# Supplemental material for: Log link informative visit processes in generalized linear mixed models

Charles E. McCulloch, John M. Neuhaus Division of Biostatistics, and Rebecca L. Olin Division of Hematology/Oncology, University of California, San Francisco, CA 94107 email: chuck@biostat.ucsf.edu November 25, 2015

1

#### Authors' Footnote:

Charles E. McCulloch and John M. Neuhaus are Professors of Biostatistics in the Department of Epidemiology and Biostatistics and Rebecca L. Olin is a Professor of Hematology/Oncology in the Department of Medicine at the University of California, San Francisco

# 1 Degree of approximation due to ignoring truncation

It is possible to calculate the exact mean of the random effects conditional on  $R_{it} = 1$  while explicitly accounting for the truncation. We start by transforming  $\mathbf{b}_i$  into independent components, the first of which is a standardized version of  $\gamma'_{it}$ **b**<sub>i</sub>, where both  $\gamma_{it}$  and **b**<sub>i</sub> are  $q \times 1$  column vectors. First define

$$
\tilde{\boldsymbol{\gamma}}_{1it} = \boldsymbol{\gamma}_{it}/\sqrt{\boldsymbol{\gamma}_{it}'\boldsymbol{\Sigma}_b\boldsymbol{\gamma}_{it}},
$$

so that  $\text{var}(\tilde{\boldsymbol{\gamma}}'_{1it}\mathbf{b}_i \mid R_{it} = 1) = 1$  and the truncation to keep the probabilities less than or equal to 1 is given by

$$
\tilde{\gamma}_{1it}' \mathbf{b}_i < -\mu_{it}/\sqrt{\gamma_{it}' \Sigma_b \gamma_{it}} \equiv -\tilde{\mu}_{it}.
$$
 (1)

Next create  $q \times 1$  column vectors  $\tilde{\boldsymbol{\gamma}}_{kit}$ ,  $k = 2, \ldots, q$ , such that  $\tilde{\boldsymbol{\gamma}}'_{kit} \Sigma_b \tilde{\boldsymbol{\gamma}}_{lit} =$  $I_{\{k=l\}}$  and denote by  $\tilde{\Gamma}_{it}$  the  $q \times q$  matrix with rows equal to  $\tilde{\gamma}'_{kit}$ . Via this construction, the conditional distribution of  $\tilde{\Gamma}_{it}$ **b** is given by

$$
\tilde{\mathbf{\Gamma}}_{it}\mathbf{b} \mid R_{it} = 1 \sim \mathcal{N}(\tilde{\mathbf{\Gamma}}_{it}\Sigma_b \boldsymbol{\gamma}_{it}, \mathbf{I}). \tag{2}
$$

Only the first component is subject to truncation because the truncation is defined by (1) and the remaining components are independent of the first.

Using the usual formula for the mean of a truncated normal we have

$$
\begin{aligned} \mathcal{E}[\tilde{\gamma}'_{1it}\mathbf{b}_i \mid R_{it} = 1, \tilde{\gamma}'_{1it}\mathbf{b}_i < -\tilde{\mu}_{it}] &= \tilde{\gamma}'_{1it}\Sigma_b \gamma_{it} \\ &- \phi(-\tilde{\mu}_{it} - \tilde{\gamma}'_{1it}\Sigma_b \gamma_{it})/\Phi(-\tilde{\mu}_{it} - \tilde{\gamma}'_{1it}\Sigma_b \gamma_{it}). \end{aligned} \tag{3}
$$

Define  $\mu_{\tilde{\Gamma} it}$  to have first entry equal to (3) and remaining entries equal to the corresponding entries of  $\tilde{\Gamma}_{it} \Sigma_b \gamma_{it}$ . Then

$$
E[\tilde{\mathbf{\Gamma}_{it}} \mathbf{b}_i \mid R_{it} = 1, \gamma'_{it} \mathbf{b}_i < -\mu_{it}] = \boldsymbol{\mu}_{\tilde{\Gamma}_{it}} \tag{4}
$$
 and

$$
E[\mathbf{b}_i | R_{it} = 1, \boldsymbol{\gamma}'_{it} \mathbf{b}_i < -\mu_{it}] = \tilde{\mathbf{\Gamma}}_{it}^{-1} \boldsymbol{\mu}_{\tilde{\Gamma}it}.
$$
 (5)

