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Estimating time to event characteristics via longitudinal threshold regression models - an application to cervical dilation progression

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Abstract

In longitudinal studies, it is sometimes of interest to estimate the distribution of the time a longitudinal process takes to traverse from one threshold to another. For example, the distribution of the time it takes a woman's cervical dilation to progress from 3 to 4 cm can aid the decision making of obstetricians as to whether a stalled labor should be allowed to proceed or stopped in favor of other options. Often researchers treat this type of data structure as interval censored and employ traditional survival analysis methods. However, the traditional interval censoring approaches are inefficient in that they do not use all of the available data. In this paper, we propose utilizing a longitudinal threshold model to estimate the distribution of the elapsed time between two thresholds of the longitudinal process from repeated measurements. We extend this modeling framework to be used with multiple thresholds. A Wiener process under the first hitting time (FHT) framework is used to represent survival distribution. We demonstrate our model through simulation studies and an analysis of data from the Consortium on Safe Labor (CSL) study.

Keywords

First hitting time; Threshold regression; Weiner process

1. Introduction

It is sometimes of interest to estimate the distribution of the time it takes a longitudinal process to progress between threshold values. For example, an important obstetrics problem is to estimate the distribution of the time it takes the cervix of a woman in labor to dilate from, say, 3 cm to 4 cm. This distribution is useful as a benchmark during labor since it gives obstetricians an idea of what proportion of women would have reached a target

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dilation within a given time period. If a woman has been within the 3 cm to 4 cm interval for 4 hours, the obstetrician may consider other delivery options depending on the proportion of women expected to have progressed. As a result, a main outcome of interest is the survival distribution of the time it takes to progress from 3 to 4 cm. For some data, when the exact time between threshold values is observed standard survival analysis methods can be applied. Difficulty arises when the observed longitudinal process is irregularly sampled. In this case, the time when the longitudinal process hits the threshold(s) may not be observed. One option is to use doubly interval censored survival analysis techniques [1], where the time the subject reached the upper and lower thresholds is known to fall within an interval. The main critique of the survival analysis method is that it does not use all of the available data. For example, if there are 10 observations known to occur within the thresholds, the interval-censored method uses at most 4 (2 to bound each threshold).

The first hitting time (FHT) approach has recently gained popularity as a survival analysis method for biomedical studies [2]. FHT models have been successfully applied to analyze the length of stay in the hospital, birth weight, risk of lung cancer of rail workers, and recurrent exacerbations in chronic obstructive pulmonary disease among others (see [3, 4, 5, 6, 7] and the references therein). FHT models utilize longitudinal threshold regression (LTR) of a latent “health process” to motivate the form for a survival model [2]. However, these models have not been applied to biomedical data when an actual marker of the “health process” is observed. The reliability literature on LTR has considered such a scenario [8, 9, 10]. However, reliability experiments produce data with lower variance than what is observed in biomedical data, with less unit to unit variability. Also, the use of multiple thresholds, which is vital to our data example, has not been addressed.

In this paper we propose a LTR model to estimate the elapsed time between two thresholds of a biological longitudinal process and draw inferences at the population level. Our method utilizes the repeated measures of the longitudinal process to estimate the distribution of the elapsed time between the thresholds. The thresholds may not cover the entire range of the outcome (e.g., a 3 to 4 cm thresholds versus 0 to 10 cm range), so we limit the range of the outcome to limit the assumptions of the model. Difficulties that arise include creating an appropriate subset of the data to limit the range of the outcome, length bias induced by left truncation, heterogeneity in the baseline measurement, and residual dependence in the curves. We also consider a conditional LTR model that alters the mean of the stochastic process based on the previous measurement. This model can be used to model the entire longitudinal process yet still provide FHT inferences for each interval of interest, conditional on the previous measurement.

We applied the proposed methods, and an analogous interval censored (IC) method to data from the Consortium on Safe Labor (CSL) study. The CSL study is a multi-center retrospective observational study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and explained elsewhere in detail [11]. A main goal of the CSL study was to estimate population-level labor curves that could be used by practicing obstetricians as a benchmark for standard labor progression. To this end, we look to estimate population level survival curves for the time it takes women to progress from D to $D + 1$ cm dilation, for multiple values of D . Previous analysis consisted

of an interval censored log normal model to examine labor patterns in contemporary obstetric practice [11, 12], see also [13, 14]. In extensive simulation studies and data analyses we compare the properties of the LTR and IC approaches.

Other examples where similar problems arise include estimating the distribution of the time it takes women to progress from different categories of bone mineral density (i.e., normal, moderate/advanced osteopenia, osteoporosis), as measured by their bone mineral density T-score (a continuous measure) traversing between thresholds [15]. Our specific aims are to develop a framework that will allow for the estimation of an LTR model for two thresholds, and extend the model to allow for inference on the entire longitudinal process.

The paper is organized as follows. In Section 2 we present the methodology on the proposed LTR model, discuss the application of the LTR to a Wiener process, propose a conditional framework useful for modeling the entire longitudinal process and give our inference procedures. In Section 3 we present a simulation study with a Wiener process and parameter estimates from both LTR and IC model (see also Appendices B, C and D which contains additional simulation studies). In Section 4, we apply both the LTR and IC models on data from the CSL study. In Section 5, we conclude our findings and give some recommendations for further study on the proposed LTR model.

