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Quantile Regression Modeling of Latent Trajectory Features with Longitudinal Data

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Abstract

Quantile regression has demonstrated promising utility in longitudinal data analysis. Existing work is primarily focused on modeling cross-sectional outcomes, while outcome trajectories often carry more substantive information in practice. In this work, we develop a trajectory quantile regression framework that is designed to robustly and flexibly investigate how latent individual trajectory features are related to observed subject characteristics. The proposed models are built under multilevel modeling with usual parametric assumptions lifted or relaxed. We derive our estimation procedure by novelly transforming the problem at hand to quantile regression with perturbed responses and adapting the bias correction technique for handling covariate measurement errors. We establish desirable asymptotic properties of the proposed estimator, including uniform consistency and weak convergence. Extensive simulation studies confirm the validity of the proposed method as well as its robustness. An application to the DURABLE trial uncovers sensible scientific findings and illustrates the practical value of our proposals.

Keywords

Corrected loss function; Latent longitudinal trajectory; Quantile regression; Multilevel modeling

1. Introduction

Longitudinal data, characterized by repeated measurements from the same subject, provide the essential platform for exploiting the temporal patterns of scientific outcomes. Such data frequently arise in biomedical research. A general account of methods for analyzing longitudinal data can be found in various texts [5, 7, 17, 25, 49, among others].

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Supplementary Materials

Supplementary Materials, which include large sample properties, justification of the proposed resampling-based inference procedure, additional simulation studies, and linear trajectory model for DURABLE data are available online.

Quantile regression [29], given its robustness in handling skewed responses and flexibility in characterizing covariate effects, has demonstrated promising utility in longitudinal data analysis. A common way to formulate longitudinal quantile regression is to specify the outcome quantile at a given time point as a function of covariates, sharing a similar spirit with the generalized estimating equation (GEE) approach [33]. A number of authors have studied such a marginal quantile regression model, including the GEE-type estimating equations and empirical-likelihood approaches [3, 10, 19, 26, 32, 35, among others]. Extensions have also been proposed to address data complications such as dropouts and censoring [31, 34, 47, 50, for example]. A more flexible modeling strategy for longitudinal quantile regression is to model outcome quantiles conditioning on covariates as well as fixed or random individual parameters that capture unobserved heterogeneity. Such conditional quantile regression models provide individual-specific interpretations and can be estimated through distribution-free or likelihood-based approaches [11, 12, 18, 27, among others]. In particular, a popular type of approaches investigated longitudinal quantile regression with random effects using asymmetric Laplace likelihood [6, 13-16, among others]. Readers may refer to [37] for a review of linear quantile regression methods with longitudinal data. It is worth noting that most (if not all) existing models are oriented to infer about the quantiles of the longitudinal outcome at given time points (i.e. cross-sectional quantiles).

In many practical scenarios, the scientific interest pertains to the within-subject trajectory of an outcome. To address such an interest, the current modeling of cross-sectional quantiles may not suffice because the changing pattern of cross-sectional quantiles over time often do not reflect the outcome changing pattern at the subject level. For example, in the DURABLE trial [1] that evaluated two starter insulin regimens in type 2 diabetes patients, how quickly HbA1c decreases over time within a patient may be a more substantive efficacy measure than the patient's HbA1c level at each follow-up visit. This is because the trajectory of HbA1c would better inform us the patient's early response of treatment which is an effective indicator of the likely need for change in (or intensification of) therapy [8]. As shown by Figure 1, the 25th, 50th, and 75th cross-sectional quartiles of HbA1c are all decreasing with time (see black solid lines), while examining the within-subject data suggests that some subjects may have underlying HbA1c trajectories roughly unchanged or even increasing over time (see dashed lines). These subjects correspond to weak responders to the assigned insulin treatment, which is of critical clinical importance but cannot be captured by evaluating the temporal trend of the cross-sectional quantiles.

