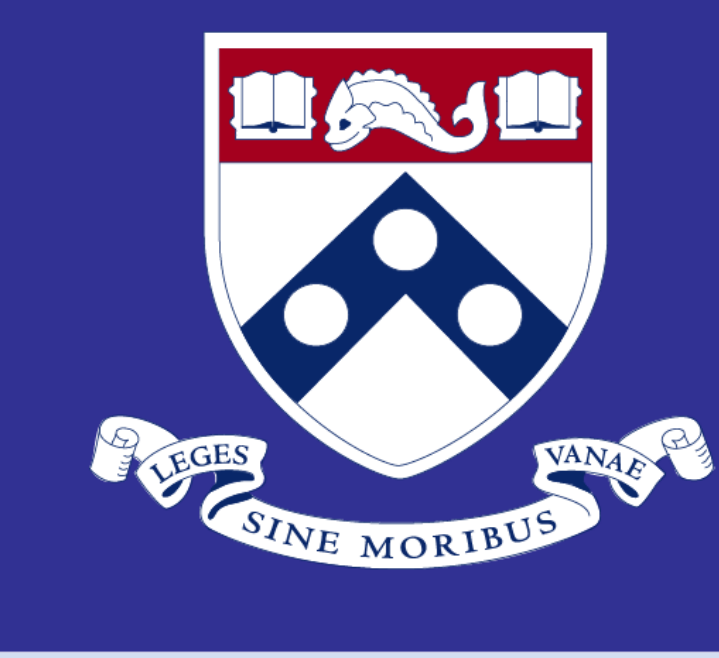


A SAS-based Solution for NONMEM Run Management and Post-processing

B. Jayaraman¹, Doug Marsteller¹, Erin Dombrowsky¹, Julia Winkler¹, Jeffrey S. Barrett¹

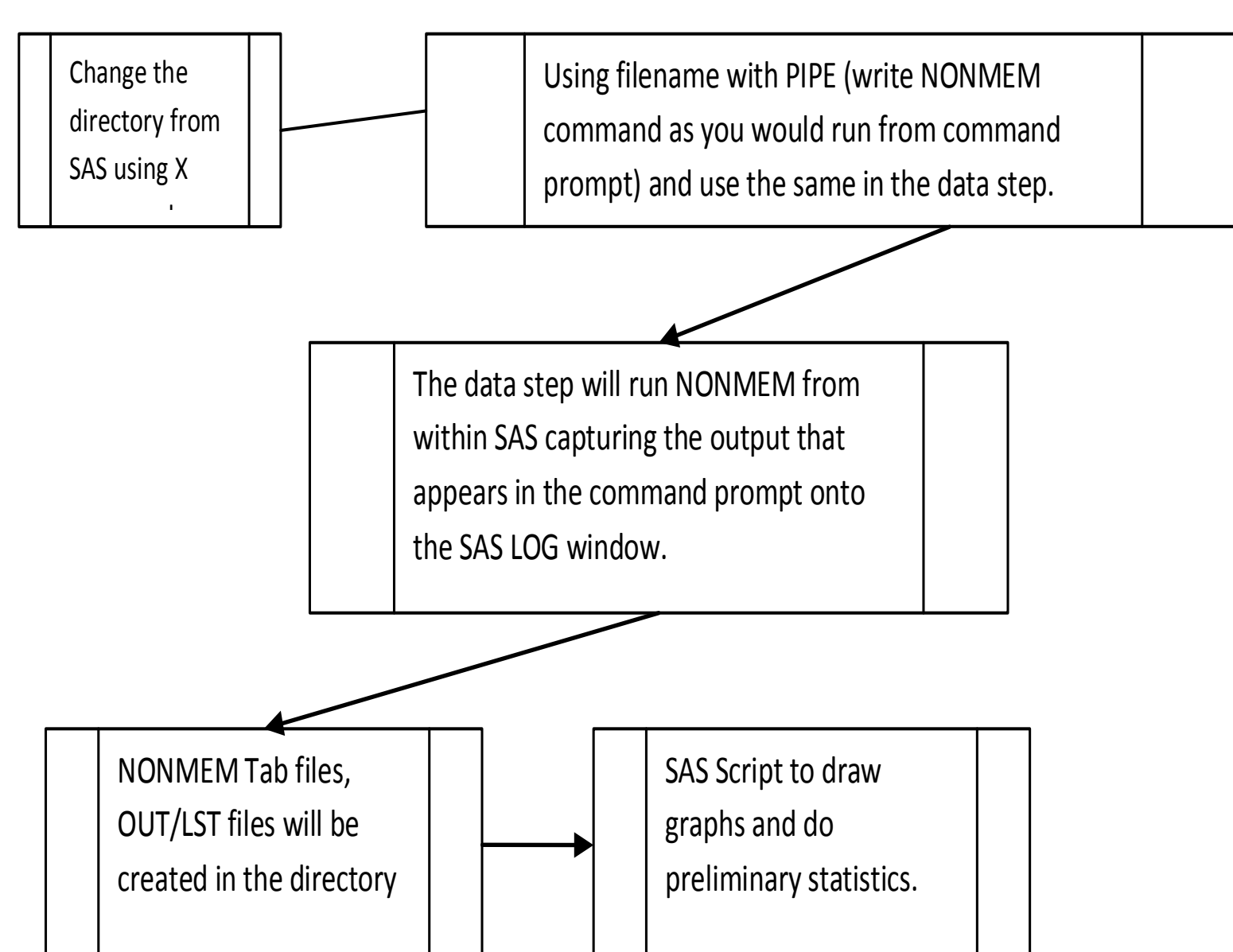
¹Laboratory for Applied PK/PD, Division of Clinical Pharmacology and Therapeutics
The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States