2. Methods

In this section, we formulate the LTR model in the interest of estimating the survival distribution for the time between thresholds. In Section 2.1 we discuss the formulation of the LTR model when we have two thresholds of interest. In Appendix A of the Supplementary Information, we discuss an extension of this approach to incorporate multiple (> 2) thresholds with varying mean structures. In Section 2.2, we discuss the estimation details under the assumption that the underlying stochastic model is a Wiener process. In Section 2.3 we propose a formulation of the Wiener process model where the slope parameter is a function of the previous measurement. This method is useful for providing conditional inferences on the entire longitudinal process, which are non-linear in time. Finally, in Section 2.4 we discuss our inference procedures.

2.1. Longitudinal threshold model

In this section, we estimate the distribution of the time it takes a longitudinal process to traverse between two thresholds when longitudinal measurements are used for analysis. We define A_1 and A_2 as the lower and upper thresholds of interest, respectively. Further, let $\mathbf{t}_i^* = \{t_{i1}^*, t_{i2}^*, \dots, t_{in_i}^*\}$ and $\mathbf{Y}_i^* = \{Y_{i1}^*, Y_{i2}^*, \dots, Y_{in_i}^*\}$ be the vectors of observed time points and measurements for the i th subject, respectively, where $Y_{ij}^* = Y_i^*(t_{ij}^*)$ for $i = 1, 2, \dots, n, j = 1, 2, \dots, n_i$. Let (t_0, y_0) denote the initial state which, initially, we assume to be the same across subjects. The observed data consist of independent pairs of $(\mathbf{t}_i^*, \mathbf{Y}_i^*)|_{i=1, \dots, n}$. The survival time of interest is defined as the difference of two first hitting times, $S_{12} = S_2 - S_1$, where $S_k = \inf\{s: Y(s) \geq A_k\}$. Notice that the definition of S_k is relative to the initial state (t_0, y_0) , which is commonly $(0, 0)$. Here we assume that $\Pr(S_{12} < \infty) = 1$.

Consider the general stochastic form of the longitudinal process

$$Y_{ij}^* = \mu_{ij} + \varepsilon_{ij} = \mu(t_{ij}; \boldsymbol{\beta}) + \varepsilon_{ij} \quad (1)$$

where μ_{ij} is the mean of i th subject at time t_{ij} , ε_{ij} is the error term with $\varepsilon_{ij} \sim \mathcal{G}(t_{ij}|\boldsymbol{\sigma})$, and $\boldsymbol{\beta}$ is a vector of parameters. The distribution of S_k can be defined as

$$F_{S_k} \{t|(t_0, y_0), \boldsymbol{\theta}\} = P\{S_k \leq t|(t_0, y_0), \boldsymbol{\theta}\} = P \left[\max_{u \in [t_0, t]} \{Y_i^*(u)\} \geq A_k | (t_0, y_0), \boldsymbol{\theta} \right], \quad (2)$$

where $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\sigma})$. There are specifications of (1) where (2) and F_{S_k} simplify to known parametric distributions. For example, when ε corresponds to a Wiener process, Gamma process, or Ornstein–Uhlenbeck process (2) corresponds to an inverse Gaussian, inverse Gamma, or Ricciardi–Sato distribution, respectively (see Lee and Whitmore [16] for other FHT models).

Many of the models used for (1) will have the Markov property where $Y_j - Y_{j-1}$ and $\varepsilon_j - \varepsilon_{j-1}$ will be independent of $y_{j-2}, y_{j-3}, \dots, y_0$. This is particularly convenient when the initial state (t_0, y_0) varies across subjects (as in our motivating example). When this is the case we can use an observation from (t_i^*, Y_i^*) as the initial state. Another benefit of the Markov property is that we need not specify a model for the entire longitudinal process. Using all the longitudinal data (t_i^*, Y_i^*) increases the efficiency of the procedure, but also increases the parametric specification required in model (1). This is unnecessary when the size of $[A_1, A_2]$ is small relative to the range of Y . As a result, we limit the range of the longitudinal observations in the interest of using a more parsimonious longitudinal model.

We consider a subset of (t_i^*, Y_i^*) denoted by $\mathcal{D}_i = (t_i, Y_i) = \{(t_{ij}, Y_{ij})_{j=1,2,\dots,m_i}\}$ where m_i is the number of observations in (t_i, Y_i) . The subset consists of only observations that are in or immediately outside of $[A_1, A_2]$ (see Figure 1). To this end, let $T_{ik}^+ = \min\{t_{ij}: Y_{ij} \geq A_k\}$ be the first time an observation is equal to or above A_k , and $T_{ik}^- = \max\{t_{ij}: t_{ij} < T_{ik}^+\}$, the time that immediately preceded T_{ik}^+ . For example, T_{i2}^+ is the first observation at or above A_2 and T_{i1}^- is the last observation before the first crossing of A_1 . The subsetted data consists of

$$\mathcal{D}_i = (t_i, Y_i) = \{(t_{ij}^*, Y_{ij}^*): T_{i1}^- < t_{ij}^* \leq T_{i2}^+\}.$$

Further, let $\mathcal{D}_{i0} = (t_{i0}, Y_{i0}) = \{(t_{ij}^*, Y_{ij}^*): t_{ij}^* = T_{i1}^-\}$ denote the initial state, and $\mathcal{D}_{ij} = \{(t_{ik}, Y_{ik})_{k=0,1,\dots,j-1}\}$ denote the observed information up to $t_{ij} - \varepsilon$ for arbitrarily small ε (assuming the t_{ij} 's are predictable). In Figure 1, we display an example of (t_0, Y_0) and (t_i, Y_i) where $m_i = 4$, $A_1 = 3$ and $A_2 = 4$.

