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Bayesian Inference for Skew-Normal Mixture Models With Left-Censoring

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Abstract

Assays to measure concentration of antibody after vaccination are often subject to left-censoring due to a lower detection limit (LDL), leading to a high proportion of observations below the detection limit. Not accounting for such left-censoring appropriately can lead to biased parameter estimates. To properly adjust for left-censoring and a high proportion of observations at LDL, this paper proposes a mixture model combining a point mass below LDL and a Tobit model with skew-elliptical error distribution. We show that skew-elliptical distributions, where the skew-normal and skew-t are special cases, have great flexibility for simultaneously handling left-censoring, skewness and heaviness in the tails of a distribution of a response variable with left-censored data. A Bayesian procedure is used to estimate model parameters. Two real datasets from a study of measles vaccine and an HIV/AIDS study are used to illustrate the proposed models.

Keywords

Bayesian inference; Censoring; Mixed-effects models; Skew-normal distribution; Tobit model

1. Introduction

Left-censored data are most commonly collected in bioassays (Hughes, 1999), occupational and environmental exposures (Singh and Nocerino, 2002; Jin et al., 2011), and dietary exposure assessment of chemical substances (EFSA, 2010). In such data, left-censoring occurs because of a lower detection limit (LDL), below which measurements cannot be accurately determined. For example, before the introduction of a large-scale vaccination program, a new vaccine is routinely tested for its immunogenicity, safety and efficacy (Feiterna-Sperling et al., 2005). Studies addressing these issues usually measure vaccine-induced antibody concentration as an outcome variable, which may often be subjected to a LDL due to the inability of a diagnostic assay to detect levels below a certain value (Moulton and Halsey, 1995; Vainio et al., 2008). Because of left-censoring, there may also be cases where there are more observations at or below LDL than would be expected according to a standard parametric distribution. The commonly used methods in the literature for analyzing such left-censored data are substitution method (Hornung and Reed, 1990), nonparametric method (She, 1997; Hu et al., 2008), and maximum likelihood estimation (MLE) method (Lynn, 2001). Among these methods, the MLE method is usually considered as ‘best’. However, it does not perform well in the situations where the data set is small, and/or the percentage of censored values is high (Helsel, 2005a). In this article, we

provide a skew-elliptical mixture model for properly adjusting for left censoring with high fraction of observations at LDL and at the same time relaxing the stringent assumption of normality for taking into account the skewness of the response variable.

Our approach is to treat all observations at or below LDL as missing values and those above it as observed values by extending the Tobit model (Tobin, 1958; Schnedler, 2005), also called a censored normal regression model, for making proper inferences about left-censored data. The standard Tobit model uses the MLE method (Lynn, 2001; Schnedler, 2005) to estimate the parameters of interest. That is, instead of treating the censored values as missing values and then predict them, the MLE method uses only the observed percentage of values below LDL and the observed values above LDL. Helsel (2005b) has shown that MLE does not perform well for small samples and also sensitive to outliers. To address these issues in the context of left-censoring and skewness, we propose a new approach which has three components: (i) a mixture Tobit model which accounts for a high proportion of left-censored observations, (ii) skew-normal and skew-t distributions for skewed response variable, and (iii) a flexible Bayesian hierarchical representation of the skew-t mixture Tobit model. These are further discussed below.

First, the Tobit specification is usually appropriate for a situation in which the sample proportion of observations below LDL is roughly equivalent to the left tail area of the assumed parametric distribution (e.g., log-normal). However, such a specification is not appropriate when there is a high proportion of left-censored observations. There are several plausible mechanisms that could result in such a high proportion. For example, in an analysis of pre-vaccination sera, the sample may include individuals who do not have a specified antibody either for lack of exposure to the associated antigen or because of genetic predisposition. That is, there may be a subpopulation of individuals who at some time may have acquired antibody, but might have lost all of it prior to serum collection. In the analysis of post-vaccination sera, there may be individuals who do not respond at all to the vaccine or respond so poorly that their antibody concentration falls below LDL. This is the case when passively acquired maternal antibody may interfere with response to measles vaccine in infants (Halsey et al., 1985; Moulton and Halsey, 1995). The data set we analyze in this paper, which is depicted in Figure 1, has a relatively higher proportion of values below the LDL than would be expected under log-normality. Thus, we hypothesize that there are at least two sub-populations of subjects: low responders and high responders of vaccine.

In general, simply substituting left-censored values with a constant such as LDL, $LDL/2$ and $LDL/\sqrt{2}$ leads to biased estimation of parameters of interest (EFSA, 2010). In addition, such a practice has two major disadvantages: (i) it assumes that all values below LDL belong to the lower tail of a parametric distribution, ignoring the possibility that some of these values may come from a different distribution with a point mass, and (ii) it fails to use appropriate statistical methods which take left-censoring, potential outliers or skewness into account. To partially overcome these drawbacks of substitution methods, a Bernoulli/lognormal mixture model (Lynn, 2001; Chu et al., 2010) or Bernoulli/gamma mixture model (Moulton and Halsey, 1996) based on MLE method has been suggested in the literature. A Bernoulli/lognormal mixture model, which has a degenerate component (Bernoulli part) and a non-degenerate component (lognormal), is a special case of a finite mixture models (Jasra

et al., 2006; Lin et al., 2007; Fruhwirth-Schnatter and Pyne, 2010), where the component distributions may all be non-degenerate. To our knowledge, there is very limited work that has been done to extend the Bernoulli/lognormal mixture model to accommodate skewness and treat left-censored values as missing values.

