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A Longitudinal Model for Repeated Highly Skewed Outcome Data

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ABSTRACT

Highly skewed outcomes are commonly encountered in longitudinal data settings. We propose a Weibull model with gamma random effects for analyzing such longitudinal data. We provide the overall likelihood and the prediction of the subject-specific response at a given time. We apply our model to the Michigan polybrominated biphenyl (MIPBB) study and evaluate the prediction using a validation sample. The model performs reasonably well in terms of prediction in the MIPBB study.

Key Words: Longitudinal data, Random effects, Skewed data, Weibull model.

INTRODUCTION

In longitudinal studies, repeated measurements of subject characteristics and outcomes are frequently available. A common objective in such studies involves the statistical modeling of longitudinal measurements incorporating observed characteristics of subjects, and investigation of associations between longitudinal outcomes and observed covariates. In some instances it is also of interest to predict subject-specific outcomes at a later time point during the study period. In particular, the goal of predicting subject-specific values at a later time requires well thought out, flexible and innovative models for longitudinal data.

When the outcome is approximately normally distributed, there is a vast literature for modeling longitudinal data (Diggle *et al.*, 1994;, Verbeke and Molenberghs, 2000). A common, convenient and often reasonable tool for this purpose is the general linear mixed model, for which there exists a wealth of well-established theory facilitating maximum likelihood (ML) and restricted maximum likelihood (REML) estimation as well as the prediction of individual-specific random effects corresponding to levels or trajectories (Verbeke and Molenberghs, 2000). This approach has become attractive for the analysis of multivariate epidemiologic data since the development of commercial software (e.g., Littell *et al.*, 1996) for its implementation.

The generalized estimation equation (GEE) approach has also been very popular in the investigation of the association between longitudinal outcomes and covariates since this approach does not require the outcome to be normally distributed (Zeger and Liang, 1988; Liang and Zeger, 1986). An attractive feature of the GEE approach is that the estimation is carried out without distributional assumptions of the outcome. Robust, easy to use approximate variances are available to accompany regression parameter estimates, thus facilitating the inferential procedures. The GEE approach only requires the specification of the mean of the marginal distribution of the outcome. This is in contrast to the linear mixed model, which requires the distributional specification of normality of the outcome conditional on the subject-specific random effects. Consequently, the interpretations of the parameters corresponding to covariate effects differ for these two approaches. The GEE estimation approach has the interpretation of population averages, while the linear mixed model provides a subject-specific covariate effects interpretation. Due to its population average interpretation, in terms of prediction of the outcome at a given time point, the GEE approach only provides the prediction of the population average of subjects. However, the linear mixed model borrows strength across other subjects to allow prediction of subject-specific effects at a given time using empirical Bayes-like estimation (Laird and Ware, 1982; Verbeke and Molenberghs, 2000). These issues have been well described in a detailed manner in several texts (Diggle *et al.*, 1994; Verbeke and Molenberghs, 2000).

In many epidemiologic studies, available repeated measurements of exposure are often highly skewed and thus may be expected to violate the normal distributional assumption. The data could be transformed (Box and Cox, 1964; Gurka *et al.*, 2006) to make the outcome approximately normal for the use of the linear mixed model. However, in this case some difficulty arises in the interpretation of parameters with respect to the original scale of the data. In particular, the prediction of the outcome on the original scale may require specifically thought-out procedures

when modeling is implemented on a transformed scale (Lyles *et al.*, 1997). When the outcome is not normally distributed. there is very limited literature on modeling longitudinal data, particularly from the viewpoint of subject-specific estimation. Several authors have used the Poisson-gamma mixture model for longitudinal counts (Thall and Vail, 1990; Jowaheer and Sutradhar, 2002). Most of the other research proposed in the literature requires solving extensive numerical integrations or making numerical approximations due to intractable likelihoods.

