Monolix

Installation Guide

Version 4.2.2

March 2013

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. 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 recommanded to use Matlab 2010b-SP1.

- Standalone versions:

  - Linux (32 bits)
  - Linux (64 bits)
  - Windows (32 bits)
  - Windows (64 bits)[1]

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[1] Monolix 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:
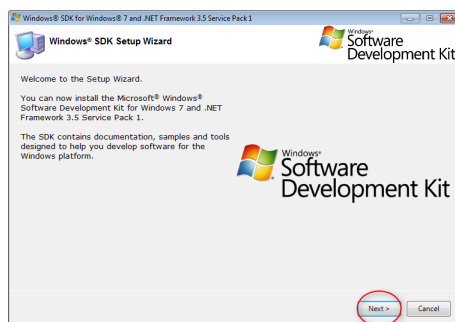
Welcome page of the SDK installer: click on 'next' button to continue;
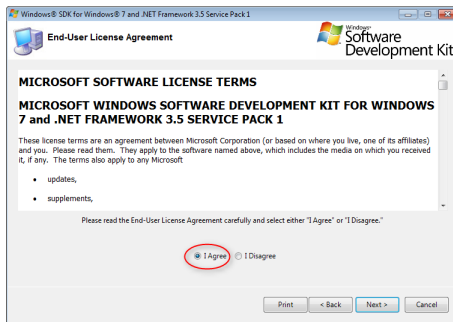
License agreement page: accept the agreement by selecting 'I agree', then click on 'next' button to continue;
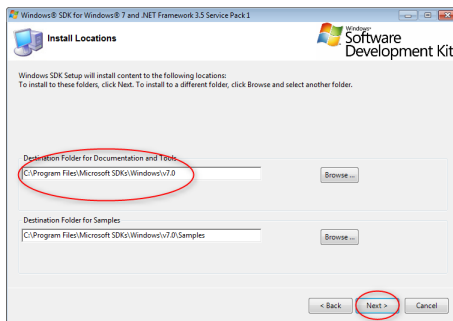
Choose the installation path. The proposed directories are required by MONOLIX ;
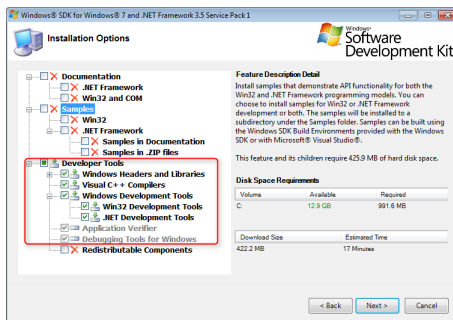
The component used by MONOLIX are the compiler only, therefore it is not necessary to install documentation and samples.
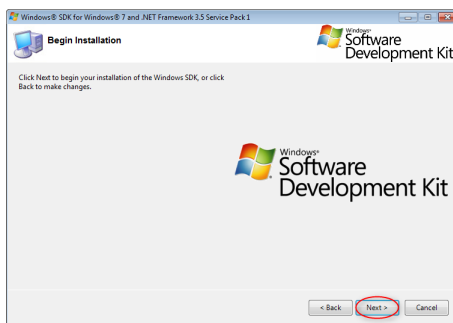
On 'Begin installation' page, click on 'next' button to continue;
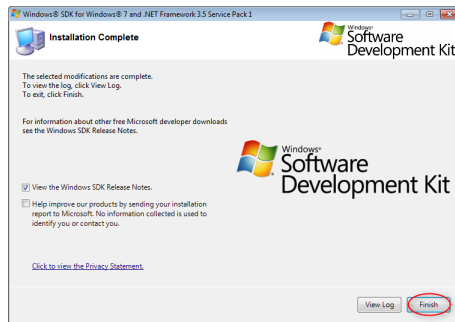
On 'Installation complete' page click on 'finish' button to continue;

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:
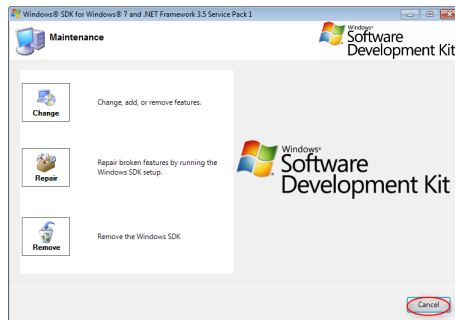
No action is necessary, click on 'Cancel';
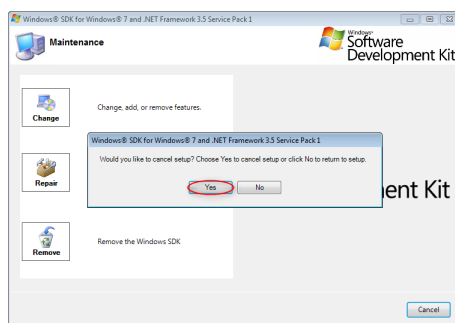
Confirm the 'Cancel' choice by clicking on 'Yes' button.

2.2 About Installer

- Linux : the installer is a self-extractable archive.