The second aspect of this paper is to relax the stringent assumption of normality for the Tobit model (Bera et al., 1984). Even though the normality assumption makes the computation relatively simple, it may be unrealistic for some concentration measurements since they seem to be highly skewed to the right, even after log-transformation. As it can be seen in Figure 1(b), the histogram of antibody concentrations (in natural log scale) for 330 infants (Moulton and Halsey, 1995) is highly skewed to the right even after log-transformation. One of the referees has suggested to use inverse hyperbolic (arsinh) transformation (Huber et al., 2002) to stabilize the variability at the lower end of concentrations. Figure 1(c) depicts the distribution of antibody concentrations after arsinh-transformation, and the lower part tends to be smoother than the log-transformation but the asymmetry still remains an issue which needs to be accounted for. In order to properly model this data set, we introduce less restrictive families of distributions that can accommodate asymmetry in a more flexible way. It is, therefore, the objective of this paper to examine the suitability of skew-normal and skew-t distributions (Sahu, Dey and Branco, 2003; Genton, 2004)) in modeling a response variable in the context of a mixture Tobit model.

The third component of this paper is to develop a parametric mixture Tobit Model using skew-elliptical distributions under a Bayesian estimation method, which is computationally feasible due to major developments of computational algorithms (Gelfand and Smith, 1990; Lunn, Thomas, Best and Spiegelhalter, 2000). A flexible hierarchical representation of the proposed skew-elliptical models (see Section 3) makes it easier to implement the Markov chain Monte Carlo (MCMC) algorithm using a freely available WinBUGS software (Lunn, Thomas, Best and Spiegelhalter, 2000).

The remainder of this paper is structured as follows. In Section 2 we introduce the motivating data and a formulation of mixture Tobit model using skew-normal distribution for the error terms. Section 3 discusses the Bayesian estimation procedures. In Sections 4 and 5, we demonstrate the potential of the proposed model by analyzing two real data sets of antibody concentrations from an immunogenicity study of measles vaccines and an HIV/AIDS study. Finally, the paper concludes with a discussion in Section 6.

2. Skew-Normal Mixture Models for Censored Data

2.1. Motivating Data

Our research was motivated by the data from a large safety and immunogenicity study of measles vaccines conducted in Haiti during 1987-1990 (Job et al., 1991; Moulton and Halsey, 1995). The main objective of the study was to assess the effectiveness of Edmonston-Zagreb vaccine strain as compared to Schwarz strain on the ability of high titer vaccines to overcome interference of maternal antibodies in infants of at least 6 months of age. Antibody assays were performed on sera from 330 children at 12 months of age. The

lower detection limit was 0.1 international units (IU) or $\log(.1) = -2.3026$ on the natural log scale. Out of the 330 total observations, 86 (26.1%) of the observations fell below this limit, and were recorded as 0.1. The relatively high proportion of left-censored observations were recorded because of a limited amount of serum having been collected on each filter paper, precluding analysis of lower dilutions. The antibody concentrations at this limit are not considered reliable, therefore we impute them based on the Tobit model discussed in the next Section.

2.2. Model Specification

An approach we present in this paper treats censored values as latent (unobserved) continuous observations that have been left-censored. This idea was popularized by Tobin (1958) and the resulting model is commonly referred to as the Tobit model. Analytically, letting y_i^* denote the latent measurement for subject i ($i = 1, \dots, n$), the Tobit model can be formulated as:

$$y_i = \begin{cases} y_i^*, & \text{if } y_i^* > \tau_i \\ \text{missing}, & \text{if } y_i^* \leq \tau_i, \end{cases} \quad (1)$$

where τ_i is a non-stochastic LDL, which in our example is equivalent to $\log(.1)$. Note that the value of y_i is missing when it is less than or equal to τ_i , though in the standard Tobit model it is replaced by zero or LDL.

We can extend (1) to allow for the possibility that only a proportion, p , of the observations come from the censored skew-elliptical (SE) distribution (e.g., skew-normal or skew-t), while the other $(1 - p)$ of the observations come from another population (e.g., low responders) whose distribution is located entirely at or below τ_i . That is, any value above τ_i may come from the SE distribution, while a censored value ($y_i^* < \tau_i$) may be from either the SE distribution or the point mass distribution. We model this mixture as the outcome of a Bernoulli random variable S_i with probability $p = \Pr(S_i = 1)$ if $y_i^* > \tau_i$, and if $S_i = 0$, then $y_i^* < \tau_i$ with probability one.

Covariates are introduced for each component random variable as follows. A logistic model for S_i is formulated as:

$$\text{logit} \{ \Pr(S_i = 1) \} = \mathbf{Z}_i \boldsymbol{\alpha}, \quad (2)$$

where $\mathbf{Z}_i$ is a $d \times 1$ vector of covariates with associated vector of coefficients $\boldsymbol{\alpha}$. A possibly distinct set of covariates, $\mathbf{X}$, may also be related to the SE distribution component where we assume that the outcome variable y_i^* follows a skew-elliptical (SE) distribution (Azzalini and Capitanio, 1999; Sahu, Dey and Branco, 2003; Arellano-Valle and Genton, 2005) in order to incorporate skewness which may be very often inherent in bioassays or exposure assessments. Thus, the response variable y_i^* for the i th subject is distributed as

$$y_i^* | \boldsymbol{\beta}, \sigma^2, \delta, g \sim SE \left(\mathbf{X}_i \boldsymbol{\beta}, \sigma^2, \delta, g \right), \quad (3)$$

where $SE(\mu, \sigma^2, \delta, g)$ refers to a skew-elliptical distribution with location parameter $\mu = \mathbf{X}\beta$, scale parameter σ^2 , skewness δ , and density generator function g . More detailed information about the density generator function is given in the appendix where skew-normal (SN) and skew-t (ST) models are discussed as special cases of SE.