It is remarkable that the trajectory-related measures, such as the decreasing rate of within-subject HbA1c values, unlike the cross-sectional measurements, are not directly observable but may be accessible through trajectory modeling of HbA1c at the individual level. To investigate whether and how a certain insulin treatment or individual characteristics lead to more rapid reductions of HbA1c, a natural approach is to consider multilevel modeling (MLM) [41]. That is, one may assume a level-1 trajectory model for the repeated HbA1c measurements within each subject, and then use a level-2 model to link covariates with the latent individual-specific features that capture the HbA1c reduction pattern based on the level-1 model. Traditional MLM for continuous longitudinal data is frequently based on the assumption of Gaussian distributed errors at every level [21, 43, for example]. While this assumption helps ensure the model identifiability and facilitates likelihood-based inferences,

it can induce potentially stringent data constraints. Integrating quantile regression into repeated measures MLM, for example in the level-2 model described above, can avoid some of unverifiable distributional assumptions. It can also offer the same flexibility to explore meaningful heterogeneous covariate effects as in the standard quantile regression.

In this paper, we propose a new longitudinal quantile regression framework that serves to investigate individual trajectory features of longitudinal data under MLM. We shall refer the new framework to as longitudinal trajectory quantile regression. Existing work on quantile regression for longitudinal data has been mostly concerned with inference on the distribution of longitudinal outcome conditional on covariates or subject-specific effects. While methods, such as linear quantile mixed models [13, 15], have the capacity to estimate longitudinal trajectories, these methods mainly target covariate effects on cross-sectional quantiles. In contrast, we directly model the quantiles of the latent trajectory feature of interest defined upon an assumed random trajectory model. This can help provide a clearer and yet comprehensive picture of how covariates influence the trajectory feature of interest. As a proof of concept, we illustrate in Section 2 the proposed framework assuming a polynomial trajectory model and taking the outcome changing rate as the targeted trajectory feature. The main thrust of our method is to deal with unobserved latent responses (e.g. decreasing rate of HbA1c) in the quantile regression context without fully parametric modeling. Our key strategy is to map the latent quantile regression model to a quantile regression problem with observed but perturbed responses. As delineated in Section 3, we show that the bias caused by the response perturbation can be corrected through adapting the technique for handling covariate measurement errors [45, 51]. Our estimation method permits a less restrictive trajectory model for the correlated within-subject measurements, for example, by allowing the error term to be non-normal. More specifically, we derive a unified estimation procedure that can accommodate trajectory random errors following either normal or Laplace distribution. We carefully examine the developed inference procedures including the associated asymptotic properties and computational features; see Section 4. Our simulations reported in Section 5 confirm the validity of the proposed longitudinal trajectory quantile regression procedures and demonstrate their satisfactory performance with finite sample sizes. The data application presented in Section 6 represents a novel secondary analysis of the DURABLE study, which reveals more robust and detailed heterogeneity patterns in longitudinal HbA1c outcomes.

2. The Proposed Longitudinal Trajectory Quantile Regression Framework

Consider a longitudinal study that consists of n subjects. For subject i , let $Y_i(t)$ denote the outcome variable of interest. We adopt a polynomial trajectory model for $Y_i(t)$ that takes the general form,

$$Y_i(t) = f(t; \boldsymbol{\alpha}_i) + \epsilon_i(t) \doteq \sum_{j=0}^k \alpha_{ij} t^j + \epsilon_i(t), \quad (1)$$

where $f(t; \boldsymbol{\alpha}_i)$ is a k -th order polynomial function of time t , $\boldsymbol{\alpha}_i = (\alpha_{i0}, \alpha_{i1}, \dots, \alpha_{ik})^\top$ is an unknown *random* parameter vector, and $\epsilon_i(t)$ is a mean zero process independent of $\boldsymbol{\alpha}_i$. Here the random parameters in $\boldsymbol{\alpha}_i$ are not subject to the mean zero constraint and so they are

general enough to capture both the fixed and random effects (of covariates) on $Y_i(t)$. Under model (1), $f(t; \alpha_i)$ represents the underlying outcome trajectory of interest for subject i determined by α_i , and $\epsilon_i(t)$ may play a role like a random noise or measurement error.

Remark 1: It is important to point out that the main interest under model (1) is the underlying trajectory for subject i , $f(t; \alpha_i)$, and is *not* the conditional mean of $Y_i(t)$ given a covariate vector, say X_i , i.e. $E(Y_i(t)|X_i) \equiv E(f(t; \alpha_i)|X_i)$. This distinguishes model (1) from the traditional conditional mean modeling of longitudinal data.

