PKPD Modeling of Continuous and Categorical data in NONMEM 7

Hands-On Session – Count data modeling

Mixed effect model analysis

Introduction:

This exercise makes use of the reflux data set in a format suitable for analysis as count data in a mixed effects analysis.

The counts of events are done for each one-hour interval. No distinction between events of different grades (mild, moderate or severe) will be made.

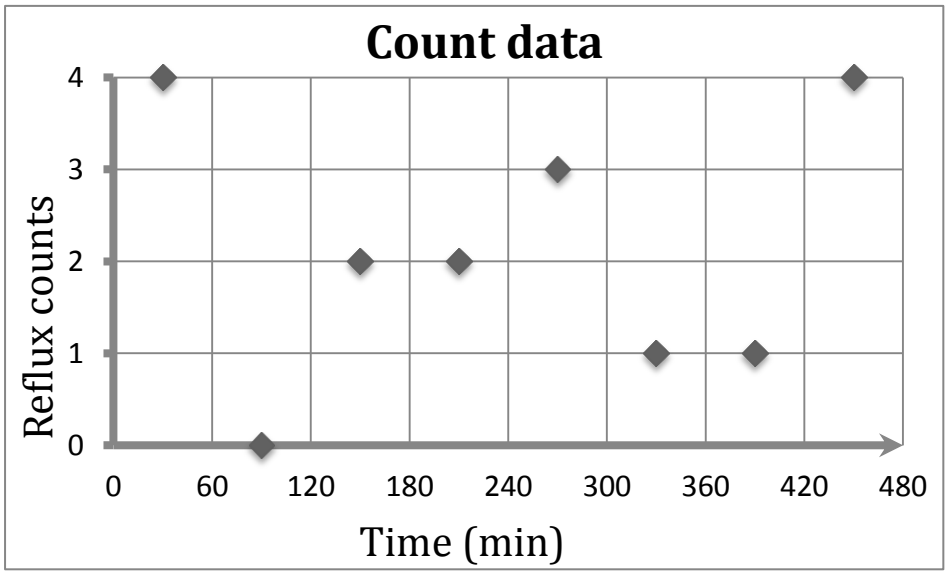

Fig 1. Data structure allowing for count data modelling strategy (ID=8, placebo) ➔ 8 intervals of counts

Please note: a naïve pooling analysis of this data is presented in the "additional material" folder of this hands-on.

Files provided:

Data set:

data.csv	The reflux data set, the model files subset this data, looking only at THR>0, the DV variable is HC ("Hourly Count"). The average concentration in each one-hour interval is given by the column "CAVH".

These data were analyzed using a mixed effects model. Baseline interindividual variability was included in the starting model.

Model files:

run65.mod = estimation model file

run65sim.mod = simulation model file for histograms

run65vpc.mod = simulation model file for vpc

Tasks:

1) Open and study the model file; run the estimation.

PSN command in DOS:

```
execute run65.mod
```

2) Run65sim.mod and categorical.plots.R contain the NONMEM code and R commands needed for creating two GOF plots for run65.mod (do not run this model or re-create these plots). Plots of data and simulation based diagnostics are given below for run65 (Figures 1-2). VPC results are shown in Figures 3-4.

Inspect the plots.

