RsNLME Installation

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RsNLME provides users with the ability to define PK/PD models from within the R environment and utilize PML (Phoenix Modeling Language) and the NLME engine to fit/simulate those models.

For these installation instructions, replace C:/NlmeStandaloneInstallation with the location of your standalone NLME installation.

1. Install the NLME standalone package

If the NLME standalone package is already installed, skip this step. Otherwise, unzip the Certara.Nlme_Windows.zip file you received from Certara in a directory of your choice (e.g., C:/NlmeStandaloneInstallation).

2. Install MPICH2 and gcc

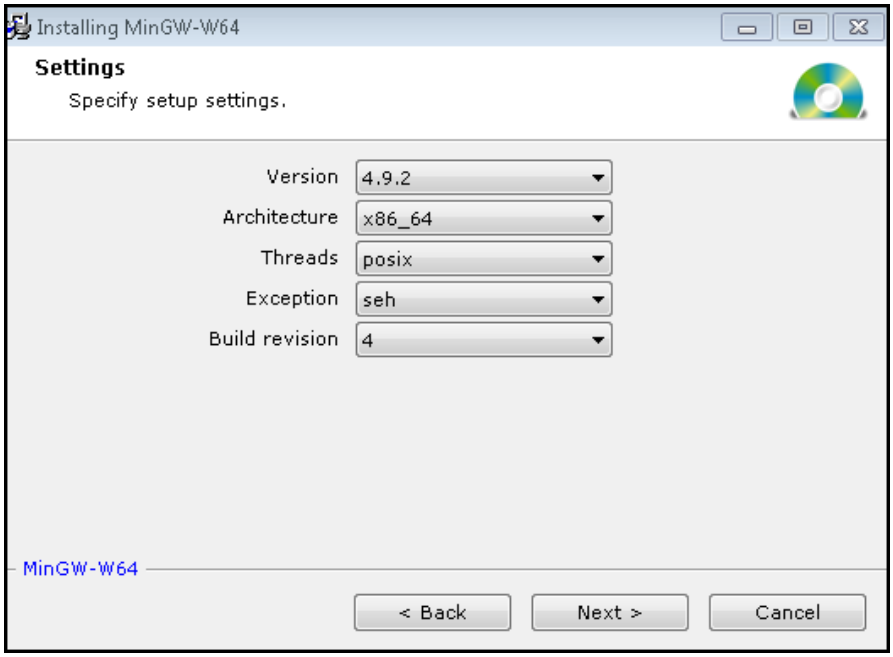
MPICH2 enables usage of multiple CPUs and CPU cores. MPI version is 1.4.1p1 is required and can be downloaded from:

http://www.mpich.org/downloads/versions/mpich2-1.4.1.p1-win-x86-64.msi

The gcc 4.9.2 compiler is used to create PML (Phoenix Modeling Language) models. This compiler is required and can be downloaded from:

https://sourceforge.net/projects/mingw-w64/

During gcc installation, define the settings as shown in the following image:



3. Install the R program

If R 3.5 is already installed, skip this step. Otherwise, go to https://www.r-project.org, click the **Manuals** link on the left side of the webpage, and follow the instructions in the *R Installation and Administration* document.

4. Install the R libraries

If the following R libraries are already installed, skip this step. Otherwise, run the R program as the administrator and use the **Packages > Install Packages** menu option to install the following libraries..

ggplot2
reshape
ssh
XML
ggforce
tidyr
Xpose (https://cran.r-project.org/src/contrib/Archive/xpose/xpose_0.4.3.tar.gz)

If you are going to run the test example provided in the last step of this document, you will also need to install the following libraries:

data.table
vpc

5. Install the Certara packages

Three packages from Certara also need to be installed in R:

Certara.NLME8_0.0.1.1000.tar.gz Located in C:/NlmeStandaloneInstallation /InstallDirNLME.

RsNlme_0.0.0.9000.tar.gz Sent from Certara.

Xpose.Nlme_0.0.0.9000.tar.gz Sent from Certara.

To install the packages:

a. Save the RsNlme_0.0.0.9000.tar.gz and Xpose.Nlme_0.0.0.9000.tar.gz files you received from Certara in a directory of your choice.

b. From an administrator run R session, type the following command for each of the three packages being installed.
`install.packages(FULL_PATH_TO_GZ_FILE, repos=NULL,type="source")`
Be sure to replace "`FULL_PATH_TO_GZ_FILE`" with the actual path to one of the .gz files.