In cases where the second term in (3) is negligible we can ignore the effects of truncation. This will be true when the value of  $\tilde{\mu}_{it}$  is negative and the values of  $\gamma_{it}$  are small in relation to the absolute value of  $\tilde{\mu}_{it}$ . This occurs under the scenarios we consider where the probability of any single visit is small (so that  $\mu_{it}$  is negative, but large in absolute value) and the informativeness is not overly strong (so that the values of  $\gamma_{it}$  are not large in absolute value).

### 2 Detailed simulation results

Details of the simulation methodology are given in the main paper. The tables in this section give the estimated mean values of the parameters and standard errors from the simulations and are more extensive than the graphical results given in the main paper. They are organized first by the outcome simulation process: linear mixed model or logistic mixed model. Within the linear mixed model section they are next organized by the informative visit process: conditional mean or random effects dependence. For the logit link we report on only the conditional mean dependence. Individual tables show the influence of varying the informativeness of the process as well as the effect of the log versus the logit link for the informative visit process for linear mixed models or the estimation method (maximum likelihood versus generalized estimating equations) for the logistic outcome models.

The data were simulated using the following outcome process. Let  $Y_{it}$ represent the measurement at time t (where t runs from 1 to  $n_i$ ) on subject i (where i runs from 1 to m). We assume that our outcome process follows a generalized linear mixed model with normally distributed random effects,  $\mathbf{b}_i$ :

$$
Y_{it}|\mathbf{b}_i \sim \text{ independent } f_Y \qquad i = 1, ..., m; t = 1, ..., n_i
$$

$$
g(\mathbf{E}[Y_{it}|\mathbf{b}_i]) = \mathbf{x}'_{it}\boldsymbol{\beta} + \mathbf{z}'_{it}\mathbf{b}_i \qquad (6)
$$

$$
\mathbf{b}_i \sim \text{ i.i.d. } \mathcal{N}(\mathbf{0}, \Sigma_b), \tag{7}
$$

In this model,  $\mathbf{x}_{it}$  represents the covariates associated with subject i at time t,  $\beta$  is the vector of covariate effects,  $z_{it}$  is the model matrix for the random effects, and  $g(\cdot)$  is the link function (either linear or logit).

The simulations fit models only to the observed data, with  $R_{it} = 1$ , where  $R_{it}$  is the binary indicator with  $R_{it} = 1$  indicating that  $Y_{it}$  is observed and is 0 otherwise. We assume that, conditional on the random effects,  $Y_{it}$  and  $R_{it}$  are independent (and independent from one another) and that the probability that  $R_{it} = 1$  is dependent on the random effects via a log link or a logit link:

$$
P(Y_{it} \text{ is observed} | \mathbf{b}_i) \equiv P(R_{it} = 1 | \mathbf{b}_i)
$$
  
= 
$$
\exp\{\mu_{it} + \gamma'_{it} \mathbf{b}_i\} \text{ or}
$$
  
= 
$$
1/(1 + \exp\{-[\mu_{it} + \gamma'_{it} \mathbf{b}_i\}]).
$$
 (8)

In this model,  $\gamma_{it}$  governs the strength and directionality of the association between the random effects and whether or not data are observed.