  - run the following command (depending on your os version):
    ```
    #> sh Monolix-4.2.2-matlab2010a-linux32.bin
    or
    #> sh Monolix-4.2.2-matlab2010bSP1-linux32.bin
    ```

```
or
#> sh Monolix-4.2.2-standalone2008b-linux32.bin
or
#> sh Monolix-4.2.2-matlab2010a-linux64.bin
or
#> sh Monolix-4.2.2-matlab2010bSP1-linux64.bin
or
#> sh Monolix-4.2.2-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 SCENARII
    │  └─ 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 xfz 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 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.

2.6.3 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

With floating license 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.

With desktop license   Monolix is installed on a remote server using a standard installation (without floating license). After the standard activation procedure, the license file is copied into the directory :

`<user directory>/monolixData/license`

At this step Monolix is only runnable by the user who launched the installation procedure. To allow an access to Monolix for each user of the application server, copy the license file (stored into the directory `<user directory>/monolixData/license`) 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 .

Each user is supposed to run Monolix from the application server.

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.
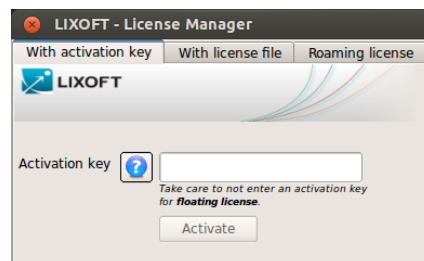
2.7.2   Floating license

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`
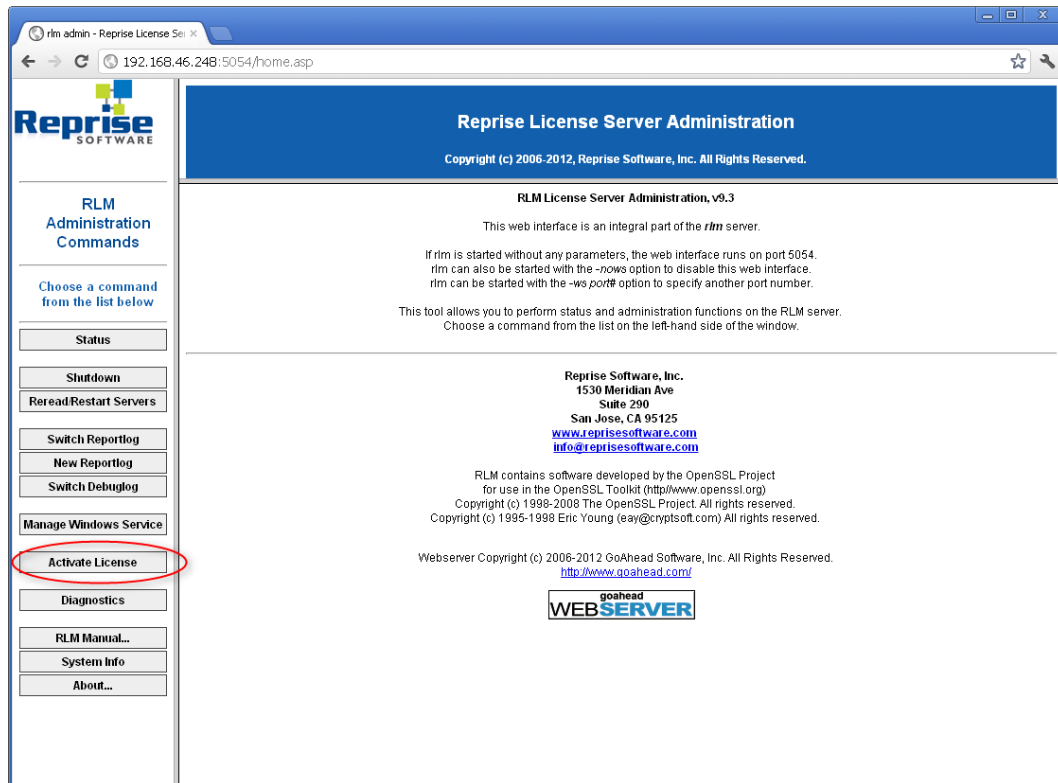
2. Begin license activation:

Monolix 4.2.2
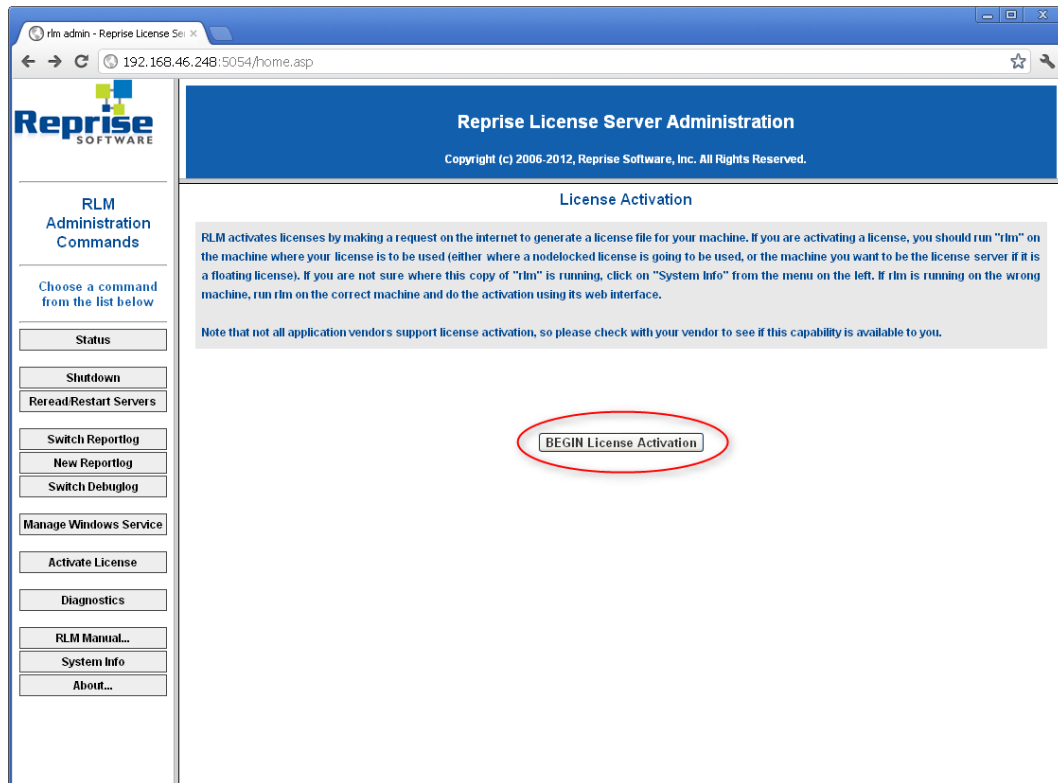
3. Enter the RLM activation url : `activate.lixoft.net`. And click on `Next` button.

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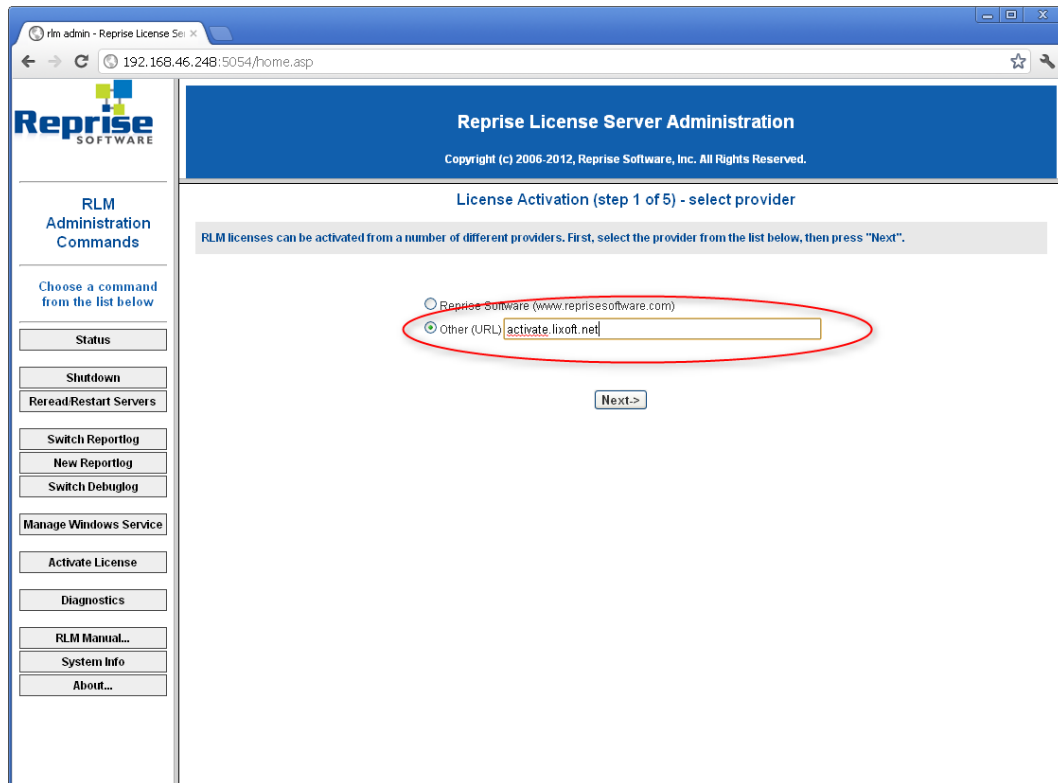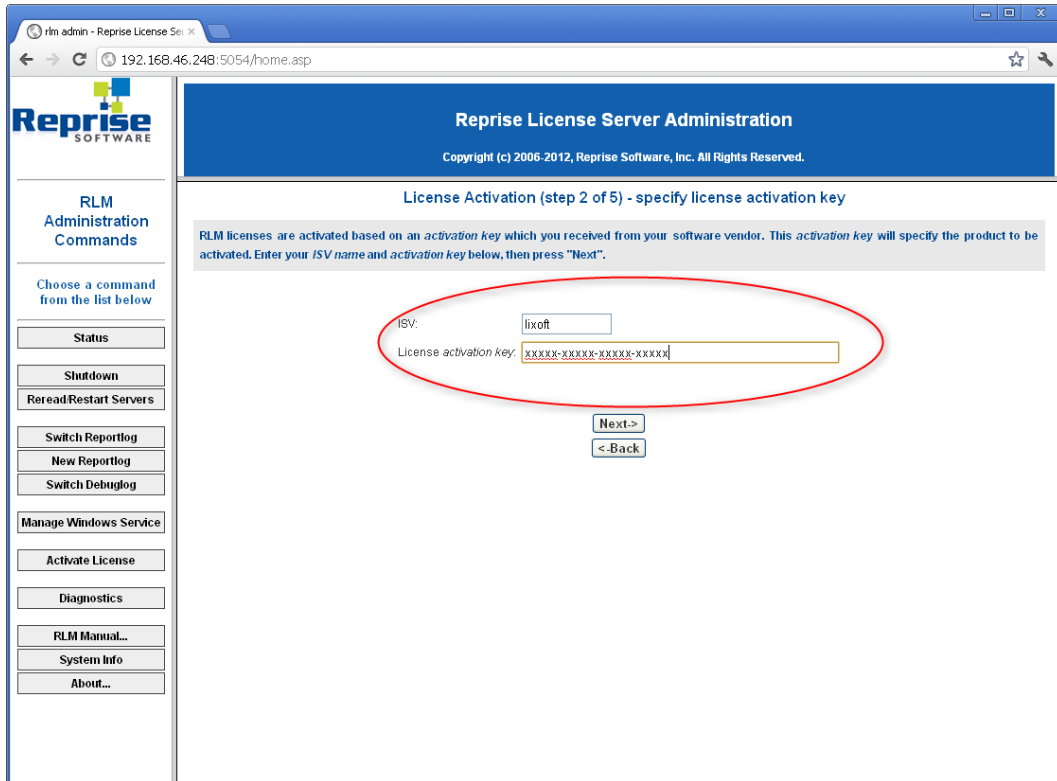
LIXOFT will send in return a `'.lic'` file which has to be copied in the directory

- `<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.

LIXOFT

