



MONOLIX INSTALLATION GUIDE

Version 4.3.1

FEBRUARY 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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Contents

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 ?? 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 ?? 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 ?? '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 ?? '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 ?? 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 ?? '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 ?? '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 ?? '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

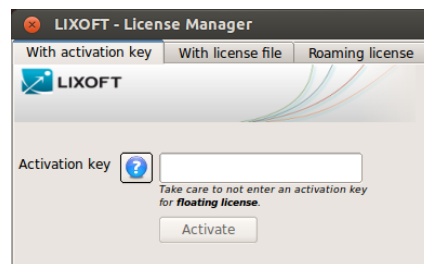
MONOLIX licenses can be of the following types:

- 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 .

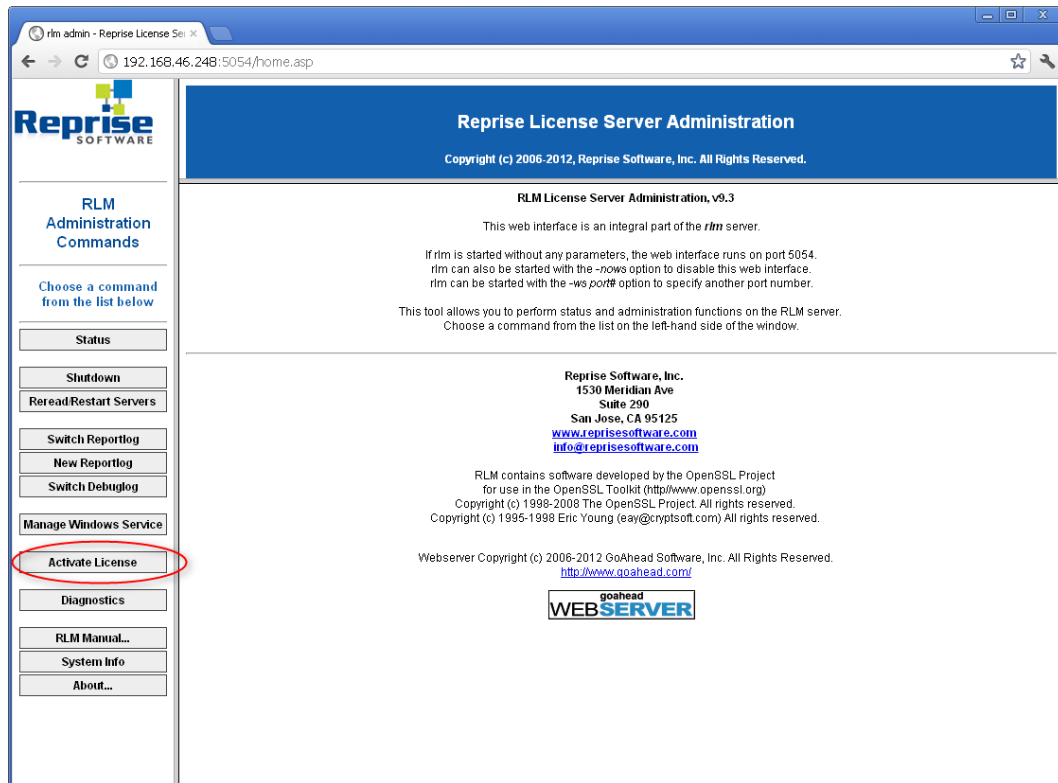
At this step there is no license available yet; the IT manager should use the RLM web server to download the license by following the procedure below:

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`).