#### 2.1 Linear mixed model for the outcome

#### 2.1.1 Conditional mean informative visit process

Table 1: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \delta E[Y|b],$ Fitting method: maximum likelihood Random effects:  $corr(b_{0i}, b_{1i})=0$ 



Table 2: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \delta E[Y|b],$ Fitting method: GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0$ 



Table 3: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \delta E[Y|b],$ Fitting method: maximum likelihood Random effects:  $corr(b_{0i}, b_{1i})=0.5$ 



Table 4: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \delta E[Y|b],$ Fitting method: GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0.5$ 



#### 2.1.2 Random effects informative visit process

Table 5:

Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \gamma_0 b_0 + \gamma_1 b_1$ , Fitting method: maximum likelihood Random effects:  $corr(b_{0i}, b_{1i})=0$ 



Table 6: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \gamma_0 b_0 + \gamma_1 b_1$ , Fitting method: GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0$ 

Info Visit Process		Simulated mean parameter estimates (SEs as subscripts)			
$\gamma_0$	$\gamma_1$	$(true=0)$ $\beta_0$	$\beta_1$ $(true=1)$	$(true=2)$ $\beta_2$	$\beta_3$ (true=3)
$log$ link					
$\theta$	$\overline{0}$	$0.013_{0.005}$	$0.981_{0.009}$	$1.983_{0.007}$	$3.014_{0.012}$
0.5	$\overline{0}$	$0.499_{0.005}$	$0.998_{0.009}$	$2.006_{0.007}$	$2.998_{0.013}$
1	$\overline{0}$	$1.004_{0.005}$	$0.997_{0.009}$	$1.986_{0.007}$	$3.016_{0.012}$
$\overline{0}$	0.5	$0.003_{\scriptstyle 0.005}$	$1.496_{0.009}$	$2.001_{0.007}$	$2.997_{\scriptstyle 0.012}$
0.5	0.5	$0.499_{0.005}$	$1.498_{0.009}$	$1.998_{0.007}$	$3.008_{0.013}$
1	0.5	$0.991_{\scriptstyle 0.005}$	$1.504_{0.009}$	$1.996_{0.008}$	$3.005_{0.012}$
$\overline{0}$	1	$0.008_{\scriptstyle 0.005}$	$1.986_{ 0.009}$	$1.996_{0.007}$	$3.017_{0.012}$
0.5	$\mathbf{1}$	$0.498_{0.005}$	$2.008_{0.010}$	$2.002_{0.008}$	$2.994_{0.013}$
1	1	$0.984_{\scriptstyle 0.006}$	$1.973_{\scriptstyle 0.008}$	$1.991_{ 0.008}$	$3.022_{0.012}$
logit link					
$\overline{0}$	$\overline{0}$	$0.012_{0.005}$	$0.982_{0.009}$	$1.983_{0.007}$	$3.015_{0.012}$
0.5	$\overline{0}$	$0.488_{0.005}$	$0.996_{0.009}$	$2.006_{0.007}$	$2.997_{0.013}$
$\mathbf 1$	$\overline{0}$	$0.962_{0.005}$	$0.999_{0.009}$	$1.985_{0.007}$	$3.017_{0.012}$
$\overline{0}$	0.5	$0.003_{\scriptstyle 0.005}$	$1.485_{0.009}$	$2.001_{0.007}$	$2.996_{0.013}$
0.5	0.5	$0.487_{0.005}$	$1.480_{0.009}$	$1.997_{0.007}$	$3.009_{0.013}$
1	0.5	$0.944_{\scriptstyle 0.005}$	$1.477_{0.009}$	$1.994_{0.008}$	$3.010_{0.012}$
$\overline{0}$	$\mathbf{1}$	$0.008_{\scriptstyle 0.005}$	$1.945_{0.009}$	$1.997_{0.007}$	$3.016_{\scriptstyle 0.013}$
0.5	$\mathbf 1$	$0.474_{0.005}$	$1.957_{0.010}$	$2.000_{0.008}$	$2.998_{0.013}$
1	1	$0.920_{\scriptstyle 0.005}$	$1.914_{0.009}$	$1.991_{ 0.008}$	$3.019_{0.013}$

