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A longitudinal Model for repeated interval-observed data with informative dropouts

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Abstract

We consider repeated measures interval-observed data with informative dropouts. We model the repeated outcomes via an unobserved random intercept and it is assumed that the probability of dropout during the study period is linearly related to the random intercept in a complementary log-log scale. Assuming the random effect follows the power variance function (PVF) family suggested by Hougaard (2000), we derive the marginal likelihood in a closed form. We evaluate the performance of the maximum likelihood estimation via simulation studies and apply the proposed method to a real data set.

Keywords

Interval-observed data; Informative dropouts; Power variance function

1 Introduction

There is extensive literature in analyzing repeated measures longitudinal data when the outcomes are continuous (Diggle et al., 1994; Verbeke and Molenberghs, 2000; Ware, 1985) or dichotomous (Agresti, 2002; Fitzmaurice and Laird, 1993). However, relatively few methods are available for analyzing repeated measures interval-observed data. Most of the existing methods for interval-observed data are computationally complex because the closed form likelihoods are not available. Chen et al. (2009) proposed a model for repeated measures interval-observed data which allows flexible random effects via PVF family of distributions. Under the assumption that responses being in different intervals were induced from an unobserved latent Weibull distributed random variable, they formulated a model to analyze an environmental data set. Since the underlying latent process was not observed, the likelihood was written for the observed responses corresponding to indicator variables being in different intervals. Another common feature of such longitudinal studies is that subjects who are highly exposed at the baseline are more likely to participate in subsequent follow-

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up studies compared to subjects with low levels of exposure. This is the case in the environmental data, where the number of measurements per subject is expected to be positively associated with the initial measurement. To address this issue, we extend the Chen et al. (2009) model by modeling the number of observations as a geometric distribution conditional on the subject's random effect. Interestingly, the extended model maintains a closed form for the marginal likelihood and allows flexible random effects via PVF family.

2 Model

Suppose we have repeated measurements of subjects which are observed in intervals. Let r be a finite number of partitions of the positive real line by means of known cutpoints $0 = \alpha_0 < \alpha_1 < \dots < \alpha_{r-1} < \alpha_r = \infty$. Let Z_{ij} take values $1, \dots, k, k \in \{1, \dots, r\}$, corresponding to the observed interval for the j th measurement of the i th subject and let X_{ij} be the corresponding vector of covariates ($i = 1, 2, \dots, I; j = 1, 2, \dots, n_i$). We consider w_i as the random effect for the i th subject with a positive support and π_{ijk} as the complementary cumulative probability for the j th measurement of the i th subject in the k th interval conditional on random effect w_i . We model this probability as

$$\log(-\log \pi_{ijk}) = \log w_i + \theta_{0k} + \theta_1 X_{ij}, \quad (1)$$

where $\log w_i$ is the random intercept, θ_1 is the regression coefficient associated with the covariate, and the parameter θ_{0k} represents the intercept corresponding to the k th baseline interval.

It is interesting to note that the model (1) can be derived by assuming additional assumptions about a latent continuous variable which generates interval-observed data. Suppose that the interval-observed data arise from a Weibull model. Let Y_{ij} be the underlying unobserved continuous variable associated with the observed interval. The relationship between the observed Z_{ij} and Y_{ij} is $\alpha_{k-1} \leq Y_{ij} < \alpha_k \Leftrightarrow Z_{ij} = k$, where $k \in \{1, \dots, r\}$. That is, the unobservable Y_{ij} belongs to the k th interval if and only if $\alpha_{k-1} \leq Y_{ij} < \alpha_k$, where α_{k-1} and α_k denote the lower and upper cutpoints of the k th interval. Assume that conditional on w_i , $Y_{ij} | w_i \sim \text{Weibull}(w_i \eta_{ij}, \lambda)$, where $\lambda > 0$ is a shape parameter and $\eta_{ij} = \exp(-\lambda \beta_0 - \lambda \beta_1 X_{ij})$. It can be shown that