To form the likelihood of the subsetted longitudinal data, we must condition on the observations being included in the subsample. Note that all observations in $\mathcal{D}_i$ are included

in the sample based on the previous observation except for (t_{i1}, Y_{i1}) . That is, $\Pr\{(t_{ij}, Y_{ij}) \in \mathcal{D}_i | \mathcal{D}_{ij}\} = 1$ for $j = 2, 3, m_i$. Conditional on $\mathcal{D}_0$, (t_{i1}, Y_{i1}) is included in $\mathcal{D}_i$ if and only if $Y_{i1} > A_1$. This creates a length-bias in $Y_{i1} = Y_{i1} - Y_{i0}$ similar to what is observed in left truncated survival analysis. Similar to the survival analysis setting we correct for the length-bias by multiplying the likelihood by the inverse probability that the observation was included in the sample, $\Pr(Y_{i1} > A_1 | \mathcal{D}_{i1})^{-1}$ (see Wang [17] or Andersen et al. [18] Chapter III.3).

To form the likelihood we assume, without loss of generality, that $Y_{i0} < A_1$, $Y_{im_i} > A_2$ and $m_i \geq 2$, alterations are straightforward and more technical in nature. So as not to extend the parametric assumption beyond A_2 , we censor the last observation at A_2 . Given the observed data $\mathcal{D} = \{(t_i, Y_i)_{i=1,2,\dots,n}\}$ the likelihood is then

$$L(\boldsymbol{\theta} | \mathcal{D}) = \prod_{i=1}^n \frac{f(Y_{i1} | \mathcal{D}_{i1}, \boldsymbol{\theta})}{\bar{F}(A_1 | \mathcal{D}_{i1}, \boldsymbol{\theta})} \left\{ \prod_{j=1}^{m_i-1} f(Y_{ij} | \mathcal{D}_{ij}, \boldsymbol{\theta}) \right\} \bar{F}(A_2 - Y_{im_i-1} | \mathcal{D}_{im_i-1}, \boldsymbol{\theta}), \quad (3)$$

where f and $\bar{F}$ are the density and survival functions, respectively, corresponding to (1). Let $\hat{\boldsymbol{\theta}} = \operatorname{argmax}_{\boldsymbol{\theta} \in \Theta} \log \{L(\boldsymbol{\theta} | \mathcal{D})\}$ denote the maximum likelihood estimate (mle) where Θ is the parameter space of $\boldsymbol{\theta}$. The inference provided by $\hat{\boldsymbol{\theta}}$ applies to the range of data used in the subsetting procedure outlined above which is approximately $[A_1, A_2]$. Thus, we can estimate the distribution of S_{12} using the plug-in estimator $F_{S_{12}}(t | \hat{\boldsymbol{\theta}})$. We discuss inference procedures for $\hat{\boldsymbol{\theta}}$ and $F_{S_{12}}(t | \hat{\boldsymbol{\theta}})$ in Section 2.4.

2.2. Wiener Process LTR model

We consider representing the underlying stochastic model as a Wiener process, given for the i th subject by

$$Y_{ij} = Y_{ij-1} + \beta(t_{ij} - t_{ij-1}) + \sigma B(t_{ij} - t_{ij-1}), \quad (4)$$

which is modeled conditionally on an initial state (t_{i0}, Y_{i0}) , where β is the drift, σ^2 is a variance parameter and $B(t)$ is a standard Brownian variate with $B(t) \sim \mathcal{N}(0, t)$. The Wiener process is a convenient choice for the underlying longitudinal process due to its mathematical applicability [4]. An advantage of the linear form of (4) is that it can be used when no benchmark time exists, this is particularly important for the data example of interest [19]. Further, the Wiener process allows for a bi-directional pattern in the observations. In our motivating example most observations are non-decreasing, but not all. A decrease from one observation to the next may be due to measurement error, but slight decreases in the mean cervical dilation have been observed via devices that allow for constant monitoring of cervical dilation. In studies with these instruments cervical dilation is observed to present a subtle wave like pattern (c.f., [20]). Though this pattern is too subtle to explicitly model with our more coarse data, it does provide motivation for a non-monotone model (the Ornstein-Uhlenbeck process is another possibility).

It might be of interest to examine the effect of some covariates on the longitudinal process. At time t_{ij} model (4) with $p + 1$ -dimensional covariate vector $\mathbf{X}_i$ is defined as

$$Y_{ij} = Y_{ij-1} + \beta \mathbf{X}_i^T (t_{ij} - t_{ij-1}) + \sigma B(t_{ij} - t_{ij-1}), \quad (5)$$

where T denotes the transpose of a vector. In matrix form (5) becomes $\mathbf{Y}_i \sim N(\beta \mathbf{X}_i^T \mathbf{t}_i, \Sigma_i)$, where $\mathbf{X}_i^T \mathbf{t}_i$ is an $m_{i1} \times (p + 1)$ matrix with $\mathbf{X}_i^T (t_{ij} - t_{ij-1})$ as row j , and Σ_i is a time dependent covariance structure given as $\Sigma_i = \sigma^2 \mathbf{U}_i$ where $(\mathbf{U}_i)_{jk} = \min(t_{ij}, t_{ik})$.

Given (4), $F_{S12}(t)$ has an inverse Gaussian distribution with density

$$f_{S12}(t) = \sqrt{\frac{\lambda}{2\pi t^3}} \exp \left[-\lambda \frac{(t - \mu)^2}{2\mu^2 t} \right] \quad (6)$$

where μ is the mean survival time and λ is a scale parameter. Thus, the distribution of the time it takes to progress from A_1 to A_2 can be estimated with an inverse Gaussian distribution characterized by $\mu = (A_2 - A_1)/\beta$ and $\lambda = (A_2 - A_1)^2/\sigma^2$. In Section 2.4, we discuss our inference procedures for μ , λ , and $\bar{F}_{S12}$.

