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Research Article

Bayesian Bent-Cable Tobit Models for Longitudinal and Survival Data: Application to AIDS Studies

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Abstract

This paper presents a new methodology for jointly identifying bent cable phasic patterns and mixture of progressors and non-progressors of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) patients based on longitudinal and time-to-event data. Using the longitudinal data, the bentcable model gives an estimate of a gradual transition period for the development of drug resistance to Antiretroviral (ARV) drug for treating HIV patients. In addition to finding such an estimate (phasic pattern identification), a two-part modeling is carried out to incorporate a relatively large percentage of left-censored data in the framework of joint analysis of time to event and longitudinal data. Even though there are some methods for separately analyzing time to event and longitudinal data, those methods may not be appropriate when time to event is dependent on the longitudinal outcome. A better approach is to extend a bent-cable To bit model that jointly incorporates patients who are potentially progressors to AIDS from those patients who do not, phasic changes of trajectories of viral load, and the association between the time to a decline of CD4/CD8 ratio and rates of change in viral load. The proposed methods are illustrated using real data from an AIDS clinical study.

Introduction

In prospective studies, there is often a response variable which may be associated with a time to an event of interest. For example, in HIV (Human Immunodeciency Virus) clinical trials, a longitudinal response variable, viral load or HIV RNA (Ribonucleic Acid), may be related to the time to the first decrease to CD4/CD8 (clusters of differentiation 4 and 8 T-cell co-receptors) ratio. Such an association throws light on important indicators of risk of disease progression [1,2]. In addition, the viral load has a Lower Detection Limit (LOD) and a developmental growth curve with phasic changes over time [3-5]. The viral load growth curves of patients, After Receiving Antiretroviral (ARV) drugs, may decrease over time up to a point and then start increasing upwards [6]. These phasic changes may also occur gradually instead of abruptly because of a biological process of developing resistance to ARV drugs over time [7]. To simultaneously model these features of viral load, we extend the bent-cable method [8,9] by incorporating (i) the relationship between viral load proles and time to first decrease of CD4/CD8 ratio; (ii) two-part modeling of left-censored viral load to account for heterogeneity of patients who are either progressing to AIDS (viral load above detection limit and rebound) or non-progressing to AIDS after receiving treatment (having viral load below detection limit and decreasing over time); and (iii) skewness of response variable.

Joint modeling of longitudinal phasic changes and event time data is substantively important [10-12]. For modeling phasic changes using repeated observations over time with an abrupt change, a piecewise linear regression is commonly used [13-16]. A piece wise model, however, may not be sensible where a trajectory may show a gradual transitional change instead of an abrupt change. For example, in the case of HIV/AIDS studies, trajectories of viral loads may show gradual transition periods between an initial decline after treatment and rebound at later time in the follow-up. This feature may manifest because of drug resistance and non-adherence [7]. To properly analyze such a feature, we use a bent-cable regression within the context of joint modeling of time to event and longitudinal data. The bent-cable model consists of two linear growth curves to describe the incoming (decline)and outgoing (rebound) phases, joined by a quadratic bend to represent the gradual transition period [9,17]. A typical graph of a bent-cable model is depicted in Figure 1 where the gradual transition period is between $\phi 1 - \phi 2$ and $\phi 1 + \phi 2$ with its center at $\phi 1$. The downward trend to the left of $\phi 1 - \phi 2$ is referred to as an incoming line while the upward trend to the right of $\phi 1+\phi 2$ is an outgoing line. These parameters have nice interpretability in the joint Tobit model focusing on growth curves and time to event (Figure 1).

Specifically, joint modeling of time to first decrease of CD4/CD8 ratio and viral load growth curves provides valuable information about the risk of disease progression [1,2]. CD4 and CD8 cells are two important types of white blood cells where CD4 cells fight against an infection, while CD8

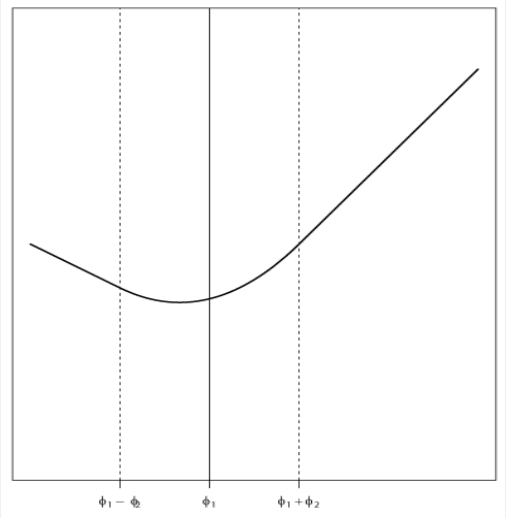

Figure 1: A hypothetical scheme of a bent-cable model. A gradual transition period is between ϕ_1-ϕ_2 and ϕ_1 + ϕ_2 where ϕ_1 is the center and ϕ_2 is the width. The transition connects two linear trends called the incoming (left side of the dotted line at ϕ_1-ϕ_2) and outgoing trends.

cells suppress the immune response [18]. For an HIV infected patient, the CD4 cell count declines while the CD8 cell count increases. The ratio of CD4 to CD8 indicates how strong patient's immune system is and helps predict how likely one may develop a progression to AIDS [19]. To fully characterize the relationship between the time to first decline of the CD4/CD8 ratio and the rate of trajectory of viral load, the heterogeneity of substantial proportion of left-censored values should be taken into account.

Recognizing the need to account for both the left-censored response variable (viral load) and heterogeneity among subjects leads to the development of a two-part Tobit model [20-25]. The standard Tobit model assumes that the underlying process generating left-censored values is the same as the process that generates the observations above LOD (26). This assumption may not always be true. It is plausible that some of the factors that influence left-censoring may be different from the factors that influence the generation of data above a LOD. In our data which will be analysed later, there may be a mixture of patients in which, after receiving antiretroviral therapy(ART), some have their HIV RNA suppressed enough to be below and stay under LOD nonprogressors to severe disease condition), while others intermittently have values below LOD due to suboptimal responses [27] (progressors). An extended version of the standard Tobit model is flexible to incorporate such heterogeneity of patients and non-normal distributions for accounting skewness in the response variable. Thus, we propose to use more flexible parametric models based on skew-elliptical distributions [28,29] to incorporate skewness of random errors. Multivariate Skew-Normal (SN) and multivariate Skew-T (ST) distributions are special cases of skew-elliptical distributions.

