

Reporting of NONMEM Models using S-PLUS

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Background

Pharmaceutical companies use NONMEM software to fit sophisticated Pharmacokinetic and pharmacodynamic models. However, NONMEM produces a large quantity of text-based outputs, which can be difficult to read and understand. This output consists of 2 sources of data:

Rectangular datasets stored in a text-based format that need to be imported, subsetting and formatted in order to be understood

Complex unstructured text files that must be parsed to extract key elements such as final estimates and covariance matrices

Importing the information and presenting it together in a user-friendly manner is key to understanding the viability of each model fit.

NONMEM

NONMEM is a FORTRAN program used for population pk/pd analysis and other modeling and simulation tasks during drug development. Results from such analysis can support internal decision making but can also support labeling claims and need therefore to be submitted to regulatory authorities.

Inputs to NONMEM are ASCII files (data and model specification) which are translated into NONMEM and then executed. Outputs are again ASCII files which need to be further processed to check the validity of the model (diagnostic plots) and to report the results.

Since NONMEM is a FORTRAN application based on text inputs and outputs, it is often criticized for being difficult to use, especially in a formal regulated environment. Also, the textual and graphical output from NONMEM can be difficult to customize and enhance.

Solution Technology

A library was developed in S-PLUS 7.0 in order to import and report on NONMEM information. Within S-PLUS, the library was enhanced with a menu system to allow non-programmers to evaluate the NONMEM models.

At the request of customers, the library was also ported to R for integration into modeling and simulation systems.

Library Functional Requirements

Functional requirements for the library were built from 2 key sources:

- Conversations during S-PLUS and R training sessions provided by Mango Solutions consultants, where the need to access such a library was discussed
- The existence of an R library from Uppsala University called "xPose", which performs some of the tasks of the developed library with a slightly different focus

The high level requirements for the library were as follows:

- Read each of the NONMEM files and store them as a single structure
- Provide graphic routines to plot the NONMEM data elements
- Provide easy access to other elements of the NONMEM run (such as the objective function and final parameter estimates)

Further enhancements and definition of requirements was achieved through the use of intradepartmental discussions and workshops. Reference was also made to the NONMEM user manuals..

We used the NONMEM User Manuals in order to investigate the format of the various types of NONMEM file. These documents were used to build the design documents for the components of the library that import and allowed access to NONMEM elements.

We also looked at presentations from the field of pharmacometrics in order to discern the graphical types that would be appropriate for inclusion in the library. The “xPose” library and conversations within pharmacometric teams were also useful for this task.

Importing NONMEM Files

The NONMEM files themselves are text based inputs and outputs to the modelling process. An example from the NONMEM "output" file can be seen here:

```
*****  
*****  
***** FINAL PARAMETER ESTIMATE *****  
*****  
*****  
*****  
  
THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****  
  
          TH 1      TH 2      TH 3  
  
    1.96E+01   8.46E+01   1.66E+00  
  
OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****  
  
          ETA1      ETA2      ETA3  
  
ETA1  
+       1.64E-01  
  
ETA2  
+       0.00E+00   1.65E-01  
  
ETA3  
+       0.00E+00   0.00E+00   1.30E+00
```

The list of the key input and output files to NONMEM are as follows:

File	Description	Structure
Control File	Also called the "model" file, this defines the model to be fit to the input data	User written file with elements defined by the "\$" symbol
Input Data File	The data to which the model is applied	Rectangular data structure with additional formatting to identify rows to be omitted
Output File	Report file produced by NONMEM, storing parameter estimates and other statistics from the model fit	Unstructured format produced by NONMEM
Table Files	User-requested dataset(s) to be produced by NONMEM	Rectangular datasets with custom NONMEM header rows (which could be repeated throughout the data)
Log Files	Contains any error or warning messages produced by NONMEM	Unstructured report files with lists of warnings and errors

The import of the files can be achieved either by naming each file in turn, or by identifying the "control file" within a directory. The "control file" can be used to deduce all other NONMEM files either by direct reference or using pattern matching on user-defined extension names.