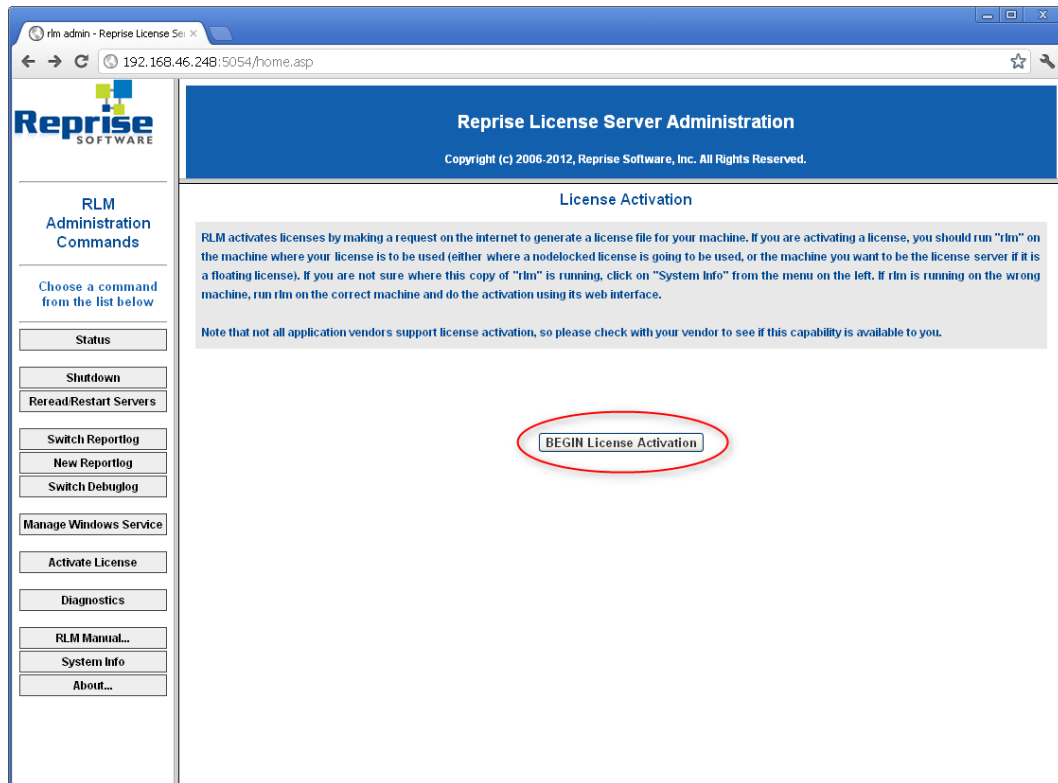
Notice that the RLM server opens two ports : 5053 and 5054. The first port (5053) is a service port used for the transactions of licenses. The second port (5054) is the RLM web server port used to access to the RLM configuration through a web browser.

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`



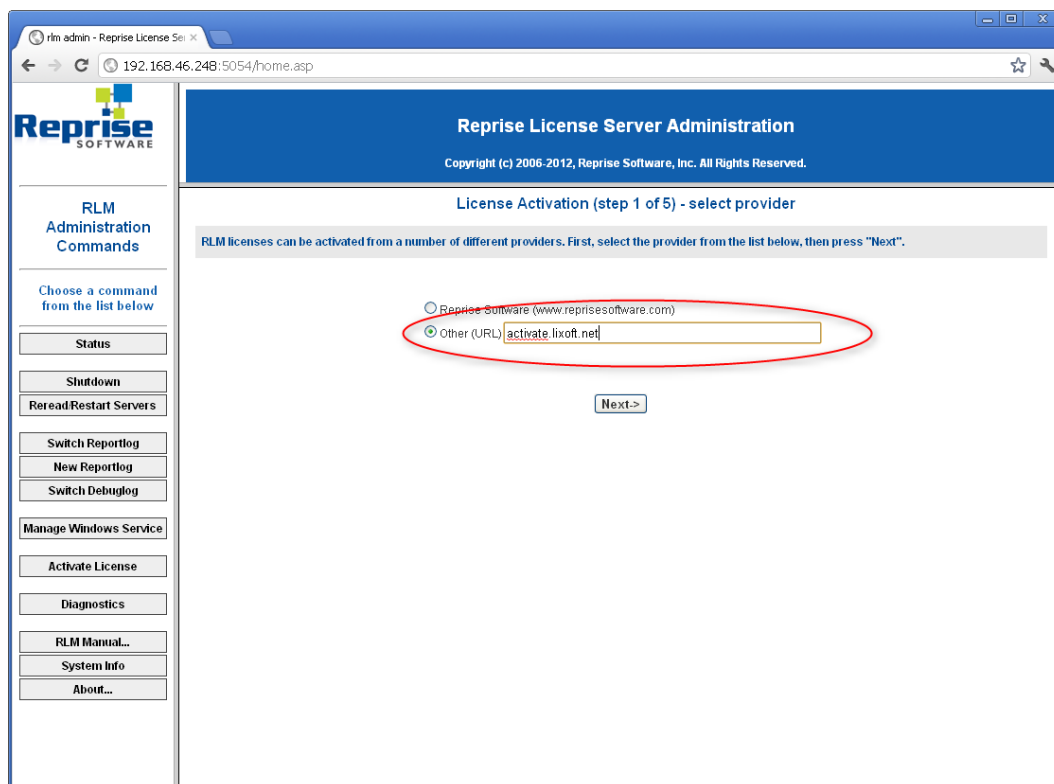
2. Begin license activation:



