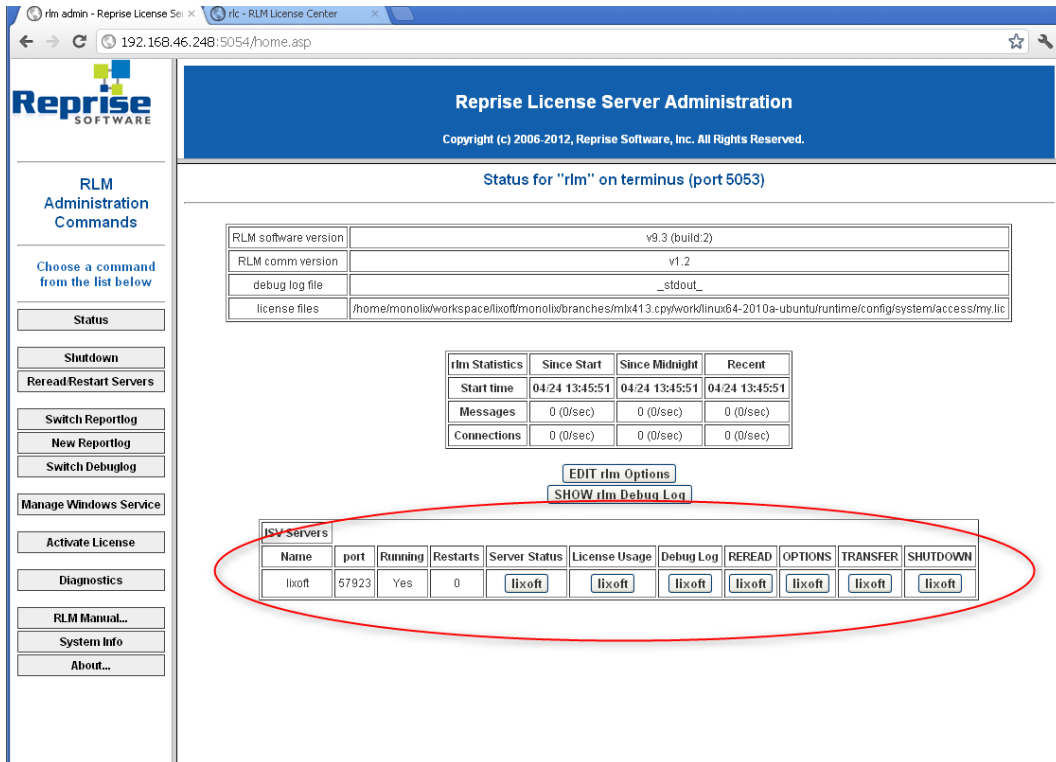
- The RLM server is executed on the computer **master-server**.
- MONOLIX is installed on each cluster node of the cluster.
- The license file is copied on **each cluster node** in the directory `<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

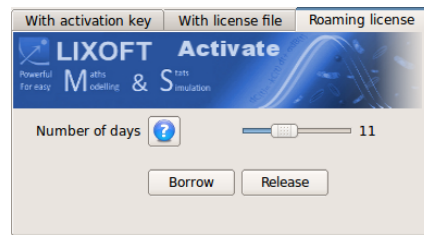
The documentation of the management of the RLM server provided by Reprise Software is available at

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

2.7.3 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.xml` (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/monolix421s/bin` in installation directory: for instance
`c:/ProgramData/Monolix/monolix421s/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 4.2.1 (2013-02-15)
2 Bugs Fixes:
3   - MLXTRAN Project : in STRUCTURAL_MODEL section resolved problem
      with path relative to %MLXPROJECT%
4   - mlxEditor, mlxPerlScript : under Suse Linux OS, conflict with
      libstdc++ and Qt librairies installed on the OS.
5   - Graphics : Kaplan Meier
6     - mean normalization
7     - survival curve: case of censored data
8   - simulations where wrong in presence of correlation between
      individual parameters
9   - MLXTRAN Model :
10     - Events could be close at a numerical epsilon for the solver,
      but not for the solver driver
11     - Rarely, it resulted into an explicit integration failure,
      returning "NaN"
12     - For the simulation of RTTE models, the ordering of the output
      names had to be alphabetical
13     - Not declaring all regression variables that where selected
      from the data set crashed the application.
14     - Declaring some PK without actual doses within the data set
      raised an error.
15     - Using the deprecated syntax with several lagged compartments
      returned "NaN"
16   - Algorithms
17   - Error when some subjects had no doses in conditinal mode
      computation
18   - GUI
19     - "Display the data" button did not update the information when
      the dataset was changed after running algorithms
20     - Convergence assessment GUI failed when there where only one
      individual parameter
21     - structural models with several dots (.) were not compiled when
      clicking in the compile button in the Model selection GUI
22     - projects with more outputs in structural model than
      observations in dataset caused an error when it is loaded
23     - the editor was not saved in the preference file
24
25 Enhancements:
26   - add possibility to configure the compiler (used to create
      Structural Model plugins) through the file 'system.xmlx'
27   - user API:
28     - it is possible now to use matlab function "ver" to know Monolix
      version and Monolix API version
29   - mlxEditor:
30     - allow multiple files selection on open file dialog box
```

