User Guide for PKreport Package

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February 8, 2011

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1 Introduction

Graphics play an important and unique role in population pharmacokinetic (PopPK) model building by exploring hidden structure among data before modeling, detecting extremity during modeling, and validating results after modeling. However, to our knowledge there are no tools available to provide an automatically pipeline for routine graphic generation and it also requires users to have expertise in statistical and computing knowledge to generate all related graphics. This may provide obstacles to users who do not have this expertise. In this work, I developed an automatically pipeline, an R package called PKreport, for testing model assumptions, visualizing data and diagnosing models. PKreport aims to 1) provide automatic pipeline for users to visualize data and models. It creates a flexible R framework with automatically generated R scripts to save time and cost for later usage; 2) implement an archive-oriented management tool for users to store, retrieve and modify figures. 3) offer powerful and convenient service to generate high-quality graphs based on two R packages: lattice and ggplot2. The general architecture, running environment and statistical methods can be easily extended to include more automatic diagnostics in the development of PopPK models.

2 Installation

You can install PKreport with the following command,

```
install.packages("PKreport")
```

For users who do not have administrative privilege for their computers, they can install this package in their own accounts:

```
install.packages("PKreport", lib.loc="User directory")
library("PKreport", lib.loc="User directory")
```

3 Software implementation

PKreport is one R package aiming to create an automatic pipeline for model assumption testing. Based on a hidden metric system matching default variables to data variables, this package turns the assumption testing to a fast, convenient and comprehensive routine. With the support of two powerful R graphical packages (*lattice* and *ggplot2*), this software can generate high-quality figures for further diagnosing, archive all figures with specific folders for report and review, and utilize web browsers as interface for viewing, archiving and analyzing.

3.1 Metric system

The default variables function as currency for communicating between data sets and packages to generate special-purpose plots (Table˜1). For example, PRED represents prediction calculated from nonlinear mixed effects model fitting, and RES is equal to the difference between observations and predictions. Users may use preferred software to calculate these related variables. As a result, each data set and fitting results have totally different variable names for further analysis. To facilitate model diagnostics, users need to match the default metric with the variables from data sets. After matching, the package can process the data, configure the functions, and generate related diagnostic plots. This system provides ways to function for diverse software such as NONMEM, Monolix, R nlme package, and SAS NLMIX procedure.

Package variable	**Description**
ID	Patient ID
TIME	Time after dose
CONC	The concentration of drug in the body
PRED	Prediction generated from model fitting
RES	Residual
WRES	Weighted residual
IPRED	Individual prediction
IWRES	Individual weighted residual
COV	Covariates

Table 1: Package metric system. The first column (Package variable) contains default variable names. These default variable names match NONMEM naming system. The second column explains the details of these variables.

3.2 Configuration

The whole system is configured by three lists: 1) graph list. This list helps user to choose proper figure format (jpg, pdf, png, etc.) as well as the graphical packages. Currently there are two graphical packages implemented for high-quality figures (*lattice* and *ggplot2*). 2) histogram list. This list specifies the configuration for the histogram generated by package. It includes type of histogram and layout setup. 3) scatterplot list. This list determines the type of scatter plot, bandwidth of smooth and layout setup.

3.3 Architecture description and features

Currently PKreport offers console user interface to test model assumptions. It has the following functions: 1) Match metrics. By matching default variables to data variables based on one-to one or one-to-many schema, this function sets up global variables for further analysis. 2). Configure figures. This module determines the figure format, figure size and other related properties of figures. 3). Generate figures. Depending on the research goals, users have access to 7 sub-functions for exploratory data analysis, overall goodness of fit plots, parameter diagnostics, random effect diagnostics, structural model diagnostics, residual model diagnostics, and covariate model diagnostics. Each sub-function will create a folder to store related figures as archives. 4). Display results. PKreport offers web browser as a management tool to explore archives created in function 3 and R scripts in function 5. The main interface includes categories matching the name of file directories. 5). Generate R scripts. To improve efficiency and help users to generate high-quality figures, users have option to modify related R scripts to meet their specific requirements. All generated R scripts match the order of figures generated in function 4. 6). Modify figures. Users can also up-date or modify certain figures with figure ID for particular purpose. 7). Clean archives. This module will delete all archives (file directories and figures) and clean global variables in R environment. The general architecture is shown in Fig.~1.