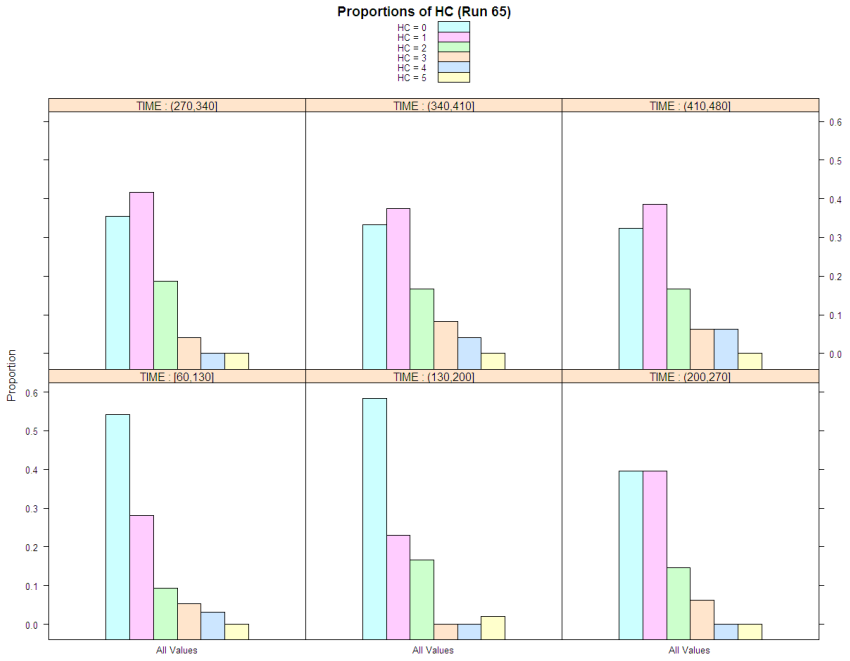

Figure 1: Histograms by time

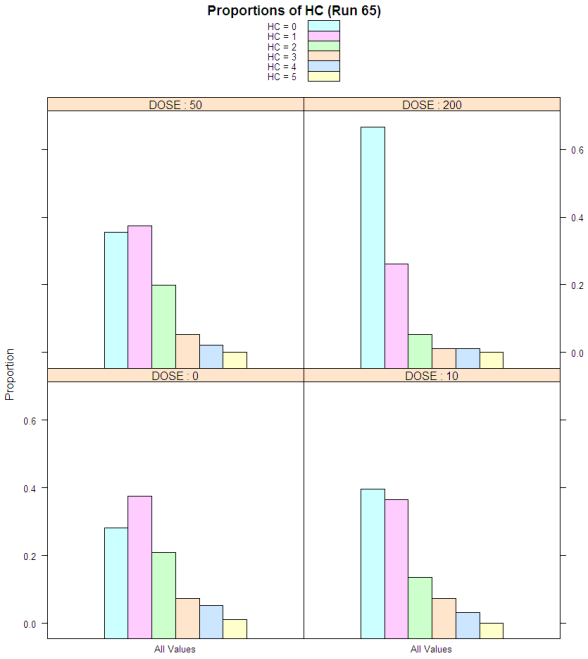

Figure 2: Histograms by dose

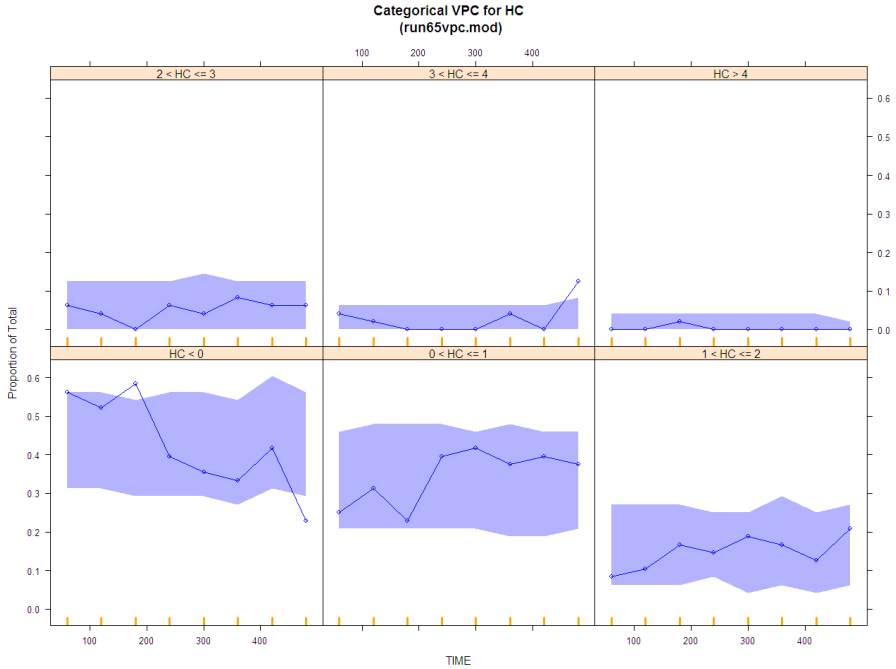

Figure 3: VPC versus time (default)

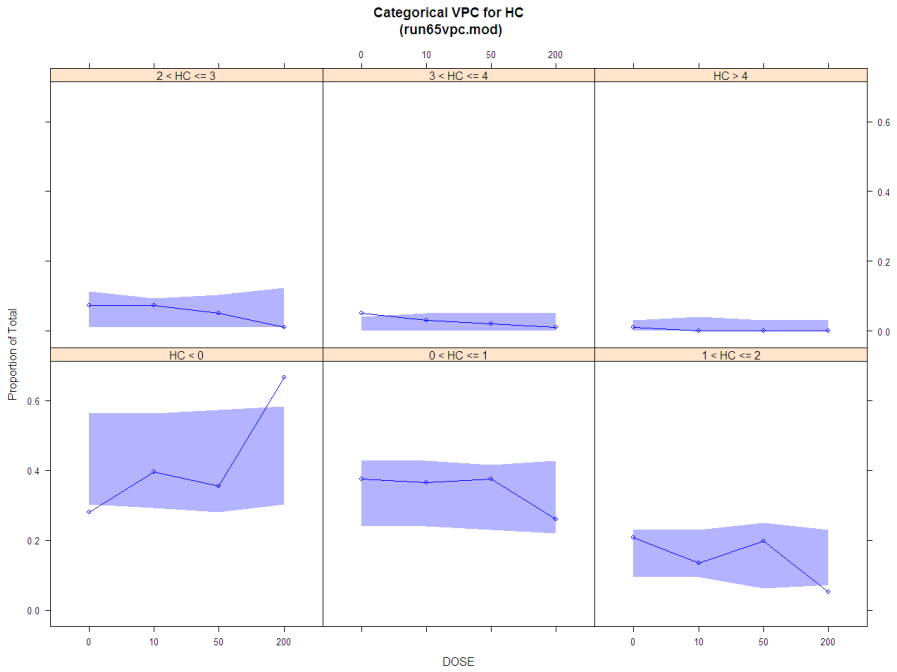

Figure 4: VPC versus dose

3) Add a dose effect into the model, assuming that at high doses the occurrence of (moderate and severe) events can be fully inhibited. Allow no interindividual variability in the PD effect. Run the model. Recreate model diagnostic graphs and simulation-based diagnostics (using run66sim.mod and categorical.plots.R). Add also the dose effect to run66sim.mod and run66vpc.mod.

PsN command in DOS:

```
vpc run66vpc.mod -lst=run66.lst -samples=100 -dir=vpc66a -seed=123 -levels=0,1,2,3,4 -nopred -dv=HC
```

PsN command in DOS:

```
vpc run66vpc.mod -lst=run66.lst -samples=100 -dir=vpc66b -seed=123 -levels=0,1,2,3,4 -idv=DOSE -nopred -dv=HC
```

Xpose command in R (directory vpc66a or b):

```
library(xpose4)

xpose.VPC.categorical()

xpose.VPC()
```

Does the model represent an improvement? Are there any signs of model misspecification?

4) Same question as previously, but use plasma drug concentration (CAVH) as the predictor of drug effect.
5) Investigate whether an IIV can be identified for the PD relation.

Extra credit: Try a model that includes overdispersion or zero-inflation. Check the dispersion of the counts.