The polynomial specification of $f(\cdot)$ can flexibly characterize various types of outcome temporal patterns. At the same time it provides the technical convenience that allows a meaningful trajectory-related feature of interest, denoted by B_i to be represented as a known parametric function of α_i , $\phi(\alpha_i)$. With real data, the polynomial order k may be determined by examining the observed within-subject longitudinal measurements. As motivated by the application to the DURABLE trial, we consider the special case where $\phi(\alpha_i)$ corresponds to the changing rate of the within-subject outcome trajectory at a given time point t_* , which, under model (1), takes the form

$$B_i \doteq \phi(\alpha_i) = \left. \frac{\partial f(t; \alpha_i)}{\partial t} \right|_{t=t_*} = \sum_{j=1}^k j \alpha_{ij} t_*^{j-1}. \quad (2)$$

When $k=1$, B_i is simply α_{i1} , the random slope of the assumed linear trajectory. In practice, t_* is often pre-specified per study protocol. Studying other forms of $\phi(\cdot)$, such as the area under curve of $Y_i(t)$ in a given time interval, can be carried out based on the same strategy presented in this work.

The focus of the proposed framework is to use quantile regression to permit a robust and comprehensive examination of the relationship between a latent outcome trajectory feature and the observed covariates. Let $\tilde{X}$ denote a $(p-1) \times 1$ vector of covariates, $X = (1, \tilde{X}^\top)^\top$, and let B stand for the population analogue of B_i . The τ th conditional quantile of B given X is defined as $Q_B(\tau|X) \doteq \inf \{b : \Pr(B \leq b|X) \geq \tau\}$. We assume the following quantile regression model:

$$Q_B(\tau | X) = X^\top \beta_0(\tau), \quad (3)$$

where $\tau \in (0, 1)$ and $\beta_0(\tau) \in \mathcal{R}^p$ is an unknown coefficient vector. The coefficients in $\beta_0(\tau)$, as interpreted in the standard quantile regression [28], reveal the change in the τ -th quantile of B per one unit covariate change. When all non-intercept coefficients in $\beta_0(\tau)$ are constant with respect to τ , model (3) reduces to a linear model where the regression coefficients represent the *location shift* to the distribution of B resulted from one unit covariate change.

Models (1) and (3) together can be viewed as a multilevel model with level-1 units consisting of the repeated measurements for each subject and level-2 units corresponding to subjects. The multilevel model perspective enables us to employ quantile regression to investigate the determinants of a latent trajectory feature of interest. The resulting multilevel model encompasses common repeated measures models such as the traditional linear mixed

models, which may also be expressed as multilevel models. The quantile regression specification of our level-2 model avoids the typical normality assumption for the individual random parameters under the traditional linear mixed models and hence leads to improved robustness.

3. The Proposed Estimation

In longitudinal studies, the outcome process $Y_i(t)$ is usually not continuously observed; rather $Y_i(t)$ is measured only at multiple discrete time points, say $t_{i1} < t_{i2} < \dots < t_{im_i}$ where m_i is the total number of observations for subject i . Let Y_{ij} denote the $Y_i(t)$ measured for subject i at time point t_{ij} . The observed data consist of $\{Y_{ij}, t_{ij}, X_i: j = 1, \dots, m_i, i = 1, \dots, n\}$. Our data scenario accommodates both regular and irregular time points for longitudinal measurements.

Model (1) implies that $Y_{ij} = \alpha_{i0} + \alpha_{i1}t_{ij} + \alpha_{i2}t_{ij}^2 + \dots + \alpha_{ik}t_{ij}^k + \epsilon_{ij}$ with $\epsilon_{ij} = \epsilon_i(t_{ij})$ for $j = 1, \dots, m_i$ and $i = 1, \dots, n$. This can further be expressed in a matrix form,

$$\mathbf{Y}_i = \mathbf{Z}_i \boldsymbol{\alpha}_i + \boldsymbol{\epsilon}_i, \quad (4)$$

where $\mathbf{Y}_i = (Y_{i1}, \dots, Y_{im_i})^\top$, $\mathbf{Z}_i = (z_{p,q})$ is a $m_i \times (k+1)$ matrix with $z_{p,q} = t_{ip}^{q-1}$, and $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, \dots, \epsilon_{im_i})^\top$, and $\boldsymbol{\alpha}_i = (\alpha_{i0}, \dots, \alpha_{ik})^\top$. Accordingly, we can write the latent response in model (3) as $B_i = \boldsymbol{\gamma}^\top \boldsymbol{a}_i$, where $\boldsymbol{\gamma} = (0, 1, 2t_{i*}, \dots, kt_{i*}^{k-1})^\top$.