In this manuscript, we take a subject-specific modeling approach for analyzing longitudinal data. Motivated by a specific study known as the Michigan Polybrominated Biphenyl study (MIPBB) involving highly skew-distributed exposure measurements, we propose a parametric longitudinal model for determining associations between these measurements and covariates. We assume that the outcome (exposure) follows a Weibull distribution conditional on the random effect. The random effect represents the intercept, indicating that the first exposure for each subject is assumed to be gamma distributed. Under this mathematical structure, we derive the explicit likelihood for the longitudinal data. We also give the formula for predicting the expected log-scale exposure for each subject at a given time point. We apply our results to the MIPBB study and compare our results to those of Terrell *et al.* (2008), who used a normal-theory linear mixed model for analyzing the same data.

The remainder of the paper is structured as follows. In Section 2, we describe the data from the MIPBB study. Section 3 describes the longitudinal model and the likelihood. In Section 4, we apply the results to the MIPBB study and compare to the results of Terrell *et al.* (2008). Finally, we conclude with a discussion.

THE MIPBB STUDY

The Michigan Long-Term PBB Study was initiated following an industrial accident on Michigan farms in the early 1970's. In brief, a commercial mixture of PBBs (a brominated flame retardant) was inadvertently delivered to Michigan farms and subsequently added to animal feed, instead of a nutritional feed supplement. The Michigan Department of Community Health (MDCH) recruited families who either lived on or received food from contaminated farms and farm animals. The cohort of approximately 4000+ individuals has been followed since its inception in 1976 and PBB has been measured repeatedly in their serum over a 17 year time frame. Further details on the cohort have been previously reported (Humphrey and Hayner 1976; Landrigan *et al.*, 1979; Fries, 1985).

PBB is stored in body fat and very persistent in humans and the environment. Half-life estimates are between 13 to 29 years in humans (Blanck *et al*, 2000a). It is similar in nature to PCBs and the more commonly known brominated flame retardant, PBDEs. Studies have shown PBB to have endocrine disrupting properties. In addition, studies have shown that PBB can transfer from mother to offspring *in utero* and during breastfeeding.

A sub-study of the MIPBB study was initiated as an effort to assess endocrine-related outcomes among the women exposed to PBB, and among their offspring who were born after the PBB exposure incident. Through this sub-study, a wealth of demographic, lifestyle, and reproductive information has been obtained. In addition, while the MIPBB study has multiple exposure measurements on these women, there have been limited PBB measurements collected for their children. Thus, a decay model was developed by Blanck *et al.* (2000) to estimate serum PBB levels in these women at various key developmental times (such as when daughters and sons of exposed women were *in utero*). A subsequent decay model was recently developed using linear mixed models, and was shown to improve the estimation of PBB (Terrell *et al.*, 2008) via the use of time dependent covariates and subject-specific effects. Despite the use of a simple logarithmic transformation for serum PBB concentrations in both decay models, there remains some departure from normality that we seek to address in the present study.

As in Terrell *et al.* (2008), the present study includes 406 women who met the following criteria: they were born before the PBB exposure incident; had at least two serum PBB measurements collected when they were at least 16 years of age; were not pregnant or breastfeeding at the time of their measurements; and had an initial serum PBB concentration of at least 2 parts per billion (ppb). The serum PBB limit of detection established by the MDCH Bureau of Laboratories is 1 ppb, and non-detectable samples were set to half the limit of detection (0.5 ppb) to facilitate the log-transformation. For additional information on the PBB analytical methods, refer to Burse *et al.* (1980) and Needham *et al.* (1981). In the MIPBB cohort, serum was collected when the participants were not fasting and lipids were not measured. Within this cohort, the distribution of serum PBB concentrations is skewed and about 30% of the measurements are below the limit of detection. However, the 406 women included in the present study had to have an initial serum PBB of at least 2 ppb. Of their remaining samples, only 5% were below the limit of detection. In the most recent prior decay modeling effort the covariates of interest were age at exposure, body mass index (BMI) at the initial measurement, smoking history, pregnancy and breastfeeding status. Time was expressed as the years from initial

PBB exposure to the serum measurement date. Smoking history, pregnancy and breastfeeding status were considered as time-dependent covariates (Terrell *et al.*, 2008).

