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SHORT REPORT

Mixed-effects beta regression for modeling continuous bounded outcome scores using NONMEM when data are not on the boundaries

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Abstract Beta regression models have been recommended for continuous bounded outcome scores that are often collected in clinical studies. Implementing beta regression in NONMEM presents difficulties since it does not provide gamma functions required by the beta distribution density function. The objective of the study was to implement mixed-effects beta regression models in NONMEM using Nemes' approximation to the gamma function and to evaluate the performance of the NONMEM implementation of mixed-effects beta regression in comparison to the commonly used SAS approach. Monte Carlo simulations were conducted to simulate continuous outcomes within an interval of (0, 70) based on a beta regression model in the context of Alzheimer's disease. Six samples per subject over a 3 years period were simulated at 0, 0.5, 1, 1.5, 2, and 3 years. One thousand trials were simulated and each trial had 250 subjects. The simulation–reestimation exercise indicated that the NONMEM implementation using Laplace and Nemes' approximations provided only slightly higher bias and relative RMSE (RRMSE) compared to the commonly used SAS approach with adaptive Gaussian quadrature and built-in gamma functions, i.e., the difference in bias and RRMSE for fixed-effect parameters, random effects on intercept, and the precision parameter were <1–3 %, while the difference in the random effects on the slope was <3–7 % under the studied simulation conditions. The mixed-effect beta regression model described the disease progression for the cognitive component of the Alzheimer's disease assessment scale from the Alzheimer's Disease Neuroimaging Initiative study. In conclusion, with Nemes' approximation of the gamma function, NONMEM provided comparable estimates to those from SAS for both fixed and random-effect parameters. In addition, the NONMEM run time for the mixed beta regression models appeared to be much shorter compared to SAS, i.e., 1–2 versus 20–40 s for the model and data used in the manuscript.

The Alzheimer's Disease Neuroimaging Initiative—Data used in preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Introduction

Continuous bounded outcome scores are measurements taking values on a finite interval, and often used in clinical studies. Examples of bounded outcome data are the cognitive component of the Alzheimer's disease (AD) assessment scale (ADAS-cog), a key measure of cognition in AD patients taking values from 0 to 70 inclusive [1], and the Disability Assessment for Dementia (DAD), a measure of activities of daily living (0–100 inclusive) [2]. Since these types of data are often bounded within a certain range, the expectation must be nonlinear due to the ceiling/

floor effects, and the error distribution must be heteroscedastic since the variance must approach zero as their mean approaches either boundary score [1]. Therefore, regular regression models, such as normal linear or nonlinear regression models, are not suitable for these scales [1, 2].

Since bounded outcome data are restricted to a finite interval, they can be viewed as proportion or percentage-like data after being normalized by the range of the scale (e.g., 70 for ADAS-cog). One of the challenges associated with this type of data is that its distribution can vary from unimodal to J-, L-, or U-shaped. Thus, standard statistical approaches such as normalizing transformations may not work well in these cases [3]. Beta regression models, an extension of the generalized linear model, are recommended for such data due to the flexibility of the beta distribution and its ability to characterize dependent variables with various skewed and bimodal distributions[3–6].

Beta regression models, including mixed-effects beta regression, have been successfully implemented using WinBugs [7, 8] and Proc NLMIXED in SAS [3, 6, 9]. However, implementing beta regression in NONMEM presents difficulties, because NONMEM does not provide gamma functions required by the beta distribution density function. Values of the gamma function can be computed numerically by asymptotic approximations. Based on Stirling-De Moivre asymptotic series approximation, Nemes developed a new approximation to the gamma function using a series transformation [10]. This new approximation was shown to be superior to the other existing approximation methods (e.g., Stirling, Laplace and Ramanujan approximations) for the gamma function [10].

The objective of this research was to implement mixed-effects beta regression models in NONMEM. In addition, in mixed-effects beta regression, the likelihood is composed of gamma functions that contain subject-specific random effects. We evaluated the sufficiency of the NONMEM implementation of mixed-effects beta regression in comparison to widely used SAS approach. We used Nemes' approximation to the gamma function to construct the likelihood of the beta regression. A simulation-reestimation exercise was performed to evaluate the performance of NONMEM (version 7.1) for mixed effects beta regression models.