Estimating $\boldsymbol{\beta}_0(\tau)$ would be a trivial quantile regression problem if B_i ($i = 1, \dots, n$) were known. In that case, a well-studied estimator is given by

$$\operatorname{argmin}_{\boldsymbol{\beta} \in \mathcal{R}^p} \sum_{i=1}^n \rho_\tau(B_i - \mathbf{X}_i^\top \boldsymbol{\beta}), \quad (5)$$

where $\rho_\tau(v) \doteq v\{\tau - \mathbb{I}(v < 0)\}$ is the quantile loss function [28] and $\mathbb{I}(\cdot)$ is the indicator function. However, B_i is a function of the latent parameter $\boldsymbol{a}_i$ in model (1), which is not observable. Therefore, the standard quantile regression method is not applicable to estimating $\boldsymbol{\beta}_0(\tau)$.

Since B_i 's are not observable, a natural thought to handle this problem is to replace the B_i in (5) by its proxy that is obtainable from the observed data. We propose to utilize an observable proxy of B_i , $\hat{B}_i = \boldsymbol{\gamma}^\top \hat{\boldsymbol{\alpha}}_i$, where $\hat{\boldsymbol{\alpha}}_i \doteq (\mathbf{Z}_i^\top \mathbf{Z}_i)^{-1} \mathbf{Z}_i^\top \mathbf{Y}_i$. Such a choice of $\hat{B}_i$ is motivated by a nice connection between B_i and $\hat{B}_i$ (as shown below in (6)) that facilitates adapting the corrected score technique [39, 44] to recover the information on B_i from $\hat{B}_i$. However, simply substituting B_i with $\hat{B}_i$ in (5) to estimate $\boldsymbol{\beta}_0(\tau)$ can lead to biased estimation. This is clearly shown by the simulation studies presented in Section 4 and can be explained as follows. First, by simple algebra, we show that under model (1),

$$\hat{B}_i = B_i + \eta_i, \quad (6)$$

where $\eta_i = \gamma^T(Z_i^T Z_i)^{-1} Z_i^T \epsilon_i$. We can see from (6) that $\hat{B}_i$ is an unbiased estimator of B_i , but its difference from B_i may not be negligible because m_i , the number of longitudinal measurements within subject i used to construct $\hat{B}_i$, is usually bounded. The error term η_i in (6) has a similar flavor to covariate measurement errors concerned in literature [2, See a summary]; both are mean zero but not negligible. Treating the observable $\hat{B}_i$'s as the true responses in model (3) constitutes a quantile regression problem with perturbed responses. While several papers [20, 51-53, for example] investigated quantile regression with covariate measurement errors, how to deal with response perturbation has not been studied. The response perturbation η_i bears a notable distinction from a typical covariate measurement error; that is, the latter is usually assumed to be independent of covariates while η_i is clearly covariate dependent and thus cannot be simply ignored in the regression setting.

In this work, we derive an appropriate bias-correction method to eliminate the bias caused by η_i . Specifically, denote the data with observed responses as $\mathcal{O}_i = \{\hat{B}_i, Z_i, X_i\}$ and the data with unobserved responses as $\mathcal{U}_i = \{B_i, Z_i, X_i\}$. Following the corrected score argument in [44] and [39], we may obtain a consistent estimator of β_0 by minimizing $\sum_{i=1}^n \rho_{\tau}^*(\mathcal{O}_i, \beta)$, where $\rho_{\tau}^*(\cdot)$ satisfies $E[\rho_{\tau}^*(\mathcal{O}_i, \beta) | B_i, Z_i, X_i] = \rho_{\tau}(B_i - X_i^T \beta)$. However finding such a $\rho_{\tau}^*(\cdot)$ is difficult because $\rho_{\tau}(v)$ involves an indicator function and thus is not differentiable at $v = 0$. To overcome this difficulty, we propose to approximate $\rho_{\tau}(v)$ by a smooth function $\rho_{\tau,h}(v)$, where h is a positive smoothing parameter. The strategy of smoothing $\rho_{\tau}(\cdot)$ was used and justified in various quantile regression settings [51, 53, for example]. Specifically, we shall adopt the smoothing scheme used in [23]. Define $\rho_{\tau,h}(v) = v\{\tau - 1 + K(v/h)\}$, where $K(\cdot)$ is a smooth function satisfying $\lim_{v \rightarrow -\infty} K(v) = 0$ and $\lim_{v \rightarrow \infty} K(v) = 1$. It is clear that $1 - K(v/h)$ converges to $I(v < 0)$ as $h \rightarrow 0$ and hence $\rho_{\tau,h}(v) = v\{\tau - 1 + K(v/h)\}$ approaches $\rho_{\tau}(v)$ as $h \rightarrow 0$.