For purpose of accounting both skewness and heaviness in tails, we focus our attention to skew-t distributions for the conditional model $y_i^*|\beta, \sigma^2, \delta \sim ST_\nu(\mathbf{X}_i\beta, \sigma^2, \delta)$, where the skew-t distribution is given by

$$f(y_i^*|\beta, \sigma^2, \delta) = \frac{2\Gamma((\nu+1)/2)}{\Gamma(\nu/2)(\nu\pi)^{1/2}} \left[1 + \frac{(y_i^* - \mathbf{X}_i\beta)^2}{\nu(\sigma^2 + \delta^2)} \right]^{-(\nu+1)/2} \times \int_0^\infty t_{\nu+1}(v|\delta Q^{-1}(y_i^* - \mathbf{X}_i\beta), \frac{\nu+D}{\nu+1}(1 - \delta^2/Q)) dv \quad (4)$$

where $t_{\nu+1}(\cdot|\zeta, \omega)$ is a t-distribution with ν degrees of freedom, location ζ , and scale ω , and $D = (y_i^* - \mathbf{X}_i\beta)^2/Q$, $Q = \sigma^2 + \delta^2$, δ controls the level of skewness. For example, if $\delta > 0$, the density is skewed to the right, while it is skewed to the left when $\delta < 0$. However, if $\delta = 0$ we get a symmetric t distribution. The skew-normal distribution is obtained when $\nu \rightarrow \infty$ and the normal distribution when both $\delta = 0$ and $\nu \rightarrow \infty$ (Azzalini and Capitanio, 2003). The mean of the distribution in (4) is given by

$$E(Y_i^*) = \mathbf{X}_i\beta + \left(\frac{\nu}{\pi}\right)^{1/2} \frac{\Gamma((\nu-1)/2)}{\Gamma(\nu/2)} \delta, \\ Var(Y_i^*) = \frac{\nu(\delta^2 + \sigma^2)}{\nu-2} - \frac{\nu}{\pi} \left\{ \frac{\Gamma((\nu-1)/2)}{\Gamma(\nu/2)} \right\}^2 \delta^2,$$

where $\nu > 2$. For a full discussion of the properties of this distribution see (Sahu, Dey and Branco, 2003; Liu and Dey, 2004). The parameters of the models are estimated using a Bayesian approach.

3. Bayesian Modeling Approach

In this section, we describe a Bayesian estimation procedure for the model in (4). A Bayesian analysis focuses on computing the posterior probability distributions for model parameters, given the prior probability distributions of parameters and the likelihood of observed data. First, we present the likelihood function for the observed data under the skew-t mixture Tobit model. Before doing this, we note that the observed dependent variable $y_i = y_i^*$ if $c_i = 1$, and y_i is left censored if $c_i = 0$, where c_i is a censoring indicator, and the latent variable y_i^* was discussed in Section 2.

Letting $\theta = (\beta, \sigma^2, \delta, \nu)$ be the collection of the parameters, the joint distribution (likelihood function) of the observed data $\mathbf{y} = (y_1, \dots, y_n)^T$ is

$$f(\mathbf{y}|\theta) = \prod_{i=1}^n [1 - Pr(S_i=1|\mathbf{Z}_i, \alpha) + Pr(S_i=1|\mathbf{Z}_i, \alpha) F(\tau_i|\mathbf{X}_i, \theta)]^{1-c_i} [Pr(S_i=1|\mathbf{Z}_i, \alpha) f(y_i|\mathbf{X}_i, \theta)]^{c_i} \quad (5)$$

where $f(\cdot)$ and $F(\cdot)$ denote the probability distribution function and cumulative density function of skew-t, respectively.

Directly using the likelihood in (5) is computationally challenging since it requires the calculation of complex integrals. An alternative is to use Markov Chain Monte Carlo (MCMC) procedure to estimate the model parameters by exploiting the conditionally symmetric representation of the skew-t distribution. Thus, following Sahu et al.(2003) and properties of skew-t distribution, it can be shown that y_i in the model (4) follows the following hierarchical representation.

$$\begin{aligned}
 y_i | \beta, \sigma^2, \delta, \nu, w_i &\sim t_\nu \left(\mathbf{X}_i \beta + \delta [w_i - (\nu/\pi)^{1/2} \Gamma((\nu-1)/2) / \Gamma(\nu/2)], \sigma^2 \right), \\
 w_i | \sigma^2 &\sim t_\nu (0, \sigma^2) I(w_i > 0), \\
 \beta &\sim N_q(\beta_0, \mathbf{\Lambda}) \\
 \sigma^2 &\sim IG(a, b), \\
 \delta &\sim N(0, \gamma), \\
 \nu &\sim \exp(\lambda) I(\nu > 3),
 \end{aligned} \tag{6}$$

where w_i is a latent variable whose distribution is a truncated t-distribution, $I(\cdot)$ is an indicator function. In the above hierarchical Bayesian specification, we have assumed conjugate prior distributions for all unknowns in the model in order to guarantee proper posteriors. The representation in (6) allows us to write WinBUGS codes in a straight forward fashion, which is also a freely available software (Lunn, Thomas, Best and Spiegelhalter, 2000).

To select the best fitting model among competing models, we use the Bayesian selection tools. We specifically use measures based on replicated data from posterior predictive distributions. A replicated data set is defined as a sample from the posterior predictive distribution,

$$f(y_{rep} | y_{obs}) = \int f(y_{rep} | \theta) f(\theta | y_{obs}) d\theta, \tag{7}$$

where y_{rep} denotes the predictive data and y_{obs} represents the observed data, and $f(\theta | y_{obs})$ is the posterior distribution of θ . One can think of y_{rep} as values that might have observed if the underlying conditions generating y_{obs} were reproduced.