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

where e_{ij} has a log unit exponential distribution. This model provides an appealing interpretation of a log linear relationship between Y_{ij} and X_{ij} . Now, $\pi_{ijk} = \Pr(Y_{ij} \geq \alpha_k | w_i) = e^{-w_i \eta_{ij} \alpha_k^\lambda}$, $\eta_{ij} = \exp(-\lambda \beta_0 - \lambda \beta_1 X_{ij})$, $\pi_{ij0} = 1$, $\pi_{ijr} = 0$. This leads to

$$\log(-\log \pi_{ijk}) = \log w_i - \lambda \beta_0 - \lambda \beta_1 X_{ij} + \lambda \log \alpha_k,$$

where the α_k 's are known constants. When $\theta_{0k} = -\lambda \beta_0 + \lambda \log \alpha_k$ and $\theta_1 = -\lambda \beta_1$, we have the model (1). Following Chen et al. (2009), we can write the conditional likelihood for the i th subject from (1) as

$$L_i^*(\beta_0, \beta_1, \lambda | w_i) = \prod_{j=1}^{n_i} \prod_{k=1}^r \Pr(Z_{ij}=k | w_i)^{\delta_{ijk}} = \prod_{j=1}^{n_i} \prod_{k=1}^r \Pr(\pi_{i,j,k-1} - \pi_{ijk})^{\delta_{ijk}}, \quad (3)$$

where δ_{ijk} is an index variable which equals 1 when $Z_{ij} = k$, otherwise 0. Using the binomial expansion as Chen et al. (2009) and Ten Have (1996), the likelihood becomes

$$L_i^*(\beta_0, \beta_1, \lambda | w_i) = \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} e^{-w_i S_i},$$

where $S_i = \sum_{j=1}^{n_i} \sum_{k=1}^{r-1} D_{ijk}$ and $D_{ijk} = \eta_{ij} \cdot \alpha_k^\lambda (\delta_{ijk} - b_{ijk} + b_{ij, k+1})$ for $k \leq r-2$ and $D_{ijk} = \eta_{ij} \cdot \alpha_{r-1}^\lambda (\delta_{ijk, r-1} - b_{ijk, r-1} + \delta_{ijr})$ for $k = r-1$.

Now the unconditional likelihood can be written as

$$L_i(\beta_0, \beta_1, \lambda) = \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} E(e^{-w_i S_i}),$$

where $E(\cdot)$ represents the expectation over the positive random variable w_i . When w_i follows

the PVF distribution, $w_i \sim \text{PVF}(\gamma, \psi^{1-\gamma}, \psi)$ with mean 1 and variance $\frac{1-\gamma}{\psi}$, the Laplace

transform of w_i is $E(e^{-S_i w_i}) = \exp \left[-\frac{\psi^{1-\gamma}}{\gamma} \{(\psi + S_i)^\gamma - \psi^\gamma\} \right]$, $0 < \gamma \leq 1$ and $\psi > 0$ (Hougaard, 2000).

Therefore, with the PVF random effect, the likelihood can be expressed as

$$L_i(\beta_0, \beta_1, \lambda, \psi, \gamma) = \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} \exp \left[-\frac{\psi^{1-\gamma}}{\gamma} \{(\psi + S_i)^\gamma - \psi^\gamma\} \right]. \quad (4)$$

The PVF distribution family includes the gamma distribution as a special case when $\gamma \rightarrow 0$,

and the inverse Gaussian distribution when $\gamma = \frac{1}{2}$. Inferential procedures can be obtained via maximum likelihood. This model provides a reasonable parametric framework for analyzing repeated interval-observed data while allowing flexible random effects within the PVF family (Chen et al., 2009).

3 Extension to informative dropouts

Now, we extend the above model to handle the monotone informative dropouts. As described in the introduction, in environmental longitudinal studies subjects who are highly exposed at the baseline are more likely to participate in the study than the subjects who are less exposed. Similar to other authors (Mori et al., 1994), we assume that the likelihood of dropout is related to the true initial exposure and we model the number of observations per subject (n_i) as a truncated geometric distribution. We write the conditional distribution of n_i as $n_i | w_i \sim \text{truncated geometric}(p_i)$, where p_i is the probability of a subject dropping out from the study and the density is

$$f(n_i | w_i) = (1 - p_i)^{n_i-2} p_i, \quad n_i \geq 2. \quad (5)$$

We model the probability of dropout in terms of w_i as $\log(1 - p_i) = -w_i\rho$, where $\rho > 0$. When all subjects are homogeneous, then $w_i = 1$ for all i and the probability of dropping-out (p_i) is a constant with $\log(1 - p_i) = -\rho$. Also, from model (2), the subject specific intercept,