Now our goal becomes finding a corrected quantile loss function $\rho_{\tau,h}^*(\mathcal{O}_i, \beta)$ such that

$$E[\rho_{\tau,h}^*(\mathcal{O}_i, \beta) | B_i, Z_i, X_i] = \rho_{\tau,h}(B_i - X_i^T \beta). \quad (7)$$

Given $\rho_{\tau,h}(B_i - X_i^T \beta) \rightarrow \rho_{\tau}(B_i - X_i^T \beta)$ as $h \rightarrow 0$, an estimator of $\beta_0(\tau)$ may be given by

$$\tilde{\beta}_{n,h_n}(\tau) = \operatorname{argmin}_{\beta \in \mathcal{R}^p} \sum_{i=1}^n \rho_{\tau,h_n}^*(\mathcal{O}_i, \beta), \quad (8)$$

with $h_n \rightarrow 0$ as $n \rightarrow \infty$.

Since the distribution of $\mathcal{O}_i$ given (B_i, Z_i, X_i) is determined by the distribution of ϵ_i , (7) suggests that the form of $\rho_{\tau,h}^*(\cdot)$ depends on the distribution of ϵ_i . In the following two subsections, we shall construct $\rho_{\tau,h}^*(\cdot)$ for the cases where ϵ_{ij} follows the normal and the Laplace distributions respectively. It is worth emphasizing that by our results, both types of error distributions for ϵ_i can be accommodated by the same estimation procedure. We also

evaluate the robustness of our method to misspecification of the distribution of ϵ_j via simulations.

3.1. Normal trajectory random error

Assume that $\{\epsilon_{ij}, j = 1, \dots, m_i\}$ are independent, and $\epsilon_{ij}|(X_i, Z_i) \sim N(0, \delta(X_i, Z_i)\sigma^2)$, where $\delta(\cdot)$ is a known positive scalar function and $\sigma^2 > 0$. In this case, the within-subject correlations in Y_{ij} 's are captured by the subject-specific latent random parameter α_i . Then $(Z_i^T Z_i)^{-1} Z_i^T \epsilon_i \sim N(0, \delta(X_i, Z_i)\sigma^2 \{Z_i^T Z_i\}^{-1})$ and $\eta_i = \hat{B}_i - B_i \sim N(0, \sigma^2 D_i)$, where $D_i = \delta(X_i, Z_i) \gamma^T \{Z_i^T Z_i\}^{-1} \gamma$. This implies

$$D_i^{-1/2}(\hat{B}_i - X_i^T \beta) | (B_i, Z_i, X_i) \sim N(D_i^{-1/2}(B_i - X_i^T \beta), \sigma^2). \quad (9)$$

Based on (9), we can derive a corrected quantile loss function $\rho_{\tau, h}^*(\cdot)$ by employing the result established in [46]. That is, given a sufficiently smooth function $g(\cdot)$, and independent random variables, $U \sim N(\mu, \sigma^2)$ and $V \sim N(0, 1)$, it holds that $E[E\{g(U + i\sigma V) | U\}] = g(\mu)$, where $i = \sqrt{-1}$. By Taylor expansion and the moment expression of standard normal distribution, $E\{g(U + i\sigma V) | U\} = \sum_{m=0}^{\infty} g^{(2m)}(U) \frac{(-\sigma^2)^m}{2^m m!}$. Therefore

$$E\left\{\sum_{m=0}^{\infty} g^{(2m)}(U) \frac{(-\sigma^2)^m}{2^m m!}\right\} = g(\mu). \quad (10)$$