2.3. Conditional LTR model for multiple thresholds

In this section we present an estimation method which is straightforward to implement on the entire range of the observed data. This can be accomplished by altering the question of interest from estimating population level quantities of F_{S12} to estimation of

$$F_k\{t|(t_0, y_0), \boldsymbol{\theta}\} = P \left\{ \max_{u \in [t_0, t_0+t)} Y^*(u) \geq y_0 + k | Y^*(t_0) = y_0, \boldsymbol{\theta}(y_0) \right\}, \quad (7)$$

the probability that the longitudinal process will reach $y_0 + k$ by time $t_0 + t$ given $Y^*(t_0) = y_0$. For example, we can use (7) to estimate the probability a woman will progress 1 cm given her previous measurement $Y^*(t_0) = y_0$. Note that the parameter vector is a function of the previous measurement which allows them to change as a function of the previous measurement. The statistical model we use to estimate (7) is

$$Y_{ij} = Y_{ij-1} + \beta_{Y_{ij-1}} (t_{ij} - t_{ij-1}) + \sigma B(t_{ij} - t_{ij-1}), \quad (8)$$

which can be extended to allow the variance parameter to vary as a function of the previous measurement. The estimation of this model is more straightforward than the procedures given in Section 2.1. That is, we can model the distribution of $\mathcal{D}_i^* = (\mathbf{t}_i^*, \mathbf{Y}_i^*)$ given $\mathcal{D}_0$ without needing the subsetting used in Section 2.1. Each observation will have a normal distribution with mean and variance given in (8). The slope parameter β_{y_0} can be modeled

using spline methods, or using a piecewise constant approach. This model can be considered as a special case of (5), where X can be constructed to capture the change in the slope.

The benefit of this approach is that all the observations can be simultaneously modeled, and we can obtain an estimate of the slope parameter for any previous measurement. This is quite practical since, for our motivating example, an obstetrician would likely be interested in the distribution of the time from y_0 to $y_0 + 1$ for a woman who was just observed to be at y_0 . As a result, this can be a valuable method for tracking the change of behavior in the longitudinal process over the range of observed values.

This model assumes that the process is linear from one observation to the next. This assumption is more believable when the observations are closer together. Further, if the true process was non-linear the observed slope could vary depending on the spacing of measurements. As a result, inference based on this model should only be applied to a population with a similar observation rate.

2.4. Inference Procedures

Under standard regularity conditions (e.g., see [21]) the estimated parameters of the proposed methods will have desirable asymptotic properties. That is, the p -dimensional vector $\hat{\theta}$ has an asymptotic normal distribution with variability that can be estimated via $-\hat{J}(\hat{\theta})^{-1}$ with $\hat{J}(\hat{\theta}) = \nabla_{\theta}^2 l(\theta|\mathcal{D})$ where ∇_{θ}^2 is a $p \times p$ matrix of second partial derivatives with respect to θ and $l(\theta|\mathcal{D}) = \log\{L(\theta|\mathcal{D})\}$. Under regularity conditions, the plug-in estimator $F_{S_{12}}(t|\hat{\theta})$ is asymptotically normal with variance that can be consistently estimated via

$$\widehat{\text{var}}\{F_{S_{12}}(t|\hat{\theta})\} = \{\nabla_{\theta} F_{S_{12}}(t|\hat{\theta})\}^T \{-\hat{J}(\hat{\theta})\}^{-1} \{\nabla_{\theta} F_{S_{12}}(t|\hat{\theta})\},$$

where $\nabla_{\theta} F_{S_{12}}(t|\hat{\theta})$ is a p -dimensional vector of derivatives with respect to θ .

Under the Wiener process specification the increments in the longitudinal process $Y_{ijk} = Y_{ijk} - Y_{ijk-1}$ are assumed to be independent of the previous measurements. This assumption is a reasonable approximation for a small $[A_1, A_2]$ interval, such as with the motivating example, but some residual dependence could exist. In practice a robust estimate of the variance [22] is preferred. The robust estimation uses the modified sandwich estimator of the variance of $\hat{\theta}$

$$R(\hat{\theta}) = \{-\hat{J}(\hat{\theta})\}^{-1} \hat{V}(\hat{\theta}) \{-\hat{J}(\hat{\theta})\}^{-1},$$

where $\hat{V}(\hat{\theta}) = \sum_{i=1}^n \{\nabla l_i(\theta|\mathcal{D}_i)\}^T \nabla l_i(\theta|\mathcal{D}_i)$ and $l(\theta|\mathcal{D}) = \sum_{i=1}^n l_i(\theta|\mathcal{D}_i)$. To estimate the variance of $F_{S_{12}}$ we then use the robust delta-method form,

$\widehat{\text{var}}_R\{F_{S_{12}}(t|\hat{\theta})\} = \{\nabla_{\theta} F_{S_{12}}(t|\hat{\theta})\}^T R(\hat{\theta}) \{\nabla_{\theta} F_{S_{12}}(t|\hat{\theta})\}$ The simulation studies and data analysis use a numerical approximation to all derivatives listed above. In Sections 3 and 4 the robust form for the variance is used. In Appendix C, we present additional simulation studies ran to investigate any biases that might arise when residual dependence is present.