Table 7: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \gamma_0 b_0 + \gamma_1 b_1$ , Fitting method: maximum likelihood Random effects:  $corr(b_{0i}, b_{1i})=0.5$ 

Info Visit Process		Simulated mean parameter estimates (SEs as subscripts)				
$\gamma_0$	$\gamma_1$	$\beta_0$ (true=0)	$\beta_1$ $(true=1)$	$\beta_2$ (true=2)	$\beta_3$ (true=3)	
$log$ link						
$\overline{0}$	$\overline{0}$	$0.004_{\scriptstyle 0.005}$	$0.997_{0.009}$	$1.999_{0.007}$	$3.000_{0.013}$	
0.5	$\overline{0}$	$0.408_{\scriptstyle 0.005}$	$1.202_{0.009}$	$2.000_{0.007}$	$3.007_{0.012}$	
1	$\boldsymbol{0}$	$0.772_{0.005}$	$1.348_{0.008}$	$2.002_{0.006}$	$2.981_{0.011}$	
$\overline{0}$	0.5	$0.158_{\scriptstyle 0.005}$	$1.490_{0.009}$	$2.004_{0.007}$	$3.011_{0.012}$	
0.5	0.5	$0.539_{\scriptstyle 0.005}$	$1.661_{0.008}$	$1.995_{0.006}$	$3.009_{0.012}$	
1	0.5	$0.863_{0.005}$	$1.779_{0.008}$	$2.004_{0.006}$	$3.000_{0.011}$	
$\overline{0}$	1	$0.281_{0.005}$	$1.963_{0.009}$	$1.997_{0.007}$	$2.997_{0.012}$	
0.5	1	$0.622_{0.005}$	$2.087_{0.009}$	$1.993_{0.007}$	$3.001_{0.011}$	
1	1	$0.935_{0.005}$	$2.160_{0.008}$	$2.001_{0.007}$	$3.004_{0.012}$	
logit link						
$\overline{0}$	$\overline{0}$	$0.002_{\scriptstyle 0.005}$	$0.999_{0.009}$	$2.002_{0.007}$	$2.995_{0.013}$	
0.5	$\overline{0}$	$0.403_{0.005}$	$1.197_{0.009}$	$1.997_{0.007}$	$3.012_{0.012}$	
1	$\overline{0}$	$0.761_{0.005}$	$1.347_{0.008}$	$2.002_{0.007}$	$2.981_{0.011}$	
$\overline{0}$	0.5	$0.156_{0.005}$	$1.482_{0.009}$	$2.002_{0.007}$	$3.012_{0.012}$	
0.5	0.5	$0.533_{0.005}$	$1.648_{0.008}$	$1.994_{0.006}$	$3.012_{0.012}$	
1	0.5	$0.853_{\scriptstyle 0.005}$	$1.774_{0.009}$	$2006_{0.006}$	$2.995_{0.012}$	
$\overline{0}$	1	$0.283_{0.005}$	$1.941_{0.009}$	$1.999_{0.007}$	$2.994_{0.012}$	
$0.5\,$	$\mathbf 1$	$0.622_{0.005}$	$2.062_{0.009}$	$1.991_{0.007}$	$3.004_{0.012}$	
1	1	$0.934_{\scriptstyle 0.005}$	$2.137_{0.009}$	$2.002_{0.007}$	$3.005_{0.012}$	

Table 8: Outcome model: linear mixed model Informative visit model:  $log(P(R_{it} = 1))$  or  $logit(P(R_{it} = 1)) = -5 + \gamma_0 b_0 + \gamma_1 b_1$ , Fitting method: GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0.5$ 