3.4 Format for input data

PKreport accepts two types of input data: data.frame or *nonmem* class:

3.4.1 data.frame as input data

PKreport accepts data.frame and diagnoses model results from NONMEM, Monolix, R nlme, etc. For NONMEM, the data.frame can be read in R directly from tab file. For Monolix, there are a few output files, and users have to combine them as one single file (demonstrated in example 6). This single file is then read in R as data.frame.

3.4.2 *nonmem* class as input data

nonmem class is specifically designed for NONMEM. The option *output.lst*, and *output.dir* is for NONMEM 7. The option *output.tab* is available for any NONMEM version.

4 Function description

This package includes 1 *nonmem* class and 5 main functions:

- *nonmem* class: this S4 class contains all NONMEM output, and users can conveniently have access to each section of output.
- PKdata: this function helps user to input data (tab file) into package (first parameter), and match the data variables to the package metric system (second parameter).
- PKconfig: this function provides a configuration tool to users for managing global parameters and figure setup. It takes three lists (global.list, hist.list, scatter.list) as parameters. If no lists are configured, the default configuration will be used.
- PKfigure: this function is the main interface for generating reports. It takes three components: data from NONMEM tab file, diagnostic methods (described in the following section), and a logical value to keep or delete previous PKfigure run.
- PKshow: this function will open web browser, load all results and generate reports.
- PKclean: this function will delete all folders and figures generated for the reports.

4.1 *nonmem* class

4.1.1 Slots in *nonmem* class

This class includes the following slots:

- file.cov: a list, includes title (character) and data (data.frame) for cov file.
- file.cor: a list, including title (character) and data (data.frame) for cor file.
- file.coi: a list, including title (character) and data (data.frame) for coi file.
- file.phi: a list, including title (character) and data (data.frame) for phi file.
- file.lst: a character vector, containing the information from NONMEM lst file.
- method: a character vector, matching #METH tag in lst file and containing the estimation method.
- analysis: a list, matching text between #TERM tag and #TERE tag in lst file and contains the analysis information.
- objt: a character vector, matching #OBJT tag in lst file and describes the objective function.
- objv: a character vector, matching #OBJV tag in lst file and describes the objective function value.
- objs: a character vector, matching #OBJT tag in lst file and describes the objective function standard deviation.
- tabid: a character vector, from the first line of tab file and describes the title of tab file
- tabdata: a data frame, matching data in tab file and describes the title of tab file. This is the main data for PKfigure.

nonmem instances are created through *new("nonmem", ...)*. The arguments to *new* should include output.lst and output.tab. If output.dir is missing, NULL will be assigned to proper slots. The option *output.lst*, and *output.dir* is for NONMEM 7. The option *output.tab* is available for any NONMEM version.

```
> myclass <- new("nonmem", output.lst="C:/nonmem7/KAKOE.lst",
                output.tab="C:/nonmem7/KAKOE.FITKAKOEST_PAR.FIT",
                output.dir="C:/nonmem7")
```

4.1.2 Methods in *nonmem* class

This class includes the following methods:

- non.cov: return file.cov slot.
- non.cor: return file.cor slot.

- non.coi: return file.coi slot.
- non.phi: return file.phi slot.
- non.lst: return file.lst slot.
- non.lst.meth: return method slot, matching #METH tag in lst file and containing the estimation method.
- non.lst.term: return analysis slot, matching text between #TERM tag and #TERE tag in lst file and contains the analysis information.
- non.lst.objt: return objt slot, matching #OBJT tag in lst file and describes the objective function.
- non.lst.objv: return objv slot, matching #OBJV tag in lst file and describes the objective function value.
- non.lst.objs: return objs slot, matching #OBJT tag in lst file and describes the objective function standard deviation.
- non.tab: return file.tab slot. This is the main data for PKfigure.
- non.select: return user-specified lines from lst file. If the length of all lines are equal, a data.frame is returned; otherwise a list is returned.

```
> non.lst(myclass)
> non.select(myclass, c(1:5))
> non.select(myclass, c(20:25))
[[1]]
[1] "MDV"  "DATA" "ITEM" "IS"   "DATA" "ITEM" "NO.:" "8"

[[2]]
[1] "0INDICES"   "PASSED"     "TO"         "SUBROUTINE" "PRED:"

[[3]]
[1] "9"  "11" "5"  "7"  "0"  "0"  "6"  "0"  "0"

[[4]]
[1] "0" "0"

[[5]]
[1] "0LABELS" "FOR"     "DATA"    "ITEMS:"

[[6]]
 [1] "ID"   "PID"  "TAD"  "DV"   "AMT"  "CMT"  "RATE" "MDV"  "EVID" "TIMB" "TIME"
```