To our knowledge, there is relatively little work done that simultaneously addresses (i) gradual phasic changes of growth curves of a response variable with skewness and heavy tails, (ii) time to event, and (iii) identifying factors that influence left-censoring. To this effect, this paper develops Joint Two Part Bent-Cable Tobit Models (JTBTM) for longitudinal and time-to-event data and analyzes real data from an HIV/AIDS study using a Bayesian approach. The remainder of the paper is organized as follows. In section 2, we develop Two-Part Bent-Cable Tobit Models (TBTM) with multivariate ST distributions for a response variable with skewness and left-censoring, and an Accelerated Failure Time Model (AFTM) for a time to event. In Section 3, a Bayesian inferential procedure will be provided. In Section 4, an illustration of the proposed methods using an AIDS data set will be given. Finally, we conclude with a discussion in Section 5.

Joint bent-cable Tobit models with skew distributions

This section describes the joint modeling of two-part bent-cable growth curves of left-censored continuous data with right-skewness and an Accelerated Failure Time Model (AFTM) for time-to-event data. Suppose we have n subjects followed over time. The *i*th subject provides a set of longitudinal quantitative measurements $y_{ij}, j = 1,...,n_i$ at times $t_{ij,i} = 1,...,n,$ and a time-to-event Ti to a certain event of interest. We assume that the timing of the observation t_{ij} is non-informative since the decision to schedule a measurement is made independently of the response or time-to-event process. To analyze such a set of data, we next present the two main components of the proposed model: Two-Part Bent-Cable Tobit Models (TBTM) for a response variable with skewness and left-censoring, and interval-censored time-to-event model.

Two-part bent-cable models for left-censored longitudinal data

In this subsection we describe the first component, TBTM, which involves two-part bent-cable Tobit modeling of left-censored longitudinal data having two parts: one part deals with the question of whether the response value is left-censored or not, and the other part determines the gradual phasic patterns of growth curves of the actual observed data of the response variable.

Let y_{ij}^* be a latent response variable that would be measured if the assay did not have a lower detectable limit ρ. A most commonly used model for y_{ij}^* is the Tobit model which is written as:

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

where ρ is a non-stochastic LOD, which in our example is equivalent to log (50). Note that the value of y_{ij} is missing when it is less than or equal to ρ.

It is straightforward to extend (1) for allowing the possibility that only a proportion, π_{ij}, of the observations comes from a population of low responders to treatment (progressors) having a skew-t (ST) distribution, while the other proportion, $1-\pi_{ij}$, of the observations are below LOD whose distribution is located entirely at or below , That is, any value above may come from the ST distribution, while a censored value ($y_{ij} < \rho$) may be from either the ST distribution or a point mass distribution. To model this feature of the response variable, we use a Bernoulli random variable S_{ij} with parameter π_{ij} , where $S_{ij} = 1$ if a patient is a progressor with probability $Pr(S_{ij} = 1) = \pi_{ij}$,

And $S_{ij} = 0$ if a patient is a nonprogressor with probability $1-\pi_{ij}$.

For the Bernoulli random variable Sij , a logistic model is formulated as:

$$logit\left\{Pr\left(S_{ij}=1\,|\,u_i,a_i\right)\right\}=\mathrm{m}^{\dagger}\left(t_{ij},\eta,Z^{*}\left(t_{ij}\right)\right)+u_i \quad 2$$

where $\mathrm{m}\dagger(.)$ is a known function which will be specified in Section 4, η are population-level parameters, u_i is a random effect which has a normal distribution with mean zero and variance σ_u^2 , and a_i is a vector of random effects associated with a time-varying covariate $Z^{*}(t_{ij})$ defined as

$$\begin{aligned} Z_{ij} &= Z_{ij}^{*}+\in_{ij} \\ &= \upsilon'_{1ij}\,\alpha+\upsilon'_{2ij}\,a_i+\in_{ij} \end{aligned} \quad 3$$

Where z_{ij} is an observed covariate with measurement error; $Z^{*}_{ij}=\upsilon_{1ij}'\alpha+\upsilon_{2ij}'a_i$ represents the true (but unobservable) covariate value at time t_{ij}; υ_{1ij} and υ_{2ij} are $r\times 1$ design vectors. Here $\alpha=(\alpha_1,\ldots,\alpha_r)$ and $a_i=(a_{1i},\ldots,a_{ri})$ are unknown population (fixed-effects) and individual-specific (random-effects) parameter vectors, respectively. $\in_i=(\in_{i1},\ldots\in_{in_i})'$ Follows a multivariate ST distribution (see Appendix A for details) with υ_1 degrees of freedom, scale parameter 2ϵ and ni ni skewness diagonal matrix $\Delta(\delta_{\varepsilon i})=\delta_{\varepsilon} I_{ni}$.

We now discuss the second part of TBTM, which is a bent-cable model for a response variable, yij . This model is specified based on an ST distribution and given as

$$y_{ij}=g\left(t_{ij},\mu_{ij},z_{ij}^{*}\right)+e_{ij},e_i\sim ST_{ni,ve}\left(0,\sigma_e^{2}I_{ni},\Delta(\delta_{ei})\right) \quad 4$$

where ij is the mean structure which is defined next; zij is a time-varying covariate, and the error vector $ei = (e_{i1},\ldots,ein_i)'$ follows a multivariate ST distribution with degrees of freedom ν_2, variance σ_e^2 and $n_i\times n_i$ skewness diagonal matrix $\Delta(\delta_{ei})=\delta_e I_{ni}$.