In describing the population, the women were exposed to PBB from early childhood up to 61 years of age. Their average age at exposure was 28 years, and their average initial BMI was 24 kg/m^2. At enrollment into the MIPBB study, their initial serum PBB concentrations reached a maximum of 560 ppb with a median of 2.4 ppb. On average, the women had 3 serum PBB measurements collected and at most 7 measurements, for a total of 1142 measurements (Terrell *et al.*, 2008). In this population there were 23% smokers, 29% had a pregnancy during follow-up, and 16% breast fed. See Table 1 for descriptive statistics of subject characteristics.

Table 1: Characteristics of Subjects (N=406)

◦ **Repeated Measurements (N=1142)**	**Mean (SD)**	**Median**	**Range**
Number of PBB measurements	2.8 (1.0)	3.0	2 - 7
Time between first and last PBB measurements (years)	9.4 (5.8)	10.8	1 - 17
Population Characteristics (N=406)			
Age at exposure (years)	28 (13.7)	26.5	2 - 61
BMI at initial measurement (kg/m^2)	24 (5.0)	23.0	15 - 62

Terrell *et al.*, 2008 performed an internal validation study to evaluate their decay model using a subset of participating women (n=151). These women had at least 3 serum PBB measurements, one of which was collected during the latest sampling time period (1991-1993). Estimates from a decay model that excluded these measurements were used to predict exposure at the actual date of the latest measurement for this subset of women. The concordance correlation coefficient between the observed and predicted 1991-1993 serum PBB measurements was

0.904. In the present work, we attempt to replicate this validation study under different distributional assumptions designed to more satisfactorily account for the skewed nature of the data.

LONGITUDINAL MODEL

Suppose that we observe N subjects each having a varying number of longitudinal measurements over time. Let Y_{ij} be the response (exposure) variable for subject i. at the jth time point (i=1, ...N; j=1,...n_i). Let $\mathbf{Y}_i$ represent the response vector for the i^{th} subject. We use x_{ij} to denote a covariate observed for the i^{th} subject at the j^{th} time, and although the model readily handles multiple covariates we consider only a single one in the following developments. Let W_i be a random variable, representing the random effect for subject i. The random effect W_i accounts for within-subject correlation, and has a distribution with a positive support . We assume that conditional on W_i, the response Y_{ij} follows a Weibull distribution, i.e.,

$$Y_{ij}|w_i \sim \text{Weibull}(w_i \eta_{ij}, \lambda), \qquad (1)$$

with a shape parameter $\lambda > 0$ and scale parameter $\eta_{ij} = \exp(\lambda\beta_0 - \lambda\beta_1 X_{ij})$ Furthermore, we assume that W_i follows a gamma distribution with mean 1 and variance θ, i.e., both shape and scale parameters are θ. For identification reasons, the mean is set to 1.

We can rewrite the model (1) as

$$\log Y_{ij} = -\frac{1}{\lambda}\log w_i + \beta_0 + \beta_1 X_{ij} + \frac{1}{\lambda}e_{ij}, \qquad (2)$$

where e_{ij} has a log unit exponential distribution. Similar to the linear mixed model, this model postulates a linear relationship between the covariates and the log of the outcome. The regression coefficient (β_1) indicates the effect of the covariate in the log-scale. Each subject has its own random intercept, $-\frac{1}{\lambda}\log(w_i)+\beta_0$, with the overall intercept β_0. We develop the corresponding likelihood assuming independence across subjects and that the repeated measurements are independent

conditional on the random effect W_i for each subject. Specifically, the likelihood for a subject (i) from model (2) is

$$L_i(\beta_0, \beta_1, \lambda|W_i) = \prod_{j=1}^{n_i} Pr(Y_{ij} = y_{ij}|W_i)$$

$$= w_i^{n_i} \lambda^{n_i} \prod_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda-1} \exp(-w_i \sum_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda})$$

since

$$Pr(Y_{ij} = y_{ij}|W_i) = w_i \eta_{ij} \lambda y_{ij}^{\lambda-1} \exp(-w_i \eta_{ij} y_{ij}^{\lambda})$$