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



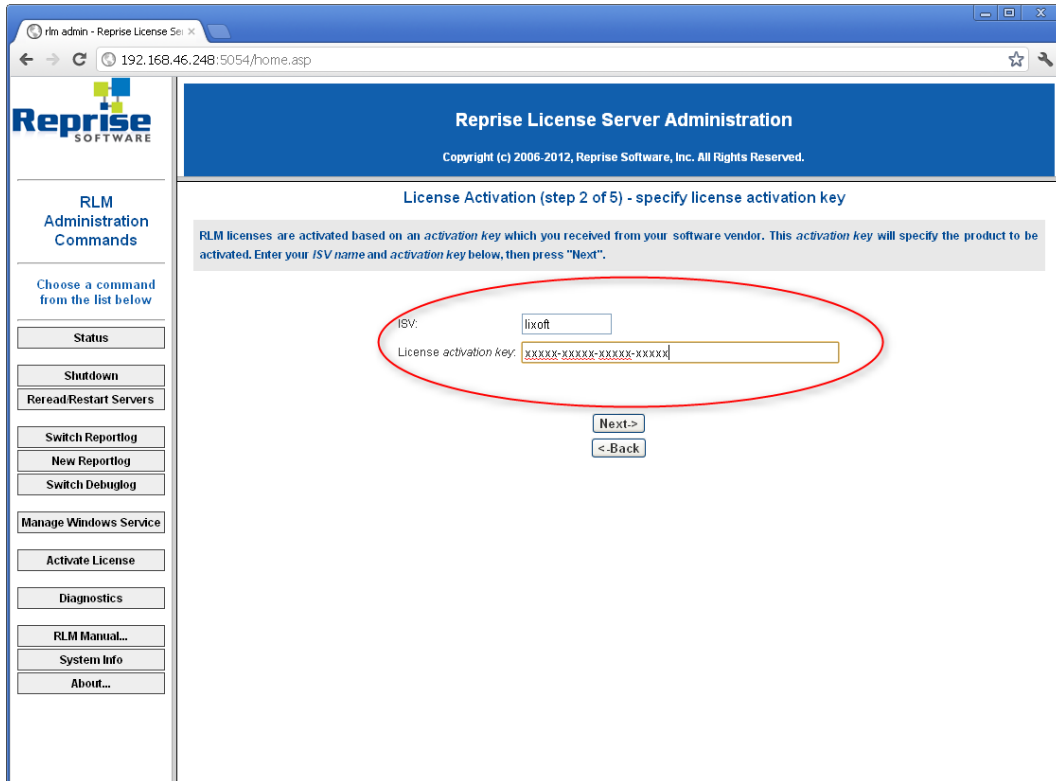
LIXOFT will send in return a '.lic' file which has to be copied in the directory

- <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.