The fact (10) provides the key insight on how to find the corrected quantile loss function. Define $\hat{\xi}_i = D_i^{-1/2}(\hat{B}_i - X_i^T \beta)$ and $\xi_i = D_i^{-1/2}(B_i - X_i^T \beta)$. Viewing $\hat{\xi}_i$ as the U in (10), we obtain from (9) and (10) that $E[\rho_{\tau, h}^{N*}(\mathcal{O}_i, \beta, \sigma^2) | B_i, X_i, Z_i] = \rho_{\tau, h}(\xi_i)$, where

$$\rho_{\tau, h}^{N*}(\mathcal{O}_i, \beta, \sigma^2) = \sum_{m=0}^{\infty} \rho_{\tau, h}^{(2m)}(\hat{\xi}_i) \frac{(-\sigma^2)^m}{2^m m!}.$$

Note $\rho_{\tau}(\xi_i) = D_i^{-1/2} \rho_{\tau}(B_i - X_i^T \beta)$ and $D_i > 0$ given $Z_i^T Z_i > 0$. Following the argument for (8), $\rho_{\tau, h}^{N*}(\mathcal{O}_i, \beta, \sigma^2)$ may serve as a corrected quantile loss function if σ^2 is known. When σ^2 is unknown, we propose to employ $\rho_{\tau, h}^{N*}(\mathcal{O}_i, \beta, \hat{\sigma}^2)$, where $\hat{\sigma}^2$ is a reasonable estimator of σ^2 discussed in Section 3.3.

To compute $\rho_{\tau, h}^{N*}(\cdot)$, it is easy to calculate that $\rho_{\tau, h}^{(0)}(v) = \rho_{\tau, h}(v)$, $\rho_{\tau, h}^{(1)}(v) = \tau - 1 + \{vK(v/h)\}^{(1)}$ and $\rho_{\tau, h}^{(j)}(v) = \{vK(v/h)\}^{(j)}$ for $j \geq 2$, where $\{vK(v/h)\}^{(j)} = \frac{j}{h^{j-1}} K^{(j-1)}\left(\frac{v}{h}\right) + \frac{v}{h^j} K^{(j)}\left(\frac{v}{h}\right)$, $j = 1, 2, \dots$. Here we choose $K(\cdot)$ as an infinitely smooth function, such as the distribution function of $N(0, 1)$, which is adopted in our

simulation studies. Solving the minimization of $\sum_{i=1}^n \sum_{m=0}^{\infty} \rho_{\tau, h}^{(2m)}(\hat{\xi}_i) \frac{(-\sigma^2)^m}{2^m m!}$ however involves an infinite series, and thus may not be feasible. Following the practical recommendation of [44] and [53], we shall keep the first two summands in $\rho_{\tau, h}^{N*}(\cdot)$ as an approximation to $\rho_{\tau, h}^{N*}(\cdot)$, which is found to be adequate in our simulation studies.

3.2. Laplace Trajectory Random Error

In this subsection, we consider the situation where the errors $\{\epsilon_{ij}, j = 1, \dots, m_i, i = 1, \dots, n\}$ follow a univariate Laplace distribution. We adopt the classical definition of univariate Laplace distribution [30, see Chapter 6]. That is, the density function of the Laplace distribution $L(\mu, b)$ is given by $f(x; \mu, b) = \frac{1}{2b} \exp\{-|x - \mu|/b\}$. Some related properties of which can be found in Lemma 1 of [51].

Assume that $\{\epsilon_{ij}, j = 1, \dots, m_i\}$ are independent and $\epsilon_{ij}|(X_i, Z_i) \sim L(0, \delta(X_i, Z_i)\sigma^2)$. Here $\delta(\cdot)$ is a known positive scalar function and $\sigma^2 > 0$. It is easy to see that

$$D_i^{-1/2}(\hat{B}_i - X_i^T \beta) | (B_i, Z_i, X_i) \sim L(D_i^{-1/2}(B_i - X_i^T \beta), \sigma^2). \quad (11)$$

