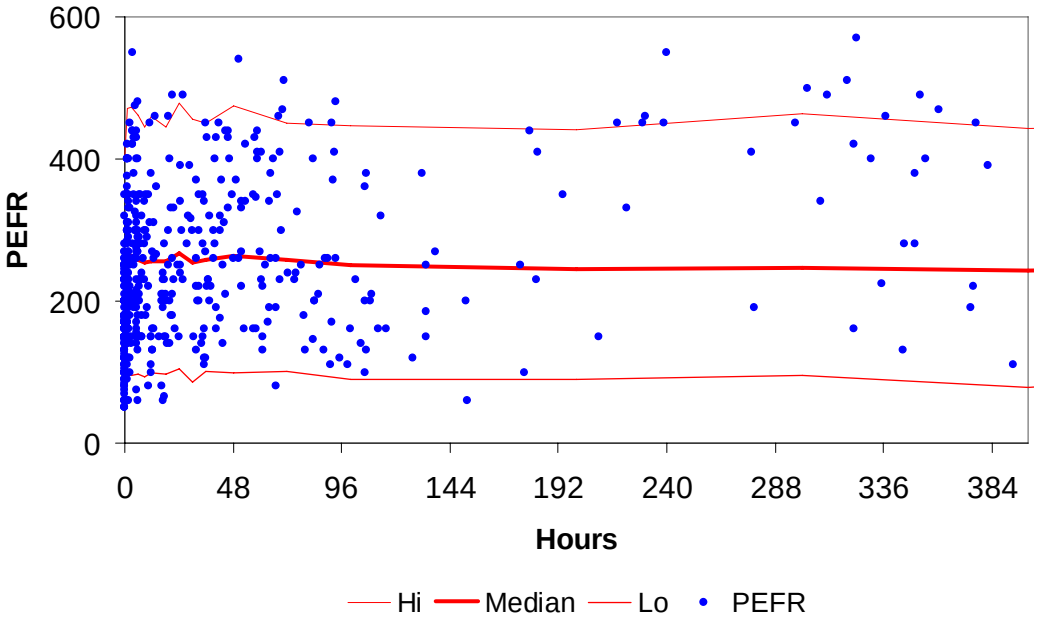
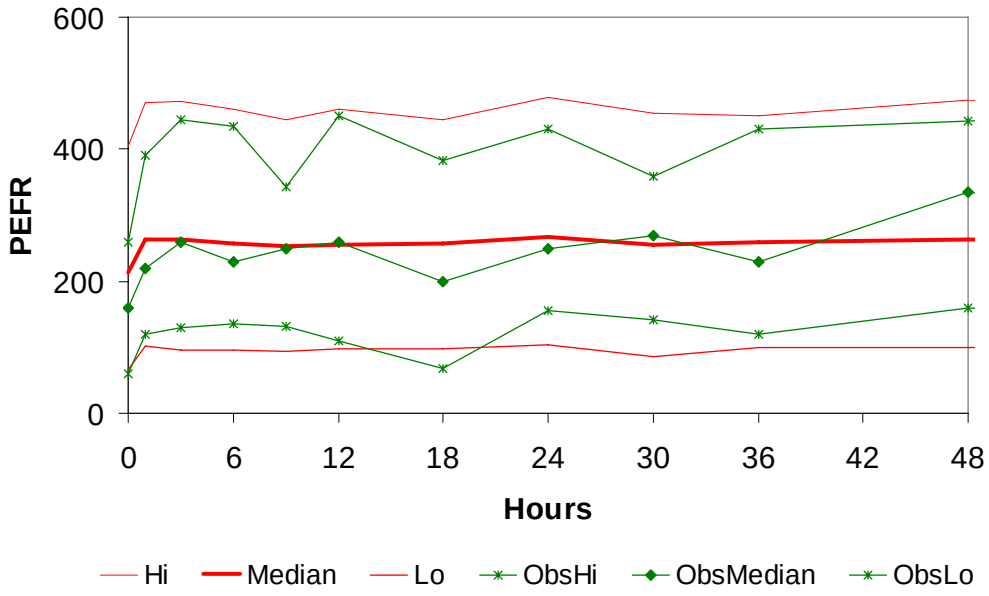
Visual Predictive Check and npde

A randomized target concentration controlled trial of theophylline in patients with severe airways obstruction and a mixed effect PD analysis was reported by Holford et al. (1, 2). The same data set and a semi-parametric analysis was used by Sheiner to illustrate his learn and confirm ideas (3).
The PD observation was peak expiratory flow rate (PEFR). A base model used measured theophylline concentration as the independent variable in an Emax PD model. The final model used time, sex, age, and diagnostic category as covariates.