If a model has good predictive validity, it expected that the observed and replicated distributions should have substantial overlap. To quantify this, we compute the *expected predictive deviance* (EPD) as

$$EPD = E \left[\sum_i (y_{rep,i} - y_{obs,i})^2 \right] \tag{8}$$

where $y_{rep,i}$ is a replicate of the observed $y_{obs,i}$, the expectation is taken over the posterior distribution of the model parameters θ . This criterion chooses the model where the discrepancy between predictive values and observed values is the lowest. That is, better models will have lower values of EPD, and the model with the lowest EPD is preferred.

4. Application to Antibody Concentration Data

This section applies the preceding models to antibody concentration data. A brief description of the data set was given in Section 2. The main variables are (1) vaccine dose (coded as $TITER = 1$ for high dose, $TITER = 0$ for low dose), (2) vaccine strain ($STRAIN = 1$ for Edmonston-Zagreb, $STRAIN = 0$ for Schwarz), (3) $GENDER$ ($= 1$ for female, $= 0$ for male), and (4) concentration of antibody (in international units (IU)), which is the response variable. This response variable has a relatively high degree of left-censoring and positive skewness as it is shown in Figure 1.

4.1. Model Framework

The plot in Figure 1 clearly suggests a mixture of a point distribution at LDL (-2.3) and a continuous distribution on the non-censored right-side of LDL. An extension of the Tobit model is presented here with two parts, where the first part contains the effect on the probability that the response variable is above LDL, while the second part contains the skew-elliptical models for the antibody data above the censoring limit.

Accordingly, the first part is the logit model which is given as

$$\text{logit} \{ \Pr(S=1) \} = \mathbf{Z}\boldsymbol{\alpha},$$

where $\mathbf{Z} = (\text{Strain}, \text{Titer}, \text{Gender})$ and these covariates are defined as $STRAIN = 1$ for Edmonston-Zagreb vaccine strain, 0 for Schwarz strain; $TITER = 1$ for high vaccine dose, 0 for low dose; $GENDER = 1$ for female infant, 0 for male.

For the second component, we posit four competing models for the censored data with mean structure

$$\log(\mu) = \mathbf{X}\boldsymbol{\beta},$$

where the covariates in $\mathbf{X}$ are the same as those in $\mathbf{Z}$ above. Because of the highly skewed nature of the distribution of the outcome, even after log-transformation, an asymmetrical skew-elliptical distribution for the error term is proposed. Accordingly, we consider the following Tobit models with skew-t and skew-normal distributions which are special cases of the skew-elliptical distribution as described in detail in Section 2.

- **Model I:** A mixture Tobit model with normal distributions of random errors;
- **Model II:** A mixture Tobit model with skew-normal distributions of random errors;
- **Model III:** A mixture Tobit model with skew-t distributions of random errors.
- **Model IV:** A standard or naive Tobit model with normal distributions of random errors.

The first three models are extensions of the standard Tobit model (Model IV). As it was discussed in Section 1, the standard Tobit model is equivalent to the MLE method (Lynn,

2001; EFSA, 2010) which ignores the mixture components but instead only takes the proportion of left-censored data combined with those above the LDL. For estimating the parameters of these models, we use a Bayesian method that requires prior distributions for the parameters. Prior distributions for the parameters involved are the same for the four models for comparison purposes. In particular, (i) fixed-effects are taken to be independent normal distribution $N(0, 100)$ for each component of the population parameter vectors β . (ii) For the variance of error terms σ^2 we assume an inverse gamma prior distribution, $IG(0.01, 0.01)$ so that the distribution has mean 1 and variance 100. (iii) The degrees of freedom, ν , is assumed to have an exponential distribution with parameter $\lambda = 5$. (iv) For the skewness parameter δ , we choose independent normal distribution $N(0, 100)$.

Based on the likelihood function and the prior distributions specified above, the MCMC sampler was implemented to estimate the model parameters and the program codes are available from the author upon request. Convergence of the MCMC implementation was assessed using standard tools (such as trace plots, ACF plots) within WinBUGS software, and it was achieved after 100,000 iterations. Thus, after initial 100,000 burn-in iterations, every 40th MCMC sample thereafter is retained from the next 400,000 iterations, obtaining 10,000 samples for subsequent posterior inferences of the unknown parameters.

4.2. Results

Table 1 presents the comparison among the four models based on log-transformation and arsinh-transformation using Bayesian model selection criteria. First, we see from the upper part (log-transformation) of Table 1 that Model IV (Naive) has the biggest expected predictive deviance (EPD) criterion value of 4.626, followed by Model I (EPD=2.898), showing that there are relatively large discrepancies between the observed data and the posterior predictive distribution. Next, Model II with skew-normal distribution has a smaller EPD value (0.183) than that of Models I and IV, confirming that accounting for skewness gives a better fit. Finally, Model III with skew t-distribution has very similar value of EPD (0.182) to that of Model II. Looking at the lower part (arsinh) of Table 1, the results also indicate that Model II is a preferred model.

The findings above are further confirmed by their residual sum of squares (RSS) which are 231.08 (Model I), 41.81 (Model II), 41.96 (Model III), and 341.381 (Model IV). Further assessment of goodness-of-fit of the four models is presented in Figure 2, where the plots of residuals against fitted values, fitted values versus observed values and $Q - Q$ plots are depicted. Looking at the plots of the observed values versus the fitted values for the four models in the second column of Figure 2, it seems that Model II and Model III provide better fit to the observed data as compared to either Model I or Model IV where the random error is assumed to be normal. The $Q - Q$ plots in the right panel suggest that Model II (skew-normal) gives a better goodness-of-fit to the data than that of both Model I (normal) and Model III (skew-t). Thus, we pick Model II as the ‘best’ model which accounts for skewness and left-censoring. The implication of the finding is that a skewed model is a better choice for fitting the logarithmic transform of the continuous component of the antibody concentration data.