The mean structure μ_{ij} in (4) represents the different growth phases of subject-specific trajectories: the incoming and outgoing linear phases, joined smoothly by a quadratic bend of non-negative width (see Figure 1). For appropriately modeling these growth phases, the following bent-cable mixed-effects model [8,9] is proposed.

$$\mu_{ij}=\eta z_{ij}^{*}+\beta_{1i}+\beta_{2i}t_{ij}+\beta_{3i}q\left(t_{ij},k_i\right) \quad 5$$

where $q(t_{ij},k_i)=(t_{ij}-\phi_{1i}+\phi_{2i})^2\backslash(4\phi_{2i})I(|t_{ij}-\phi_{1i}|\le\phi_{2i})+(t_{ij}-\phi_{1i})I(t_{ij}>\phi_{1i}+\phi_{2i}),I(.)$ is an indicator function; β_{1i} and β_{2i} are the incoming random intercept and slope, respectively; β_{3i} is the change in slope between the in-coming and outgoing linear phases; $K_i=(\phi_{1i},\phi_{2i})$ in which ϕ_{1i} is the center of the bent-cable model; and ϕ_{2i} is the half-width of the bend. Note that the bent-cable model is a generalization of the piecewise model by replacing the kink in a broken-stick model with a quadratic bend with midpoint ϕ_{1i} and half-width ϕ_{2i}. To account for between-subject and within-subject variations, the random coefficient parameters in (5) are further specified as

$$\beta_{1i}=\beta_1+b_{1i},\ \beta_{2i}=\beta_2+b_{2i},\beta_{3i}=\beta_3+b_{3i},\ \phi_{1i}=\phi_1+b_{4i},\ \phi_{2i}=\phi_2+b_{5i} \quad 6$$

where $\beta=(\beta_1,\beta_2,\beta_3,\phi_1,\phi_2)'$ are population-based parameters. The random effects $(b_{1i}, b_{2i}, b_{3i}, b_{4i}, b_{5i})'$ have a multivariate normal distribution $N_5(0,\Sigma_b)$ where Σ_b is a variance-covariance matrix with dimension of 5. This proposed bent-cable model is applied to t the HIV/AIDS data (see Section 4 for more information). The first segment of the bent-cable curve represents a decline in viral load after treatment; the middle part represents a gradual growth. This gradual growth period occurs as a result of the release of HIV from macrophages or other long-lived cells from the lymphoid tissues. The outgoing segment models the viral load rebound as a result of drug resistance. Next, we present a model for a time to event measured within the same trials.

Interval-censored time-to-event models

In this subsection we now describe the second component of the joint modeling framework. It is an accelerated failure time model (AFTM) for a time to event. The timing of the event of interest may not sometimes be available except that it is known to lie in an interval obtained from a sequence of visit times. This type of data is referred to as interval censored data. For such data, the exact time T to an event of interest is only known to fall within a time interval (L, *R*], such that $0<L<T\le R<\infty$. A commonly used method for modeling interval-censored data is an AFTM which assumes that the covariates speed up or slow down the expected event time [30,11,31]. As an extension of AFTM, we consider the random effects accelerated failure time model which takes into account covariates in (3) and longitudinal response in (4) process by including individual-specific random effects, a_i; *bi*, in a linear mixed model [32]. Thus

$$\begin{aligned} \zeta_i &= \log\left(T_i\right)=\gamma_o+\gamma_1^{+'}a_i+\gamma_2^{+'}b_i+\varepsilon_i \\ &= \mu\zeta_i+\varepsilon_i, \end{aligned} \quad 7$$

where T_i is the event time of the *i*th subject, $\mu_{\zeta_i}=\gamma k_i$, and $\gamma=(\gamma_0,\gamma_1^{+'},\gamma_2^{+'})$ are unknown parameters, $k_i = (1, a'_i, b'_i)'$ contains the random-effects from models in (3) and (4). We assume that k_i are independent of ε_i and ε_i follows a normal distribution with mean zero and variance σ_ζ^2 . The AFTM in (7) can also be written as, $T_i=\exp(\gamma k_i)\exp(\varepsilon_i)$, and T_i is only known to lie in the interval

$$(L_i,R_i]=\begin{cases}(0,t_{i,1}], & \text{if } T_i\le t_{i,1}\\ (t_{i,L},t_{i,R}], & \text{if } t_{i,L}<T_i\le t_{i,R}\\ (t_{i,n_i},\infty), & \text{if } T>t_{i,n_i},\end{cases} \quad 8$$

Where $(t_{i,1},\ldots,t_{i,n_i})$ are the clinic visit times for the *i*th patient, *i* = 1,…., *m*.

In the above model, the event times are assumed to depend on individual-specific random effects from the rates of response bent-cable trajectories and associated covariate measurement error process (e.g. CD4). Thus, Model (7) is closely related to the so-called shared

parameter models [30]. These shared random effects may be viewed as latent processes that govern the longitudinal process, the covariate measurement error process and the time-to-event process, leading to a joint modeling approach.

Joint Model

As presented in (3, 4, 7), the association among the longitudinal trajectories, covariate measurement error, and time-to-event processes can be jointly described through the shared random-effects *ai* and *bi*. This joint modeling gives less biased and more efficient inferences than separate analyses. Denote the observed data by $D=\{(y_i,Z_i,L_i,R_i),i=1,...,n\}$ where $y_i=(y_{i1},...,y_{in_i})'$, $Z_i=(Z_{i1},...,Z_{in_i})'$ and $(L_i,R_i]$ is the smallest observed interval containing the event time Ti. Let = $\theta=\{\alpha,\beta,\gamma,\sigma^2_\zeta,\sigma_u{}^2,\eta,\sigma_\varepsilon{}^2,\sigma_e{}^2,\sum a,\sum b,\nu_1,\nu_2,\delta_\varepsilon,\delta_e\}$ be the collection of unknown population parameters in models (3), (4) and (7). Let $f(.|.)$ and $F(.|.)$ denote a Probability Density Function (PDF) and Cumulative Density Function (CDF), respectively. Conditional on the random variables and some unknown parameters, a detectable measurement y_{ij} contributes $f(y_{ij}|a_i b_i)$, where as a non-detectable measurement contributes $F(\rho|a_i,b_i)\equiv Pr(y_{ij}<\rho|a_i,b_i)$ in the likelihood. The likelihood function for the joint model becomes

$$L(\theta;D)=\prod_{i=1}^{n}\int\int\int\prod_{j=1}^{ni}\left[Pr(S_{ij}=1|u_i,a_i)\,f(y_{ij}|a_i,b_i)\right]^{c_{ij}}$$

$$\times\left[1-p_r\left(s_{ij}=1|u_i,a_i\right)\right)+p_r\left(s_{ij}=1|u_i,a_i\right)F\left(\rho|a_i,b_i\right)\Big]^{1-c_{ij}}$$

$$\times f\left(z_{ij}|a_i\right)\left[F_\zeta\left(\log(R_i)|a_i,b_i\right)\right]-F_\zeta\left(\log(L_i)|a_i,b_i\right]^{di}S^*\left(\zeta_i|a_i,b_i\right)^{1-d_i}$$

$$\times f(u_i)\,f(a_i)\,f(b_i)\,du_i\,da_i\,db_i \qquad 9$$

Where

$$\zeta_i=\log(T_i),S^*(\zeta_i|a_i,b_i)=\int_{\zeta_i}^{\infty}f(\zeta_i|a_i,b_i)d\zeta_i=1-\Phi(\zeta_i);f(\zeta_i|a_i,b_i)=\phi\frac{\left(\zeta_i-\gamma_0-\gamma_1^{+\prime}a_i-\gamma_2^{+\prime}b_i\right)}{\sigma_\zeta}/T_i$$