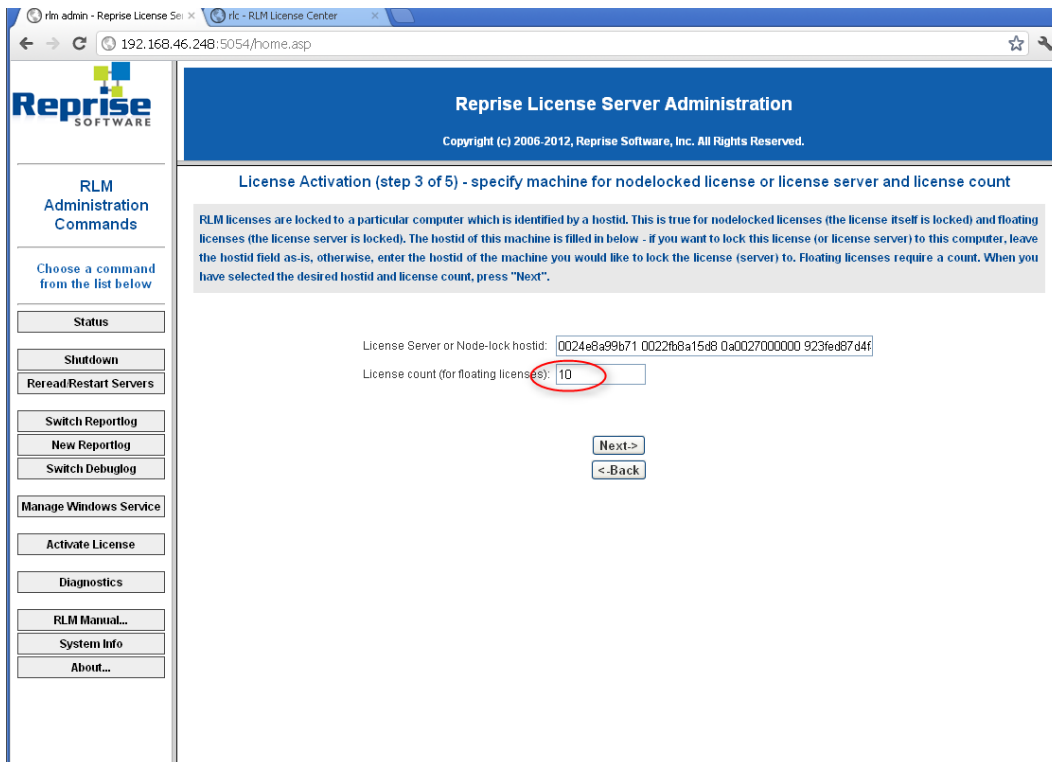
4. Activate the license.

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 :

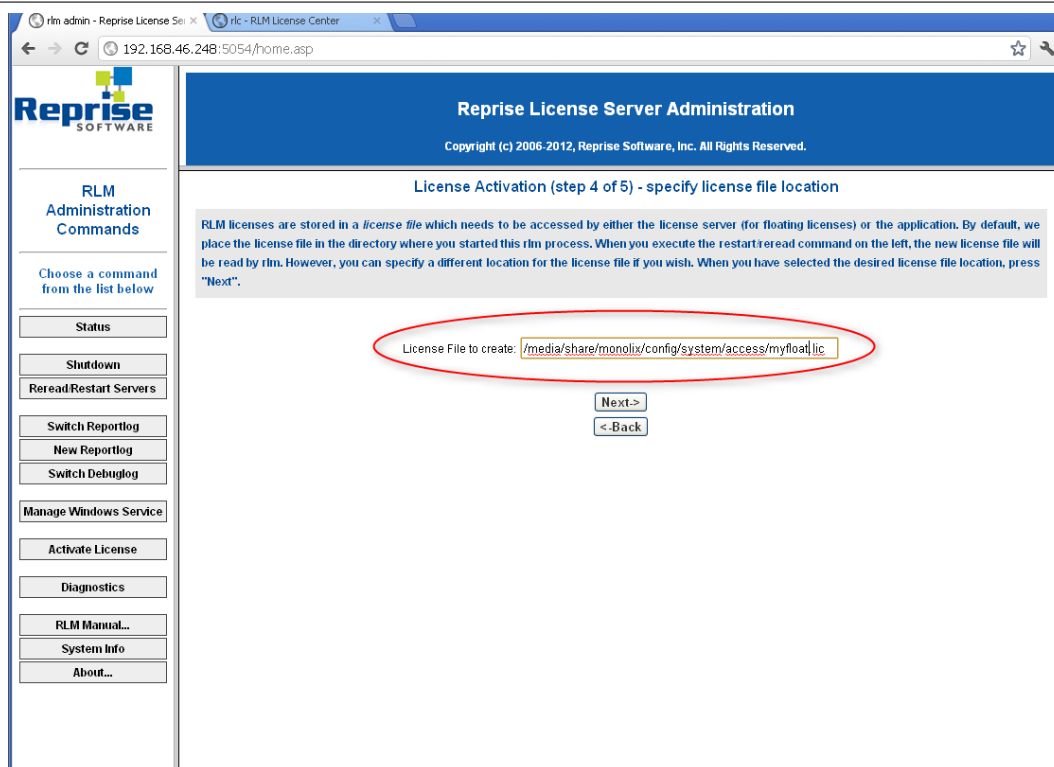
- If Monolix is installed on a shared space (i.e. each node of the cluster has an access to this directory), copy the license file into the directory
`<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