Methods

Beta regression

The mixed-effects beta regression assumes that conditional on the random effects, the response variable follows a beta distribution as denoted by:

$$y_{ij}|\eta_i, \theta, \tau \sim beta\,(\mu_{ij}\tau, (1-\mu_{ij})\tau) \quad (1)$$

where y_{ij} is the response variable ($0 < y_{ij} < 1$) for the ith subject ($i = 1\ldots m$) at the jth time ($j = 1\ldots n_j$), μ_{ij} is the conditional expectation (mean) of the response process ($0 < \mu_{ij} < 1$), η_i's are the random effects following a multivariate normal distribution ($\eta_i \sim N(0, \Sigma)$), θ's are the fixed effects (parameter coefficients), and τ is the precision parameter ($\tau > 0$). In addition, conditional on η_i, θ, and τ, y_{ij}'s are independent and have a beta density as follows:

$$f(y_{ij};\theta,\eta_i,\tau) = \frac{\Gamma(\tau)}{\Gamma(\mu_{ij}\tau)\Gamma((1-\mu_{ij})\tau)} y_{ij}^{(\mu_{ij}\tau-1)}(1-y_{ij})^{(1-\mu_{ij})\tau-1} \quad (2)$$

Using a logit link function, a beta regression model can be formed as:

$$\log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = g(\theta, \eta_i, x_{ij}) \quad (3)$$

$g(\theta, \eta_i, x_{ij})$ is some function of the regression covariates, the fixed, and random effects. Other link functions, including probit and complementary log–log, can be used as well. Selection of link functions in data analysis can be assisted by statistical tests [11, 12]. Interpretation of the parameters of the link functions is not always straightforward. One solution is to evaluate the covariates (e.g., slope) on the probability scale through rate of change functions [8, 13]. In this manuscript, we assume that the precision parameter, τ, is constant over all observations. However, τ may be modeled as a function of covariates using the log link function to assure a positive value for this parameter [6].

Nemes' approximation to the gamma function

Nemes has shown that the closed form approximation to the gamma function can be expressed as follows [10, 14]:

$$\Gamma(x) \sim \sqrt{\frac{2\pi}{x}}\left(\frac{x}{e}\right)^x \left(1+\frac{1}{15x^2}\right)^{\frac{5}{4}x} \quad (4)$$

Simulations

The simulation data were generated in the context of disease progression in patients with AD. The hypothetical AD response ($R(t)$) is assumed to be Alzheimer's disease assessment scale-cognitive subscale 11 (ADAS-cog/11) Scores, which has scores between 0 and 70. We assume that the normalized response scores (i.e., $R(t)/70$) follow a beta distribution as shown in Eq. 1. Conditional on the random effects, the expected response (μ_{ij}) for the ith subject at the jth time point is a linear function of time on the logit scale [7, 8]:

$$log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = \theta_0 + \eta_{0i} + (\theta_1 + \eta_{1i}) \cdot t_{ij} \quad (5)$$

where θ_0 is the intercept that characterizes baseline disease state, and θ_1 characterizes the rate of disease progression. The random effects of intercept and slope (η_{0i} and η_{1i}, respectively) are assumed to follow a multivariate normal distribution with mean equal to the null vector and variance–covariance matrix:

$$\begin{pmatrix} \omega_{00} = 0.4^2 & \omega_{01} = 0 \\ \omega_{01} = 0 & \omega_{11} = 0.3^2 \end{pmatrix} \quad (6)$$

Monte Carlo simulations were conducted based on the beta regression model in R 2.14.0. The R code for the simulation can be made available upon request. Six samples per subject over a 3 years period were simulated at 0, 0.5, 1, 1.5, 2, and 3 years. One thousand trials were simulated, and each trial contained 250 subjects. This sample size is relevant to a Phase 2 clinical study for AD. The intercept and slope were: $\theta_0 = 1$and $\theta_1 = 0.3$, respectively. The precision parameter, τ, was set to 3, 5, and 7 to generate approximately 50, 40, and 30 % data near the boundaries (Supplementary Fig. 1). The simulations were inspired by the example given in the Application section of this manuscript. The parameters were tweaked to move the data closer to the boundaries. It should be noted that the conditional likelihood cannot be computed at the boundaries because the beta density is not defined for these values. As a result of the numeric rounding, a very small portion of the simulated data (i.e., 0.19 % for $\tau = 3$; 0.05 % for $\tau = 5$; and 0.02 % for $\tau = 7$) were on the boundaries of the scale. Since the percent of data points at the boundaries was negligible, we analyzed the simulated data after excluding the data on the boundaries.