6. Select the license directory and file.

   In the field named `License file to create` write the full path to license file
   `<monolix install path>/config/system/access/myfloat.lic` for the MATLAB version
   of MONOLIX
   or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the
   standalone version.
   e.g: if the MONOLIX (matlab version) installation directory is `/media/share/monolix` the
   input field name `License file to create` should contain
   `/media/share/monolix/config/access/myfloat.lic`

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

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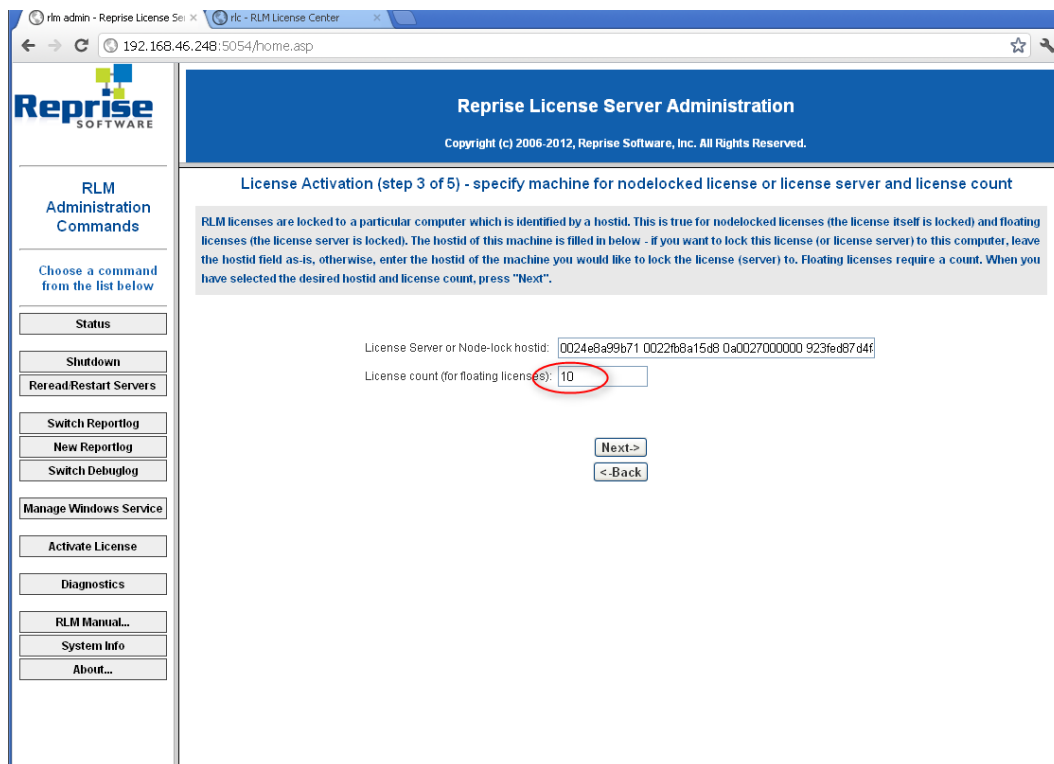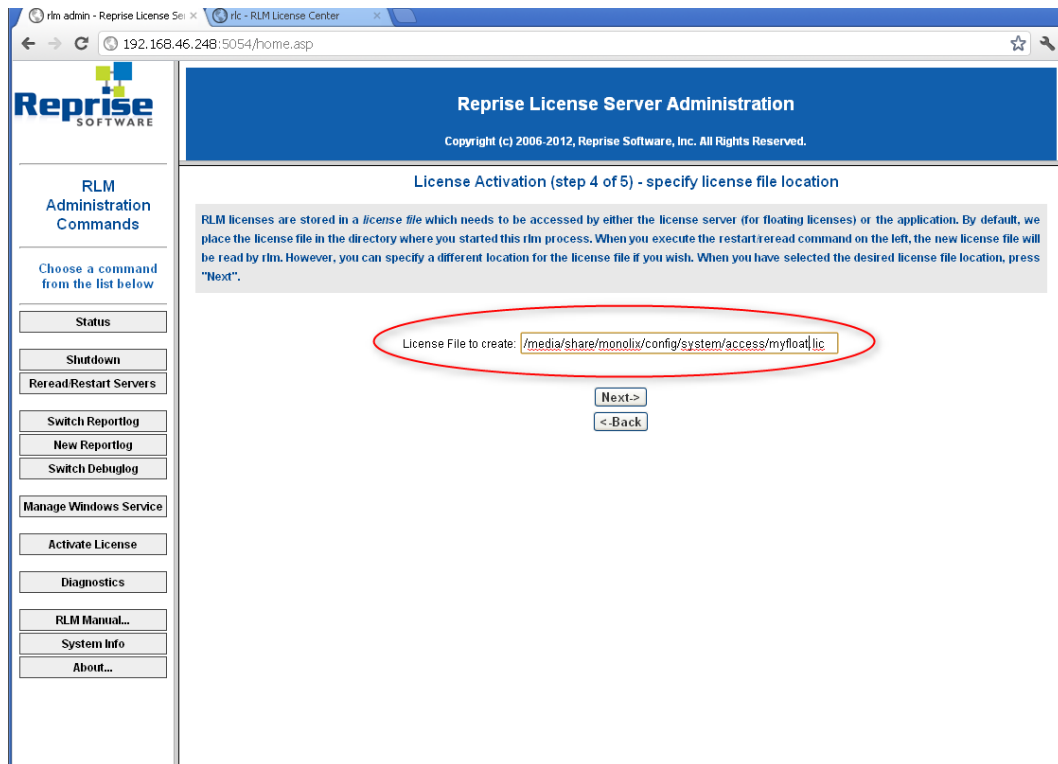   to this directory), copy the license file into the directory
     `<monolix install path>/config/system/access/` for the MATLAB version of MONOLIX
     or `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for
     the standalone version.
     Make sure that the MONOLIX directory is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

Example (with a MATLAB version of MONOLIX)

- – MONOLIX is installed on the computer `master-computer` in the directory:
  `/usr/local/monolix/`.
  The license is in the directory :
  `/usr/local/monolix/config/access/`
- – The RLM server is run on the computer `master-computer`.
- – Cluster computers mount the directory `/usr/local/monolix/`.
- – Each monolix user runs MONOLIX from the previously mounted directory.

- If Monolix is installed on each node of the cluster, copy the license file on each computer in the directory `<monolix install path>/config/system/access` for the MATLAB version of MONOLIX or
  `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version.

Example

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

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

   - `<monolix install path>/config/system/access/` for the MATLAB version
   - `<monolix install path>/bin/Monolix_mcr/runtime/config/system/access` for the standalone version of MONOLIX .