Covariates are added to both logit and skew-elliptical models so as to study the effect of asymmetry of the distribution of antibody concentration data. The same set of covariates (STRAIN, TITER, GENDER) are entered in all the models. Table 2 reports posterior means, standard deviations, and the 95 percent credible intervals (in terms of the 2.5 and 97.5 percentiles) of the parameters of the four models. The findings in Table 2, particularly for Model II which gives the best model fit, show that most covariates in both components of the two-part models contribute little in explaining the variation in the post-vaccination antibody concentrations. However, STRAIN (α_2) is found to strongly explain the probability of being a responder. The effect of STRAIN (posterior mean = 0.751 with 95% credible interval of (0.247, 1.274)) is significant in the logit component of Model II since the 95% credible interval does not contain zero. Expressed differently, this means is that the odds ratio of an infant having post-vaccination antibody concentrations higher than LDL as compared to the low responder group is $\exp(0.751) = 2.119$. The interpretation is that young infants who had received Edmonston-Zagreb vaccine stain at 6 months are 2.12 times more likely to have high concentrations of antibody at 12 month than those with Schwarz vaccine. Note that GENDER and TITER are no longer significant as they were found in Moulton and Hasley (1995)'s study whose approach did not account for skewness and uncertainty in the model parameters.

Estimates of the skewness parameters are also given in Table 2. The posterior mean of the skewness parameter (δ) of Model II (skew-normal) is 1.681 with 95% credible intervals (1.521, 1.855); suggesting that there is a positive and significant skewness in the antibody concentration data; this confirms the fact that the distribution of the original data is skewed even after taking log-transformation or arsinh-transformation (see Figure 1). Thus, incorporating skewness parameter in the modeling of the data is recommended. Furthermore, when heaviness in the tails is taken into account using skew-t distribution, the estimate of the skewness parameter is 1.517 which is positive and significant but not much different from that of Model II.

A referee suggested to use some other transformations (e.g., arsinh) to see how much the impact of left-censoring on model fitting. Accordingly, we fitted the four models to the arsinh-transformed data and the results are given in Tables 1 and 3. According to the EPD criterion in Table 1, the best model is Model II based on the arsinh-transformation. In addition, most of the posterior parameter means from Table 3, based on arsinh-transformation, look similar to those in Table 2 based on the log-transformation. There are, however, some differences in the estimates of variance and skewness parameters. For example, under Model III, the posterior mean for δ is -0.136 with 95% credible interval (-0.232, -0.063), implying that the outcome variable is negatively skewed which is contrary to what Figure 1(c) suggests. In contrast, the estimate of δ based on log-transformation (see Table 2) for Model III is 1.517 which confirms the feature shown in Figure 1(b). Moreover, we believe that log-transformation may be easier to interpret than arsinh-transformation.

The posterior means of proportions (p) of high responders under the four competing models are 75.4%, 74.0% and 73.9% for Model I, Model II and Model III, respectively. Especially the estimated proportions for Model II (skew-normal) and Model III (skew-t) are very close to the observed percentage 73.9%, confirming the results obtained earlier regarding the

goodness-of-fit of these two models to the data after allowing skewness. Thus, a skewed model is recommended for fitting the logarithmic transform of the continuous component of the antibody data.

Although several potential covariates are examined in this paper using the skew-normal mixture Tobit model, few of them played any role at all. We found that there is a significant effect of STRAIN on the probability of having an antibody concentration above the detection limit. The clinical importance of this finding is that it is important to use an effective vaccine strain for increasing the protective antibody concentration above the detection limit 0.1 IU/mL. Other predictors have not been found strong enough to classify observations into low and high responders. For example, the effect of gender (posterior mean = -0.190) on the probability of having an observation greater than the lower detection limit (LDL) is not significant since its 95% credible interval contains zero. These findings are partially in agreement with that of Moulton and Halsey (1995) who analyzed the same data set but using a different approach which did not account for skewness exhibited in the observed data.

5. Application to HIV/AIDS data

The second example we use to illustrate the proposed methods is a data set obtained from an AIDS clinical trial (Acosta et al., 2004). In this study, 44 HIV-1 infected patients were treated with a potent antiretroviral regimen. RNA viral load was measured in copies/mL at study days 0, 7, 14, 28, 56, 84, 112, 140 and 168 of follow-up. Covariates such as CD4 cell counts were also measured throughout the study on similar scheme. The viral load detectable limit is 50 copies/mL, and there are 107 out of 357 (30 percent) of all viral load measurements that are below the LDL. Previous studies show that change in viral load may be associated with change in CD4 cell counts, and we use CD4 as covariate in the models below.

For the initial stage of viral decay after treatment, a biologically reasonable viral load model can be formulated by the uniexponential form (Ho et al., 1995), $V(t) = V(0) \exp(-\lambda t)$, where $V(t)$ is the total virus at time t and λ is the rate of change in viral load. To model the complete viral load trajectory, we allow λ to vary over time. A simple determinant for time-varying λ is the linear function $\lambda(t) = a + bt$. For HIV viral dynamic models, it is typical to take log-transformation of the viral load in order to stabilize the variance and to speed up estimation algorithm (Ding and Wu, 1999). After log-transformation of $V(t)$ and substituting λ by the linear function $\lambda(t) = a + bt$, we obtain the following quadratic linear mixed-effects model

$$y_{ij} = \beta_{i0} + \beta_{ij1}t_{ij} + \beta_{ij2}t_{ij}^2 + e_{ij}, \quad (9)$$

where $y_{ij} = \log(V(t_{ij}))$, parameter β_{i0} represents the initial viral load in log scale for the i^{th} subject at j^{th} time point, and parameters β_{ij1} and β_{ij2} incorporate change in viral decay rate over time, with $\lambda_{ij} \equiv -(\beta_{ij1} + \beta_{ij2}t_{ij})$ being the time-varying exponential decay rate.

