Semiparametric distributions with estimated shape parameters: Implementation and Evaluation

UPPSALA UNIVERSITET

K. Petersson, E. Hanze, R.M. Savic, M.O. Karlsson

Division of Pharmacokinetics & Drug Therapy, Uppsala University, Sweden

Background and Objective

In parametric population analysis interindividual random effects are assumed to be normally distributed and PK and PD parameters a fixed, often exponential, transformation of this distribution. It is possible to also estimate parameters that relates to the shape of the transformed distribution [1],[2], but this has not become common practise, possibly because of implementation difficulties of the previously suggested transformation functions. We therefore investigate two transformations that can be easily implemented.

The aims of this work were: **(i)** to evaluate if such transformations can improve model fit; **(ii)** to assess the actual significance level for inclusion of these transformations into the models [3]

Methods

The analysis was done using NONMEM VI. Two transformations were evaluated.

(i) The Box-Cox transformation (Eq. 1) can transform the normal distribution into a skewed one. The direction and magnitude of the skewness is determined by one parameter (θ_1). The sign of the parameter controls direction and the value controls the magnitude (Fig. 1). This shape parameter was estimated simultaneously from the data along with other parameters as fixed effects (thetas) in NONMEM. The η_1 in the equation is transformed into $\eta_{1Transformed}$ which then can be related to the population value in a suitable manner, e.g. Eq. 2.

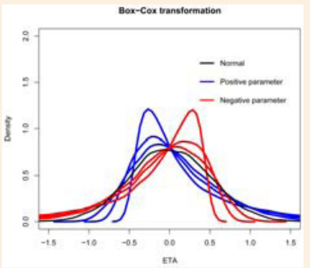

Figure 1. Normal distribution transformed with the Box-Cox transformation. Shape parameter values were 0.5, 1, 2, -0.5, -1, -2. (SD= 0.5)

$$\eta_{i_{Transformed}} = \frac{((e^{\eta_i})^{\theta_i} \text{ -1 })}{\theta_i} \quad \text{Eq. 1}$$

$$CL_i = CL_{Pop} \cdot e^{\eta_{i_{Transformed}}} \quad \text{Eq. 2}$$

(ii) The Logit transformation (Eq. 3) can transform a normal distribution both into a skewed distribution and into a bimodal one. This transformation has two parameters to estimate and offers a more flexible way to transform the gaussian distribution. One parameter (θ_1) controls the skewness and it can vary between 0 and 1 with 0.5 being no skewness at all.

The other parameter (θ_2) determines the width of the distribution. This must be a positive value. If the standard deviation of the parametric distribution is large the transformed distribution becomes bimodal.

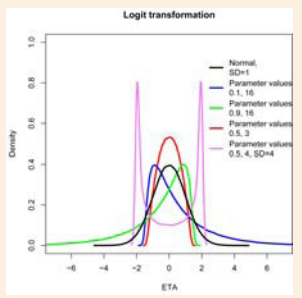

Figure 2. Normal distribution transformed with the Logit transformation. The standard deviation and parameter values for θ_1, θ_2 are shown.

$$\Phi = LOG(\frac{\theta_i}{(1-\theta_i)}) \quad \text{Eq. 3}$$

$$\eta_{i_{Transformed}} = ((\frac{e^{\Phi+\eta_i}}{(1+e^{\Phi+\eta_i})} - \theta_i) \cdot \theta_{ii}$$

Important features of these transformations are that they both retain rank order and that the typical values remain the same. The transformations were applied to parameter distributions (etas) in 27 already existing PK and PD models, both to a single parameter and to multiple parameters within the same model. Monte Carlo simulation studies were performed to assess cut-off values for statistical significance for both transformations. [3]

Results and Discussion

New transformations significantly improved the model fit in 14 models out of 27 with drops in OFV ranging from 4 to 239 (Fig. 3) As we can see both transformations create drops in roughly the same models and for the same parameters. Both transformations could also estimate similar shapes with similar drops in OFV (Fig. 4)

The cut-off values (i.e. drop in OFV) for significant inclusion of the Logit and Box-Cox transformations were 7 and 4 (p=0.05). Thus nominal and actual significance levels agree.

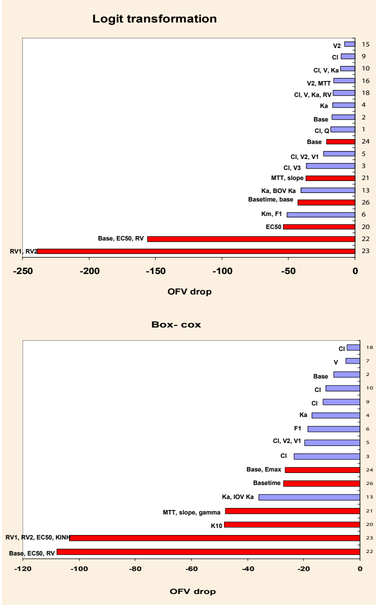

Figure 3. Drops in OFV for the 27 investigated models (model # in y-axis). PD models in red. Also shown are which parameter distributions that are transformed.

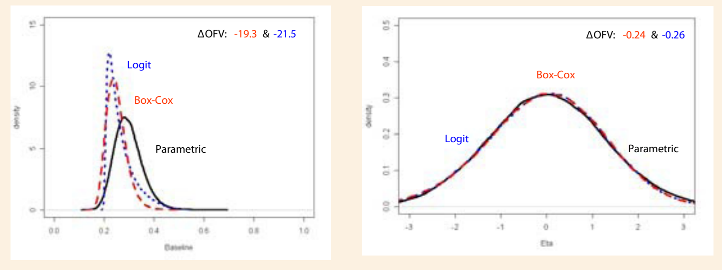

Figure 4. Estimated non-normal shapes creates significant drops in OFV and when no transformation occur there is no drop in OFV.

Conclusion

A novel method for parameter distribution estimation is introduced, which allows for estimation of flexible semi-parametric shapes. Transformations are easy to implement and powerful to detect deviations from normality, thus model fit may be improved.

References:

[1] Davidian M., Gallant R. A. Smooth Nonparametric Maximum Likelihood Estimation for Population Pharmacokinetics, with Application to Quinidine. J Pharmacokinet Biopharm 1992; 20(5):529-56

[2] Fattinger KE, Sheiner LB, Verotta D. A New Method to Explore the Distribution of Interindividual Random Effects in Non-Linear Mixed Effects Models Biometrics. 1995 Dec;51(4):1236-1251

[3] Wahlby U, Jonsson EN, Karlsson MO. Assessment of act ual significance levels for covariate effects in NONMEM. J Pharmacokinet Pharmacodyn. 2001 Jun;28(3):231-52.