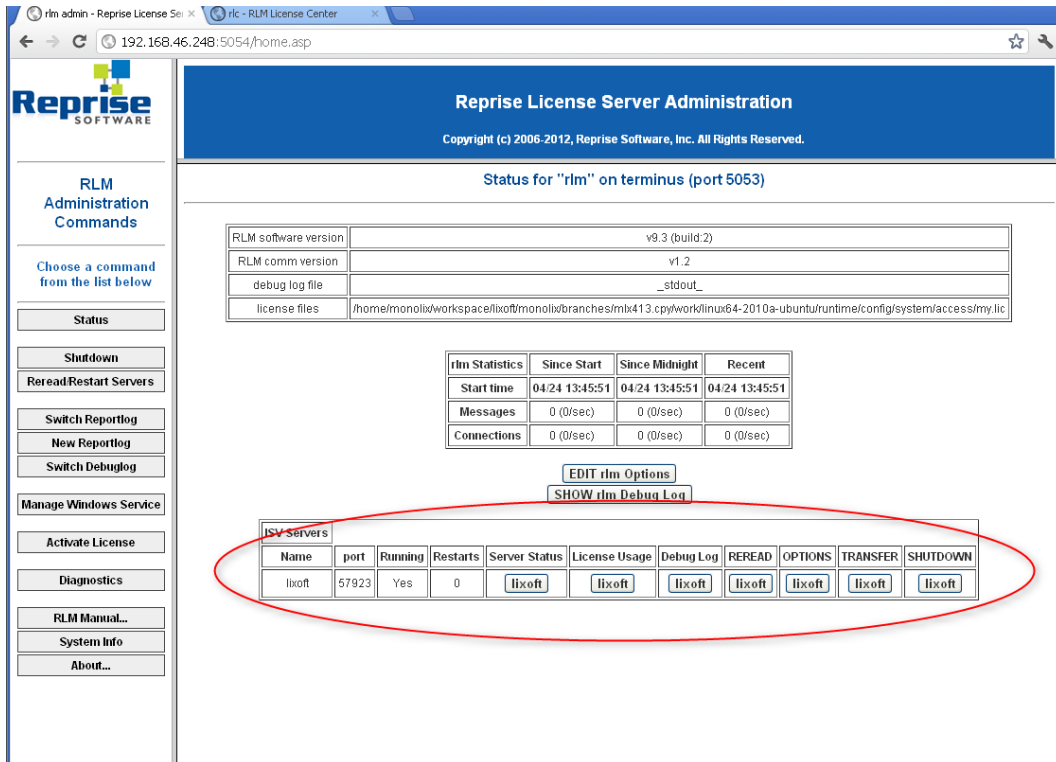
   Now RLM is running with the provided license. This is verified in the web interface by clicking on `status` button.

8. RLM Server : server hostname and port considerations.
   If for any reason, the server port or the server hostname is not registered in a DNS, it is possible to change these informations directly on licence file.
   The line `HOST <hostname> <mac> <port>` can be changed by `HOST <rlm server ip> <mac> <new port>`.

9. RLM Server : firewall considerations.
   If the RLM server is behind a firewall, the port 5053, 5054 and the ISV port have to be opened.
   The ISV port can be set directly in license file by changing the ISV line as follow:

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

10. Managing RLM server :
    The documentation of the management of the RLM server provided by Reprise Software is available at
    `http://www.reprisesoftware.com/RLM_Enduser.html`

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)
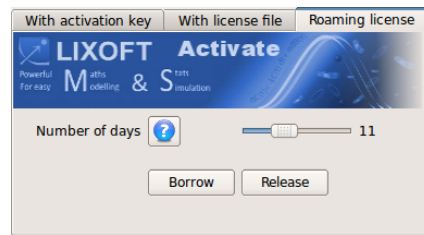
This feature is enabled on demand. An extra activation key will be provided by LIXOFT and the procedure to get the roaming license feature is identical to the installation of a floating license. To enable this feature, the file `system.xmlx` (stored in directory `<monolix install path>/config/`-MATLAB 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 embers 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/monolix422s/bin` in installation directory: for instance `c:/ProgramData/Monolix/monolix422s/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 4.2.2 (?)
2  Bugs Fixes:
3          - Graphics : Spaghetti plot
4              - Error when there are censored data on several outputs (
                  index out of bounds)
5          - MLXTRAN model :
6              - the autocorrelation was not correctly set when the error
                  model is defined inside the structural model
7
8          - GUI
9              - When the error model is defined in the structural model
                  and  it is changed from constant or proportional to
                  combined, some parameters became fixed to 0
10                 - problem handling IOV + categorical covariates
                     dependency on omegas
11                 - problem with Extensive workflow
12
13 ------------------------------
14 Monolix 4.2.1 (2013-02-15)
15 Bugs Fixes:
16     - MLXTRAN Project : in STRUCTURAL_MODEL section resolved problem
             with path relative to %MLXPROJECT%
17     - mlxEditor, mlxPerlScript : under Suse Linux OS, conflict with
             libstdc++ and Qt librairies installed on the OS.
18     - Graphics : Kaplan Meier
19         - mean normalization
20         - survival curve: case of censured data
21     - simulations where wrong in presence of correlation between
             individual parameters
22     - MLXTRAN Model :
23         - Events could be close at a numerical epsilon for the solver,
               but not for the solver driver
24           Rarely, it resulted into an explicit integration failure,
                 returning "NaN"
25         - For the simulation of RTTE models, the ordering of the output
             names had to be alphabetical
26         - Not declaring all regression variables that where selected
             from the data set crashed the application.
27         - Declaring some PK without actual doses within the data set
             raised an error.
28         - Using the deprecated syntax with several lagged compartments
             returned "NaN"
29     - Algorithms
30         - Error when some subjects had no doses in conditional mode
               computation
31     - GUI
```

```
32              - "Display the data" button did not update the information when
                   the dataset was changed after running algorithms
33              - Convergence assessment GUI failed when there where only one
                   individual parameter
34              - structural models with several dots (.) were not compiled when
                     clicking in the compile button in the Model selection GUI
35              - projects with more outputs in structural model than
                   observations in dataset caused an error when it is loaded
36              - the editor was not saved in the preference file
37                    - Convergence assessment graphics did not handled
                        correctly when there were not variances on some
                        parameters or their covariate dependence
38
39    Enhancements:
40        - add possibility to configure the compiler (used to create
             Structural Model plugins) through the file 'system.xmlx'
41        - user API:
42          - it is possible now to use matlab function "ver" to know Monolix
               version and Monolix API version
43        - mlxEditor:
44          - allow multiple files selection on open file dialog box
45          - add 'Find and replace'
46          - set tabs movable
47        - MLXTRAN Model :
48            - Continuous observations can be declared within the model.