$\tau_i = -\frac{1}{\lambda} \log w_i + \beta_0$. Using this, we can write $\log\{-\log(1 - p_i)\} = -\lambda\tau_i + e$, where $e = \lambda\beta_0 + \log\rho$. Therefore, the probability of dropout on the complementary log-log link scale has a linear regression relationship with the subject-specific intercept. This representation provides a useful way of interpreting the relationship between the subject's dropout probability and his/her baseline value.

The corresponding marginal likelihood for the i th subject becomes

$$\begin{aligned} L_i(\beta_0, \beta_1, \lambda, \rho) &= \int L_i^*(\beta_0, \beta_1, \lambda | n_i, w_i) f(n_i | w_i) dF(w_i) \\ &= \int \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} e^{-w_i S_i} f(n_i | w_i) f(w_i) dw_i. \end{aligned}$$

Since n_i has a truncated geometric distribution conditional on w_i , we apply (5) to the above equation and obtain

$$L_i(\beta_0, \beta_1, \lambda, \rho) = \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} \times \left[E\left(e^{-w_i(S_i + \rho(n_i - 2))}\right) - E\left(e^{-w_i(S_i + \rho(n_i - 1))}\right) \right].$$

When $w_i \sim \text{PVG}(\gamma, \psi^{1-\gamma}, \psi)$, the likelihood can be expressed as

$$\begin{aligned} L_i(\beta_0, \beta_1, \lambda, \rho, \psi, \gamma) &= \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} \\ &\times \left[\exp\left(-\frac{\psi^{1-\gamma}}{\gamma} [\{\psi + S_i + \rho(n_i - 2)\}^\gamma - \psi^\gamma]\right) - \exp\left(-\frac{\psi^{1-\gamma}}{\gamma} [\{\psi + S_i + \rho(n_i - 1)\}^\gamma - \psi^\gamma]\right) \right]. \end{aligned} \quad (6)$$

As $\gamma \rightarrow 0$, $w_i \sim \text{Gamma}(\psi, \psi)$, the likelihood takes the form

$$L_i(\beta_0, \beta_1, \lambda, \rho, \psi) = \sum_{b_{i11}=0}^{\delta_{i11}} \sum_{b_{i12}=0}^{\delta_{i12}} \cdots \sum_{b_{in_i, r-1}=0}^{\delta_{in_i, r-1}} \left\{ \prod_{j=1}^{n_i} \prod_{k=1}^{r-1} (-1)^{\delta_{ijk} - b_{ijk}} \right\} \times \left[\left(\frac{\psi}{\psi + S_i + \rho(n_i - 2)} \right)^\psi - \left(\frac{\psi}{\psi + S_i + \rho(n_i - 1)} \right)^\psi \right].$$

Compared to (4), the marginal likelihood (6) adjusts for the dependence between the initial PBB exposure level and the number of observations. The explicit expression promotes convenient maximum likelihood estimation and hypothesis testing procedures.

4 Simulations

We conduct simulation studies to evaluate the performance of the proposed models. Five hundred simulations are performed for two sample sizes ($I = 500, 1000$) under model (6). In each simulation, the latent variable Y_{ij} is generated from a Weibull($w_i \eta_{ij}, \lambda$) distribution with subject-specific random effect $w_i \sim \text{Gamma}(\psi, \psi)$. Here $\eta_{ij} = e^{-\lambda\beta_0 - \lambda\beta_1 X_{ij}}$, $i = 1, \dots, I$, $j = 1, \dots, n_i$, $(\beta_0, \beta_1, \rho, \lambda, \psi) = (2.0, -0.5, 1.5, 2.5, 1.0)$. The number of measurements n_i is

generated according to the geometric distribution specified in model (5). We set the maximum value of n_i as 5. The covariate X_{ij} corresponding to the four time points that are set to be 0, 1, 2, 3. To derive observed-interval data, we group the data into 12 intervals.