The unconditional likelihood for subject i is

$$L_i(\beta_0, \beta_1, \lambda) = \int w_i^{n_i} \lambda^{n_i} \prod_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda-1} \exp(-w_i \sum_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda}) dF(w_i).$$

where F(.) denotes the distribution function of the random effect W. By noting that the Laplace transform of W is $p(s)=\int \exp(-w\, s)\, dF(w)$, we can rewrite the likelihood as

$$L_i(\beta_0, \beta_1, \lambda) = (-1)^{n_i} \lambda^{n_i} \prod_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda-1} P^{(n_i)}(\sum_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda})$$

where $P^{(ni)}(.)$ denotes the n_i^{th} derivative of the Laplace transform. Since we assume W has a gamma distribution, the specific Laplace transform for random effect, W is

$$p(s) = \left(\frac{\theta}{\theta + s}\right)^{\theta}$$

We can show that the n_i^{th} derivative of this Laplace transform leads to the following:

$$(-1)^{n_i} p^{n_i}(s) = \theta^{\theta} \theta(\theta + 1)...(\theta + n_i - 1)(\theta + s)^{-\theta - n_i}$$

Using this result, the likelihood for the i^{th} subject becomes

$$L_i(\beta_0, \beta_1, \lambda) = \lambda^{n_i} \prod_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda-1} \theta^{\theta} \theta(\theta+1)\ldots(\theta+n_i-1)(\theta+\sum_{j=1}^{n_i} \eta_{ij} y_{ij}^{\lambda})^{-\theta-n_i}$$

Therefore, the overall likelihood can be obtained as a multiplication of this expression over all N subjects. Consequently, we can write the log-likelihood and obtain the maximum likelihood estimates using the Newton-Raphson algorithm. The standard errors are obtained via inverting the observed information matrix. One of the advantages of this method is that the likelihood is explicit, so that hypotheses testing can readily be carried out using likelihood ratio tests.

PREDICTION

We can also use this Weibull-gamma random effects model to predict the subject's response for a given value of the covariate x_{ij} (for instance, at a given time t). Since the response y_{ij} is Weibull and W has a gamma distribution with parameter θ, we can show that the posterior distribution of W given the data is also gamma distributed with shape parameter $(\theta+B_i)$ and scale parameter $(n_i+\theta)$ where $B_i = \sum_{j=1}^{n_i} n_{ij} y_{ij}^{\lambda}$ Using the properties of the gamma distribution, we can subsequently show that

$$E(\log W | y_i) = \Psi(\theta + n_i) - \log(\theta + B_i)$$

where ψ is the digamma function (Abromovitz and Stegun (1972)). Since $E(e_{ij})= \psi(1)$, from equation (2), the predicted value on the log scale for the i^{th} subject is

$$-\frac{1}{\lambda}[\psi(\theta+n_i)-\log(\theta+B_i)]+\beta_0+\beta_1 x_{ij}+\frac{1}{\lambda}\varphi(1) \qquad (3)$$

It is also of interest to determine the predicted value on the original scale. In this case, we first show that the expectation of y_{ij} given w may be written as

$$E(y_{ij}|W_i) = \frac{\Gamma(1+\frac{1}{\lambda})}{(W_i \eta_{ij})^{\frac{1}{\lambda}}}$$

because of the assumed Weibull distribution for y_{ij} given W. Since W given the data is also gamma distributed, we can show that the expectation of $W^{-\frac{1}{\lambda}}$ given the data is

$$(\theta + B_i)^{\frac{1}{\lambda}} \frac{\Gamma(\theta + n_i - \frac{1}{\lambda} - 1)}{\Gamma(\theta + n_i - 1)}$$

Therefore the predicted value on the original scale may be derived as:

$$\frac{(\theta + B_i)^{\frac{1}{\lambda}}}{(\eta_{ij})^{\frac{1}{\lambda}}} \frac{\Gamma(1 + \frac{1}{\lambda})\Gamma(\theta + n_i - \frac{1}{\lambda} - 1)}{\Gamma(\theta + n_i - 1)}$$

In the current manuscript, we use equation (3) to predict the random effect for each subject and to obtain the expected value of the PBB on the log scale.