49            - Macro for a depot absorption , with a target ODE component.
50        - Permutation kernel for mcmc included
51
52    Other:
53        - Licensing system : '.ini' files desactivated (only the '.lic'
             files are allowed)
54        - residual error models in main interface are shown now with their
             full name (those used in MLXTRAN project and model)
55    --------------
56
57      Monolix 4.2.0 (2012-11-26)
58
59    Bugs Fixes:
60        - MLXTRAN Project : in OBSERVATION section when a prediction has the
               same name as an individual parameter the project parses fail
61        - PerlScript : bug with parameter '--use-matlab=false' was taken as
             'true'
62        - Identity line works in observations vs predictions graphic
63        - Prediction distribution : percentiles are correctly displayed
64        - Color when stratify in covariables graphic
65        - Problem with prior (by default prior is Variance and not Standard
             Deviation , this implies a syntax error (standardDeviation <->
             variance)
```

```
66        - Wrong data file for the demonstration project
                rtteWeibullCount_project.mlxtran
67        - "Display the data" button did not work
68        - bug when unchecking and checking "random effects" variability in
             simulation interface
69
70   Enhancements:
71        - Interval censoring for continous data
72        - Extended priors on fixed effects
73        - Mlxtran model and Mlxtran project editor
74        - Perl script HMI
75        - Autosave
76        - Multiple covariate definitions
77        - Add batch-mode demo
78        - Add a doc package and a rlm server package (floating license
             server)
79        - Graphic
80           - BLQ graphic : possibility to choose his own interval of
                censored data
81           - Reorganisation of panel for list of graphics
82           - Background color for each graphic in preferences
83           - When split, limits are the same  for all axes
84           - Obs. vs Pred., observations can be relied by individual
85           - Optimal bandwidth setting for parameter distribution
86           - CvSaem graphic : choice of axes number
87        - Interval-censored data and maximum number of events for time-to-
             event and drop-out data models
88        - Markov chain for categorical data
89        - Continuous-time Markov process for categorical data
90        - probit and normal cdf for Mlxtran model
91        - New user API including simulation-estimation, convergence
             assessment and simulations tools
92        - Possibility to define new covariates as transformation of already
             defined ones
93
94   New graphics:
95        - Posterior and prior functions for bayesian
96        - Individual contribution for the LL
97        - Transition probabilities
98        - Kaplan-Meier survival function
99
100  New tables:
101       - Individual contribution to log-likelihood
102       - Covariates summary
103  --------------
104
105     Monolix 4.1.4 (2012-07-16)
106
```

```
107  Bugs Fixes :
108       - Saving preferences from tools menu failed .
109       - Display remaining time ( license ) correctly .
110       - Problem with license activation file path .
111       - Add license agreement into Linux installer .
112       - The horizontal slider in " Check initial fixed effects " interface
              did not appear for some number of individual parameters .
113
114  Enhancements :
115       - Windows 64 RC .
116       - Management of the maximum number of threads for MLXTran models (
              can be set from the preference tools : MonolixGUI -> Tools ->
              Preference )
117       - License activate : inform user to not set activation key
118         if the license is a floating license .
119       - Documentation :
120           * Installation guide : Windows 64 bits .
121           * User Guide : Cluster section revised .
122           * Model MLxTRAN : list of keywords of the language .
123
124
125  --------------
126
127    Monolix 4.1.3 - sp2 (2012 -05 -29)
128
129  Enhancements :
130       - system . xmlx : possibility to not display Lixoft Activate .
131       - Lixoft Activate : add the possibility to send an email with
              encoded computer information to create license @Lixoft .
132       - Lixoft Activate : manage " cannot connect to url " error by asking
              user to go on a web site or send an email .
133
134  Bugs Fixes :
135       - IOV Problem with R2010bSP1
136       - perlScripts : bug in the management of the configuration file for
              [ program - execute - options ] and run on a cluster .
137       - add ' rlmutil . exe ' for windows packages ( forgotten in previous
              packages ).
138       - problem floating license .
139       - warnings for occasions without dose were removed .
140       - when the last Individual / Occasion had no dose , Monolix crashed .
141       - When there were syntax errors in the structural model , monolix
              said that it could not find the file instead giving the MLXTRAN
              message
142       - NaN observations are now mentionned as error when algorithms are
              launched .
143       - Update documentation : in batch mode section , there is a bad path .