$\phi(.)$ and $\Phi(.)$ are standard normal density and cumulative density distribution, respectively. For time to event, d_i = 0 if right censored, and d_i = 1 if interval censored. Note that the observed dependent variable y_{ij} = y^*_{ij} if c_{ij} = 1, and y_{ij} is left censored if *cij* = 0, where *cij* is a censoring indicator, and the latent variable y^*_{ij} was discussed in Section 2.

Bayesian Inference

The unknown parameters in (9) are estimated using the Bayesian approach via a Markov Chain Monte Carlo (MCMC) algorithm which can replace the integrals in (9) by sampling of exact event times and values of latent random effects from appropriate posterior distributions. In order to carry out MCMC, we exploit the stochastic representation of the ST distribution by introducing two random variables W_{eij} and $W_{\epsilon ij}$. Based on such stochastic representations, the ST distributions of Z_{ij} and Y_{ij} can be hierarchically formulated in conjunction with model (7) as follows.

$$\begin{aligned}
&y_{ij}|b_i,\omega_{eij},\xi_{ei};\beta,\sigma_e^2,\delta e_{ij}\sim N(g(t_{ij},z_{ij}^*,\beta,b_i)+\delta e_{ij}\omega_{eij},\xi_{ei}^{-1}\sigma_e^2),\\
&\omega_{eij}\sim N(0,1)I(\omega_{eij}>0),\xi_{ei}|\nu_e\sim G(\nu_e/2,\nu_e/2),\\
&z_{ij}|a_i,\omega_{eij},\xi_{ei};\alpha,\sigma_\epsilon^2,\delta\in_{ij}\sim N(g(z_{ij}^*+\delta_{\epsilon ij}\omega_{\epsilon ij},\xi_{\epsilon i}^{-1}\sigma_\epsilon^2),\\
&\omega_{\epsilon ij}\sim N(0,1)I(\omega_{\epsilon ij}>0),\xi_{\epsilon i}|\nu_e\sim G(\nu_\epsilon/2,\nu_\epsilon/2),\\
&\zeta_i|a_i,b_i,\gamma,\sigma_\zeta^2\sim N(\mu\zeta_i,\sigma_\zeta^2),u_i|\sigma_u^2\sim N(0,\sigma_u^2),\\
&a_i|\Sigma_a\sim N_\gamma(0,\Sigma_a),\quad b_i|\Sigma_b\sim N_{S4}(0,\Sigma_b),
\end{aligned} \qquad 10$$

Where $G(.)$ is a gamma distribution, I ($W_{eij}>0$) is an indicator function. It is noted that the hierarchical model with the ST distribution (10) can be reduced to the following three special cases: (i) a model with a skew-normal (SN) distribution as $\nu_e\to\infty$ and $\xi_{ei}\to1$ with probability 1, (ii) a model with a standard t-distribution as $\delta_{eij}=0$, or (iii) a model with a standard normal distribution as $\nu_e\to\infty$ and $\delta_{eij}=0$.

To complete the Bayesian formulation, we need to specify prior distributions for unknown parameters in as follows.

$$\begin{aligned}
&\alpha\sim N_p(\alpha_0,\Lambda_1),\sigma_\epsilon^2\sim IG(\omega_1,\omega_2),\Sigma_a\sim IW(\Omega_1,\rho_1),\sigma_u^2\sim IG(\omega_3,\omega_4),\\
&\beta\sim N_{S2}(\beta_0,\Lambda_2),\sigma_e^2\sim IG(\omega_5,\omega_6),\Sigma_b\sim IW(\Omega_2,\rho_2),\delta_{ei}\sim N_{ni}(0,\Gamma_1),\\
&\gamma\sim N_{S3}(\gamma^*,\Lambda_3),\nu_e\sim G(\nu_{e0},\nu_{e1})I(\nu_e>3),\sigma_\zeta^2\sim IG(\omega_7,\omega_8),\\
&\nu_\epsilon\sim G(\nu_{\epsilon0},\nu_{\epsilon1})I(\nu_\epsilon>3),\delta_{\epsilon i}\sim N_{ni}(0,\Gamma_2)
\end{aligned} \qquad 11$$

where the mutually independent Inverse Gamma (*IG*), Normal (*N*), Gamma(*G*) and Inverse Wishart (*IW*) prior distributions are chosen to facilitate computations [32]. The hyper-parameter matrices $\Lambda_1,\Lambda_2,\Lambda_3,\Omega_1,\Omega_2,\Gamma_1$ and Γ_2 are assumed to be diagonal for implementation convenience.

Combining the likelihood of the observed data and the prior distributions for the unknown model parameters, we can make Bayesian inference for the parameters based on their posterior distributions using the Gibbs sampler algorithm. A freely available WinBUGS software [33] is used for fitting the proposed models. Note that when using the WinBUGS soft-ware, it is not necessary to specify the full conditional distributions explicitly since they are generated automatically by the software. Thus, we omit those here to save space.