Both n_i unadjusted (4) and n_i adjusted (6) models are fitted to each simulated data. Table 1 presents the maximum likelihood parameter estimate, the estimated standard error (SE), and the empirical standard deviation (SD). As expected, when n_i is adjusted, the parameter bias is small for all cases, decreasing as the sample size increases. The estimated standard error and the empirical standard deviation agrees well. When the adjustment is ignored, the slope parameter is mostly affected, showing a moderate bias.

5 Application

We illustrate the model by using data from the Michigan polybrominated biphenyl study (Chen et al., 2009). This study consists of women who were exposed to a chemical called polybrominated biphenyl (PBB) through an accidental contamination of cattle feed in Michigan in 1973 (Blanck et al., 2000). To determine the pattern of PBB decay and its association with characteristics such as body mass index (BMI), we include a total of 3706 observations contributed by 1369 women over the year 1976 to 1993. Since data are sparsely distributed and PBB values are concentrated around integers with relatively few observations occurring between integers (Chen et al., 2009) we consider data as observed into the following intervals: < 1.0 , $1.0 - 1.5$, $1.5 - 2.5$, $\dots$, ≥ 10.5 .

For each woman we take the time since her first measurement t_{ij} (measured by year) as a primary covariate. We also include the log transformed initial BMI for the i th woman, denoted by $\log \text{BMI}_i$. The model for PBB decay over time is as follows:

$$\log Y_{ij} = -\frac{1}{\lambda} \log w_i + \beta_0 + \beta_1 t_{ij} + \beta_2 \log \text{BMI}_i + \beta_3 t_{ij} \times \log \text{BMI}_i + \frac{1}{\lambda} e_{ij}.$$

The results are presented in Table 2. The model with PVF-distributed random effects is not significantly different from that with gamma-distributed random effects ($\gamma = 0$) based on the Wald test ($Z=1.17$, $p=0.12$). The classical likelihood ratio test draws the same conclusion

($\text{LR}=0.06$, $p=0.27$). With a mixed chi-square distribution $\left(\frac{1}{2}\chi_0^2 + \frac{1}{2}\chi_1^2\right)$ the resulting likelihood ratio is 0.06 with $p = 0.38$, indicating that we cannot reject the null hypothesis of ($\gamma = 0$) and we choose the parsimonious gamma random effects model in this case.

As the profile likelihood CIs may perform better than the Wald CIs particularly when the parameter is near or on the boundary of the parameter space (Meeker and Escobar, 1995; Pawitan, 2000), we investigate both Wald-type and profile likelihood asymptotic 95% CIs for ψ and ρ in the gamma model. The 95% Wald-type CI for ψ is (0.889, 1.093), and the corresponding profile likelihood based CI is (0.894, 1.098). The two CIs for ρ are (1.436, 1.738) and (1.445, 1.750), respectively. The differences between the two approaches appear to be insignificant. The results are similar for other parameters.

To assess the adequacy of the models, we display plots of the observed proportions and the estimated probabilities of $Z_{ij} = k$ conditional on n_i , $\Pr(Z_{ij} = k | n_i)$, where n_i changes from 2 to 5 and k ranges from 1 to 12 (see Figure 1). Fitted values from both models, adjusted for n_i and unadjusted are plotted. The plots indicate that the model with n_i adjusted seems to agree with the PBB data somewhat better than the unadjusted one.

To evaluate the fit of the extended model we also compare the observed distribution of n_i to the estimated marginal distribution. The marginal probability density is given by

$$\begin{aligned} f(n_i) &= \int f(n_i|w_i) f(w_i) dw_i \\ &= \int \left[e^{-w_i(n_i-2)\rho} - e^{-w_i(n_i-1)\rho} \right] f(w_i) dw_i. \end{aligned}$$

When w_i has a PVF distribution, we have

$$\begin{aligned} f(n_i) &= \exp\left(-\frac{\psi^{1-\gamma}}{\gamma} [\{\psi + (n_i - 2)\rho\}^\gamma - \psi^\gamma]\right) \\ &\quad - \exp\left(-\frac{\psi^{1-\gamma}}{\gamma} [\{\psi + (n_i - 1)\rho\}^\gamma - \psi^\gamma]\right). \end{aligned}$$

Similarly, for the gamma distribution,

$$f(n_i) = \left(\frac{\psi}{\psi + (n_i - 2)\rho}\right)^\psi - \left(\frac{\psi}{\psi + (n_i - 1)\rho}\right)^\psi.$$

Based on the gamma distribution, we find a reasonable fit of the model-based probability and the observed proportion for most n_i except when n_i is very small (plot not shown).