4.2 PKdata

This function includes two parameters:

- data: a data frame to analyze. Generally it is from tab file generated from NONMEM.

- match.term: a list. It matches the package metrics to the variable names in the data. For ID, DV, TIME, PRED, RES, WRES, IPRE, the package only allows one variable to match these terms. Users can use CWRES, NWRES to match WRES based on their research goals. For COV, PARA, ETA, the package accepts multiple variables a character vector.

```
> head(pdata)
  ID PID    TIME    DV  IPRED    CWRES EVID
1  1   1 0.00000  0.00  0.000  0.00000    0
2  1   1 0.49861  0.00  0.000  0.00000    1
3  1   1 0.49861  0.00  0.000  0.00000    1
4  1   1 0.99917 15.84 12.674  1.49810    0
5  1   1 1.49940 27.20 46.562 -1.69600    0
6  1   1 1.99920 62.90 73.010 -0.57653    0
         TAD    ETA1    ETA2    ETA3 ETA4 ETA5
1 -0.49833000 0.32094 0.16727 0.26971    0    0
2  0.00027778 0.32094 0.16727 0.26971    0    0
3  0.00027778 0.32094 0.16727 0.26971    0    0
4  0.50083000 0.32094 0.16727 0.26971    0    0
5  1.00110000 0.32094 0.16727 0.26971    0    0
6  1.50080000 0.32094 0.16727 0.26971    0    0
      ETA6 ETA7  DV.1   PRED      RES     WRES
1 -0.34748    0  0.00  0.000   0.0000  0.00000
2 -0.34748    0  0.00  0.000   0.0000  0.00000
3 -0.34748    0  0.00  0.000   0.0000  0.00000
4 -0.34748    0 15.84 16.384  -0.5443  0.94749
5 -0.34748    0 27.20 62.534 -35.3340 -1.10160
6 -0.34748    0 62.90 99.985 -37.0850 -0.38250

> var.name <- list(ID="ID", DV="DV", TIME="TIME", PRED="PRED",
                   RES="RES", WRES=c("WRES"),
                   IPRE="IPRED", IDV=c("EVID"),
                   ETA=c("ETA5", "ETA1"), COV="EIVD",
                   PARA=c("ETA2", "ETA3")
                   )

> PKdata(data=pdata, match.term=var.name)
Data is read successfully.
```

4.3 PKconfig

This function includes two parameters:

- general.list: a list. It includes figure configuration: save.format (png format will be generated automatically as the default format for html report) , width, height, and also graphic packages (0: use only lattice package. 1: use only ggplot2 package. 2: use both packages).

- hist.list: a list. It includes histogram configuration: type, layout, ind.layout (for individual plots).

- scatter.list: a list. It includes scatterplot configuration: type, layout, span, ind.layout (for individual plots).

This function only supports simple configuration for figures. If you need more complex configuration for figures, please go to R code page in HTML report and regenerate proper figures with those codes.

```
> global.list <- list(    save.format=c("jpeg", "bmp"),
                         width = 480, height = 480,
                         package=2
                     )
> hist.list <- list(type=c("count"), layout=c(1,1), ind.layout=c(5,5))
> scatter.list <- list(type=c("p", "smooth"), layout=c(1,1), ind.layout=c(5,5))
> PKconfig(global.list, hist.list, scatter.list)
```

4.4 PKfigure

This function includes three parameters:

- data: a data frame to analyze. Generally it is from tab file generated from NONMEM.
- methods: a numeric vector. It includes all diagnostics methods according to Census,
  - 1: Exploratory data analysis
  - 2: Individual plots
  - 3: Goodness-of-fit plots
  - 4: Structural model diagnostics
  - 5: Residual model diagnostics
  - 6: Parameters diagnostics
  - 7: Covariate model
  - 8: Random effects
- clean: a logical value indicating whether or not to keep results from previous PKfigure for final report.

```
> PKfigure(pdata, c(1,5,8))
```