The performance of beta regression in NONMEM was evaluated by re-estimating the model parameters for each simulated dataset and by comparing bias (%) and the relative root mean squared error (RRMSE, %) as follows:

$$BIAS = \frac{1}{N}\sum_{n=1}^{N}\frac{(\hat{\phi}_n - \phi)}{\phi} \times 100 \quad (7)$$

$$RRMSE = \left(\frac{1}{N}\sum_{n=1}^{N}\left[\frac{(\hat{\phi}_n - \phi)}{\phi}\right]^2\right)^{1/2} \times 100 \quad (8)$$

where N is the total number of simulated datasets, ϕ is the true value of the parameters (i.e., θ or ω) in Eq. 2 and $\hat{\phi}_n$ is the estimate for the nth simulated dataset.

The simulated data were analyzed with the beta regression using both NONMEM and SAS. The implementation of the beta regression model in NONMEM used Nemes' approximation to gamma function and Laplace approximation of the likelihood function (hereafter NONMEM), while adaptive Gaussian quadrature of PROC NLMIXED was used to numerically solve the integrals over the random effects to compute the marginal likelihood (hereafter SAS). Because implementation of beta regression in SAS with adaptive Gaussian quadrature has been widely accepted in the literature [3, 6, 9], comparison of the performance of the NONMEM implementation using Laplace approximation with that of the SAS could be used to gauge the proposed NONMEM method in this manuscript. We also estimated the simulated data using SAS with Laplace approximation (hereafter SAS-Laplace) to understand the sources of difference in the performance of NONMEM and SAS by comparing Nemes' approximation to the built-in gamma functions in SAS. The number of quadrature points was set to 10 and 1 for SAS and SAS-Laplace, respectively. The quasi-Newton optimization was used for SAS, while double-dogleg optimization method was used for SAS-Laplace.

Application of beta regression implemented in NONMEM

Study details

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5 years public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1,500 adults, ages 55–90, to participate in the research,

consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. The dataset for the current analysis consisted of 191 AD subjects. All AD subjects had clinical/neuropsychological assessments and 1.5T MRI measurements, and were assessed at 0, 6, 12, and 24 months.

We demonstrate the application of a mixed-effects beta regression model in NONMEM for modeling the deterioration of cognitive function (measured by ADAS-cog) in patients with AD. ADAS-cog scores patients on an aggregate of 11 components (i.e.,measures deterioration of memory, language, praxis, attention and other cognitive abilities in AD). A recent large meta-analysis has modeled ADAS-cog data using beta regression implemented in WinBugs [8]. The purpose of the current analysis is to demonstrate the implementation of beta regression in NONMEM. It is worth mentioning that various structural models such as linear and logistic models have been applied to this type of data [15–17]. In this analysis, the simple logistic structural model was used in the simulation-reestimation exercise (Eq. 5), which assumed linear progression on the logit scale. The NONMEM code for the application is presented in the Appendix.

Goodness-of-fit and visual predictive check

Diagnostics of goodness of fit included plots of residuals against the predicted score and time and the observed versus predicted values. For beta regression, raw response residuals are not suitable for model diagnostics due to the heteroscedasticity associated with the data and the model. Pearson's residuals (also called standardized ordinary residuals) were first proposed to diagnose the beta regression models [5]. In addition, deviance residuals and standardized weighted residuals were also proposed to measure goodness-of-fit of the beta regression model [4, 5, 18]. We used standardized ordinary residuals to diagnose the beta regression model for the ADNI ADAS-cog data. The definition of standardized ordinary residuals was the following [5]:

$$r_{ij} = \frac{y_{ij} - \mu_{ij}}{\sqrt{\mathrm{var}(y_{ij})}} \tag{9}$$

where μ_i and $\mathrm{var}(y_{ij}) = \frac{\mu_{ij}(1-\mu_{ij})}{1+\tau}$ were the estimated mean and variance of the response scores, respectively.

The percentile VPC [19] was used to assess the model. The median, and 5th and 95th percentiles of the observed data were computed, and then the median and 90 % prediction intervals of these quantities were computed based on 1000 simulations and compared to the observed percentiles. The uncertainties of the parameter estimates were not used in the simulations for the VPC. The unscheduled sparse samples at 1.5 and 3 years were binned with samples at 1 and 2 years, respectively. It is worth mentioning that theoretically, simulations from beta distribution will not generate 0 and 1 (i.e., boundary values). However, the simulated values that are very close to 0 or 1 will be automatically rounded to 0 and 1 by the software.