Application to HIV/AIDS Clinical Data

For illustrating the proposed methods, we analyze real data from a clinicalstudy [34]. The study involved 44 HIV-infected patients, who were treated with a potent antiretroviral regimen. The outcome variable was a viral load which was measured by the number of HIV-1 RNA copies/mL in plasma, and it was subjected to left-censoring due to detection limitation of the assay. Even though it was designed that the viral load would be measured at study days 0, 7, 14, 28, 56, 84, 112 and 140, patients had different follow-up times because of missing scheduled visits. Some patients had at most 5 time points for follow-up (11%), 6 time points (9.1%), 7 time points (27.3%), and 8 time points (52.3%). Associated CD4 and CD8 cell counts were also measured throughout the study on a similar scheme. In this study, the viral load detectable limit was 50 copies/mL, and the RNA viral load measures below this limit are not considered reliable and thus

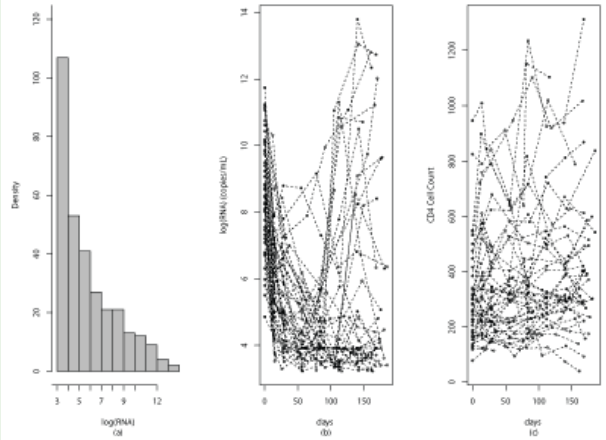

Figure 2: (a) Histogram of viral load on log scale; (b) spaghetti plot of viral load on log scale; (c) spaghetti plot of CD4 cell count, measured from 44 patients in an AIDS clinical trial study.

treated as missing. The natural logarithmic transformation of viral load is used in the following analyses. Even after log transformation, the distribution of viral load is nonsymmetric as shown in Figure 2a.

Specification of models

In the next subsections, the specific components of the proposed joint two-part bent-cable Tobit models (JTBTM) will be described and fitted to this data set.

Logistic mixed-effects model: HIV/AIDS data suffer from left censoring. As the result, a Tobit model can be extended to involve two parts: (i) the first part contains the effect on the probability that the response variable is above LOD, and (ii) the second part contains the bent-cable skew-t models presented in Section 4.1.3 for the viral load data. The first part is modeled using a mixed-effect logistic regression given as

$$\log it = \{\Pr(S_{ij} = 1 \mid u_i, a_i)\} = m^{\dagger}(t_{ij}, \eta, z_{ij}^{*}) = \eta_1 + \eta_2 t_{ij} + \eta_3 z_{ij}^{*} + u_i \quad 12$$

where $Pr\left(S_{ij}=1|u_i, a_i\right)$ is the probability of an HIV patient being a progressor (having viral load greater than LOD or rebound), the parameter vector $\eta = \left(\eta_1, \eta_2, \eta_3,\right)'$ represents population-level coefficients, and $u_i \sim N\left(0, \sigma_u^2\right)$. The covariate z_{ij}^{*} is the true value estimated from the following covariate measurement error model for z_{ij}

$$z_{ij} = (\alpha_1 + \alpha_{i1}) + (\alpha_2 + \alpha_{i2}) t_{ij} + (\alpha_3 + \alpha_{i3}) t_{ij}^2 + \in_{ij}, \quad 13$$

where

$$z_{ij}^{*} = \left(\alpha_1 + a_{i1}\right) + \left(\alpha_2 + a_{i2}\right) t_{ij} + \left(\alpha_3 + a_{i3}\right) t_{ij}^2, \alpha = \left(\alpha_1, \alpha_2, \alpha_3,\right)'$$

is a vector of fixed-effects parameters and $a_i = \left(a_{i1}, a_{i2}, a_{i3}\right)' \sim N_3\left(0, \Sigma_a\right)$ are individual-specific random-effects. To simplifying the estimation process of the model in (13), we standardized the time-varying covariate CD4 cell counts by subtracting 375.46 and dividing by 228.57. We also rescaled the original time t_{ij} (in days) to be between 0 and 1.

Response model: For the JTBTM, the response variable is the viral load. The goal is to assess the structure of the phasic changes of the viral load over time, from being a decreasing trend in the first segment to an increasing one at later stage (see Figure 1 and Figure 2(b)). Identifying these phasic changes is also central to making sound decisions for treatment management and care of patients with AIDS. Based on this substantive consideration, we t the following bent-cable Tobit model to the HIV viral load data over time t_{ij}

$$\left(i=1,\ldots,n=44,\ j=1,\ldots,n_i\right).$$

$$y_{ij} = \eta z_{ij}^{*} + \beta_{1i} + \beta_{2i} t_{ij} + \beta_{3i} q(t_{ij}, \alpha_i) + e_{ij}, \quad 14$$

where Y_{ij} is the natural logarithmic transformation of the viral load for the i_{th} subject at time t_{ij}; $\beta_{1i}, \beta_{2i}, \beta_{3i},$

are defined in (6) and q(.) is described below (5). Another useful parameter is the critical time point at which the response mean trajectory takes an upward trend from a decreasing trend. This time point is located at $\frac{\phi_1 - \phi_2 - 2\beta_2\phi_2}{\beta 3}$ [6]. $ei = (e_{i1}, \ldots, e_{in_i})' \sim S\Gamma_{ni,v2}\left(0, \sigma_e^2 I_{ni}, \delta_e I_{ni}\right)$.

Time-to-event model: Along with the response variable in the HIV/AIDS data, the time to the first decline in the CD4/CD8 ratio for the i^{th} subject, Ti, is also jointly modeled. Ti cannot be observed but is only known as being contained in some time interval, giving interval-censored data. Using the interval-censored data, we consider the following specification of AFTM for time to first decline of the CD4/CD8 ratio.

$$\log(T_i) = \gamma k_i + \varepsilon_i, \ \ \varepsilon_i \sim N(0, \sigma_\zeta^2), \quad 15$$

where $K_i = \left(1, a_{i1}, a_{i2}, b_{i2}, b_{i4}\right)'$ with associated unknown coefficients $\gamma = (\gamma_0, \gamma_1, \gamma_2, \gamma_3, \gamma_4)$ In model (15), the random-effects b_{i2} and b_{i4} represent individual variations in the r stand second-phase viral decay rates, respectively, so they may be predictive of event times. While bi1 and bi3 represent variations in the baseline viral loads, they do not appear to be highly predictive of event times, so they are excluded from the model to reduce the number of parameters. The random-effects a_{i1} and a_{i2} capture the main features of individual CD4 trajectories. For the HIV/AIDS data analysis, Model (15) formulates the dependence between the longitudinal model in (14) and the time-to-event model by making them share common random effects.