4.5 PKshow

This function includes three optional parameter: nonmemObj, a object of class nonmem; table.Rowv, a logical value determining whether the row dendrogram should be reordered in the heatmap-like table; table.Colv, a logical value determining whether the column dendrogram should be reordered in the heatmap-like table.

```
# Generate both graphical report and numeric report
> PKshow(myclass, tableRowv=TRUE, tableColv=TRUE)
# Only generate graphical report
> PKshow()
```

4.6 PKclean

This function is to delete all archives (file directories and figures) and clean global variables in R environment.

```
> PKclean()
```

5 Demonstration

To illustrate how to use this package, five examples are used. The first and the second example demonstrate the main functions, the third example focuses on the configuration, and the last two examples explain the methods related to *nonmem* class.

5.1 Example 1

We would like to generate a simple report (only graphical report and no numerical report),

```
> data(pdata)
> var.name <- list(ID="ID", DV="CONC", TIME="TIME",
  PRED="PRED", RES="RES", WRES="WRES",
                  IDV=c("ISM"), IPRE="PRED",
                  ETA=c("ETA1", "ETA2"), COV=c("WT","AGE"),
                  PARA=c("CL", "V")
                  )

> PKdata(pdata, match.term=var.name)
> PKfigure(pdata, c(3,6,8))
> PKshow()
```

5.2 Example 2

The NONMEM output directory is in *c:*
nonmem7, and it includes lst, tab, cov, cor, coi and phi files. We would like to generate a complete report, including both graphical report and numeric report.

```
> myclass <- new("nonmem", output.lst="C:/nonmem7/KAKOE.lst",
               output.tab="C:/nonmem7/KAKOE.FITKAKOEST_PAR.FIT",
               output.dir="C:/nonmem7")
> var.name <- list(ID="ID", DV="DV", TIME="TIME", PRED="PRED",
                  RES="RES", WRES=c("WRES"),
                  IPRE="IPRED", IDV=c("EVID"),
                  ETA=c("ETA5", "ETA1"), COV="TIME",
                  PARA=c("ETA2", "ETA3")
                  )

> pdata <- myclass@tabdata
> PKdata(data=pdata, match.term=var.name)

> PKfigure(pdata, 3)
> PKfigure(pdata, 7, FALSE)
> PKshow(myclass, table.Rowv=TRUE, table.Colv=TRUE)
```

5.3 Example 3

We would like to generate report only with R package lattice, and change figure width and height to 500 px.

```
> global.list <- list(    save.format=c("jpeg", "bmp"),
                        width = 500, height = 500,
                        package=0
                      )
> hist.list <- list(type=c("count"), layout=c(1,1), ind.layout=c(5,5))
> scatter.list <- list(type=c("p", "smooth"), layout=c(1,1), ind.layout=c(5,5))

> PKconfig(global.list, hist.list, scatter.list)
> PKfigure(pdata, c(3,6,8))
> PKshow(myclass)
```

5.4 Example 4

There are some methods for *nonmem* class. These methods help users to extract specific information from NONMEM output, including estimation method, objective function value, and file contents.

```
> non.lst(myclass)
> non.lst.meth(myclass)
[1] "First Order Conditional Estimation with Interaction"
> non.lst.objv(myclass)
[1] "2351.625"
> non.tab(myclass)
> non.cov(myclass)
```

5.5 Example 5

The standard output file (lst file) does not have a tabular format. There are two methods in this packages that can help users to access any line in the lst file. User can check the line number by some text edit software or use `non.lst` function.

```
> non.lst(myclass)
# select lines from 50 to 56 in lst file
> exp.data <- non.select(myclass, c(50:56))
> options(scipen=100)
> PKnum(exp.data)
     [,1]   [,2]       [,3]
[1,]    1  44.80 1000000.00
[2,]    1 410.00 1000000.00
[3,]    0   0.25 1000000.00
[4,]    6  17.00 1000000.00
[5,]    0   0.28 1000000.00
```

```
[6,]    0   0.50       0.95
[7,]    0   0.50 1000000.00
> options(scipen=-100)
> PKnum(exp.data)
      [,1]     [,2]    [,3]
[1,] 1e+00 4.48e+01 1.0e+06
[2,] 1e+00 4.10e+02 1.0e+06
[3,] 0e+00 2.50e-01 1.0e+06
[4,] 6e+00 1.70e+01 1.0e+06
[5,] 0e+00 2.80e-01 1.0e+06
[6,] 0e+00 5.00e-01 9.5e-01
[7,] 0e+00 5.00e-01 1.0e+06
```