Results and discussion

The beta regression model implemented in NONMEM had no difficulties with model convergence. No unsuccessful terminations were observed during the simulation-reestimation exercise. The run time on an Intel® Core™ i5 CPU (M520 @ 2.4 GHz) for the reestimation of the simulated datasets (e.g., a sample size of 250 per trial) was 1–2 s per model run for NONMEM, 20–40 s for SAS, and 10–20 s for SAS-Laplace.

Table 1 shows the bias and RRMSE for the parameter estimates of the mixed-effects beta regression model for NONMEM, SAS, and SAS-Laplace for different simulation scenarios (different skewness of the data when $\tau = 3, 5,$ and 7). Overall, except for the random effects of the slope, the bias for the other model parameters was small (<5 %) for all the three estimation methods. However, it appears that there were some difficulties in estimating the random effect of the slope for all the estimation methods. The bias of the random effects of the slope for SAS ranged from −2 to −9 % while the bias of the NONMEM results ranged from approximately −6 to −16 %. In general, the bias and RRMSE for the parameters of beta regression decreased with less skewed data for all the three investigated estimation approaches. When the data is highly skewed (i.e. $\tau = 3$ and 50 % of data near the edge), the bias of the random effect of the slope for SAS and NONMEM was −9 and −16 %, respectively. The bias of the random effects on slope was reduced to −2 and −6 % for SAS and NONMEM, respectively as τ increased to 7 (30 % data near the edge). Overall, the RRMSE of the parameter estimates of the beta regression using SAS was less than 15 %, while the RRMSE using NONMEM was less than 20 %. Therefore, compared to the widely used SAS implementation of beta regression (i.e., adaptive Gaussian quadrature and built-in gamma function), the NONMEM implementation using Laplace and Nemes' approximations provided similar performance with only 3 to 7 % higher bias and RRMSE for the random effect of slope under the current simulation conditions. The differences in bias and RRMSE among different estimation methods became less noticeable when the data were less skewed.

Table 1 Model performance of the beta regression model using SAS and NONMEM

Parameter	$\tau = 3$		$\tau = 5$		$\tau = 7$	
	Bias	RRMSE	Bias	RRMSE	Bias	RRMSE
NONMEM (Laplace approximation/Nemes' approximation to gamma function)						
Intercept (β0)	0.13	5.56	0.09	4.53	−0.13	4.32
Slope (β1)	−4.26	11.64	−2.15	10.01	−1.27	9.56
SD of IIV on intercept (b0)	−2.89	12.39	−2.35	11.16	−1.50	9.89
SD of IIV on slope (b1)	−16.20	20.15	−8.71	13.51	−6.01	10.92
Precision parameter (τ)	−3.59	5.65	−1.70	4.58	−1.04	4.49
SAS (adaptive Gaussian quadrature)						
Intercept (β0)	0.32	5.44	0.32	4.49	0.03	4.27
Slope (β1)	−0.39	4.39	−0.04	4.29	0.13	4.38
SD of IIV on intercept (b0)	−0.22	11.81	−0.34	10.75	0.29	9.62
SD of IIV on slope (b1)	−9.39	14.17	−4.05	10.27	−2.23	9.04
Precision parameter (τ)	−0.39	4.39	−0.04	4.29	0.13	4.38
SAS (Laplace approximation)						
Intercept (β0)	0.05	5.40	−0.07	4.47	−0.54	4.36
Slope (β1)	−2.91	10.40	−1.70	9.58	−1.28	9.44
SD of IIV on intercept (b0)	−2.13	11.87	−2.60	11.02	−2.51	10.04
SD of IIV on slope (b1)	−12.63	16.33	−7.39	11.97	−6.02	10.79
Precision parameter (τ)	−1.05	4.32	−1.38	4.46	−2.73	5.62

RRMSE relative root mean square error

Laplace approximation was also attempted with SAS to identify which approximation (Laplace or Nemes' approximation) contributed to the higher bias and RRMSE for the NONMEM implementation compared to the SAS approach. SAS-Laplace generally had slightly higher bias and RRMSE than SAS, but lower or comparable bias and RRMSE compared to NONMEM. When data is less skewed (i.e., $\tau = 7$), the difference in bias and RRMSE between NONMEM and SAS may mainly be a result of difference in Laplace and adaptive Gaussian quadrature approximations because the bias and RRMSE of NONMEM was similar to that of SAS-Laplace in this simulation scenario. However, when $\tau = 3$, both Laplace and Nemes' approximations may contribute to the difference between SAS and NONMEM as the bias and RRMSE of SAS-Laplace is in the middle between the values for NONMEM and SAS.