```
31         - add 'Find and replace'
32         - set tabs movable
33     - MLXTRAN Model :
34         - Continuous observations can be declared within the model.
35         - Macro for a depot absorption, with a target ODE component.
36     - Permutation kernel for mcmc included
37
38 Other:
39     - Licensing system : '.ini' files desactivated (only the '.lic'
40       files are allowed)
41     - residual error models in main interface are shown now with their
42       full name (those used in MLXTRAN project and model)
43 -----
44 Monolix 4.2.0 (2012-11-26)
45 Bugs Fixes:
46     - MLXTRAN Project : in OBSERVATION section when a prediction has the
47       same name as an individual parameter the project parses fail
48     - PerlScript : bug with parameter '--use-matlab=false' was taken as
49       'true'
50     - Identity line works in observations vs predictions graphic
51     - Prediction distribution : percentiles are correctly displayed
52     - Color when stratify in covariables graphic
53     - Problem with prior (by default prior is Variance and not Standard
54       Deviation, this implies a syntax error (standardDeviation <->
55       variance)
56     - Wrong data file for the demonstration project
57       rtteWeibullCount_project.mlxtran
58     - "Display the data" button did not work
59     - bug when unchecking and checking "random effects" variability in
60       simulation interface
61
62 Enhancements:
63     - Interval censoring for continous data
64     - Extended priors on fixed effects
65     - Mlxtran model and Mlxtran project editor
66     - Perl script HMI
67     - Autosave
68     - Multiple covariate definitions
69     - Add batch-mode demo
70     - Add a doc package and a rlm server package (floating license
71       server)
72     - Graphic
73         - BLQ graphic : possibility to choose his own interval of
74           censored data
75         - Reorganisation of panel for list of graphics
76         - Background color for each graphic in preferences
```

```
69         - When split, limits are the same for all axes
70         - Obs. vs Pred., observations can be relied by individual
71         - Optimal bandwidth setting for parameter distribution
72         - CvSaem graphic : choice of axes number
73     - Interval-censored data and maximum number of events for time-to-
      event and drop-out data models
74     - Markov chain for categorical data
75     - Continuous-time Markov process for categorical data
76     - probit and normal cdf for Mlxtran model
77     - New user API including simulation-estimation, convergence
      assessment and simulations tools
78     - Possibility to define new covariates as transformation of already
      defined ones
79
80 New graphics:
81     - Posterior and prior functions for bayesian
82     - Individual contribution for the LL
83     - Transition probabilities
84     - Kaplan-Meier survival function
85
86 New tables:
87     - Individual contribution to log-likelihood
88     - Covariates summary
89 -----
90
91 Monolix 4.1.4 (2012-07-16)
92
93 Bugs Fixes:
94     - Saving preferences from tools menu failed.
95     - Display remaining time (license) correctly.
96     - Problem with license activation file path.
97     - Add license agreement into Linux installer.
98     - The horizontal slider in "Check initial fixed effects" interface
      did not appear for some number of individual parameters.
99
100 Enhancements:
101     - Windows 64 RC.
102     - Management of the maximum number of threads for MLXTran models (
      can be set from the preference tools: MonolixGUI->Tools->
      Preference)
103     - License activate: inform user to not set activation key
104       if the license is a floating license.
105     - Documentation :
106       * Installation guide : Windows 64 bits.
107       * User Guide : Cluster section revised.
108       * Model MLxTRAN : list of keywords of the language.
109
110
```

```
111 -----
112
113     Monolix 4.1.3-sp2 (2012-05-29)
114
115 Enhancements:
116     - system.xmlx : possibility to not display Lixoft Activate.
117     - Lixoft Activate : add the possibility to send an email with
118       encoded computer information to create license @Lixoft.
119     - Lixoft Activate : manage "cannot connect to url" error by asking
120       user to go on a web site or send an email.
121
122 Bugs Fixes:
123     - IOV Problem with R2010bSP1
124     - perlScripts : bug in the management of the configuration file for
125       [program-execute-options] and run on a cluster.
126     - add 'rlmutil.exe' for windows packages (forgotten in previous
127       packages).
128     - problem floating license.
129     - warnings for occasions without dose were removed.
130     - when the last Individual/Occasion had no dose, Monolix crashed.
131     - When there were syntax errors in the structural model, monolix
132       said that it could not find the file instead giving the MLXTRAN
133       message
134     - NaN observations are now mentionned as error when algorithms are
135       launched.
136     - Update documentation : in batch mode section, there is a bad path.
137
138 -----
139
140     Monolix 4.1.3-sp1 (2012-05-21)
141
142 Bug Fixes:
143     - GUI:
144       * Check Initial Fixed Effects interface crashed when creating
145         covariate and parameter's sliders for some sizes
146
147 -----
148
149     Monolix 4.1.3 (2012-05-02)
150
151 New Features:
152     - MLXTran model: allows negative categories
153     - License management: uses RLM as license provider
154     - Compiler manager: adds the possibility to choose the embedded
155       compiler
156     - The Monolix and Matlab versions are now stored in the algorithm
157       result files
```

