Fitting Proportional Odds Model for Ordered Categorical Data with the NLMIXED Procedure.

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Introduction

Ordered categorical data are frequently used to assess response and often a majority of the observations is at one extreme of the possible outcomes, i.e. the distribution of response is skewed. This type of data is usually analysed using proportional odds models with an overall interindividual variability (IIV)[1-4]. Applying this modelling approach in NONMEM[5] using the Laplacian option will result in biased parameter estimates[6]. The Laplacian method conditions the estimation on the empirical Bayes estimates of ηs. Since the ηs are assumed to be normally distributed, when they, for skewed ordered categorical data, are not, the estimates will be biased. In the NLMIXED procedure in SAS®, the estimation method, Gauss-Hermite quadrature, do not condition the estimation on the Bayes estimates and thus, this method is expected to produce less biased parameter estimates, even though the ηs are non-normally distributed.

Objective

To investigate the bias in parameter estimates for the proportional odds model for ordered categorical data using NLMIXED in SAS®.

Method

A population logistic regression model for ordered categorical data was used for simulations in NONMEM and estimations in SAS®. The model predicts for each individual observation, Y_{it}, the probability of having a score that is greater than or equal to a given score m = 0, 1, 2, 3 and has the general structure below. η_i is the individual random effect, N ∈ (0, ω^2).

$$P\left(Y_{it} \geq m \,|\eta_i\right) = \frac{e^{logit+\eta_i}}{\left(1+e^{logit+\eta_i}\right)}$$

$$logit = \sum_{j=1}^{m} \theta_j + \theta_{plc} \cdot PLC + \theta_{dose} \cdot Dose$$

Three sets of nominal parameter estimates were set up to simulate data with *(i)* a non-skewed distribution of responses with low IIV, *(ii)* a skewed distribution with low IIV and *(iii)* a skewed distribution with high IIV. The last condition was simulated to mimic a real study (Table I)

Table I. Distribution of responses in the simulated original data sets, presented as percent of the total population. Nominal parameter estimates were set to simulate three conditions: *(i)* non-skewed distribution of response with low IIV, *(ii)* skewed distribution with low IIV and *(iii)* skewed distribution with high IIV.

	None/mild/moderate/severe at baseline (%)	Severe following placebo (%)	Severe following highest dose (%)
(i) (ω^2 = 4)	24 / 26 / 26 / 24	30	50
(ii) (ω^2 = 4)	96.5 / 1.22 / 1.44 / 0.84	3	6
(iii) (ω^2 = 40)	96.5 / 1.22 / 1.44 / 0.84	3	6

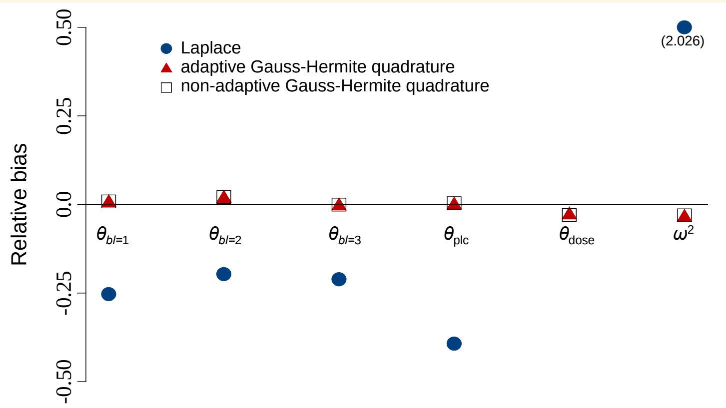

Figure 1. Relative bias for parameters estimated from skewed data with high IIV, condition *(iii)*, using non-adaptive and adaptive Gauss-Hermite quadrature in SAS and using Laplacian method in NONMEM.