The run time of the beta regression model on the ADNI dataset was 2.3 s. The parameter estimates for the beta regression model of the ADAS-cog data obtained from SAS and NONMEM are listed in Table 2. The parameter estimates based SAS and NONMEM are virtually the same. This is not surprising since very small amount of the ADAS-cog scores of the ADNI AD patients were near the boundaries (Supplementary Fig. 2). Diagnostic plots based on the NONMEM model for residuals (Fig. 1) show that there is no obvious pattern in the individual standardized ordinary residuals versus time and population predictions. The plots of the observed versus both population and individual predicted ADAS-cog (Fig. 1) shows that the data are generally distributed around the line of identity, indicating an overall reasonable model fitting of ADAS-cog scores. The percentile VPC plot (Fig. 2) suggests that overall, the beta regression disease progression model described the longitudinal progression of ADAS-cog well, as the predicted percentiles (the 5th, 50th, and 95th) closely matched the corresponding observed percentiles. It should be noted that the median predicted curve is slightly above the observed median. This may be probably due to the influence of the missing data (30 % missing data at year 2 in the current dataset) on the observed data because patients with slower disease progression tended to stay in the study, while patients with worsening progression tended to drop out. Therefore, the observed data at later times (i.e., 1 and 2 years) are probably from the subjects with less severe disease status (i.e., lower ADAS-cog scores) owing to the selection bias caused by the missing data. The mixed-effects beta regression model assumed missing at random to account for the missing data. Therefore, the prediction based on the beta regression model represents an ideal situation where no dropout occurred inspite of disease worsening. This may explain the mismatch between the predicted and observed median curves.

The main focus of the manuscript is the continuous bounded outcome scores when data are not on the boundaries. In presence of data on the boundaries, a rescaling

Table 2 Parameter estimates of the beta regression model implemented in NONMEM and SAS for ADAS-cog progression based on the ADNI dataset

Parameter	SAS			NONMEM		
	Estimate	95 % CI		Estimate	95 % CI[a]	
Intercept (β0)	−1.07	−1.01	−1.13	−1.06	−0.99	−1.13
Slope (β1)	0.311	0.258	0.364	0.32	0.270	0.372
SD of IIV on intercept (b0)	0.41	0.36	0.45	0.43	0.39	0.48
SD of IIV on slope (b1)	0.278	0.243	0.313	0.28	0.259	0.309
Precision parameter (τ)	4.55	4.40	4.70	4.59	4.44	4.74