By Lemma 2 of [51], for a random variable U following the univariate Laplace distribution $L(\mu, \sigma^2)$ and a twice-differentiable function $g(\cdot)$,

$$E\left\{g(U) - \frac{\sigma^2}{2} g^{(2)}(U)\right\} = g(\mu). \quad (12)$$

Choose $K(\cdot)$ be a twice-differentiable function, and denote

$$\rho_{\tau, h}^{L*}(v, \sigma^2) = \rho_{\tau, h}(v) - \frac{\sigma^2}{2} \frac{\partial^2 \rho_{\tau, h}(v)}{\partial v^2} = v\left\{\tau - 1 + K\left(\frac{v}{h}\right)\right\} - \frac{\sigma^2}{2} \left\{\frac{2}{h} K^{(1)}\left(\frac{v}{h}\right) + \frac{v}{h^2} K^{(2)}\left(\frac{v}{h}\right)\right\}. \text{ We then}$$

obtain from (11) and (12) that $E[\rho_{\tau, h}^{L*}(\hat{\xi}_i, \sigma^2) | B_i, X_i, Z_i] = \rho_{\tau, h}(\xi_i)$, where

$\hat{\xi}_i = D_i^{-1/2}(\hat{B}_i - X_i^T \beta)$ and $\xi_i = D_i^{-1/2}(B_i - X_i^T \beta)$ are the same as those defined in Section 3.1. A corrected quantile loss function for the Laplace error case (with known σ^2) is thus given by

$$\begin{aligned} \rho_{\tau, h}^{L*}(\mathcal{O}_i, \beta, \sigma^2) &= \rho_{\tau, h}^{L*}(\hat{\xi}_i, \sigma^2) \hat{\xi}_i \left\{ \tau - 1 + K\left(\frac{\hat{\xi}_i}{h}\right) \right\} \\ &\quad - \frac{\sigma^2}{2} \left\{ \frac{2}{h} K^{(1)}\left(\frac{\hat{\xi}_i}{h}\right) + \frac{\hat{\xi}_i}{h^2} K^{(2)}\left(\frac{\hat{\xi}_i}{h}\right) \right\}. \end{aligned} \quad (13)$$

It is interesting to note that the corrected quantile loss function for the Laplace error case is exactly the same as the approximate corrected loss function derived for the normal error case (that uses the first two summands in the infinite series). This fact enables a unified corrected quantile loss function for estimating $\beta_0(\tau)$ in the presence of normal or Laplace trajectory errors. When σ^2 are unknown, we shall plug in the estimator of σ^2 presented in Section 3.3.

3.3. Estimation of σ^2

In this subsection, we discuss how to estimate σ^2 . Define $\tilde{\mathbf{Y}}_i = \mathbf{Y}_i / \sqrt{\delta(\mathbf{X}_i, \mathbf{Z}_i)}$, $\tilde{\mathbf{Z}}_i = \mathbf{Z}_i / \sqrt{\delta(\mathbf{X}_i, \mathbf{Z}_i)}$, and $\tilde{\boldsymbol{\epsilon}}_i = \boldsymbol{\epsilon}_i / \sqrt{\delta(\mathbf{X}_i, \mathbf{Z}_i)}$. Write $\tilde{\boldsymbol{\epsilon}}_i = (\tilde{\epsilon}_{i1}, \tilde{\epsilon}_{i2}, \dots, \tilde{\epsilon}_{im_i})^\top$. By the definition, $\{\tilde{\epsilon}_{ij}, j = 1, \dots, m_i; i = 1, \dots, n\}$ are independent and identically distributed (i.i.d.) with $E(\tilde{\epsilon}_{ij}) = 0$ and $\text{var}(\tilde{\epsilon}_{ij}) = \sigma^2$.

