The Visual Predictive Check
Superiority to Standard Diagnostic (Rorschach) Plots

Nick Holford
Dept of Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

Warfarin First-Order Input (KA1L)

Objective: NONMEM users typically demonstrate the adequacy of a model by displaying plots of PR2D or CV or IPRED vs DV along with weighted and unweighted residuals. These are often called the standard diagnostic plots. An alternative way of evaluating a model is to simulate from the final estimates and compare the simulated time course of the observations and prediction intervals with the observed data. The visual predictive check is a plot that compares the distributions of the observations with the simulated distribution. The advantage of the visual predictive check is that it does not require any strong assumptions about the distribution of the observations and prediction intervals, and it can be used to compare the standard diagnostic plots with the visual predictive check in terms of their ability to suggest improvements to the model structure and confirm the suitability of the final model.

Methods: Plasma warfarin concentrations and effects on prothrombin complex activity have been reported by O’Reilly et al. (1, 2). These data were fitted with a 1 compartment disposition model with first-order input and elimination plus a prothrombin complex observation. The resulting turnover model was not performing well at the time of the earliest post treatment time point. The visual predictive check demonstrated the lack of fit of the direct and effect compartment models both for structural and stochastic components.

Results: The standard diagnostic plots did not give a clear indication of the best model. There was some indication in the residual plot that the immediate effect model was not performing well at the time of the earliest post treatment prothrombin complex observation. The visual predictive check demonstrated the lack of fit of the direct and effect compartment models both for structural and stochastic components. The standard diagnostic plots should be called Rorschach plots because their interpretation is dependent on the mind of the observer. The visual predictive check is diagnostic of both the fixed and random effects parts of a PKPD model.

References:

Warfarin Immediate SIM

Warfarin Data
- PKPD Studies in Healthy Subjects
  - 1.5 mg/kg single oral dose
  - Total racemic warfarin plasma concentration
  - Prothrombin complex activity
- 32 subjects, 250 concentrations, 232 PCA

Warfarin Predictive Check
- Estimate parameters with original data set
- Simulate using model and parameters with original data set as simulation template input
- Set NSUBPROB to get ~1000 simulated observations at each time point
- Plot median and 90% prediction intervals with observed data

Warfarin Turnover
- Standard ‘diagnostic’ plots lose one dimension (time or prediction)
- Visual check is more informative and diagnostic

Warfarin CE ADVAN4

Rorschach Blot