The S-PLUS (and R) reading and parsing functions were used in order to import and store the elements from the NONMEM files in a single structure. The structure was designed as an "SV4" class object within the environment, with associated printing, summary and extractor functions. This allowed the creation of reports involving (for example) a tabulation of initial parameter estimates (from the control file) vs final parameter estimates (from the output file).

Meta Data

In fully integrating the library within a company's internal modelling and simulation process, metadata around the library was carefully designed and implemented. This metadata includes elements within the library which can be easily modified by a system administrator.

Some examples of the use of metadata in the library are as follows:

- Allow the setting of shortcut "paths" (very much like "libnames" in SAS) in order to identify and easily reference directories from which data is to be read
- Associate recognised variable names with default labels to avoid repetition, including a method for altering default labels associated with each variable
- Integrate a set of graphic stylesheets, that can control graphic and tabular output. This allows a user to create reports with custom formats for different audiences.
- Each company typically has a set of naming conventions for the different NONMEM files. The library allows the user to set the naming conventions to be used when deducing file types (eg. "lst" or "rep" for output files)
- The graphic functions provide the capabilities to draw a standard set of headers and footers on each graph, based on a user-defined function

Graphics

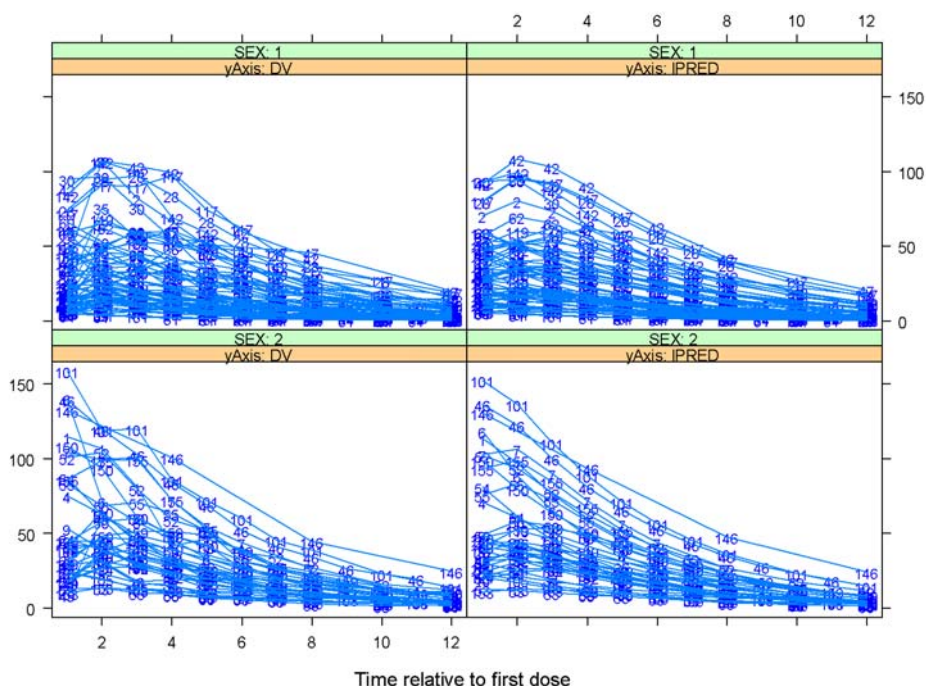
The idea for the graphical components of the library was to extend the trellis capabilities of S/R in order to provide the plotting support required. In particular, the trellis functions were extended in the following ways:

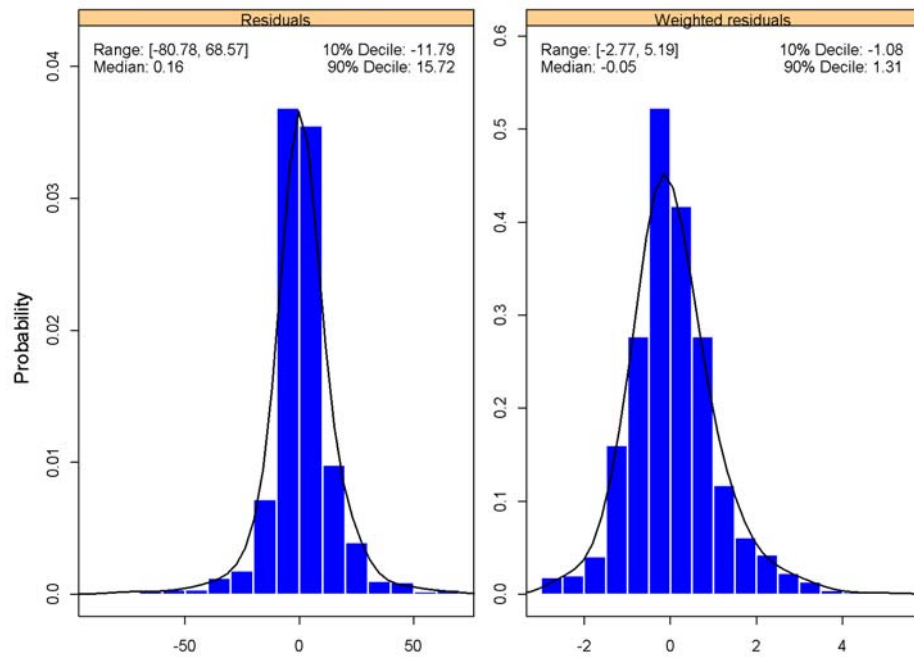
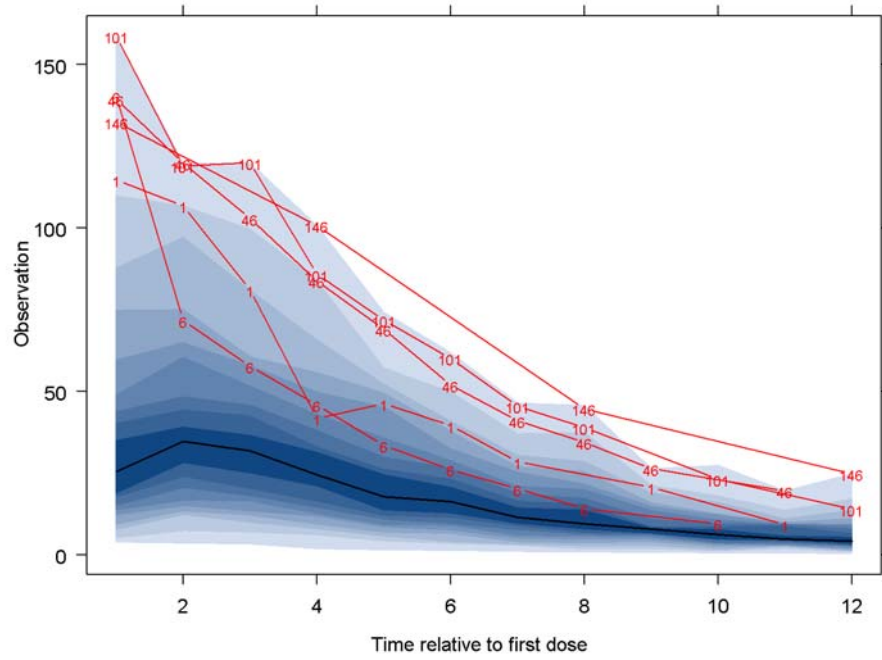
- Wrapper functions to the trellis commands were built to provide user friendly interfaces to such activities as "adding smoother lines" or "using multiple X or Y axes"
- The ability to add customisable standard headers and footers on every graphic output
- The ability to set stylesheets for the format of each graphical output
- Default variable axis labels based on the choice of plot variables
- Extended functionality to the trellis engine, such as the provision of more plot types (for example, plot types such as "Filled Polygon" and "Text and Lines")