Data analysis

For the JTBTM, the distribution of the viral load is highly skewed even after log-transformation. Thus, a nonsymmetrical skew-elliptical distribution for the error term is proposed. Accordingly, we consider (i) Model I: A joint bent-cable Tobit model with independent multivariate normal distributions of random errors for both the

response model (14) and the covariate model (3); (ii) Model II: A joint bent-cable Tobit model with independent multivariate skew-normal distributions of random errors for both the response model (14) and the covariate model (3); and (iii) Model III: A joint bent-cable Tobit model with independent multivariate skew-t distributions of random errors for both the response model (14) and the covariate model (3). The parameters of JTBTM are estimated using the Bayesian approach. For the Bayesian inference, we specify the prior distributions of these pa-rameters. Accordingly, we take non informative prior distribution for (i)fixed-effects as independent normal distribution N(0; 100) for each component of the population parameter vectors α, β, η and γ (ii) variances as an inverse gamma prior distribution IG(0:01; 0:01) each for $\sigma_e^2, \sigma_\varepsilon^2$ and σ_u^2 ,so that the distribution has mean 1 and variance 100. (iii) The priors for the variance-covariance matrices of the random-effects Σ_a and Σ_b are taken to be inverse Wishart distributions IW($\Omega 1;\rho_1$) and IW($\Omega 2;\rho_2$) with covariance matrices $\Omega 1$ = diag(0:01; 0:01; 0:01), $\Omega 2$ = diag(0:01; 0:01; 0:01; 0:01) and 1 = 3; 2 = 4, respectively. (iv)The degrees of freedom parameters ν_1 and ν_2 follow truncated exponential distribution with $\nu_{10} = \nu_{20} = 0{:}5$. (v)

For each of the skewness parameters δ_e and δ_ε, we choose independent normal distribution N(0; 100), where we assume that $\delta_{ei} = \delta_e 1_{ni}$ and $\delta_{\varepsilon i} = \delta_\varepsilon 1_{ni}$. Estimation of model parameters was carried out using the MCMC algorithm via WinBUG [33]. Convergence of the MCMC algorithm was assessed using several available tools within WinBUGS. First, we inspected how well the chain was mixing by inspecting trace plots of the iteration number against the values of the draw of parameters at each iteration. Few parameters took longer iterations to mix well, up to 100,000 iterations,

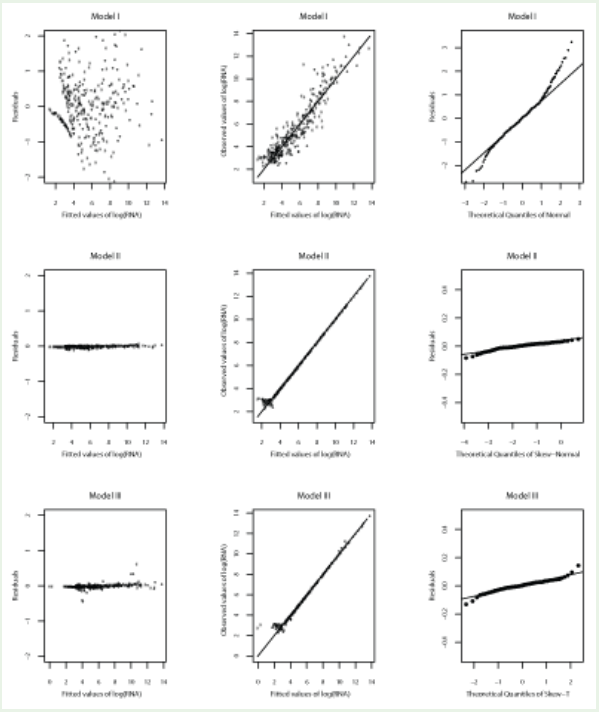

Figure 3: Plots of goodness-of-t statistics for the three Models: (i) The left panel shows the residual against the fitted values, (ii) the middle has plots of the fitted against observed log(RNA) values and (iii) the right panel has the Q-Q plots of residuals.

and thus we discarded the first 100,000 iterations as burn-in. Second, assessment of convergence was done by monitoring autocorrelations between the draws of the MCMC sampler after additional 400,000 iterations. Auto-correlations were small after using a thinning of 40, giving a good mixing.

Third, the Markov chain (MC) errors were less than 5% of posterior standard eviation values for the parameters, indicating good precision and conver-gence of MCMC [35]. Finally, we obtained 10,000 samples for subsequent posterior inference of the unknown parameters of interest. The computational burden to run MCMC for Model II, for example, was close to14 hours on Latitude E5540, Intel(R) Core(TM)i7-4600U @2.10GHz.

Analysis results

The results of fitting JTBTM to the HIV/AIDS data are given in Tables 1-3. Table 1 presents the comparison among Models I-III using Bayesian model selection criteria (DIC = Deviance Information Criterion, EPD = Expected Predictive Deviance and RSS = Bayesian Residual Sum of Squares). According to these criteria, Model II have the smallest DIC (354.617) and RSS (.203) values, while the EPD (.064) value is very close to that of Model III. Overall the results suggest that Model II is relatively the best model as compared to Models I and III. In addition, the goodness-of-t diagnosis plots of (i) residuals *versus* fitted values (left panel), (ii) observed values versus fitted values (middle panel) and (iii) Q-Q plots of the residuals (right panel) for Models I-III are displayed in Figure 3. It can be seen from the plots in the left and middle panels that Model II (skew-normal) provides a better t to the observed data as compared to Model I (normal) and Model III (skew-t). This finding is further confirmed by the Q-Q plots of the residuals (right panel) in which Model II has few extreme values showing a better goodness-of fit to the data than either Model I or Model III. Thus, Model II is considered as the 'best' model which accounts for phasic changes, skewness, left-censoring and time to event. The implication of the finding is that a skewed bent-cable model is a better choice for fitting the logarithmic transform of the continuous component of the viral load (RNA) data (Table 1 and Figure 3).

JTBTM is also flexible to predict missing values below LOD. The predicted values are depicted in Figure 4. Figure 4(a) displays the distribution of the observed but inaccurate values, while Figures 4(b-d) show the histograms of the Bayesian predicted values under normal, skew-normal, and skew-t, respectively. Note that the dotted vertical line represents log (50) = 3.912 (LOD). We can see from the histograms that the left-censored, inaccurate values are stacked up in the lower end of Figure 4(a), whereas the predicted values are spread out as expected for the other plots. Thus, JTBTM under skew-normal gives relatively more compact predictions of missing values below LOD than both JTBTM under normal and JTBTM with skew-t, implying that JTBTM with skew-normal (Model II) is a better model.