3. Simulation Studies

To evaluate the performance of our model numerous simulation studies were performed. We simulated a longitudinal Wiener process where at time t_{ij}^* the cervical dilation measurement was generated as $Y_{ij}^* = Y_{ij-1}^* + \beta_1(t_{ij}^* - t_{ij-1}^*) + \sigma \sqrt{(t_{ij}^* - t_{ij-1}^*)} \varepsilon_{ij}$ where t_{ij}^* were N equally dispersed time points over $(0, 25)$, and $\varepsilon_{ij} \sim N(0, 1)$. The initial states of the process across all subjects were $Y_{i0}^* \sim N(1, 1)$. We generated 1000 datasets each with sample size of 500 where (A_1, A_2) is $(4, 5)$ and (β_1, σ) is $(1, 1)$, or $(0.5, 1)$ corresponding to (μ, λ) equal to $(1, 1)$, and $(2, 1)$, respectively. Further, we mimicked sparse and frequently measured longitudinal data by setting N to 7 (sparse) or 36 (frequent). We subsetting the longitudinal observations using the methods in Section 2.1. For the sparse setting this resulted in an average m_i of 2.3 and 2.6 for $\beta_1 = 1$ and 0.5, respectively, and for the frequent setting an average m_i of 3.5 and 4.9 for $\beta_1 = 1$ and 0.5, respectively. In our data analyses the average m_i was 2.3 and 2.6. All models were fitted using R [23].

We compare the results of our model to estimates obtained from the inverse Gaussian model for doubly interval censored data. Using the notation in Section 2.1, the survival times $S_{ik} = \inf\{s : Y(s) = A_k\}$ have the property $T_{ik}^- < S_{ik} \leq T_{ik}^+$. Thus, for the interval (A_1, A_2) we have $T_{i2}^- - T_{i1}^+ < S_{i12} \leq T_{i2}^+ - T_{i1}^-$ which can be used to form a standard interval censored likelihood.

Table 1 displays the average estimated parameter, Monte Carlo standard error, mean squared error (MSE), and empirical coverage probabilities of Wald-type confidence intervals using the robust delta method presented in Section 2.4 for the μ and λ parameters, along with estimates of the quantile function denoted by $F_{S_{12}}^{-1}(q)$ for the q th quantile of S_{12} . The table also contains the observed relative efficiency of estimates from the IC model to estimates from the LTR model (measured by the ratio of their MSE's). For the sparsely measured data the interval censored (IC) model produces erratic estimates of the λ parameter. Further, the coverage probabilities for all parameters are well below the nominal 0.95 level. The LTR model produces estimates that are relatively unbiased, with coverage probabilities close to the nominal level. Moreover, the MSE of the LTR model is markedly lower than the MSE for the IC model. For the frequently measured setting, both models estimate the true mean survival time and the scale parameter closely. For the $\mu = 1$ setting the LTR model has preferable bias, MSE, and empirical coverage probabilities. For the $\mu = 2$ setting the IC model appears to have more precise estimates of the μ parameter, while the LTR model produces more accurate estimates of the λ parameter.

In Appendix D of the Supplementary Information we present further empirical studies of the LTR and IC models for varying μ and spacing of the measurements (δ). These simulations found that as β increased or δ decreased the IC model for the μ and F^{-1} parameters improved relative to the LTR model. For the λ parameter the LTR model markedly outperformed the IC model in all settings.

Usually the cervical dilation measurements are rounded to the nearest 0.5 cm. We thus evaluated the performance of our model on data that were rounded to the nearest 0.5. Table 2

presents results from the LTR model for this setting with sparsely measured data (the results for the frequently measured data were similar to the pattern observed in Table 1). For this model there is some additional variation induced by the rounding mechanism. That is, let Y'_{ij} denote the continuous outcome. Here, we observe $Y_{ij} = Y'_{ij} + \delta_{ij}$ where δ_{ij} is the rounding error (i.e., if $Y'_{ij} = 4.2$ then $\delta_{ij} = -0.2$). The variability in δ_{ij} will be absorbed in the estimate of the variance of the error term, σ^2 . Thus, we expect some positive bias in σ^2 and negative bias in λ . Accounting for this, the results are similar to those from the continuous outcome.

In Appendix B in the Supplementary Information, we present a simulation study using the conditional LTR model presented in Section 2.3. In this simulation study we found that the parameters were unbiased with standard errors that were accurately estimated using the robust variance estimator. Further, in Appendix C, we examined the robustness of the proposed methods with simulation studies. Specifically, we examined the ability of the proposed method to estimate the marginal survival function from a Weiner process model with a random slope term. Overall, we found that the proposed method resulted in survival function estimates that had relatively low biases.

4. Application to Consortium on Safe Labor data

We applied the proposed model and the analogous doubly interval censored model on the CSL data. We randomly selected a sample of 2,000 out of 11,521 nulliparous women from the Utah site of the CSL study. We carried out three analyses. First, we compared the estimates from unadjusted analyses using the LTR and IC models. Second, we fit the LTR model adjusting for maternal BMI levels (adjusted model). Maternal BMI has been established to be a key factor in labor progression and management [13, 14], however this has never been investigated for specific portions of the labor curve. Third, we analyzed the data using the conditional LTR model given in Section 2.3. This analysis gives a complete picture of the labor curve conditional on the previous measurement. For the first two analyses we used both (3, 4) and (7, 8) as the thresholds, which respectively correspond to early and late stages of labor. The average m_i was 2.6 and 2.3 for the (3, 4) and (7, 8) thresholds, respectively. For the third analysis we use all of the data and the average m_i was 7.0 measurements.