BACKGROUND

- While the NONMEM algorithm remains the centerpiece of the workflow for pharmacometric analyses, data assembly, pre and post processing are functions typically handled outside of NONMEM.
- The analyst has many choices for software solutions for these tasks with Excel, SPLUS and R being the most common solutions employed.
- While SAS offers an excellent platform for these tasks, it has often been excluded from such analyses because the user community is not as invested with SAS, the licensing is more attractive to groups of users, and the graphics have historically been inferior to other algorithms.
- We have created a SAS-based environment to assemble NONMEM datasets from template input files, perform data checking, manage NONMEM runs, summarize run output within and across projects, and provide flexible post-processing including the management of scripts written in other 4th generation languages and compilers (R, FORTRAN, etc).

METHODS



SAS / NONMEM Flow:

1. Assemble NONMEM ready input datasets
2. Create graphs to visually look at the data
3. Calculate preliminary statistics and to visualize data errors
4. Calculate CMAX, TMAX, AUC and other relevant secondary parameters
5. Create RUN directories to run control files from SAS
6. Call NONMEM (5, 6 or 7) from SAS
7. For NONMEM 6, call the CWRES R script from SAS
8. Import NONMEM tab files and other relevant files (subroutines) into SAS
9. Create all the goodness of fit lots using SAS 9.2 or 9.1

Two different versions of SAS graph codes are created – one using PROC TEMPLATE and macro variables which will allow users to run the script as is generating standard run output including the tables, graphs etc. The other version of the “open” code allows experienced users to modify the existing graph code and define additional graphs and statistics. This code can also be run automatically without user input on the graphic design.

User input is required in the first part of the code to define run and environment conditions (e.g., directory, name of the control file, name of the input data file, etc). User input is collected as macro variables which are then passed on the later elements of the SAS code. A portion of the code which collects this information is displayed below.

```
DM 'clear output';
DM 'clear log';
DM 'odsresults' clear;
%let dir =*****; /*DIRECTORY WITH CONTROL FILE
AND DATA FILE -- PARENT DIRECTORY*/
%let datafile=*****; /*THE DATA FILE IS ALWAYS IN
CSV FORMAT - IF IT IS IN DIFFERENT FORMAT THE IMPORT CODE NEEDS
TO BE CHANGED*/
%let cfile=*****; /*WITHOUT THE CTL EXTENSION*/
%LET TFILE=*****; /*THE TAB FILE*/
%LET PRIOR=NULL; /*NULL IF THERE IS NO PRIOR SUBROUTINE*/
%let N=002; /*PARTICULAR RUN NUMBER AND FOLDER NAME - CHANGED
FOR DIFFERENT DIAGNOSTIC PLOTS; SEPARATE FOLDER CREATED */
```

Directory structure is now created; NONMEM and R can be run from SAS.

```
x 'cd\';
x "cd &dir";
X "MD &N";
x "cd &n";
%LET DIR1=&DIR\&N;
X "CD &DIR1";
%put &dir1 &dir;
X "%str(copy %"&DIR\COMP.R %" %"&DIR1\COMP.R %" )";
```

```
filename nonmem pipe "perl -S nmvi.pl &CFILE1..CTL
&CFILE1..out";
/*Running NONMEM from SAS using Metrum Perl script*/
```