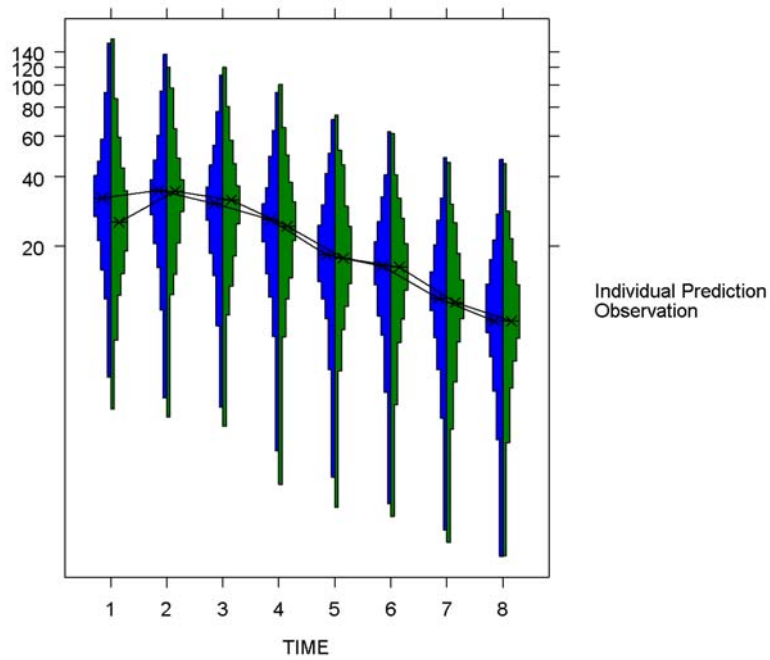
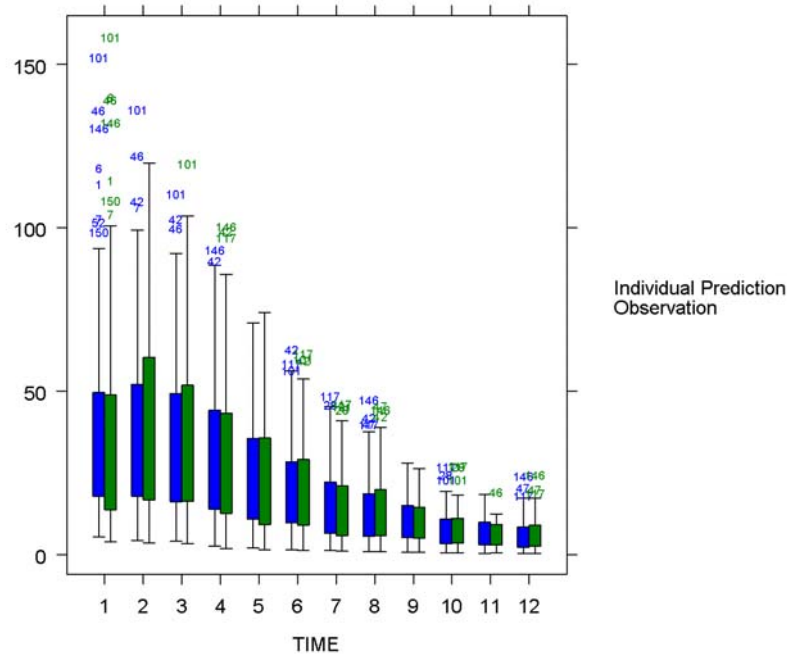
The standard graphical functions provided include the following functions:

Function	Description
graphNm	Creates scatter plots with one or more X/Y axis variables
qqNm	Creates QQ plots of one or more variables
yErrorPlot	Creates boxplots, range plots and other plots designed to assess the error in one or more Y axes against a categorical or numeric X axis
histNm	Creates histograms of one or more variables
barPlotNm	Create bar plots of variables that can be considered as categories
mirrorPlot	Creates scatter plots comparing simulated and observed data
simBarPlot	Creates bar plots comparing simulated and observed data

Some examples of graphical outputs produced by the library are shown here:







Summary

Working closely with pharmaceutical companies, Mango have produced a library for S-PLUS (and R), which is able to process NONMEM information and produce graphical and tabular report items. This library is available under a "free to use" license and is used by many pharmaceutical companies globally.

The library allows a user to:

- Extract key information from the unstructured NONMEM "output" file format and present this information in tabular reports for evaluating and comparing models
- Import and format the rectangular data outputs so they can be used for tabular and graphical reports
- Create a variety of graphical outputs to evaluation model fit, including scatter plots, error plots, histograms and bar plots
- Compare standard data with "simulated" data to see how well the model performs when parameters are varied