4.1. Application of LTR and IC models

The maternal BMI levels were categorized as normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²) and obese (above 30 kg/m²). The mean survival times for the three BMI groups are denoted by $\hat{\mu}_1 = (A_2 - A_1)/(\hat{\beta} + \hat{\beta}_{1BMI})$, $\hat{\mu}_2 = (A_2 - A_1)/(\hat{\beta} + \hat{\beta}_{2BMI})$ and $\hat{\mu}_3 = (A_2 - A_1)/\hat{\beta}$ for normal, overweight and obese (reference) BMI's, respectively. The regression coefficients, $\hat{\beta}_{1BMI}$ and $\hat{\beta}_{2BMI}$ estimate the difference in the rate of change of cervical dilation per hour (cm/hr) between the obese women and the normal and overweight women, respectively. For the adjusted model, we performed a likelihood ratio test for allowing λ to vary by BMI categories. This test failed to reject the null model with one λ parameter value. The parameter and percentile estimates, denoted by $F_{S_{12}}^{-1}(q)$ for the q th percentile of S_{12} , can

be viewed in Table 3. Wald-type confidence intervals were constructed using the robust delta method presented in Section 2.4.

From the unadjusted analysis, both the LTR and IC models provide similar estimates of the mean and the median survival time. For example, for the LTR (IC) model we estimate a mean survival time of 2.50 (2.58) hours and median time of 1.21 (1.79) hours to progress from 3 to 4 cm. However, it will take 9.18 hours and 7.34 hours for 95% of women's cervical dilation to progress from 3 to 4 cm based on the LTR model and the IC model, respectively. To progress from 7 to 8 cm, we estimate the mean and median survival time as 1.29 hours and 0.40 hours, and 95th percentile of 5.45 hours for the LTR model. In comparison the IC model finds mean and median survival times of 0.71 hours and 0.37 hours, respectively, with 95% of women crossing the two thresholds within 2.52 hours. The estimates from the LTR model have smaller standard errors on most occasions. In Figure 2 we display the estimated unadjusted survival curves for both threshold definitions for the LTR and IC models.

The results from adjusted LTR model show that, the estimated rate of change in cervical dilation per hour is significantly faster for women with normal BMI compared to obese women for early ($\beta_{1_{BMI}} = 0.11$, 95%CI : [0.04, 0.18]) and late ($\beta_{1_{BMI}} = 0.29$, 95%CI : [0.27, 0.31]) stages of labor. However the rate for the overweight women is significant only for the early stage ($\beta_{2_{BMI}} = 0.07$, 95%CI : [0.069, 0.07]). Overall, the rate of change appears to be slower at the early stage of labor and gradually accelerates in the later stage. For example, for obese women the rate is 0.32 cm/hr for the early stage and 0.57 cm/hr at the later stage. Overall, the mean and median values show small differences between the BMI groups, which are unlikely to be significant in practice. The biggest difference between BMI groups is in the latter percentiles of the distributions. For example, in the later stage of labor the 95th percentile is estimated to be 4.92 and 7.79 hours for normal and obese women, respectively, a difference of 2.87 hours.

4.2. Application of Conditional LTR model

To fit the conditional LTR model we allowed the slope parameter to vary by the previous measurement. We did this in a piecewise manner where the slope parameter for Y_{ik} was equal to β_D if $Y_{ik-1} \in [D, D+1)$ for $D \in \{0, 1, \dots, 9\}$. The resulting estimates were then used to estimate the expected FHT to $Y_{ik-1} + 1$, a one unit increase over the previous measurement, denoted by $\mu_D = 1/\beta_D$ for $Y_{ik-1} \in [D, D+1)$. In Table 4 we present estimates, standard errors and 95% confidence intervals for $\{\mu_0, \mu_1, \dots, \mu_9\}$ obtained using the robust delta method. We also present the number of women with at least one measurement in $[D, D+1)$, denoted by n_D .

In Table 4 we observe that the μ_D 's decrease until μ_6 then slowly increase. This indicates that the rate of cervical dilation is becoming faster over $[0, 7)$ and then starts to slow down. This pattern has been noted before in nulliparous woman [24, 25], however others have found an accelerating rate of increase through 10 cm [12]. The increase in adjacent cervical dilation measurements can be 3 or 4 cm, thus women can skip over some of the $[D, D+1)$ regions. Women will only contribute to the estimate of μ_D if they have at least one measurement in $[D, D+1)$. In Table 4 we report n_D , the number of women that will

contribute to the estimate μ_D for $D = 0, 1, \dots, 9$. It is important to note the estimated μ_D 's are conditional on a woman being observed at dilation $[D, D + 1)$ during the previous measurement. As a result, they are not population level estimates of the expected time from D to $D + 1$ cm since being observed within $[D, D + 1)$ could be informative. However, the results can give obstetricians the expected time before a woman will first hit $D + 1$ cm given she was just observed at D cm. In Appendix E of the Supplementary Information we give further parameter estimates from this model.

5. Conclusion

In this article, we have demonstrated that the distribution of the elapsed time between two pre-specified thresholds can be estimated via a LTR model. By relying on the repeated measurements we incorporate the impact of the intermittent changes of the underlying process. A key step in implementing the LTR model to multiple thresholds is subsetting the longitudinal data as discussed in Section 2.1, which limits the parametric assumption required by the model to the area of interest. Our proposed method enables the utilization of all the available data within a bounded interval, and appears to have more favorable properties than the competing interval censored approach especially when the longitudinal measurements are sparse. We have demonstrated that our threshold model can be generalized to estimate an entire longitudinal process via the use of a conditional slope parameter or the use of multiple thresholds (see Appendix A).