144
```

```
145
146   --------------
147
148      Monolix 4.1.3-sp1 (2012-05-21)
149
150   Bug Fixes:
151      - GUI:
152          * Check Initial Fixed Effects interface crashed when creating
                 covariate and parameter's sliders for some sizes
153
154   --------------
155
156      Monolix 4.1.3 (2012-05-02)
157
158   New Features:
159      - MLXTran model: allows negative categories
160      - License management: uses RLM as license provider
161      - Compiler manager: adds the possibility to choose the embedded
             compiler
162      - The Monolix and Matlab versions are now stored in the algorithm
             result files
163
164   Bug Fixes:
165      - MLXTRAN project:
166          - continuous transformation can take a mathematical expression
167          - problem with structural model path
168      - MLXTRAN model:
169          - Under Linux 64 bits, due to library conflicts with Matlab
                 R2010b and better, the multi-threaded
170            loading of the model description for the project occasionally
                 fails
171          - Only the last table variable is recorded, overwriting the
                 first one
172      - Graphics:
173          - log / linear works on all graphics
174          - when log-log scale is set for "observed versus predicted', the
                 diagonal line isn't displayed anymore
175      - GUI:
176          - editor call did not work
177      - Algorithms:
178          * bug for individuals without some type of observations and with
                 IOV computing conditional mode
179          * bug when there were continuous outputs after discrete outputs
180          * Fisher Information Matrix by Stochastic Appoximation does now
                 handle better the case when there are
181            no parameters to estimate in the residual error
182      - Session:
183          * when the directory monolixData/monolix<version> is renamed
```

```
                     during an active Monolix session, stopping
184                 Monolix caused an exit of Matlab.
185

186

187   --------------
188

189     Monolix 4.1.2: (2012-03-05)
190

191   --------------
192

193   New Features:
194       - PerlScripts : possibility to save the results in the project
              directory instead of the output directory
195       - In system.xmlx : automatically creates a directory hierarchy for '
              monolixData' path
196

197   Enhancements:
198       - MLXTran (structural model) multi-threading processing enhancement
199

200   Bug Fixes:
201       - Batch Processing failed when a very large number of projects were
              launched
202       - MDV column: when MDV=2 only the regression variables were taken
              into account
203       - Fixed a bug in graphics saving
204       - Fixed error when an empty result folder was timestamped
205       - Simulation of categorical data, whenever no category 0 is defined
206       - Fixed take into account UserPath defined in 'system.xmlx' for the
              preference file saving
207

208

209   --------------
210

211     Monolix 4.1.1: (2012-02-13)
212

213   --------------
214

215   New Features:
216       - timestamped backup
217       - preferences interface
218       - tools menu for activating license and preferences
219       - option for locking structural model modifications
220       - Project-MLXTRAN grammar modification : initialization of parameter
              is written now as beta_{pi,cov}, pop_{pi}, omega_{pi}, ...
221       - save graphics as png / ps / jpg / bmp or tiff
222       - selection of graphics/tables to be saved
223

224   Bug Fixes:
```

```
225        - Project - MLXTran : user can define the result folder
226        - LoQ difference between 3.2 and 4.1
227        - statistical test for error model and covariate model
228        - xmlx loading from 3.2 to 4.1
229        - correlation ( levelName consistence with IOV ) + parser error
230        - observation model ( prediction = observation name )
231        - path for MONOLIX user profile can include special characters
232
233
234
235   --------------
236
237      Monolix 4.1.0: (2012 -01 -23)
238
239   --------------
240
241   psmlx :
242        - compatible with the mlxtran format of projects
243        - available on Windows OS
244
245   mlxtran :
246        - new syntax
247        - PK macros
248        - RTTE models
249
250   license :
251        - interface for installing the license file
252
253   Interface :
254        - setting for axes ' limits
255        - information for the observation model
256        - shortcut for model libraries
257
258   File system :
259        - improved handling of special characters for filepaths
260
261   Demos :
262        - updated for the new mlxtran syntax
263        - dispatch of the model library for demos
264
265   Known Bugs :
266        - under Windows OS , user directory cannot contain special characters
              other than spaces
267
268
269
270   --------------
271
```

```
272    Monolix 4.0.1: (2011-10-27)
273
274    -------------
275
276   psmlx:
277       - use-matlab option didn't work in command line mode
278       - multi-threading : multhreading didn't work
279       - take account the p.coded files
280
281   mlxtran
282       - problem with FIM options : both linearization and
              stochasticApproximation appeared after a save with
              stochasticApproximation option set
283       - avoid the unloading of project when settings files does not exist
            : default settings are loaded
284   license:
285       - multi write database didn't work well in multi-threading mode
286
287   Interface:
288       - save lists
289       - configuration panel
290       - launching some graphics alone is now possible
291       - the graphics were closed when "Use last estimates" were used
292       - when monolix was launched twice without loading or creating a
            project, two toolbars were created
293
294   Algorithm and simulations:
295       - simulation works now with dataset without EVID column and with MDV
            column
296
297   Results:
298       - the graphics fit now to the paper in .ps files
299       - xLabels were wrong for some graphics when several regression
            variables were present
300       - some graphics  crashed when launched after some hypotheses tests
            were done
301       - Visual studio redistribuable problem
```