6 Discussion

We propose a model for interval-observed repeated longitudinal data. As an extension of the model proposed by Chen et al. (2009), this approach adjusts for the dependence between the initial exposure levels and the dropout. Goodness of fit and model diagnostics are important issues in selecting these models. Plots based on marginal and conditional distributions suggested in this manuscript could be used as a guidance in selecting a proper model. Model selection criterion for non-nested models such as Akaike's information criterion (AIC) can also be helpful in determination of a suitable model. The likelihood of the proposed model is in a closed form facilitating likelihood-based inference. The PVF family random effect provides a class of distributions including gamma and inverse Gaussian. Several parametric assumptions involving interval-observed data, random effect and number of observations are made in the modeling process. Sensitivity of the results to these assumptions needs further investigation.

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Figure 1.
Plots of observed and the average of model-based conditional probabilities $\Pr(Z_{ij} = k|n_i)$

Table 1Simulation results with 500 replicates and $(\beta_0, \beta_1, \rho, \lambda, \psi) = (2.0, -0.5, 1.5, 2.5, 1.0)$

# Subj.	Param.	True	n_i adjusted			n_i unadjusted		
			Est.	Est. SE	Emp. SD	Est.	Est. SE	Emp. SD
500	β_0	2.0	1.998	0.079	0.078	1.923	0.077	0.077
	β_1	-0.5	-0.499	0.037	0.036	-0.339	0.029	0.027
	λ	2.5	2.514	0.146	0.145	2.498	0.151	0.151
	ψ	1.0	1.015	0.126	0.131	1.107	0.303	0.312
	ρ	1.5	1.510	0.168	0.175			
	β_0	2.0	1.999	0.056	0.055	1.923	0.055	0.055
1000	β_1	-0.5	-0.500	0.026	0.025	-0.339	0.020	0.019
	λ	2.5	2.504	0.103	0.103	2.488	0.107	0.106
	ψ	1.0	1.005	0.087	0.090	1.070	0.199	0.215
	ρ	1.5	1.504	0.118	0.121			

Table 2

Estimation results from the MIPBB adjusting for the informative number of repeated measurements *

Parameter	$w_i \sim \text{PVF}(\gamma, \psi^{1-\gamma}, \psi)$		$w_i \sim \text{Gamma}(\psi, \psi)$	
	Estimate (SE)	Z	Estimate (SE)	Z
β_0	1.998(0.189)	10.57*	1.990(0.192)	10.36*
β_1	-0.164(0.025)	-6.56*	-0.163(0.025)	-6.52*
β_2	-0.622(0.060)	-10.37*	-0.620(0.061)	-10.16*
β_3	0.049(0.008)	6.13*	0.049(0.008)	6.13*
ρ	1.593(0.079)	20.16*	1.588(0.078)	20.36*
λ	2.612(0.052)	50.23*	2.610(0.052)	50.19*
ψ	0.970(0.051)	19.02*	0.983(0.051)	19.27*
γ	0.007(0.006)	1.17 [†]		
$-\log L$	8429.13		8429.19	

*Model: $\log Y_{ij} = -\frac{1}{\lambda} \log w_i + \beta_0 + \beta_1 t_{ij} + \beta_2 \log \text{BMI}_i + \beta_3 t_{ij} \times \log \text{BMI}_i + \frac{1}{\lambda} e_{ij}$, where $i = 1, \dots, I$; $j = 1, \dots, n_i$. Also, $f(n_i | w_i) = (1 - P_i)^{n_i - 2} P_i$, $n_i \geq 2$ and $\log(1 - p_i) = -w_i \rho$.

* P-value < 0.05 for the hypothesis test that the null value equals zero based on the Wald test.

[†] P-value = 0.12.