SAS PROC NLMIXED with adaptive Gaussian quadrature and built-in gamma functions

NONMEM Laplace approximation and Nemes' approximation to gamma function

[a] Based on standard error provided in NONMEM

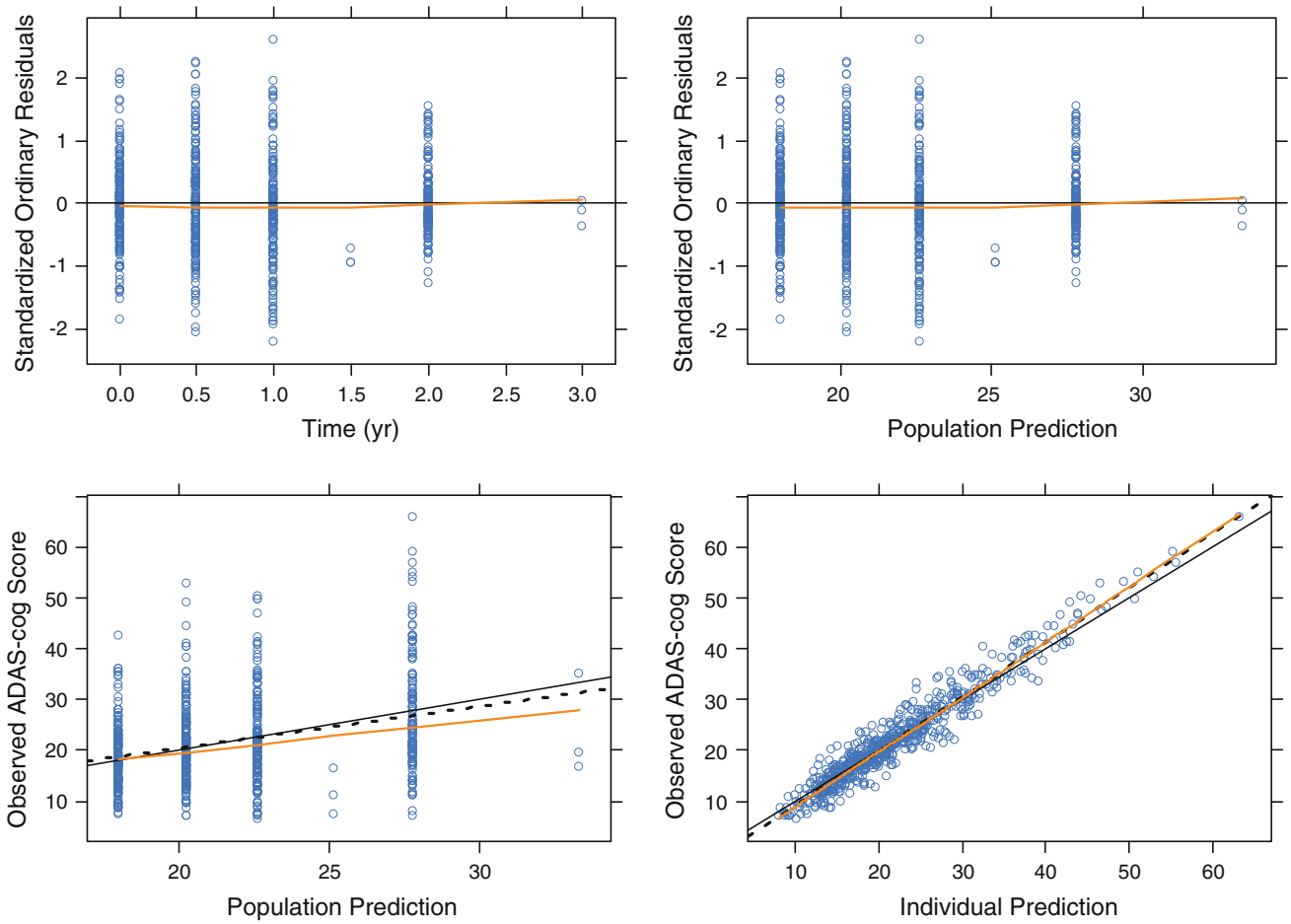

Fig. 1 Goodness of fit plots for the model of Alzheimer's disease assessment scale (ADAS-cog). The *orange line* represents a LOWESS smoother. In the residual plots, the ordinate value of zero is presented (*solid horizontal line*). In the plots of observed versus population and individual predictions, the *solid line* represents the line of identity, and the *dashed line* represents the linear regression line (Color figure online)

method proposed by Verkuilen and Smithson may be applied to the data before analysis using beta regression [4, 6, 9]. In addition, zero- and one-inflated beta regression [20, 21] and transformation approaches [22, 23] have been proposed to analyze continuous bounded outcome scores in presence of boundary data. For longitudinal, discrete bounded outcome data, random-effects coarsened models and ordinal probit models have been considered sensible approaches [24, 25]. For the current simulation data, we also analyzed the simulated data using beta regression after