$e_i = (e_{i1}, \dots, e_{in_i})^T \sim SN_{n_i}(\mathbf{0}, \sigma_e^2 \mathbf{I}_{n_i}, \delta_e \mathbf{I}_{n_i})$, $\boldsymbol{\beta}_{ij} = (\beta_{ij0}, \beta_{ij1}, \beta_{ij2})^T$ is a vector of individual-

level parameters for the i^{th} subject at time t_{ij} . We assume that the individual-specific and time-varying parameters β_{ij} are related to the CD4 values z_{ij} in the following models

$$\beta_{i0} = \beta_1 + b_{i1}; \quad \beta_{ij1} = \beta_2 + \beta_3 z_{ij} + b_{i2}; \quad \beta_{ij2} = \beta_4 + \beta_5 z_{ij} + b_{i3}, \quad (10)$$

where $\mathbf{b}_i = (b_{i1}, \dots, b_{i3})^T$ is individual level random-effects, having a multivariate normal distribution with variance-covariance matrix Σ ; and $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_5)^T$ is a vector of population parameters.

Similar to equation (2), here also the logit model is expressed as

$$\text{logit} \{Pr(S_{ij}=1)\} = \alpha + a_2 z_{ij} + a_3 t_{ij} + v_i, \quad (11)$$

where z_{ij} is the CD4 value for the i th subject at occasion j and t_{ij} is a time variable. The subject-specific random effects, v_i , is normally distributed with mean zero and variance, σ_v^2 , and $\mathbf{a} = (a_1, a_2, a_3)^T$ is a vector of coefficients.

Here also we assumed a skew-normal distribution for the error terms and compared the results to those of the usually assumed normal distribution. According to the EPD criterion, Skew-normal (SN) model fitted to the RNA data has 0.334 and Normal (N) model has 5.497, suggesting that SN is a better suited model for viral loads and CD4 covariate by taking into account skewness in the data. From Table 4 the estimated skew parameter for SN model is 2.484 with 95% credible interval (2.127, 2.837), showing that there is a positive and significant skewness in the data. Looking now at the estimated population initial stage of viral decay after treatment bases on the SN model, we get $\hat{\lambda}(t) = -(-15.5 - 1.75z * t + 12.75t - 3.32z * t^2)$, where z is the CD4 value at time t . Thus, the population viral load process may be approximated by $\hat{V}(t) = \exp[5.90 - \hat{\lambda}(t)t]$ which may be used for future prediction of viral loads.

In the logit component, the estimated value of the coefficient of the CD4 cell count, under the Skew-normal model, is 1.15 with 95% credible interval (0.626, 1.753) which does not include zero, suggesting that a typical patient with higher value of CD4 count is more likely to have her viral load measurement be left-censored. That is, the higher the CD4 value, the higher the chance of being non-progressor (viral load < LDL) towards AIDS.

6. Conclusion

Using a Bayesian framework, this paper presents methods which can be applied to analyze left-censored data (e.g., antibody concentrations) based on a mixture skew-normal Tobit model. Such model formulation of a mixture of two populations has enabled us to account for the excess of observations at or below detection limit, and skewness in the response variable. The assumption of normality after log-transformation of antibody concentrations may simplify computation but, if there is a noticeable skewness as shown in Figure 1, may give unreliable results. The inappropriateness of Model I (mixture Tobit normal) and Model IV (standard Tobit normal) fit to the data can be readily seen from Figure 2. In contrast, our proposed skew-normal and skew-t models give strongly better fits than the normal model.

Among the proposed models, the skew-normal mixture tobit model (Model II) provides relatively the best fit to both the measles vaccine data and HIV/AIDS data.

The skew-elliptical distributions, where skew-normal and skew-t distributions are special cases, have important practical advantages as compared to other computationally challenging non-parametric models and Box-Cox type models (Box and Cox, 1964; Handelsman, 2002). First, skew-elliptical distributions accommodate asymmetry directly by eliminating the need for searching for a suitable transformation for achieving normality. Second, the associations between the response and explanatory variables are more directly interpretable than those employing a transformation on the response. Finally, a hierarchical Bayesian representation given in (6) provides a straightforward implementation of Bayesian estimation using a freely available WinBUGS software programs.

The current study also extends the Tobit model (Tobin, 1958) in three ways. First, in fitting skew-elliptical models, we consider a mixture of two subpopulations of participants potentially classified as nonresponders and responders to measles vaccine. A nonresponder is an individual who do not respond at all to the vaccine or respond so poorly that her antibody concentration falls below LDL. This may be due to a passively acquired maternal antibody which may interfere with response to measles vaccine in infants (Halsey et al., 1985; Maldonado et al., 1995). Second, skew-elliptical distribution is introduced to account skewness and heaviness in the tails. Third, instead of a quasi-Newton maximization method we use a Bayesian approach to directly impute observations below or at lower detection limit. Thus, our proposed models are novel in that they allow for non-symmetry (skewness), and they can be easily fitted using freely available software. This makes our approach quite powerful and accessible to practitioners and applied statisticians.