Our analysis of the CSL study data showed some important practical differences between the LTR and IC models. While these models estimated similar means and medians, marked differences in the later percentiles were evident. For example, for women going from 7 to 8 cm dilation the LTR model estimated the 95th percentile to be 5.45 hours (95%CI [4.95, 5.96]) while the IC model estimated the same quantity to be 2.52 hours (95%CI [1.76, 3.27]). This is a stark difference when one considers that an obstetrician might use the 95th percentile as a cutoff for stopping natural labor in favor of other options (e.g., Cesarean section). When using the results from the LTR model the cutoff is almost 3 hours later. Consequently, if the IC results were used it would result in a higher rate of unnecessary Cesarean sections. The longitudinal measurements were sparse (average m_i was 2.6 and 2.3 for (3, 4) and (7, 8), respectively), thus the simulation studies suggest that the IC results should be used with caution. The adjusted LTR model found larger differences in cervical dilation progression among the BMI groups at earlier stages of labor versus the later stages. Women with normal BMI levels have a significantly higher rate of change in cervical dilation in both early and late stages of labor compared to obese women. Further, at early stages of labor the cervical dilation of overweight women progressed at a significantly faster rate than for obese women.

The proposed inference procedure is likelihood-based, and is thus valid as long as the data are missing at random (MAR). An examination of the data showed a positive association between the rate of measurements and the rate of cervical dilation is apparent. That is, women who are dilating faster appear to be measured at a more frequent rate. We assume that the measurement process is independent conditional on the previous measurements. Under this assumption, the timing of the current measurement is independent of the current

measurement given the previous measurements, which results in an MAR mechanism. Further, some women will dropout of the study due to a stalled labor. This dropout is MAR as long as the reason for the stalled labor can be characterized by the observed dilation process and covariate data. We are comfortable with this assumption since recent literature suggests that the predominant reason for a stalled labor, and subsequent Cesarean section, is directly assessed by an observed dilation process [26].

The proposed model assumes a linear trend over time, which will not always hold. For our motivating data, we consider 1 cm differences in cervical dilation where we believe the assumption of linearity is a reasonable approximation. If the interest lies in examining larger intervals, a model relaxing this assumption might be more appropriate. Typically we expect women's cervical dilation to progress differently over time due to inherent heterogeneity. Several authors [27, 28] have modeled degradation data as a Wiener process with random effects to examine mean failure time given a single threshold. When interest lies in subject-specific inferences a LTR model with random effects is appropriate. This type of approach will result in conditional inferences on the survival functions of interest. It was the goal of this research to provide population-level inference to use as a standard for labor progression that will be observed in the hospital. The survival function estimates, as well as the regression estimates for the effect of BMI on labor progression, can all be interpreted on the population-level of women that will be observed in the hospital within the range of interest. As we have shown in our robustness simulation studies (see Appendix C of the Supplemental Information) our method accurately estimates the marginal survival function for data with a random slope, however, a random effects model will be beneficial when prediction is of interest. In the future, we look to develop a method that can predict a woman's survival curve based on her past measurements via the random effects approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Example of subsetting the longitudinal data (t_i^*, Y_i^*) if $A_1 = 3$ and $A_2 = 4$, which includes the subset of observations (t_i, Y_i) denoted by ●, the initial state (t_0, Y_0) denoted by ▲, and observations excluded from the subset (x).

(a) 3 cm to 4 cm

(b) 7 cm to 8 cm

Figure 2.

The figure shows the estimated unadjusted survival curves for nulliparous women given (a) $(A_1, A_2) = (3, 4)$ cm, and (b) $(A_1, A_2) = (7, 8)$ cm. The black line is the estimated curve for the LTR model and the gray line is for the IC model.

Table 1

Summary of 1000 simulated datasets with $n = 500$ for the longitudinal threshold regression (LTR) model and the interval censored (IC) model. The table displays the average estimated parameter (EST), empirical standard error (SE), empirical coverage probabilities (ECP) of 95% confidence intervals, mean squared error (MSE), and the relative efficiency of the IC model to the LTR model (RE). The sparsely measured setting had 7 measurements, while the frequently measured setting had 36 measurements.

	LTR model				IC model			
	TRUE	EST (SE)	ECP	MSE	EST (SE)	ECP	MSE	RE
Sparse measurements								
μ	1	1.00 (0.04)	0.944	0.001	1.04 (0.68)	0.293	0.462	348
λ	1	1.01 (0.07)	0.955	0.006	10.87 (15.64)	0.200	342.1	60486
$F_{S12}^{-1}(0.5)$	0.68	0.68 (0.02)	0.960	<0.001	0.81 (0.79)	0.266	0.647	2376
$F_{S12}^{-1}(0.75)$	1.24	1.24 (0.04)	0.947	0.002	1.15 (0.82)	0.314	0.678	427
$F_{S12}^{-1}(0.95)$	2.92	2.92 (0.18)	0.939	0.032	2.39 (0.52)	0.793	0.551	17.4
μ	2	2.02 (0.12)	0.955	0.015	1.75 (0.18)	0.702	0.095	6.27
λ	1	1.00 (0.06)	0.945	0.004	0.64 (0.22)	0.526	0.178	45.4
$F_{S12}^{-1}(0.5)$	1.03	1.03 (0.04)	0.961	0.001	0.75 (0.16)	0.582	0.103	77.6
$F_{S12}^{-1}(0.75)$	2.28	2.30 (0.11)	0.952	0.011	1.83 (0.26)	0.616	0.280	24.7
$F_{S12}^{-1}(0.95)$	7.11	7.17 (0.59)	0.955	0.358	6.74 (0.69)	0.877	0.616	1.72
Frequent measurements								
μ	1	1.00 (0.05)	0.947	0.002	0.99 (0.05)	0.928	0.003	1.33
λ	1	1.00 (0.05)	0.946	0.002	0.96 (0.13)	0.917	0.020	8.31
$F_{S12}^{-1}(0.5)$	0.68	0.68 (0.02)	0.952	<0.001	0.66 (0.04)	0.920	0.002	4.16
$F_{S12}^{-1}(0.75)$	1.24	1.24 (0.05)	0.947	0.003	1.23 (0.06)	0.927	0.004	1.58