APPLICATION TO MIPBB STUDY

We apply model (2) to the MIPBB study consisting of 406 women. The covariates of interest include time, age at exposure, body mass index (BMI) at the initial measurement, smoking history, pregnancy and breastfeeding status. Following Terrell *et al.* 2008, we incorporate a linear predictor in (2) that consists of time, together with the interactions of the other covariates with time. The fixed part of the model is thus written as $\beta_0 + [\beta_1 + \beta_2 \text{BMI} + \beta_3 \text{ age} + \beta_4 \text{ smoke} + \beta_5 (\text{pregnancy and no breastfeeding}) + \beta_6 (\text{pregnancy and breastfeeding})] * \text{time}$, where BMI and age are centered and where the latter three covariates inside the brackets represent time-dependent indicator variables.

The model in Table 2 gives the estimates based on the Weibull-gamma random effects model. We obtain an average rate of decay of -0.007 log (ppb/yr) for a woman with an initial BMI of 24 kg/m^2, age 28 years, non-smoker, with no history of pregnancies. While there is no smoking or pregnancy effect on PBB decay, we observe slower decay rates with increases in initial BMI or age at exposure above their means. Alternatively, breastfeeding was found to accelerate a woman's decay of PBB over time.

Table 2: Results of the longitudinal Model for Women in the MIPBB Study Using PBB Measurements 1976-1993 (n=406)

Variable	Parameter	Estimate	Standard Error	P-value
Intercept	β_0	0.512	(0.035)	<0.0001
Time: PBB decay rate in log(ppb/yr)[a]	β_1	–0.007	(0.002)	0.001
(BMI – 24) kg/m^2	β_2	0.001	(0.0004)	0.006
(Age – 28) yrs	β_3	0.0004	(0.0002)	0.006
Smoker				
No	—	—	—	—
Yes	β_4	–0.003	(0.004)	0.212
Pregnancy and Breastfeeding[b]				0.020
None	—	—	—	—
Pregnancy and no breastfeeding	β_5	0.005	(0.005)	0.173
Pregnancy and breastfeeding	β_6	–0.009	(0.004)	0.013
λ		3.675	(0.108)	<0.0001
Ψ		0.258	(0.017)	<0.0001

[a] Decay rate for a woman with BMI 24 kg/m^2, age 28 years, non–smoker, and no pregnancies.

[b] Test for the decay rate difference between having a pregnancy and no breast-feeding and having a pregnancy and breast-feeding (p=0.011)

Comparing the results in Table 2 with the Gaussian mixed-effects model estimates from Terrell *et al.*'s Table 3 (2008), we find that the overall PBB decay rates are almost identical (-0.007 log(pbb/yr) Weibull-gamma model; -0.011 log(ppb/yr) Gaussian model). In terms of covariates impacting the decay rate, the largest difference occurs with smoking history (-0.003 log(pbb/yr) Weibull-gamma model; -0.008 log(ppb/yr) Gaussian model). No differences are seen in the decay rates for BMI or age, and the pregnancy and breastfeeding effects are similar and in the same direction.

We next evaluate our model using a validation sample. Using equation (3), we calculate the predicted values for serum PBB levels for 151 women collected during 1991-1993. We note that our model is built based on the data collected during 1976-1988. The mean squared error is 0.318. The correlation between the observed and the predicted values is 0.92. The concordance estimate which measures the agreement between the observed and predicted value is 0.903. From Terrell *et al.* (2008) using the linear mixed model the MSE is 0.325 and the concordance

coefficient is 0.904. These summary statistics indicate that the results we obtain via the Weibull model are very much similar to the results from the linear mixed model in this application.

DISCUSSION

In this manuscript we propose a Weibull-gamma random effects model for modeling highly skewed repeated measures data. We derive the likelihood and obtain the expression for predicting the subject-specific response at a given time point. Since the likelihood expression is explicit, the maximum likelihood estimates can easily be obtained and numerical approximations of the likelihood are not necessary.