In particular, as the associate editor suggested, the proposed methods can easily be applied to food risk assessment and therapy studies for properly handling non-detects (values below LDL or LOQ (limit of quantification)). An LOQ is the minimum concentration value that can be quantified with accuracy and precision, while an LDL is the minimum concentration value that can be detected using a given assay or instrument (Keith et al., 1983; EFSA, 2010). Note that an LDL is often lower than an LOQ (EFSA, 2010). Instead of treating both non-detected and non-quantified values as simply left-censored data, non-quantified values (measurements between LDL and LOQ) may be modeled with an extension of the proposed method for interval-censored data when information on both LDL and LOQ is available. Until an assay that can reliably recover nondetects below LDL or LOQ is developed, the role of an appropriate biostatistical method is crucial in assessing the extent of risk of exposure in the case of risk assessment or formulating therapy in the case of HIV/AIDS study. For example, accurately estimating the magnitudes of nondetects of viral loads is crucial in developing therapy for viral eradication. An HIV infected patient may maintain a residual viremia even when suppressed by a highly active antiretroviral regimen to below the detection limit (viral load of < 50 copies/ml). If therapy becomes ineffective or is discontinued, a small number of latently-infected cells can lead to viral rebound (Shen and Siliciano, 2008).

To an important question raised by an associate editor “Do you propose to apply in other applications all models and then select that model which fits best or do you propose to select one of the models?”, we argue that, based on the findings in this paper, one can directly adopt skew-normal mixture tobit models for cases where there is a high proportion of nondetects and skewed response variable. For cases where there are heavy tails and skewness, one may also use skew- t models. However, the advantages of these proposed methods over the traditional models as a function of censoring, skewness and the number of mixture components have not been fully investigated via a simulation study. We are currently investigating these problems and will report the findings in the near future.

In conclusion, we have empirically examined the use of flexible skew-elliptical Bayesian methods for analyzing left-censored and skewed data. For making reliable conclusions and appropriate clinical decisions, we believe that these proposed methods may have important applications to areas where there exist left-censoring and skewness in the tails of response variables.

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Appendix

Skew Elliptical Distributions

Different versions of skew-elliptical (SE) distributions have been proposed and used in the literature (Sahu et al., 2003; Genton, 2004; Arellano and Genton, 2005). We adopt a class of SE distributions proposed by Sahu et al. (2003), which is obtained based on transformation and conditioning and contains skew- t (ST) and skew-normal (SN) distributions as special cases. An k -dimensional random latent vector $\mathbf{Y}^*$ follows an k -variate SE distribution if its probability density function (pdf) is given by

$$f(\mathbf{y}^* | \boldsymbol{\mu}, \boldsymbol{\Sigma}, \boldsymbol{\Delta}(\boldsymbol{\delta}); g_{\nu}^{(k)}) = 2^k f(\mathbf{y} | \boldsymbol{\mu}, \mathbf{A}; g_{\nu}^{(k)}) P(V > 0), \quad (\text{A.1})$$

where $\mathbf{A} = \boldsymbol{\Sigma} + \boldsymbol{\Delta}^2(\boldsymbol{\delta})$, $\boldsymbol{\mu}$ is a location parameter vector, $\boldsymbol{\Sigma}$ is a covariance matrix, $\boldsymbol{\Delta}(\boldsymbol{\delta})$ is a skewness diagonal matrix with the skewness parameter vector $\boldsymbol{\delta} = (\delta_1, \delta_2, \dots, \delta_k)^T$; V

follows the elliptical distribution $SE(\boldsymbol{\Delta}(\boldsymbol{\delta}) \mathbf{A}^{-1}(\mathbf{y}^* - \boldsymbol{\mu}), \mathbf{I}_k - \boldsymbol{\Delta}(\boldsymbol{\delta}) \mathbf{A}^{-1} \boldsymbol{\Delta}(\boldsymbol{\delta}); g_{\nu}^{(k)})$ and

the density generator function $g_{\nu}^{(k)}(u) = \frac{\Gamma(k/2)}{\pi^{k/2}} \frac{g_{\nu}(u)}{\int_0^{\infty} r^{k/2-1} g_{\nu}(u) dr}$, with $g_{\nu}(u)$ being a function such that $\int_0^{\infty} r^{k/2-1} g_{\nu}(u) dr$ exists. The function $g_{\nu}(u)$ provides the kernel of the original elliptical density and may depend on the parameter ν . We denote this SE distribution by $SE(\boldsymbol{\mu}, \boldsymbol{\Sigma}, \boldsymbol{\Delta}(\boldsymbol{\delta}); g_{\nu}^{(k)})$. Two examples of $g_{\nu}(u)$, leading to important special cases used throughout the paper, are $g_{\nu}(u) = \exp(-u/2)$ and $g_{\nu}(u) = (u/\nu)^{-(\nu/k)/2}$, where $\nu > 0$. These two expressions lead to the ST and SN distributions, respectively. In the latter case, ν corresponds to the degree of freedom parameter. Note that the SN distribution is a special case of the ST distribution when the degree of freedom approaches infinity. An ST

distribution introduced by Sahu et al. (2003) is suitable for a Bayesian inference since it is built using conditional models.

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Figure 1.

The histograms of antibody concentrations: (a) raw data, (b) *log* scale, and (c) *arsinh* scale.

Figure 2.

Plots of goodness-of-fit statistics for four models: (i) The first column has the residual plots against the fitted values, (ii) the second has plots of the fitted against observed log(antibody) values, and (iii) the last column has the Q-Q plots of residuals.