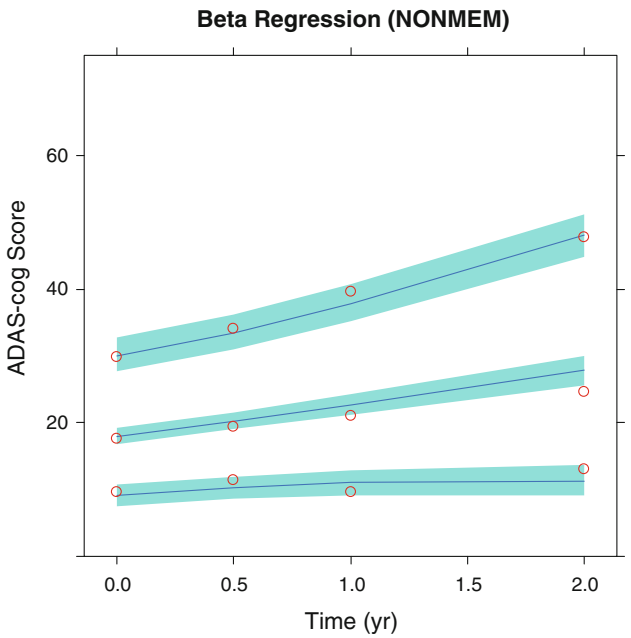

Fig. 2 Visual predictive check for the model of Alzheimer's disease assessment scale (ADAS-cog). The *upper*, *middle*, and *lower* profiles indicated by the *open circles* represent the 95th, 50th, and 5th percentiles of the observed data. The *upper*, *middle*, and *lower curves* indicated by the lines are the median model based prediction for the 95th, 50th, and 5th percentiles and these predictions account for missing data. The *shaded areas* are the 90 % prediction intervals of the corresponding percentiles of the simulations based on the model

applying the rescaling method to the data [6, 9]. The bias and RRMSE for each parameter were almost identical after rescaling the data and excluding the boundary data (data not shown), indicating that the impact of the small percentage of boundary data on the simulation-reestimation exercise was minimal. Further investigations may be needed in the future if large amount of data are located at the boundaries.

Conclusions

It is possible to implement mixed-effects beta regression in NONMEM with Nemes' approximation to the gamma function. The simulation-reestimation exercise demonstrated that compared to SAS, NONMEM provided similar bias and RRMSE (with only a relatively small difference) for estimating both fixed- and random-effect parameters of the mixed effects beta regression model. This is consistent with previous findings which suggested that the Laplace and adaptive Gaussian approximations give the best mix of efficiency and accuracy [26]. In addition, when being applied to implementation of mixed-effects beta regression, Nemes' approximation reasonably matched the SAS built-in gamma functions with less than approximately 3 % difference in bias and RRMSE in our present simulations.

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Appendix

A sample NONMEM code for the mixed effects beta regression model for the ADNI data is presented.

Code	Comments
$PROB beta regression	; Data specification
$INPUT	
$DATA ADNI.csv	
$PRED	; Mean model
B0 = THETA(1) + ETA(1)	; Define parameters for
B1 = THETA(2) + ETA(2)	baseline and slope
LINP = B0 + B1 * TIME	; Linear predictor on logit scale
MU = EXP(LINP)/	; Conditional mean by anti-logit
(1 + EXP(LINP))	transforming the linear predictor
LTAU = THETA(3)	; precision parameter
TAU = EXP(LTAU)	
	; specify the log likelihood based on the density function for beta distribution (Eq. 2)
X1 = TAU	
X2 = MU * TAU	
X3 = (1−MU) * TAU	

Appendix continued

Code	Comments
LG1 = 0.5 * (LOG(2 * 3.1415) − LOG(X1)) + X1 * (LOG(X1) − 1) + (5/4) * X1 * (LOG (1 + (1/(15 * X1 * 2))))	; Approximation of the log(gamma) function (Eq. 4)
LG2 = 0.5 * (LOG(2 * 3.1415) − LOG(X2)) + X2 * (LOG(X2) − 1) + (5/4) * X2 * (LOG (1 + (1/(15 * X2 * 2))))	; The first part of the log likelihood, 0.5 * (LOG(2 * 3.1415), can be omitted if computation of full likelihood is not required.
LG3 = 0.5 * (LOG(2 * 3.1415) − LOG(X3)) + X3 * (LOG(X3) − 1) + (5/4) * X3 * (LOG (1 + (1/(15 * X3 * 2))))	; Log Likelihood of the beta distribution (Eq. 2)
LOGL = LG1 − LG2 − LG3 + (MU * TAU−1) * LOG(DV) + ((1−MU) * TAU−1) * LOG(1−DV)	
Y = −2 * LOGL	
SOR = (DV − MU)/ SQRT(MU * (1−MU)/ (1 + TAU))	; Pearson residuals (standardized ordinary residuals)
$THETA	; specify initial values
$OMEGA	
$EST MAX = 9999 PRINT = 5 METHOD = COND − 2LOGLIK LAPLACIAN NOABORT	; estimation step
$COV PRINT = E MATRIX = R	
$TABLE	

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