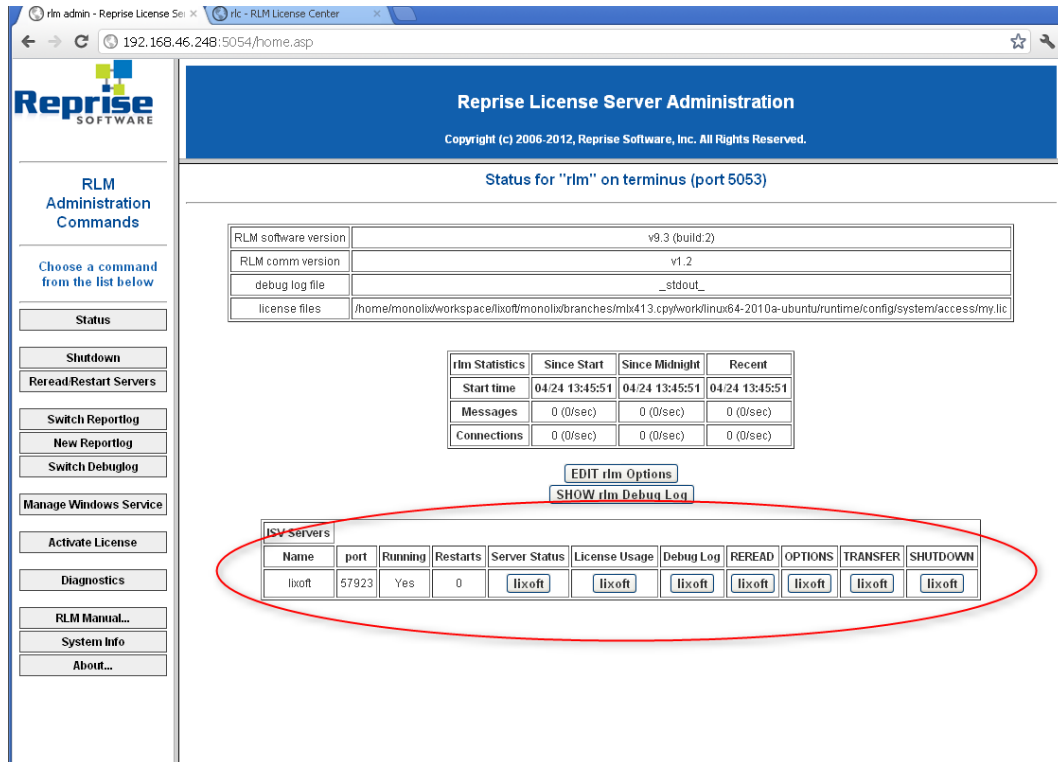
- The RLM server is executed on the computer **master-server**.
- MONOLIX is installed on each cluster node of the cluster.
- The license file is copied on **each cluster node** in the directory `<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access`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

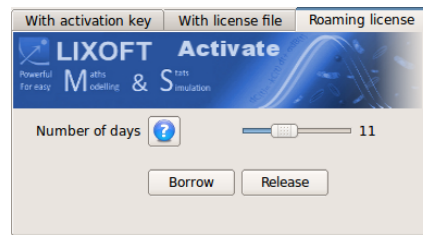
The documentation of the management of the RLM server provided by Reprise Software is available at

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