6. Set up the environment variables

Define your working directory:

```
setwd("C:/NlmeStandaloneInstallation")
```

Type the following to set the necessary variables:

```
Sys.setenv("NLME_ROOT_DIRECTORY"="C:/NlmeStandaloneInstallation")
Sys.setenv("INSTALLDIR"="C:/NlmeStandaloneInstallation/InstallDirNLME")
```

7. Run a test example

Enter the following to verify that RsNLME has been set up correctly.

```
#
# Load library
#
library(Certara.NLME8)
library(RsNlme)
library(ssh)
library(ggplot2)
library(xpose)
library(Xpose.Nlme)

|

dataset=NlmeDataset()
#
#Engine parameters
#
engineParams = NlmeEngineExtraParams(PARAMS_METHOD=METHOD_FOCE_ELS,
                                     PARAMS_NUM_ITERATIONS=1000,
                                     PARAMS_SAND="TRUE")
#
#Run locally with MPI enabled
#
host = NlmeParallelHost(sharedDirectory=Sys.getenv("NLME_ROOT_DIRECTORY"),
                        parallelMethod=NlmeParallelMethod("LOCAL_MPI"),
                        hostName="MPI",numCores=4)
#
#Look at the data
#
input=read.csv("16subjects.csv")
View(input)
#
#Graph time vs. Conc
#
df=data.frame(time=input$Act_Time,conc=input$Conc,subject=input$Subject)

ggplot(data=df,aes(x=time,y=conc))+scale_y_log10()+
geom_point(colour=df$subject)+geom_line(aes(x=df$time,y=df$conc,
group=df$subject,colour=df$subject))
#
#Model definition
#
model = pkmodel(numComp=2,
                isPopulation=TRUE,
                absorption = Intraveneous,
                modelName="InitialModel")
#
#Looks at model variables and map them to data columns
#
dataset=defaultDataset(model,input)
initColMapping(model)=input

modelColumnMapping(model)
colnames(input)
print(modelVariableNames(model))

modelColumnMapping(model)=c(id="Subject", CObs="Conc",A1="Amount")
#
#Set initial estimates on model variables
#
```

```
initFixedEffects (model)
initFixedEffects(model)=c(tvV=16,tvCl=41,tvV2=7,tvCl2=14)

print(model)
#
#Do the model fitting
#
job=fitmodel(host,dataset,engineParams)
library(xpose)
library(Xpose.Nlme)
xp=xposeNlme(dir="./",modelName="Initial Model")
#
#NOTE: If you are prompted for a TIME column names
#      (as it does not exist in the file), pick Act_Time
#
list_vars(xp)
dv_vs_pred(xp)
#dv_vs_ipred(xp)
res_vs_pred(xp,res="IWRES")
ind_plots(xp, res="IWRES")
#res_vs_idv(xp,res="WRES")
eta_distrib(xp)
```

Remote Linux host setup

Note: Please consult your IT professional for Linux grid/ssh authentication setup.

1. If the NLME standalone package is already installed on the Linux machine, skip this step. Otherwise, untar the Certara_Nlme_Linux.tar file you received from Certara in a directory of your choice (e.g., /share/NlmeStandaloneInstallation).
2. If R 3.5 is already installed, skip this step. Otherwise, go to https://www.r-project.org, click the **Manuals** link on the left side of the webpage, and follow the instructions in the *R Installation and Administration* document.
3. If the following R libraries are already installed, skip this step. Otherwise, run the R program as the administrator and use the **Packages > Install Packages** menu option to install the following libraries.

   Batchtools: Handles submission of NLME replicates to a Linux/Windows GRID.
   Reshape: Summarizes NLME spreadsheets.
   XML: Manages reading/writing progress.xml.
4. Install the Certara packages

   Three packages from Certara also need to be installed in R:

   Certara.NLME8_0.0.1.1000.tar.gz Located in C:/NlmeStandaloneInstallation /InstallDirNLME.

   RsNlme_0.0.0.9000.tar.gz Sent from Certara.

   Xpose.Nlme_0.0.0.9000.tar.gz Sent from Certara.

   To install the packages:

   a. Save the RsNlme_0.0.0.9000.tar.gz and Xpose.Nlme_0.0.0.9000.tar.gz files you received from Certara in a directory of your choice.

   b. From an administrator run R session, type the following command for each of the three packages being installed.
   `install.packages(FULL_PATH_TO_GZ_FILE, repos=NULL,type="source")`
   Be sure to replace "`FULL_PATH_TO_GZ_FILE`" with the actual path to one of the .gz files.
5. Install SSH/Sftp

   SSH/Sftp needs to be installed on all Linux machines that will be used with the MultiCore parallelization method or act as a submission host to a GRID. SSH is installed by default on Red Hat Enterprise Linux (RHEL) version 6.x. To facilitate job submission from Windows to Linux, NLME in RsNlme (on Windows) contains an SSH library.
6. Install Openmpi

   For grid execution (SGE/LSF/TORQUE), installation of Openmpi (v 1.10.6) as a parallel platform on the grid is recommended. Please refer to https://www.open-mpi.org/faq/ for information. Standard GRIDS have Openmpi installed by default.