Bias in the population estimates was studied based on Monte Carlo simulated data sets (n=100). Data sets comprising of 1000 patients, belonging to either of four dose groups (0, 1, 2 and 4 units) with four observations each were simulated. Data was simulated using NONMEM and the model used for simulation was fitted to each simulated data set using the NLMIXED procedure in SAS with the estimation methods *(a)* adaptive Gauss-Hermite quadrature with varied quadrature tolerance and *(b)* non-adaptive Gauss-Hermite quadrature with varied number of quadrature points.

Table II. Relative bias in parameter estimates for the three conditions, *(i)* non-skewed with low IIV, *(ii)* skewed with low IIV and *(iii)* skewed with high IIV for different quadrature tolerance in the estimation method, *(a)* the adaptive Gauss-Hermite quadrature.

	QTOL	$\theta_{bl=1}$	$\theta_{bl=2}$	$\theta_{bl=3}$	θ_{plc}	θ_{dose}	ω^2
(i)	0.0001	$-3.85\cdot10^{-5}$	$-6.92\cdot10^{-4}$	$-1.38\cdot10^{-4}$	$8.78\cdot10^{-3}$	$-5.88\cdot10^{-3}$	$-8.75\cdot10^{-3}$
	0.00001	$-7.96\cdot10^{-4}$	$-2.83\cdot10^{-4}$	$2.82\cdot10^{-4}$	$8.90\cdot10^{-3}$	$-6.21\cdot10^{-3}$	$-1.26\cdot10^{-2}$
	0.000001	$-9.12\cdot10^{-4}$	$-2.15\cdot10^{-4}$	$3.53\cdot10^{-4}$	$8.94\cdot10^{-3}$	$-6.24\cdot10^{-3}$	$-1.32\cdot10^{-2}$
(ii)	0.001	$1.02\cdot10^{-2}$	$-5.45\cdot10^{-3}$	$1.42\cdot10^{-2}$	$-1.29\cdot10^{-2}$	$1.36\cdot10^{-3}$	$-4.62\cdot10^{-2}$
	0.0001	$6.82\cdot10^{-3}$	$-6.81\cdot10^{-3}$	$1.29\cdot10^{-2}$	$-1.46\cdot10^{-2}$	$7.37\cdot10^{-3}$	$-3.27\cdot10^{-2}$
	0.00001	$6.82\cdot10^{-3}$	$-6.81\cdot10^{-3}$	$1.29\cdot10^{-2}$	$-1.46\cdot10^{-2}$	$7.37\cdot10^{-3}$	$-3.27\cdot10^{-2}$
(iii)	0.0001	$1.02\cdot10^{-2}$	$2.05\cdot10^{-2}$	$-6.17\cdot10^{-4}$	$1.76\cdot10^{-3}$	$-2.11\cdot10^{-2}$	$-3.16\cdot10^{-2}$
	0.00001	$8.60\cdot10^{-3}$	$2.12\cdot10^{-2}$	$5.65\cdot10^{-5}$	$1.98\cdot10^{-3}$	$-2.55\cdot10^{-2}$	$-3.22\cdot10^{-2}$
	0.000001	$8.70\cdot10^{-3}$	$2.12\cdot10^{-2}$	$1.46\cdot10^{-4}$	$1.74\cdot10^{-3}$	$-2.48\cdot10^{-2}$	$-3.22\cdot10^{-2}$

Conclusion

The Gauss-Hermite quadrature, used in the NLMIXED procedure in SAS® performs without appreciable bias in all conditions tested, including those conditions when the Laplacian method in NONMEM performs with bias. Thus, this is an alternative method for analyzing skewed ordered categorical data using proportional odds models.

Results and Discussion

In all conditions tested, *(i)*, *(ii)* and *(iii)*, the NLMIXED procedure performs without appreciable bias in parameter estimates when the quadrature tolerance of the adaptive method and the quadrature points of the non-adaptive method is set low and high enough, respectively (Table II and III)

In the situation when the Laplacian method in NONMEM produces the greatest bias, i.e. skewed distribution of response with high IIV, the NLMIXED procedure needed in the case of adaptive method, a quadrature tolerance of $1\cdot10^{-5}$ and in the case of non-adaptive method, 100 quadrature point for the methods to give stable estimates (Table II and III).