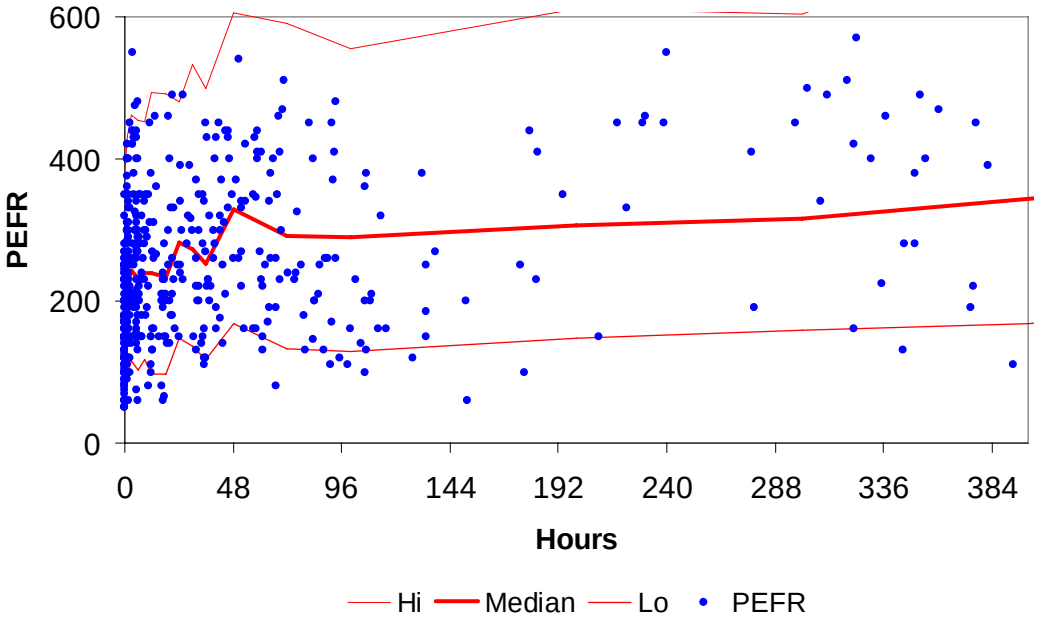
VPC Theopd Base model

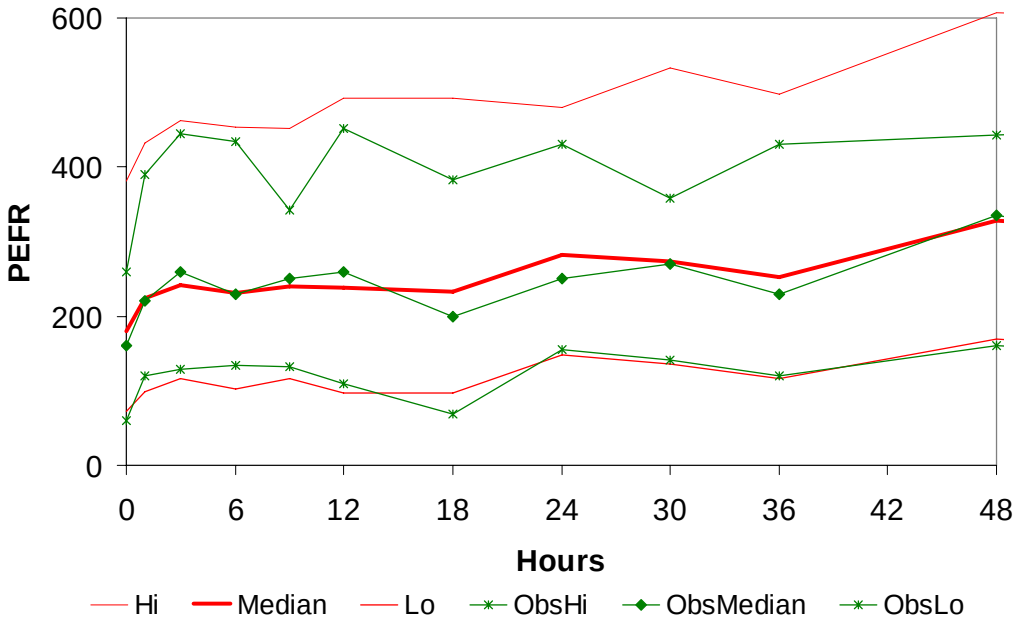




There is an improvement in the VPC when the final model is compared to the base model. This is shown by a closer match of the median observed PEFR compared with the predicted median. The upper 90% prediction interval exceeds the observed 90% interval in both models.

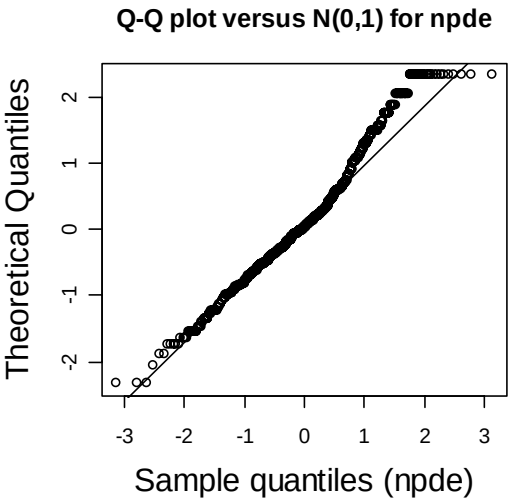