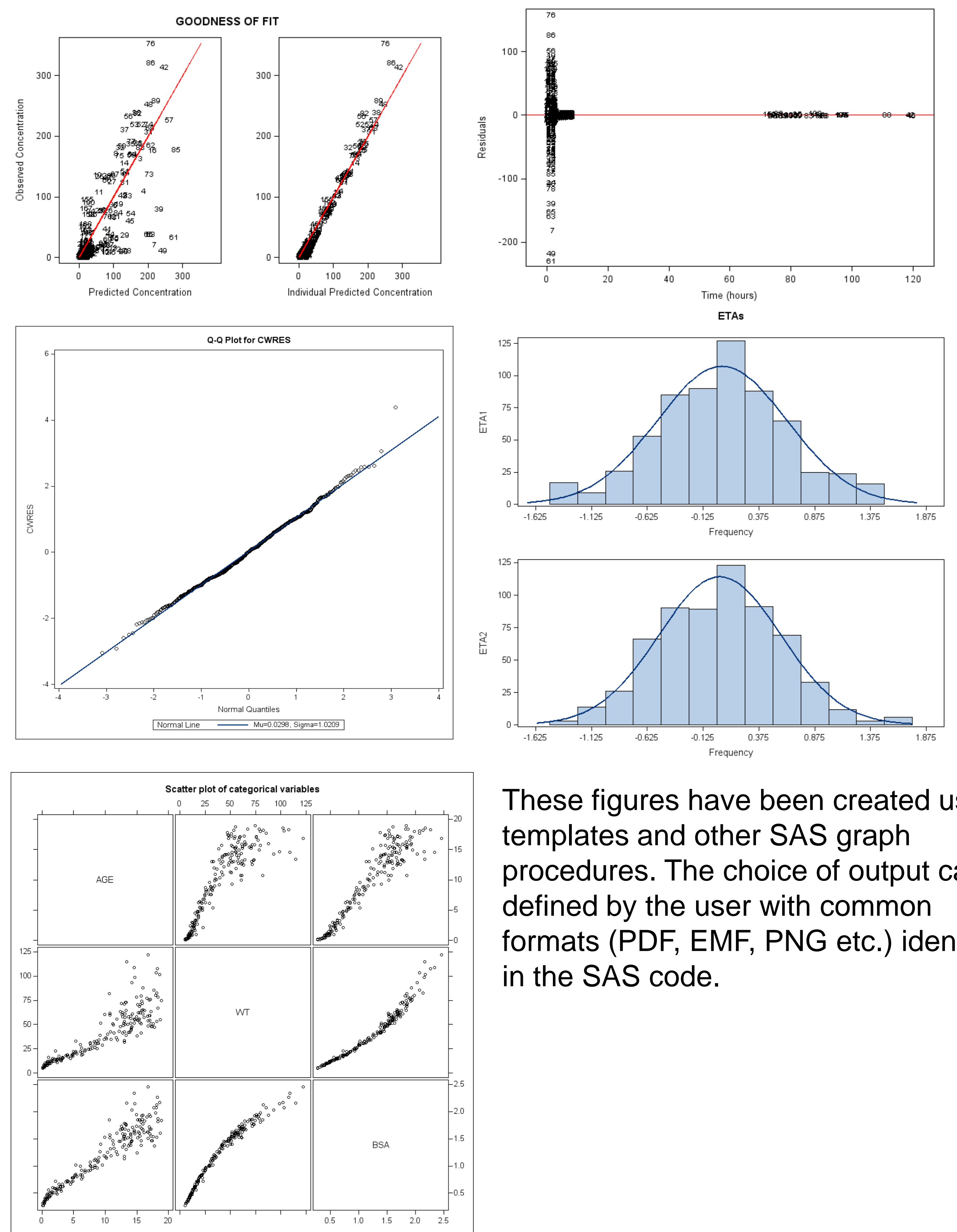
```
%PUT &DIR &DIR1 &CFILE1 &DATAFILE &TFILE1;
data _null_;
infile nonmem;
input;
list;
Run;
OPTIONS XWAIT XSYNC;
x "'C:\Program Files\R\R-2.9.2\bin\r.exe' --no-save --no-
restore <"&dir1\comp.r"> "&dir1\tsdiag.out" ||;
```

RESULTS

Current SAS / NONMEM Solution Functionality:

- Data management - creates the NONMEM-ready analysis datasets
- Visual data checks - scatter plots, panel plots by patient of time vs DV (i.e., concentration)
- Histogram of data density (collection) within time bins to verify sampling design against model parameterization
- Calculation of Tmax, Cmax, etc
- Plots - goodness of fit plots - dv vs pred, dv vs ipred, res vs time, wres vs time, cwres vs time, qqplots, plots with confidence intervals, stacked histograms of ETA, mean and standard error plot
- Customizable plots for the above
- EMF or pdf plots

Representative Graphical Output:



These figures have been created using templates and other SAS graph procedures. The choice of output can be defined by the user with common formats (PDF, EMF, PNG etc.) identified in the SAS code.

CONCLUSION

- This SAS-based solution provides a viable option to the pre-and post-processing requirements for analysis of data with the NONMEM algorithm.
- Given the considerable experience with SAS from the statistical, regulatory and medical communities, the integration of NONMEM-generated output with regulatory reporting should be further facilitated by this solution.
- This solution is provided to the pharmacometrics community (<http://www.med.upenn.edu/kmas/code>) in the hope that its future development and functionality will be expanded via open collaboration of the pharmacometrics community.

REFERENCES

- Xpose4 Generic version http://xpose.sourceforge.net/generic_chm/compute.cwres.html
- Perl Speaks Nonmem <http://psn.sourceforge.net/>
- MIFuns - <http://metruminstitute.org/>
- SAS technical support, SAS Institute, NC
- Jayaraman B, Gupta M, Barrett JS: A SAS based solution to the Rapid Assembly, Execution and Processing of NONMEM jobs for population based Analyses (ACCP 2006)