Comparing the parameters estimated from the skewed data with high IIV, using Laplacian method in NONMEM with the parameters estimated using the NLMIXED procedure in SAS®; it is obvious that the parameters estimated using NLMIXED are less biased (Figure 1), which supports the conclusion that the bias in parameters estimated using Laplacian method is due to the estimation being conditioned on the empirical Bayes estimates of ηs and the normality assumption of the ηs.

Table III. Relative bias in parameter estimates for the three conditions, *(i)* non-skewed with low IIV, *(ii)* skewed with low IIV and *(iii)* skewed with high IIV for different number of quadrature points in the estimation method, *(b)* the non-adaptive Gauss-Hermite quadrature.

	QPOINTS	$\theta_{bl=1}$	$\theta_{bl=2}$	$\theta_{bl=3}$	θ_{plc}	θ_{dose}	ω^2
(i)	10	$-2.64\cdot10^{-3}$	$2.35\cdot10^{-4}$	$5.51\cdot10^{-4}$	$1.12\cdot10^{-2}$	$-6.47\cdot10^{-3}$	$-1.38\cdot10^{-2}$
	15	$-2.66\cdot10^{-3}$	$2.43\cdot10^{-4}$	$5.59\cdot10^{-4}$	$1.12\cdot10^{-2}$	$-6.47\cdot10^{-3}$	$-1.38\cdot10^{-2}$
	20	$-2.66\cdot10^{-3}$	$2.43\cdot10^{-4}$	$5.59\cdot10^{-4}$	$1.12\cdot10^{-2}$	$-6.47\cdot10^{-3}$	$-1.38\cdot10^{-2}$
(ii)	10	$5.81\cdot10^{-3}$	$-5.44\cdot10^{-3}$	$1.28\cdot10^{-2}$	$-1.67\cdot10^{-2}$	$1.030\cdot10^{-2}$	$-2.37\cdot10^{-2}$
	15	$5.99\cdot10^{-3}$	$-7.43\cdot10^{-3}$	$1.24\cdot10^{-2}$	$-1.33\cdot10^{-2}$	$6.89\cdot10^{-3}$	$-2.81\cdot10^{-2}$
	20	$6.04\cdot10^{-3}$	$-7.40\cdot10^{-3}$	$1.24\cdot10^{-2}$	$-1.34\cdot10^{-2}$	$6.84\cdot10^{-3}$	$-2.84\cdot10^{-2}$
(iii)	90	$8.46\cdot10^{-3}$	$2.11\cdot10^{-2}$	$-5.09\cdot10^{-5}$	$3.18\cdot10^{-3}$	$-2.98\cdot10^{-2}$	$-3.16\cdot10^{-2}$
	95	$9.07\cdot10^{-3}$	$2.15\cdot10^{-2}$	$5.02\cdot10^{-4}$	$4.00\cdot10^{-5}$	$-1.95\cdot10^{-2}$	$-3.43\cdot10^{-2}$
	100	$8.59\cdot10^{-3}$	$2.08\cdot10^{-2}$	$-3.25\cdot10^{-4}$	$3.60\cdot10^{-3}$	$-3.01\cdot10^{-2}$	$-3.07\cdot10^{-2}$

References

1. Gupta SK *et al* Quantitative characterization of therapeutic index: Application of mixed-effects modeling to evaluate oxybutynin dose-efficacy and dose-side effect relationships. CPT 1999; 65: 672-84.
2. Sheiner LB. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. CPT 1994; 56: 309-22.
3. Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. CPT 1996; 60: 619-35.
4. Mould DR *et al* Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors. CPT 2002; 71: 334-48.
5. Beal SL, Sheiner LB. NONMEM users guides, Hanover, Maryland: GloboMax, 1989-1998.
6. Jönsson S, Karlsson MO. Estimating Bias in Parameters for some NONMEM Models for Ordered Categorical Data. AAPS PharmSci. 2002; 4: W4228.