Info Visit Process		Simulated mean parameter estimates (SEs as subscripts)				
$\gamma_0$	$\gamma_1$	$(true=0)$ $\beta_0$	$\beta_1$ $(true=1)$	$\beta_2$ (true=2)	$\beta_3$ $(true=3)$	
$log$ link						
$\overline{0}$	$\overline{0}$	$0.006_{\scriptstyle 0.005}$	$0.993_{0.009}$	$1.999_{0.007}$	$2.998_{0.014}$	
0.5	$\overline{0}$	$0.497_{0.006}$	$1.252_{0.010}$	$1.995_{0.007}$	$3.018_{0.013}$	
1	$\overline{0}$	$0.996_{0.005}$	$1.508_{0.009}$	$2.002_{0.008}$	$2.971_{0.013}$	
$\overline{0}$	0.5	$0.248_{0.005}$	$1.490_{0.010}$	$2.005_{0.007}$	$3.011_{0.014}$	
0.5	0.5	$0.756_{\scriptstyle 0.005}$	$1.745_{0.009}$	$1.995_{0.007}$	$3.001_{0.014}$	
$\mathbf{1}$	0.5	$1.245_{0.006}$	$1.978_{0.009}$	$1.997_{0.008}$	$3.000_{0.013}$	
$\overline{0}$	1	$0.506_{0.006}$	$1.994_{0.010}$	$1.997_{0.008}$	$2.997_{0.014}$	
0.5	1	$0.995_{0.006}$	$2.231_{0.010}$	$1.987_{0.008}$	$3.008_{0.014}$	
1	1	$1.426_{0.006}$	$2.43^{\circ}_{0.010}$	$2.000_{0.009}$	$3.004_{0.014}$	
logit link						
$\theta$	$\overline{0}$	$0.005_{\scriptstyle 0.005}$	$0.995_{0.009}$	$2.000_{0.007}$	$2.995_{0.014}$	
0.5	$\overline{0}$	$0.487_{\scriptstyle 0.006}$	$1.244_{0.010}$	$1.994_{0.008}$	$3.019_{0.014}$	
1	$\overline{0}$	$0.957_{0.005}$	$1.484_{0.010}$	$1.999_{0.007}$	$2.976_{0.013}$	
$\overline{0}$	0.5	$0.242_{0.005}$	$1.478_{0.010}$	$2.005_{0.007}$	$3.011_{0.014}$	
0.5	0.5	$0.729_{0.005}$	$1.719_{0.009}$	$1.996_{0.007}$	$3.001_{0.014}$	
$\mathbf{1}$	0.5	$1.168_{0.005}$	$1.922_{0.010}$	$2.000_{0.008}$	$2.997_{0.014}$	
$\overline{0}$	$\mathbf{1}$	$0.487_{\scriptstyle 0.006}$	$1.954_{0.010}$	$1.999_{0.008}$	$2.995_{\scriptstyle 0.014}$	
0.5	$\mathbf 1$	$0.935_{\scriptstyle 0.006}$	$2.159_{0.010}$	$1.988_{0.008}$	$3.009_{0.014}$	
1	1	$1.327_{\scriptstyle 0.006}$	$2.319_{0.011}$	$1.998_{0.008}$	$3.010_{\scriptstyle 0.015}$	

## 2.2 Logistic mixed model for the outcome

#### 2.2.1 Conditional mean informative visit process

Table 9:

Outcome model: logistic mixed model Informative visit model:  $logit(P(R_{it} = 1)) = -1 + \delta E[Y|b],$ Fitting method:

maximum likelihood or GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0$ 



#### Table 10: Outcome model: logistic mixed model Informative visit model:  $logit(P(R_{it} = 1)) = -1 + \delta E[Y|b],$ Fitting method: maximum likelihood or GEE (independence working correlation) Random effects:  $corr(b_{0i}, b_{1i})=0.5$



### 3 Additional dependence on the covariates

The log link informative visit process allows arbitrary dependence on the covariates since they can be incorporated in the  $\mu_{it}$  portion of equation (3). The theory in Section 3.2 shows that the marginal distribution is unaffected by  $\mu_{it}$  and hence dependence on covariates does not influence the marginal distribution. To check whether this result carries over to the logistic link visit process, (30), we redid the simulation of Figure 1, but modified the informative visit process to allow additional dependence on the covariates. We simulated the realistic situation where the visit probability differs by the group variable in (19),  $x_2$ . Specifically, we considered a modification of (21):

$$
logit P(Rit = 1 | bi) = \mu + \delta E[Yit|bi] + \lambda x_2.
$$
 (9)