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	LTR model				IC model			
	TRUE	EST (SE)	ECP	MSE	EST (SE)	ECP	MSE	RE
$F_{S12}^{-1}(0.95)$	2.92	2.92 (0.18)	0.939	0.032	2.93 (0.20)	0.935	0.040	1.23
μ	2	2.09 (0.14)	0.932	0.029	1.99 (0.13)	0.937	0.016	0.55
λ	1	1.00 (0.04)	0.945	0.001	0.97 (0.10)	0.924	0.012	8.88
$F_{S12}^{-1}(0.5)$	1.03	1.05 (0.04)	0.921	0.002	1.01 (0.06)	0.930	0.005	2.20
$F_{S12}^{-1}(0.75)$	2.28	2.37 (0.13)	0.922	0.023	2.26 (0.13)	0.928	0.017	0.75
$F_{S12}^{-1}(0.95)$	7.11	7.27 (0.64)	0.934	0.432	7.14 (0.59)	0.950	0.347	0.80

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Table 2

Summary of 1000 simulated datasets with $n = 500$ for LTR model with data rounded to the nearest 0.5 with sparsely sampled measurements.

	TRUE	EST(SE)	ECP	TRUE	EST(SE)	ECP
μ	1	1.00 (0.06)	0.943	2	2.03 (0.15)	0.949
λ	1	0.98 (0.06)	0.935	1	0.98 (0.05)	0.936
$F_{S12}^{-1}(0.5)$	0.68	0.70 (0.03)	0.951	1.03	1.04 (0.04)	0.965
$F_{S12}^{-1}(0.75)$	1.24	1.26 (0.06)	0.948	2.28	2.38 (0.11)	0.942
$F_{S12}^{-1}(0.95)$	2.92	2.92 (0.19)	0.934	7.11	7.17 (0.59)	0.934

Parameter estimates from unadjusted and adjusted LTR model and an unadjusted IC model with n=2000 nulliparous women. We display the point estimates (EST), robust standard errors (SE) and corresponding 95% confidence intervals (CI).

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	EST (SE)	95% CI	EST (SE)	95% CI
Overweight women				
$F_{S12}^{-1}(0.5)$	1.15 (0.002)	(1.14, 1.15)	0.38 (0.0001)	(0.38, 0.38)
$F_{S12}^{-1}(0.75)$	2.62 (0.11)	(2.41, 2.82)	1.05 (0.19)	(0.68, 1.42)
$F_{S12}^{-1}(0.95)$	8.48 (1.62)	(5.31, 11.66)	4.92 (0.18)	(4.57, 5.26)
Obese women				
μ_2	2.58 (0.24)	(2.11, 3.06)	1.46 (0.14)	(1.18, 1.75)
$F_{S12}^{-1}(0.5)$	1.21 (0.30)	(0.62, 1.79)	0.40 (0.001)	(0.40, 0.41)
$F_{S12}^{-1}(0.75)$	2.83 (0.40)	(2.04, 3.63)	1.20 (0.03)	(1.14, 1.26)
$F_{S12}^{-1}(0.95)$	9.63 (1.55)	(6.61, 12.66)	6.35 (2.61)	(1.23, 11.46)
Obese women				
μ_3	3.14 (0.37)	(2.41, 3.87)	1.77 (0.10)	(1.58, 1.96)
$F_{S12}^{-1}(0.5)$	1.32 (0.04)	(1.24, 1.40)	0.43 (0.03)	(0.37, 0.48)
$F_{S12}^{-1}(0.75)$	3.27 (0.07)	(3.13, 3.42)	1.32 (0.03)	(1.27, 1.38)
$F_{S12}^{-1}(0.95)$	12.24 (2.03)	(8.26, 16.23)	7.79 (0.50)	(6.81, 8.78)

Estimated expected FHT of a one centimeter increase from the previous measurement from the unadjusted conditional LTR model with $n=2000$ nulliparous women. We display the point estimates (EST), robust standard errors (SE), corresponding 95% confidence intervals (CI) and the number of women with at least one measurement in $[D, D + 1)$ (n_D). The model resulted in $\hat{\lambda} = 0.59$ with 95% CI (0.57, 0.60)

Table 4

	μ_0	μ_1	μ_2	μ_3	μ_4
EST (SE)	6.40 (1.38)	3.45 (0.21)	2.23 (0.09)	1.96 (0.06)	1.18 (0.03)
95% CI	(3.70, 9.10)	(3.04, 3.85)	(2.05, 2.42)	(1.84, 2.09)	(1.13, 1.23)
n_D	120	575	833	1219	1194
		μ_5	μ_6	μ_7	μ_8
EST (SE)		0.86 (0.02)	0.74 (0.02)	0.77 (0.02)	0.85 (0.03)
95% CI		(0.82, 0.89)	(0.71, 0.77)	(0.73, 0.81)	(0.80, 0.90)
n_D		928	778	658	729
					1086