5.6 Example 6

In the final example, I will demonstrate how to use this package for the output from Monolix. These output files are "predictions.txt", "indiv_eta.txt", "indiv_parameters.txt".

```
# read in Monolix output files
> mpred <- read.table(file.path(
   paste(system.file("monolix", package="PKreport"),
   "predictions.txt", sep="/")),
+          header=T, sep="\t")
> meta <- read.table(file.path(
           paste(system.file("monolix", package="PKreport"),
   "indiv_eta.txt", sep="/")),
+          header=T, sep="\t")
> mpara <- read.table(file.path(
   paste(system.file("monolix", package="PKreport"),
   "indiv_parameters.txt", sep="/")),
+          header=T, sep="\t")
>
# combine three files together as one file
> merge.1 <- merge(mpred, meta, by="ID")
> mdata <- merge(merge.1, mpara, by="ID")
> colnames(mdata) <- gsub("_", ".", colnames(mdata))
> no.index <- which(colnames(mdata) %in% c("X.1", "X.y", "X"))
> mdata <- mdata[, - no.index]
>
> PKdata(mdata, match.term=var.name)
Data is read successfully.
> PKfigure(mdata, c(3))
> PKshow()
```

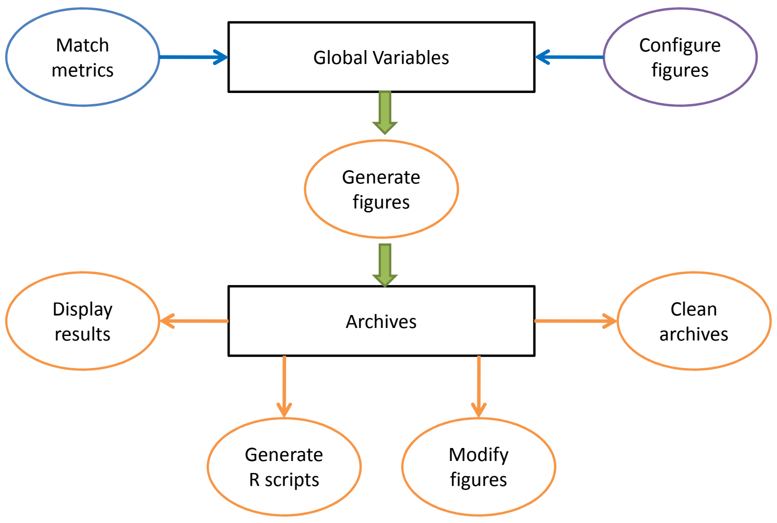
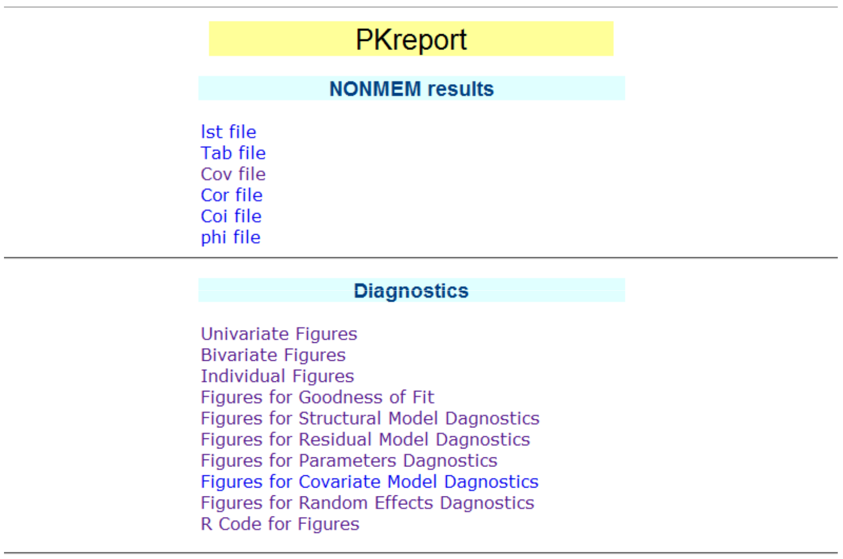


Figure 1: Software architecture of PKreport. It has three main functions: 1) match metrics; 2) configure figures; 3) generate figures; 4) display results; 5) generate R scripts; 6) modify figure; 7) clean archives. The first two functions set up working environment, and the other functions help to generate related figures.