Table 1: Model comparison using Bayesian model selection criteria (RSS = Residual Sum Of Squares, EPD= Expected Predictive Deviance).

Criterion	Model I	Model II	Model III
DIC	1322.11	354.617	598.5
RSS	266.905	0.203	1.432
EPD	2.603	0.064	0.053

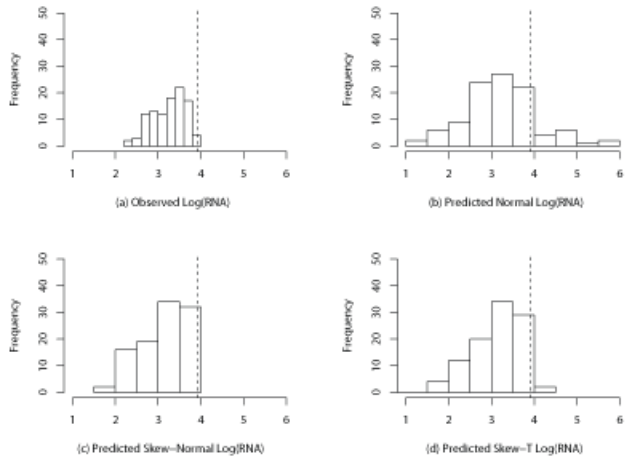

Figure 4: Predicted values below limit of detection for viral load (RNA). The limit of detection is at log (50), shown by the dotted vertical line.

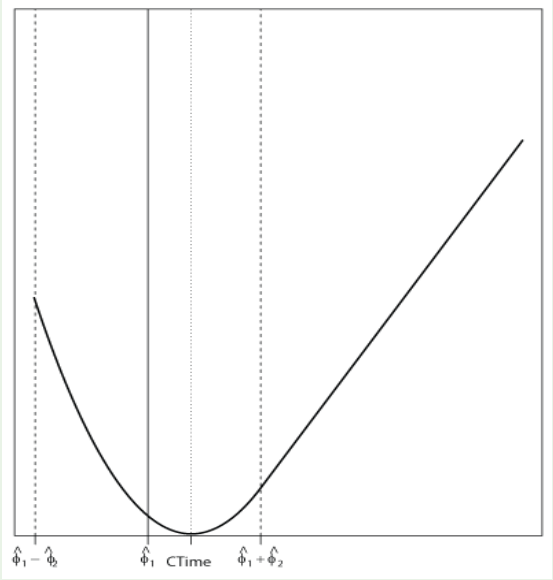

Figure 5: Fitted bent-cable growth curve for log (viral load). The dotted vertical lines represent the lower (Ψ_1) and upper (Ψ_2) limits of the gradual transition period with center at ϕ_1 = 9:327 weeks (solid vertical line); an estimated critical time point is C Time = 12:877 weeks.

Next, we discuss and interpret the results of fitting Model II to the AIDS data.

Results of Model II: The Baysian analysis results for the response model (14), particularly for Model II which gives the best model t, are presented in the middle row of Table 2. The first part of the response model is the logit model (12) which describes the probability of an HIV patient having viral loads above the lower detection limit, leading to progression to AIDS. Looking at the logit part for Model II in Table 2, the posterior mean for the coefficient of time effect (2) on the probability of an HIV patient becoming a progressor over time is 2.601 with a 95% credible interval (1.354; 3.916) which does not contain zero. The corresponding odds ratio is exp(2:601) = 13.477, suggesting that over time after the initial treatment, patients are approximately 13.477 times more likely to have viral loads above detection limit. That is, as time increases, the probability that the value of viral load is coming from the skew-normal distribution also increases. It is noted that the effect of CD4 turned out to be nonsignicant after adjusting for the effect of time.

The second part of the response model is the log-nonlinear model (14), which describes the bent-cable model for viral loads. The posterior means for β_1 and β_2, which are the incoming intercept and slope of the first phase, are 4.48 and -747, respectively; the posterior mean of the parameter 3 rep-resenting the change in slope between the incoming first phase and outgoing linear phase is 1.079. The posterior mean of the center of the bent-cable model, $\phi 1$, is 9.327, and for $\phi 2$, which is the half-width of the bend, the estimate is 9.239. These results suggest that the typical viral load phasic patterns approximately begin from the time of initiation of treatment and last for about 9.327 + 9.239 = 18.566 weeks, followed by a linear rebound of viral load with a slope of 1.079. The posterior mean of the scale parameter σ_e^2 is .032 which is relatively small as the result of taking into account skewness of the data. The posterior mean of the skewness parameter δ_e is 2.013 with a 95% credible interval of (1.663, 2.458). This positive and strong estimate confirms the fact that the distribution of the HIV/AIDS data is skewed even after taking

Table 2: A summary of the Posterior Means (PM) of population parameters along with the Corresponding Lower Limit (LCI) and upper limit (UCI) of 95% equal-tail credible interval.

		Log-nonlinear Part						Logit Part					
Model		β_1	β_2	β_3	ζ	ϕ_1	ϕ_2	η_1	η_2	η_3	σ_e^2	σ_u^2	δ_e
I	PM	7.656	-1.182	1.318	-1.107	4	5.198	-3.573	2.595	0.448	1.349	1.507	-
	L_{CI}	5.006	-1.994	0.858	-1.567	0.923	2.771	-4.726	1.328	-0.057	1.069	0.097	-
	U_{CI}	8.493	-0.732	2.145	-0.682	6.202	8.18	-2.631	3.947	1.06	1.689	4.381	-
II	PM	4.48	-0.747	1.079	-1.05	9.327	9.239	-3.574	2.601	0.417	0.032	1.498	2.013
	L_{CI}	3.355	-1.537	0.606	-1.503	2.46	3.49	-4.703	1.354	-0.113	0.004	0.14	1.663
	U_{CI}	5.459	-0.356	1.712	-0.626	22.18	21.25	-2.657	3.916	1.033	0.142	4.355	2.458
III	PM	4.595	-0.767	1.54	-0.889	13.52	21.15	-3.561	2.597	0.408	0.02	1.482	2.203
	L_{CI}	3.685	-0.9225	1.186	-1.306	10.29	16.78	-4.69	1.368	-0.111	0.003	0.091	1.959
	U_{CI}	5.462	-0.638	2.105	-0.505	19.53	27.94	-2.631	3.921	1.031	0.077	4.33	2.465

Table 3: A summary of the Posterior Means (PM) of parameters of covariate and time-to-event models along with the Corresponding Lower Limit (LCI) and Upper Limit (UCI) of 95% equal-tail credible interval.