```
149
150 Bug Fixes:
151   - MLXTRAN project:
152     - continuous transformation can take a mathematical expression
153     - problem with structural model path
154   - MLXTRAN model:
155     - Under Linux 64 bits, due to library conflicts with Matlab
156       R2010b and better, the multi-threaded
157       loading of the model description for the project occasionally
158       fails
159     - Only the last table variable is recorded, overwriting the
160       first one
161   - Graphics:
162     - log / linear works on all graphics
163     - when log-log scale is set for "observed versus predicted", the
164       diagonal line isn't displayed anymore
165   - GUI:
166     - editor call did not work
167   - Algorithms:
168     * bug for individuals without some type of observations and with
169       IOV computing conditional mode
170     * bug when there were continuous outputs after discrete outputs
171     * Fisher Information Matrix by Stochastic Appoximation does now
172       handle better the case when there are
173       no parameters to estimate in the residual error
174   - Session:
175     * when the directory monolixData/monolix<version> is renamed
176       during an active Monolix session, stopping
177       Monolix caused an exit of Matlab.
178
179 -----
180 Monolix 4.1.2: (2012-03-05)
181 -----
182
183 New Features:
184   - PerlScripts : possibility to save the results in the project
185     directory instead of the output directory
186   - In system.xmlx : automatically creates a directory hierarchy for '
187     monolixData' path
188
189 Enhancements:
190   - MLXTran (structural model) multi-threading processing enhancement
191
192 Bug Fixes:
193   - Batch Processing failed when a very large number of projects were
```

```

    launched
188   - MDV column: when MDV=2 only the regression variables were taken
      into account
189   - Fixed a bug in graphics saving
190   - Fixed error when an empty result folder was timestamped
191   - Simulation of categorical data, whenever no category 0 is defined
192   - Fixed take into account UserPath defined in 'system.xmlx' for the
      preference file saving
193
194
195 -----
196
197   Monolix 4.1.1: (2012-02-13)
198
199 -----
200
201 New Features:
202   - timestamped backup
203   - preferences interface
204   - tools menu for activating license and preferences
205   - option for locking structural model modifications
206   - Project-MLXTRAN grammar modification : initialization of parameter
      is written now as beta_{pi,cov}, pop_{pi}, omega_{pi}, ...
207   - save graphics as png / ps / jpg / bmp or tiff
208   - selection of graphics/tables to be saved
209
210 Bug Fixes:
211   - Project-MLXTRAN: user can define the result folder
212   - LoQ difference between 3.2 and 4.1
213   - statistical test for error model and covariate model
214   - xmlx loading from 3.2 to 4.1
215   - correlation (levelName consistence with IOV) + parser error
216   - observation model (prediction = observation name)
217   - path for MONOLIX user profile can include special characters
218
219
220
221 -----
222
223   Monolix 4.1.0: (2012-01-23)
224
225 -----
226
227 psmplx:
228   - compatible with the mlxtran format of projects
229   - available on Windows OS
230
231 mlxtran:
```

```
232     - new syntax
233     - PK macros
234     - RTTE models
235
236 license:
237     - interface for installing the license file
238
239 Interface:
240     - setting for axes' limits
241     - information for the observation model
242     - shortcut for model libraries
243
244 File system:
245     - improved handling of special characters for filepaths
246
247 Demos:
248     - updated for the new mlxtran syntax
249     - dispatch of the model library for demos
250
251 Known Bugs:
252     - under Windows OS, user directory cannot contain special characters
      other than spaces
253
254
255
256 -----
257
258 Monolix 4.0.1: (2011-10-27)
259
260 -----
261
262 psmlx:
263     - use-matlab option didn't work in command line mode
264     - multi-threading : multithreading didn't work
265     - take account the p.coded files
266
267 mlxtran
268     - problem with FIM options : both linearization and
      stochasticApproximation appeared after a save with
      stochasticApproximation option set
269     - avoid the unloading of project when settings files does not exist
      : default settings are loaded
270
271 license:
272     - multi write database didn't work well in multi-threading mode
273
274 Interface:
275     - save lists
276     - configuration panel
```

```
276     - launching some graphics alone is now possible
277     - the graphics were closed when "Use last estimates" were used
278     - when monolix was launched twice without loading or creating a
        project, two toolbars were created
279
280 Algorithm and simulations:
281     - simulation works now with dataset without EVID column and with MDV
        column
282
283 Results:
284     - the graphics fit now to the paper in .ps files
285     - xLabels were wrong for some graphics when several regression
        variables were present
286     - some graphics crashed when launched after some hypotheses tests
        were done
287     - Visual studio redistribuable problem
```