PKreport

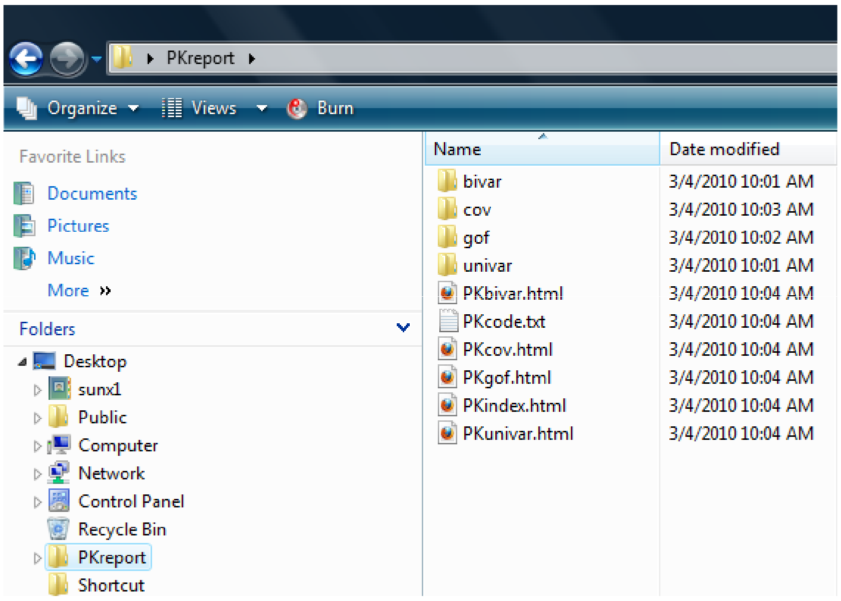
NONMEM results

lst file
Tab file
Cov file
Cor file
Coi file
phi file

Diagnostics

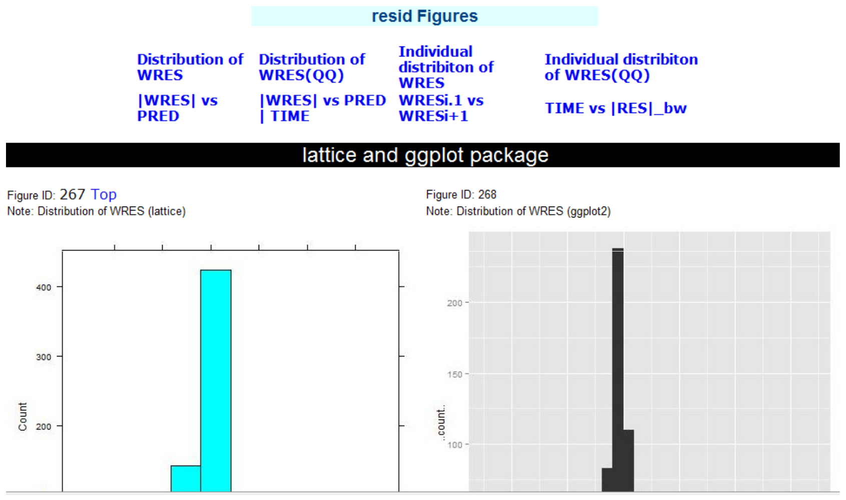
Univariate Figures
Bivariate Figures
Individual Figures
Figures for Goodness of Fit
Figures for Structural Model Dagnostics
Figures for Residual Model Dagnostics
Figures for Parameters Dagnostics
Figures for Covariate Model Dagnostics
Figures for Random Effects Dagnostics
R Code for Figures

Figure 2: PKreport web interface. The first section: NONMEM result is numerical report. The second section: Diagnostics is the graphical report. The R code is the last section of graphical report.