Table 1

Model comparison using Bayesian model selection criteria

Transformation	Criterion	Model I	Model II	Model III	Model IV
Log	Deviance	916.200	298.400	320.200	1116.0
	RSS	231.091	41.810	41.961	341.381
	EPD	2.898	0.183	0.182	4.626
Arsinh	Deviance	586.5	58.25	983.5	1227.0
	RSS	146.224	4.090	374.136	60.956
	EPD	3.43	2.519	3.398	5.724

(RSS=residual sum of squares, EPD=expected predictive deviance)

Table 2

A summary of the estimated posterior mean (PM) of population parameters along with the corresponding lower limit (L_{CI}) and upper limit (U_{CI}) of 95% equal-tail credible interval based on the log-transformation.

Model		Log-normal Component				Logit Component				σ^2	δ
		$\beta_1(\text{intercept})$	β_2	β_3	β_4	$\alpha_1(\text{intercept})$	α_2	α_3	α_4		
I	PM	0.740	-0.310	-0.142	0.394	0.613	1.531	0.669	-0.532	1.603	-
	L_{CI}	-0.818	-0.730	-0.538	0.001	-0.172	0.453	-0.152	-1.606	1.159	-
	U_{CI}	0.156	0.102	0.266	0.799	1.728	4.152	1.573	0.302	2.281	-
II	PM	-2.852	-0.087	0.034	0.091	0.643	0.751	0.407	-0.190	0.034	1.681
	L_{CI}	-3.076	-0.240	-0.115	-0.058	0.176	0.247	-0.089	-0.697	0.015	1.521
	U_{CI}	-2.641	0.064	0.185	0.245	1.118	1.274	0.914	0.314	0.064	1.855
III	PM	-2.824	-0.090	0.045	0.089	0.645	0.750	0.404	-0.193	0.0298	1.517
	L_{CI}	-3.064	-0.242	-0.106	-0.059	0.183	0.226	-0.097	-0.691	0.014	1.318
	U_{CI}	-2.598	0.060	0.204	0.239	1.107	1.278	0.910	0.298	0.056	1.720
IV	PM	-1.269	0.339	0.171	0.080	-	-	-	-	2.848	-
	L_{CI}	-1.632	-0.040	-0.201	-0.301	-	-	-	-	2.35	-
	U_{CI}	-0.903	0.717	0.549	0.453	-	-	-	-	3.465	-

Table 3

A summary of the estimated posterior mean (PM) of population parameters along with the corresponding lower limit (L_{CI}) and upper limit (U_{CI}) of 95% equal-tail credible interval based on the arsinh-transformation.

Model		Arsinh-normal Component				Logit Component					
		β_1 (intercept)	β_2	β_3	β_4	α_1 (intercept)	α_2	α_3	α_4	σ^2	δ
I	PM	0.940	-0.109	-0.107	0.194	0.645	0.745	0.408	-0.193	0.517	-
	L_{CI}	0.762	-0.287	-0.284	0.012	0.187	0.229	-0.089	-0.704	0.436	-
	U_{CI}	1.118	0.071	0.072	0.379	1.122	1.275	0.915	0.302	0.612	-
II	PM	-0.725	-0.033	0.007	0.043	0.642	0.747	0.411	-0.191	0.013	1.081
	L_{CI}	-0.865	-0.124	-0.082	-0.044	0.184	0.232	-0.087	-0.688	0.007	0.984
	U_{CI}	-0.602	0.057	0.096	0.134	1.114	1.266	0.916	0.315	0.022	1.189
III	PM	1.012	-0.057	0.010	0.120	0.648	0.757	0.407	-0.195	0.265	-0.136
	L_{CI}	0.771	-0.206	-0.138	-0.025	0.180	0.234	-0.106	-0.707	0.202	-0.232
	U_{CI}	1.291	0.098	0.163	0.273	1.117	1.282	0.915	0.307	0.340	-0.063
IV	PM	-0.570	0.541	0.254	-0.023	-	-	-	-	4.212	-
	L_{CI}	-1.017	0.087	-0.201	-0.479	-	-	-	-	3.462	-
	U_{CI}	-0.130	0.997	0.708	0.432	-	-	-	-	5.116	-

Table 4

Estimated posterior means (PM) of fixed-effects, precision, skewness, and 95% credible intervals with lower limit (L_{CI}) and (U_{CI}) from skew-normal and normal models fitted to HIV/AIDS data.

Parameter	Normal			Skew-Normal		
	PM	L_{CI}	U_{CI}	PM	L_{CI}	U_{CI}
<i>Lognormal Component</i>						
β_1	7.701	7.169	8.230	5.902	5.406	6.430
β_2	-14.78	-17.52	-12.07	-15.0	-17.870	-12.240
β_3	-1.425	-4.252	1.389	-1.747	-4.782	1.125
β_4	12.84	9.539	16.03	12.75	9.383	16.09
β_5	-3.409	-7.484	0.526	-3.322	-7.377	0.734
<i>Logit Component</i>						
a_1	-2.729	-3.651	-1.934	-2.735	-3.659	-1.935
a_2	1.149	0.620	1.749	1.15	0.626	1.753
a_3	3.738	2.583	5.01	3.74	2.608	5.005
Deviance	1128.0	1091.0	1171.0	712.6	185.1	1187.0
δ_e	—	—	—	2.484	2.127	2.837
σ_e^2	2.735	2.162	3.474	0.123	0.005	0.552
σ_v^2	2.267	0.756	5.032	2.274	0.750	4.949
Σ_{11}	1.54	0.625	2.91	1.434	0.601	2.692
Σ_{12}	0.344	-2.325	3.154	0.764	-1.93	3.685
Σ_{13}	-1.495	-5.22	0.975	-2.323	-6.103	0.375
Σ_{22}	7.714	0.678	26.13	7.571	0.510	28.65
Σ_{23}	1.697	-14.7	8.694	-2.028	-27.86	7.281
Σ_{33}	12.16	0.858	43.82	19.83	1.726	64.43