In our application, the resulting predicted model is very similar to the linear mixed model fitted by Terrell *et al.* (2008). When we assess the predicted equation using the validation sample, similar results are obtained. In the linear mixed model, the marginal distribution of PBB values is considered to be log-normal. In the Weibull-gamma mixture model the marginal distribution takes a different form. Conceivably, therefore, one might expect markedly different results in other applications. The comparison between these two models needs further investigation, potentially including simulation studies to assess the potential for invalid results when applying the more standard linear mixed model when the Weibull-gamma model holds.

The methods that we describe here are parametric, so they are powerful when the assumptions are met. However, when assumptions are violated the results may not hold. The goodness of fit of the model is an important future research topic, though not part of the focus in the current manuscript.

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REFERENCES

Blanck, H.M., M. Marcus, V. Hertzberg, P.E. Tolbert, C. Rubin, A.K. Henderson and R.H. Zhang (2000a). Determinants of polybrominated biphenyl serum decay among women in the Michigan PBB cohort. *Environ Health Perspect*, 108(2): 147-152.

Box, G.E.P. and D.R. Cox (1964). An analysis of transformations. *Journal of the Royal Statistical Society B*, 26: 211–252.

Burse, V.W., L.L. Needham, J.A. Liddle, D.D. Bayse, and H.A. Price (1980). Interlaboratory comparison for results of analyses for polybrominated biphenyls in human serum. *Journal of Analytical Toxicology*, 4(1): 22-26.

Diggle, P.J., Liang, K.Y. and Zeger, S.L. Analysis of Longitudinal Data. *Oxford University Press*, 1994.

Fries, G.F. (1985). The PBB episode in Michigan: an overall appraisal. *Crit Rev Toxico*, 16(2): 105-156.

Gurka, M.J., L.J. Edwards, K.E. Muller and L.L. Kupper (2006). Extending the Box-Cox transformation to the linear mixed model. *Journal of the Royal Statistical Society*, 169: 273-288.

Humphrey, H. and N. Hayner (1976). Polybrominated Biphenyls: An agricultural incident and its consequences: An epidemiological investigation of human exposure. *Trace Substances in Environ Health*, 9: 57-63.

Jowaheer, V. and B.c. Sutradhar (2002). Analyzing longitudinal count data with overdispersion. *Biometrika*, 89: 389-399.

Landrigan, P.J., Jr. K.R. Wilcox, Jr. J. Silva, H.E. Humphrey, C. Kauffman and Jr. C.W. Heath (1979). Cohort study of Michigan residents exposed to polybrominated biphenyls: epidemiologic and immunologic findings. *Annals of the New York Academy of Sciences*, 320: 284-294.

Liang, K.Y. and S.L. Zeger (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, 73: 13-22.

Littell, R.C., G.A.Milliken, W.W. Stroup, and R.D. Wolfinger (1996). *SAS System for Mixed Models*. SAS Institute, Inc.: Cary, NC, USA.

Lyles, R.H., L.L. Kupper and S.M. Rappaport (1997). On prediction of lognormal-scale mean exposure levels in epidemiologic studies. *Journal of Agricultural, Biological, and Environmental Statistics*, 2: 417-439.

Needham, L.L., V.W. Burse and H.A. Price (1981). Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. *Journal of* Association *of Official Analytical Chemists*, 64(5): 1131-1137.

Terrell, M.L., A.K. Manatunga, C.M. Small, L.L. Cameron, J. Wirth, H. Michels Blanck, R.H. Lyles and M. Marcus (2008). A Decay model for assessing polybrominated biphenyl exposure among women in the Michigan long-term PBB study. *Journal of Exposure* Science *and Environmental Epidemiology*. 18: 410-420.

Thall, P.F. and S.C. Vail (1990). Some covariance models for longitudinal count data with over-dispersion. *Biometrics*, 46: 657-671.

Verbeke, G. and G. Molenberghs (2000). *G. Linear Mixed Models for Longitudinal Data, 1st Edition*. Springer-Verlag, New York.

Zeger, S. and K.Y. Liang (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, 42: 121-130.