

Implementing “best practice” in Pop PK modelling

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The aim of this work is to implement guidance from our Pop PK Guidance document, identifying the best tools & processes and support these. We aim to make it easier for analysts to switch to new tools and methods by providing examples, snippets of code, code templates.

PROCESS

- From our Best Practice document ¹, we identify implementation details, discuss these.
- Work with example models, data to illustrate and test that methods work as expected.
- Trial the proposed methods, feedback and refine.

DOCUMENT

- Document Pop PK Guidance advice alongside implementation detail, reproducible code examples.
- Use rmarkdown and bookdown packages to combine descriptive text, embed code and output.
- The document can be compiled to GitBook (HTML), PDF or EPUB formats.

CORE TOOLS, PACKAGES AND ROUTINES

- R packages including,
 - tidyverse²
 - xpose³
 - tables⁴
 - xtable⁵
- NONMEM-7.4.1⁶
 - MU referencing
 - FOCEI or SAEM + IMP
 - xpose \$TABLE files
- PsN-4.7.9⁷
 - linearize, cdd, simeval, frem, xv-scm, boot-scm, ncappc



EXPLORATORY DATA ANALYSIS

- Embed data manipulation in R markdown notebooks to capture rationale as well as code and output. Render to HTML or PDF for QC.
- Data display viewing within Rstudio
- Filtering, variable selection, transformation via the dplyr functions.
- Pipelining code using the R magrittr package pipe command %>%
- Data checkout and quick tabulation of data using the tables package tabular function.

```
tables::tabular((SEX=as.factor(SEX)) *
Justify(c)*(AGE + WT) ~
((N=length)*Format(fmt="%1f")+
(Range = rangeBuild) +
(Median = median)*Format(fmt="%1f") +
(Mean = mean) +
(SD = sd)),
data=mysub)
```

SEX	N	Range	Median	Mean	SD
1	AGE	59 (43-78)	67	65.63	7.823
	WT	59 (54-125)	80	82.41	13.653
2	AGE	15 (55-78)	61	63.40	7.827
	WT	15 (41-100)	60	63.20	14.674
- Data visualisation using ggplot2.
 - Allows the user to add, transform plots quickly.

```
concPlot1 <- ggplot(data = myobs,
aes(x = TAD, y = DV)) +
geom_point(alpha=0.2)

concPlot1 + scale_y_log10()
```
- Coding standards makes code sharing and QC easier, allows users to concentrate on content rather than implementation.

BASE MODEL DEVELOPMENT

- Coding standards for parameter specification.

```
POP_parameter = THETA(n)
TVparameter = POP_parameter
MU_n = LOG(TVparameter)
parameter = EXP(MU_n + ETA(n))
```
- Template code snippets for different absorption and elimination models, BLQ handling (M3 method) ⁸.
- Coding standards for residual error models.

```
$ERROR (ONLY OBSERVATIONS)
LNCC = LOG(0.025)
IF (F.GT.0) LNCC = LOG(F)
RUV_ADD = THETA(5)
RUV_PROP = THETA(6)
EPS_Y = EPS(1)
W = SQRT(RUV_PROP**2 +
(RUV_ADD**2/LNCC**2))
Y = LNCC + W*EPS_Y
IPRED = LNCC
IRES = IPRED-DV
IWRES = IRES/W
```

 - Can test additive, proportional, combined simply by fixing terms to zero.
- Template code for \$ESTIMATION records
 - FOCEI
 - SAEM + IMP
- Template code for \$TABLES output:

```
$TABLE ID TIME AMT DVID MDV PRED RES WRES DV
IPRED IWRES CWRES NPDE Y
ESAMPLE=10000 NOAPPEND NOPRINT
FILE=sdtabl

$TABLE ID CL V KA TLAG
ETA_CL ETA_V ETA_KA ETA_TLAG
NOAPPEND NOPRINT FILE=patabl

$TABLE ID WT LOGTWT NOAPPEND NOPRINT FILE=cotabl
$TABLE ID NWRES WRESI CWRESI
ECWRES EWRES NPDE
ONEHEADER NOPRINT FILE=mytabl
```

 - Aim to produce consistent output table files that can then be passed to the xpose package for diagnostics.

MODEL DIAGNOSTICS

- Use R package xpose for model diagnostics.
 - Modern R, “tidy” handling of data and graphics.

```
xpose_data('moxonidine.lst', dir='Example') %>%
dv_vs_pred(facets = "VISI",
panel_labeller = "label_both")

res_distrib(xpdb, type = "dr")
```
- NPDE plots

```
xplot_scatter(xpdb,
aes(x=TAD,y=NPDE),
type = "ps",
guide = 0,
title = 'NPDE vs. Time after dose | @run',
subtitle = 'Ofv: @ofv')
```
- VPC via PsN and xpose / xpose4
 - Using auto-binning, prediction correction (predcorr), handling of log DV, handling of BLQ observations.
 - Plot with xpose (uses vpc package plotting) or xpose4.
- Additional xpose functions to extract run information
 - summary(xpdb) - # individuals, # observations, OFV, shrinkage, condition number, sig digits, warnings.
 - prm_table(xpdb) - parameter estimates, RSEs
- Can embed xpose function calls in markdown / RStudio notebooks so that analysts can describe and annotate model diagnostic output, capture reasoning for next steps in modelling.

PARAMETER UNCERTAINTY

- Recommend PsN SIR ⁹ procedure over bootstrap.

```
sir-4.7.9 run1.mod
-samples=1000,1000,1000,2000,2000
-resamples=200,400,500,1000,1000
-rplots=2 -directory=sir
```

 - More robust to small sample sizes
 - Avoids problems of NONMEM crashes, lack of convergence with bootstrap – uses MAXEVAL = 0.
- R functions written to read PsN bootstrap or SIR results .csv files.
 - Preparing PsN output for use in reporting.

MODEL QUALIFICATION

- PsN procedures help us qualify key steps in the model building process (base model, following covariate modelling, candidate final model):
 - Simulation & evaluation (simeval)
 - Case deletion diagnostics (cdd)
 - NCA PPC (ncappc)
- Linearization of the NONMEM model using PsN linearize procedure allows us to use methods that would be computationally expensive if we had to fit and estimate the full nonlinear mixed effects model.
 - Cross-validation of Stepwise Covariate Model (xv-scm)
 - Bootstrap of Stepwise Covariate Model (boot-scm)

- Promising, recently released functionality in PsN like frem and qa is discussed.
 - We can describe and show implementation for these new methods within the document through working examples.

REPORTING

- Implementation document describes how to get “quick” tables and figures for review of ongoing modelling.
- Also describes how to produce “report-ready” tables and figures.
 - Using tidyverse functionality (dplyr and tidyr) to prepare table content as data frame.
 - Export this data frame to LaTeX format for inclusion in report using xtable.
 - Prepare figures based on ggplot2 functionality, then tweak titles, footnotes, legends, themes while core content is unchanged.

- Prepare parameter tables for reporting by using xpose get_prm functionality with purrr mapping across runs.

DISCUSSION

- We aim for analysts to spend more time on the clinical pharmacology aspects of their models and less on coding.
 - Standardise code where possible
 - Provide code “snippets” to assist analysts in building scripts.
 - Worked examples illustrate HOW to implement recommendations from our Pop PK Guidance documentation.
 - Example code can also provide a basis for training on these topics.

- Implementation documentation is a living document. Can be updated at any time with updates to code, methods, recommendations.
 - Update with new methods, new template code.
 - Extend to additional topics e.g. prediction & simulation

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