		Model I			Model II			Model III	
	PM	*LCI*	*UCI*	PM	*LCI*	*UCI*	PM	*LCI*	*UCI*
Covariate Model									
α_1	-0.913	-1.214	-0.606	0.362	-0.029	0.701	-0.872	-1.175	-0.453
α_2	0.67	0.166	1.175	0.727	0.133	1.208	0.67	0.239	1.108
α_3	-0.292	-0.84	0.262	-0.324	-0.873	0.282	-0.277	-0.748	0.236
σ_ϵ^2	0.062	0.031	0.097	0.082	0.052	0.117	0.069	0.039	0.112
Time-to-event Model									
γ_0	3.142	2.893	3.388	3.175	2.941	3.413	3.155	2.932	3.367
γ_1	-0.053	-0.849	0.6	-0.297	-1.087	0.429	-0.248	-1.043	0.331
γ_2	0.444	-1.326	1.711	0.954	-0.723	2.078	1.378	0.678	2.351
γ_3	-1.86	-4.384	1.5	-1.083	-3.677	1.482	-0.377	-2.227	1.352
γ_4	-0.512	-2.033	0.827	-0.29	-1.688	0.803	-0.046	-0.831	0.659
σ_4^2	0.133	0.111	0.161	0.133	0.11	0.161	0.134	0.111	0.161

the log-transformation. Thus, incorporating skewness parameter in modeling the data is highly recommended.

Graphically, the log-nonlinear model (bent-cable curve) is displayed in Figure 5. It can be seen that patients show decline in viral load after receiving the ARV treatment with a gradual transition period up until ^ϕ1 + ^ϕ2 =18.566 weeks. This shows that the reduction of production of viral load after treatment is stronger at the beginning of the study but does not last long. Right after approximately 19 weeks in the study, patients experiencea significant linear increase at the rate of 1.079 log viral load per week (the right dotted line in Figure 5). The Critical Time (C Time) point at which the response mean trajectory takes an upward trend from a decreasing trend is estimated to be 12.877 weeks after the start of treatment. Thus, the bent-cable curve of viral load after receiving treatment suggests that the effect of treatment decreases over time and thus providing less protection against the multiplication of HIV virus. This explains why we see the upward linear curves towards the latter stage of the study.

For Model II, the posterior means of the parameters of the CD4 covariate model (3) are presented in the upper part of Table 3. The posterior mean of the time effect (α_2) on observed CD4 cell counts with measurement error is .727 with a 95% credible interval of (:133; 1.208). The 95% credible interval does not contain zero, suggesting that there is a strong, positive linear relationship between CD4 cell count and measurement time. The quadratic effect (α_3) of time on CD4 count is found to be nonsignificant as the corresponding 95% credible interval includes zero. The posterior mean of the scale parameter σ_ε^2 of the covariate model is .082 for Model II which accounts for skewness. The lower part of Table 3 contains the estimates of parameters of AFTM in (15) for the first decline of CD4/CD8 ratio. The posterior means of these parameters have 95% credible intervals containing zeros, indicating that time to first decrease of the CD4/CD8 ratio is not strongly associated with either the bent-cable rates or the CD4 covariate measurement error rates over time. This finding is similar to that of [31].

Discussion and conclusion

The focus of this paper is to develop a bent-cable mixed-effects Tobit model which simultaneously incorporates two-part censored response process and time to event process. The processes are joined by using random effects that characterize the slopes of individual-specific bent-cable trajectories, CD4 covariate measurement error and time to first decrease of CD4/CD8 ratio. The bent-cable trajectories of the HIV/AIDS data is assumed to have a mixture of two distributions: a point mass below the limit of detection with non-zero probability and a skew-normal distribution that was found to be the best fit to the data. These two parts of the mixture are modeled using a logistic mixed-effects regression (12) and a log-nonlinear bent-cable regression (14). The former regression assesses the effects of covariates on the probability of classifying patients as having their viral loads coming from the skew-normal distribution, leading potentially to higher chance of disease progression. The findings indicate that patients, who received a treatment at baseline, are approximately 13.477 times more likely to have viral loads above detection limit over time, increasing the chance of progression to AIDS. The results of fitting the log-nonlinear bent-cable regression (see Figure 5) show that a significant decline (incoming trend with a slope β_2 = -.747) in viral load is followed by a gradual transition period upward until 18:566 weeks since initiation of treatment. Thus, the bent-cable mixed-effects Tobit model has flexibility to account for heterogeneity in the left-censored response variable and provide precise estimate of the time at which drug resistance will develop (rebound).

Though the proposed bent-cable mixed-effects Tobit model deals with clumped data at lower detection limit, the model can also are used to analyze right-censored data. Either way, it is important to properly incorporate censoring effects in a longitudinal data analysis. Our proposed models with skew distributions make best use of both censored and uncensored data information. In addition to the presence of censoring effects, when there is skewness in the longitudinal data and covariate measurement errors, the Bayesian approach is a powerful tool to jointly model time-to-event and longitudinal response with skewness and left-censoring. The Bayesian estimation of the parameters of the proposed models was carried out using the publicly avail-able WinBUGS package [33], making the procedure quite powerful and accessible to practicing statisticians in the field.

Despite being the best fit to the longitudinal viral load and time-to-event data, JTBTM has a limitation. It is not intended to be an exhaustive study of the HIV/AIDS dynamic profiles. We considered a small number of covariates, particularly CD4, which are related to viral load, a priori. However, it would be straightforward to extend the proposed methods for incorporating several covariates. Goodness-of fit of the proposed models to the data could have been improved by using more stringent methods such as cross-validation prediction. Unfortunately, in our case we have a small data set (44 patients) and splitting such a data set into two subsets for cross-validation would reduce the precision of the model fits. In summary, we have illustrated that the Joint Two-Part Bent-Cable Tobit Models (JTBTM) are very flexible and capable of fitting phasic patterns of a response process with a high proportion of data at a detection limit and skewness, covariate measurement error and time-to-event process simultaneously. For making reliable conclusions and appropriate clinical decisions, particularly for intervention studies, JTBTM with skew distributions holds a promising future for applications in various areas such as hepatitis C virus (HCV) RNA [36].

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