Name	Date modified
bivar	3/4/2010 10:01 AM
cov	3/4/2010 10:03 AM
gof	3/4/2010 10:02 AM
univar	3/4/2010 10:01 AM
PKbivar.html	3/4/2010 10:04 AM
PKcode.txt	3/4/2010 10:04 AM
PKcov.html	3/4/2010 10:04 AM
PKgof.html	3/4/2010 10:04 AM
PKindex.html	3/4/2010 10:04 AM
PKunivar.html	3/4/2010 10:04 AM

Figure 3: Archives directories for figures. In this example, *univar* and *bivar* folders match exploratory data analysis; *gof* folder matches goodness of fit plots; *cov* folder matches covariate model diagnostics. These folders contain all related diagnostic figures. *PKcode.text* has all related R scripts for these figures.



resid Figures

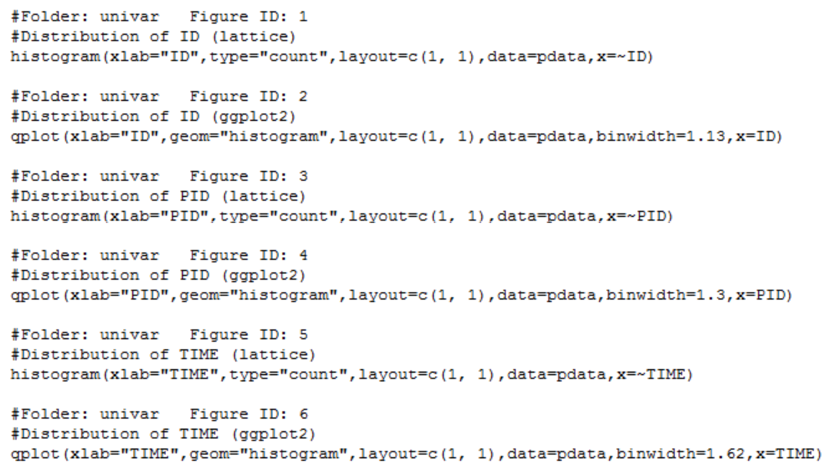
Distribution of WRES	Distribution of WRES(QQ)	Individual distribiton of WRES	Individual distribiton of WRES(QQ)
|WRES| vs PRED	|WRES| vs PRED | TIME	WRESi.1 vs WRESi+1	TIME vs |RES|_bw

lattice and ggplot package

Figure ID: 267 Top
Note: Distribution of WRES (lattice)

Figure ID: 268
Note: Distribution of WRES (ggplot2)

Figure 4: Figures for residual model diagnostics. A summary list for all figures is on the top. The figure ID matches that in the R code web page, and users can easily regenerate the figure with this ID. Left figure: histogram for distribution of WRES generated with lattice package. Right figure: histogram for distribution of WRES generated with ggplot2 package.



```
#Folder: univar   Figure ID: 1
#Distribution of ID (lattice)
histogram(xlab="ID",type="count",layout=c(1, 1),data=pdata,x=~ID)

#Folder: univar   Figure ID: 2
#Distribution of ID (ggplot2)
qplot(xlab="ID",geom="histogram",layout=c(1, 1),data=pdata,binwidth=1.13,x=ID)

#Folder: univar   Figure ID: 3
#Distribution of PID (lattice)
histogram(xlab="PID",type="count",layout=c(1, 1),data=pdata,x=~PID)

#Folder: univar   Figure ID: 4
#Distribution of PID (ggplot2)
qplot(xlab="PID",geom="histogram",layout=c(1, 1),data=pdata,binwidth=1.3,x=PID)

#Folder: univar   Figure ID: 5
#Distribution of TIME (lattice)
histogram(xlab="TIME",type="count",layout=c(1, 1),data=pdata,x=~TIME)

#Folder: univar   Figure ID: 6
#Distribution of TIME (ggplot2)
qplot(xlab="TIME",geom="histogram",layout=c(1, 1),data=pdata,binwidth=1.62,x=TIME)
```

Figure 5: R scripts generated for graphical report. Each R code command includes two comments and one script. The first comment explains the folder name for this figure and figure ID matching the graphical report. The second comment describes the title of the figure.