Figure 1 shows the results for the linear mixed model under the conditional mean informative visit model with additional covariates, (9), using maximum likelihood to fit the model. Each panel includes four curves, corresponding to values of  $\lambda$  ranging from 0 to 0.75 in steps of 0.25. All of the curves lie nearly on top of one another demonstrating there is, at most, minor effect on the means values and that is restricted to those cases with strongly informative visit processes (e.g.,  $\delta$  and  $\lambda$  greater than 0.25).

Figure 2 shows similar results when the linear mixed model is fit using generalized estimating equations. Again, all of the curves lie nearly on top of one another, demonstrating the minor effect of dependence of the visit

Figure 1: Simulated mean values of the maximum likelihood regression coefficient estimators. Simulated under a conditional mean informative visit process with a logit link, i.e.,  $\text{logit}(P(R_{it} = 1)) = -5 + \delta E[Y \mid b] + \lambda x_2$ , and linear mixed outcome model with random intercepts and slopes. Curves within each panel show the results as  $\lambda$  ranges from 0 to 0.75.



Figure 2: Simulated mean values of the generalized estimating equations regression coefficient estimators. Simulated under a conditional mean informative visit process with a logit link, i.e.,  $logit(P(R_{it} = 1)) = -5 + \delta E[Y|$  $b$  +  $\lambda x_2$ , and linear mixed outcome model with random intercepts and slopes. Curves within each panel show the results as  $\lambda$  ranges from 0 to 0.75.



process on the covariate,  $x_2$ .

# 4 Theory for dependence on random intercept or random slope only

In this section we consider an informative visit process where the probability of observing Y depends only on the random intercept,  $b_{0i}$ :

$$
P(Y_{it} \text{ is observed} \mid b_i) \equiv P(R_{it} = 1 \mid b_i) = \exp\{\mu + \gamma_0 b_{0i}\}, \qquad (10)
$$

so that  $\gamma_{it}^T = (\gamma_0 \, 0)$ . For the above model and using the results of Section 3 of the manuscript, the expected value of the linear predictor conditional on being observed is equal to

$$
x_{it}^T \beta + z_{it}^T \Sigma_b \gamma_{it} = \beta_0 + \beta_1 x_{1it} + \beta_2 x_{2i} + \beta_3 x_{3it} + \sigma_0^2 \gamma_0 + \sigma_{01} \gamma_0 x_{1it}
$$
  
=  $(\beta_0 + \sigma_0^2 \gamma_0) + (\beta_1 + \sigma_{01} \gamma_0) x_{1it} + \beta_2 x_{2i} + \beta_3 x_{3it}.$ 

This result indicates that fitting the usual model to observed data will result in a biased estimate of the intercept, with bias equal to  $\sigma_0^2 \gamma_0$  and a biased estimate of  $\beta_1$  with bias equal to  $\sigma_{01}\gamma_0$ . So, even though the informative visit process depends only on the random intercept, estimators of  $\beta_1$  will be biased if the random intercept and slope are correlated.

A similar result holds for the random slope when  $P(R_{it} = 1 | b_i) =$ 

 $\exp{\{\mu + \gamma_1 b_{1i}\}}$ . Estimators of  $\beta_1$  will be biased by  $\sigma_1^2 \gamma_1$  and the intercept will be biased by  $\sigma_{01}\gamma_1$  if the random intercept and slope are correlated.

In either case, we can obtain consistent estimates of the coefficients unconnected to the random effects,  $\beta_2$  and  $\beta_3$ , using estimation methods that ignore the informative visit process. This can be achieved, for example, by using an analysis that only requires correct specification of the marginal mean.