VPC Theopd Final Model

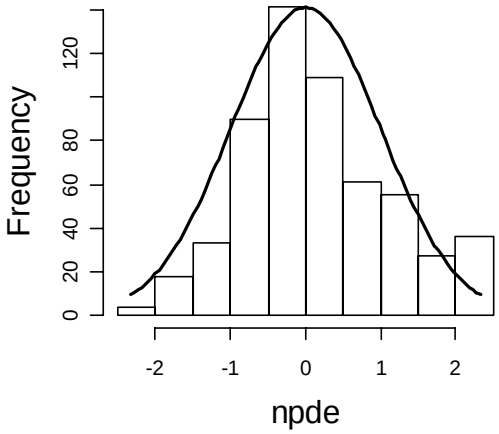


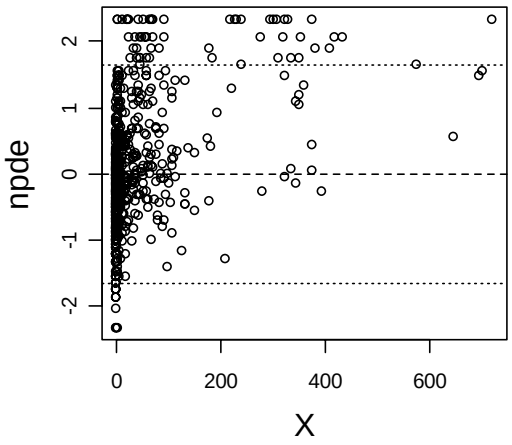


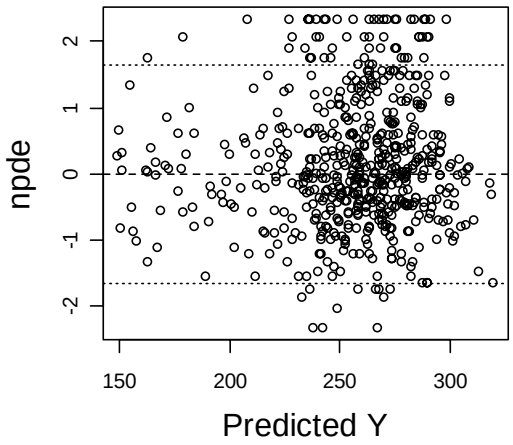
The npde procedure (4, 5) shows visually that the base model npde values are not normally distributed. The final model distribution of npde is visually much more satisfying but the normal distribution hypothesis is rejected when formally tested.

Npde 1.1 Theopd Base model







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Distribution of npde:
           mean= 0.1461
       variance= 0.975
       skewness= 0.3571
       kurtosis= -0.2418
------------------------------------------------

Statistical tests
  Wilcoxon signed rank test  : 0.0233 *
  Fisher variance test       : 0.683
  SW test of normality       : 7.47e-08 **
Global adjusted p-value      : 2.24e-07 **
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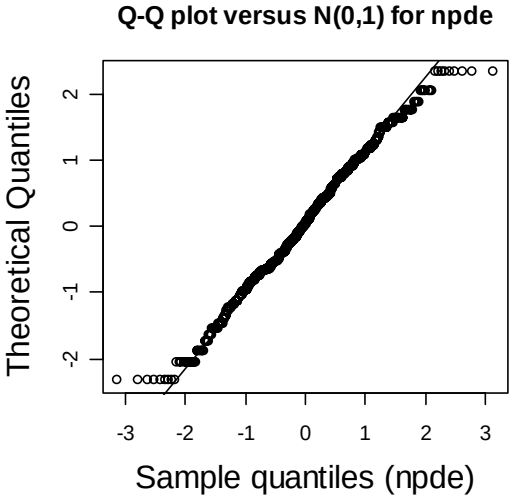
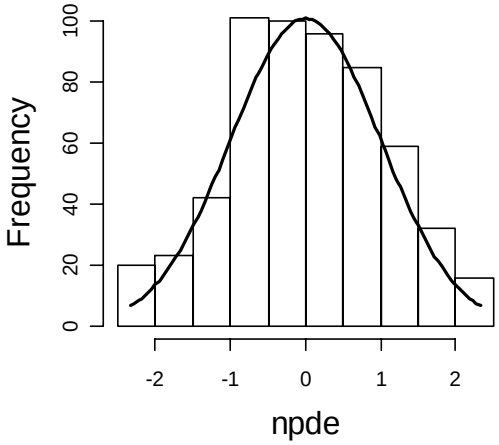
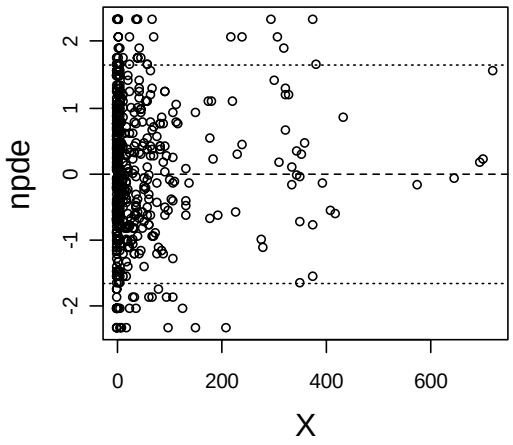
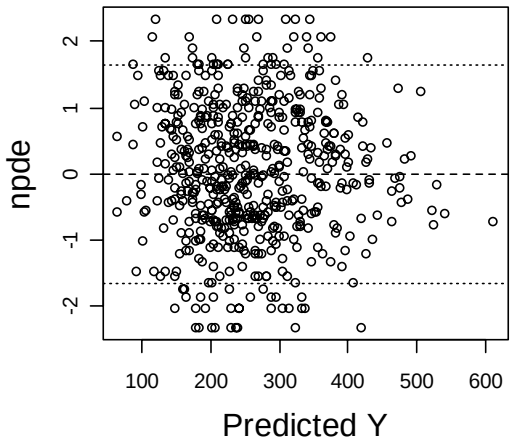
Npde 1.1 Theopd Final Model










```
Distribution of npde:
           mean= 0.04148
       variance= 1.065
       skewness= -0.058
       kurtosis= -0.483
------------------------------------------------

Statistical tests
  Wilcoxon signed rank test  : 0.294
  Fisher variance test       : 0.269
  SW test of normality       : 0.00214 **
Global adjusted p-value      : 0.00642 **
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References

1. Holford NHG, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? Clin Pharmacokinet. 1993;25(6):495-505.
2. Holford NHG, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Clin Pharmacokinet. 1993;25(6):506-15.
3. Sheiner LB. Learning versus confirming in clinical drug development. Clinical Pharmacology & Therapeutics. 1997;61(3):275-91.
4. Brendel K, Comets E, Laffont C, Laveille C, Mentre F. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. Pharm Res. 2006 Sep;23(9):2036-49.
5. Comets E. npde. 2007 [cited 2007 27 July]; Version 1.1:[Available from: http://www.npde.biostat.fr]