Suppose there exists a constant M such that $m_i < M < \infty$. Following the idea of [48], we estimate σ^2 based on the residuals, $\hat{\boldsymbol{\epsilon}}_i = \tilde{\mathbf{Y}}_i - \tilde{\mathbf{Z}}_i \hat{\boldsymbol{\alpha}}_i = \tilde{\mathbf{Y}}_i - \tilde{\mathbf{Z}}_i (\tilde{\mathbf{Z}}_i^\top \tilde{\mathbf{Z}}_i)^{-1} \tilde{\mathbf{Z}}_i^\top \tilde{\mathbf{Y}}_i = (\mathbf{I}_{m_i} - \mathbf{P}_i) \tilde{\mathbf{Y}}_i$, $i = 1, \dots, n$, where $\mathbf{P}_i = \tilde{\mathbf{Z}}_i (\tilde{\mathbf{Z}}_i^\top \tilde{\mathbf{Z}}_i)^{-1} \tilde{\mathbf{Z}}_i^\top$. Let $\text{RSS}_i = \hat{\boldsymbol{\epsilon}}_i^\top \hat{\boldsymbol{\epsilon}}_i = \tilde{\mathbf{Y}}_i^\top (\mathbf{I}_{m_i} - \mathbf{P}_i) \tilde{\mathbf{Y}}_i$, and $q = k + 1$, which correspond to the number of columns of $\tilde{\mathbf{Z}}_i$. Pooling all RSS_i ($i = 1, \dots, n$) together naturally leads to an estimator of σ^2 , $\hat{\sigma}^2 = \frac{1}{N - qn} \sum_{i=1}^n \text{RSS}_i$, where $N = \sum_{i=1}^n m_i$. By Lemma 1 of the Appendix, $\hat{\sigma}^2$ is consistent and asymptotically normal.

With the consistent estimator, $\hat{\sigma}^2$, our proposed estimator $\hat{\boldsymbol{\beta}}(\tau)$ when σ^2 is unknown is given by $\hat{\boldsymbol{\beta}}_{n, h_n}(\tau) = \arg\min_{\boldsymbol{\beta} \in \mathcal{B}} \sum_{i=1}^n \rho_{\tau, h_n}^*(\mathcal{O}_i, \boldsymbol{\beta}, \hat{\sigma}^2)$. Here and in the sequel, the notation $\rho_{\tau, h}^*(\mathcal{O}_i, \boldsymbol{\beta})$ in (7) is expanded to incorporate the additional argument from σ^2 or $\hat{\sigma}^2$. The $\rho_{\tau, h_n}^*(\cdot)$ above stands for either $\rho_{\tau, h}^{N*}(\cdot)$ or $\rho_{\tau, h}^{L*}(\cdot)$.

3.4. Choose the smoothing parameter h_n

Motivated by the work of [4] and [51], we propose a modified simulation-extrapolation-type strategy to choose the smoothing parameter h_n . For notation simplicity and clarity, in this subsection we drop the τ in $\hat{\boldsymbol{\beta}}(\tau)$ and use $\hat{\boldsymbol{\beta}}(h)$ to denote the estimator associated with smoothing parameter h .

For a given dataset, we define $M_n(h) = E[\{\hat{\boldsymbol{\beta}}(h) - \boldsymbol{\beta}_0\}^\top \hat{\boldsymbol{\Omega}}^{-1} \{\hat{\boldsymbol{\beta}}(h) - \boldsymbol{\beta}_0\}]$, where $\hat{\boldsymbol{\Omega}} = \text{cov}\{\hat{\boldsymbol{\beta}}(h)\}$, and aim to identify the optimal smoothing parameter defined as $h_{0,n} \doteq \arg\min_{\mathcal{H}_n} M_n(h)$, where $\mathcal{H}_n$ is a sequence of candidate values for h_n conforming to the technical requirement, $h_n \rightarrow 0$ as $n \rightarrow \infty$. However, since $M_n(h)$ depends on the unknown $\boldsymbol{\beta}_0$, the minimization of $M_n(h)$ cannot be carried out directly in practice. We propose to approximate $h_{0,n}$ through the following procedure:

- Step 0: Set $c = 1$.
- Step 1: Generate $\eta_{c,i}^*$ and $\eta_{c,i}^{**}$ independently from the normal distribution $N(0, \hat{\sigma}^2 D_i)$ (if the normal trajectory error is assumed) or the Laplace distribution $L(0, \hat{\sigma}^2 D_i)$ (if the Laplace trajectory error is assumed) for $i = 1, \dots, n$.
- Step 2: Compute $\hat{\boldsymbol{\beta}}_c^*(h)$ and $\hat{\boldsymbol{\beta}}_c^{**}(h)$ as estimator (8) based on samples $\{(\hat{B}_{c,i}^*, \mathbf{X}_i)\}_{i=1}^n$ and $\{(\hat{B}_{c,i}^{**}, \mathbf{X}_i)\}_{i=1}^n$, respectively, where $\hat{B}_{c,i}^* = \hat{B}_i + \eta_{c,i}^*$ and $\hat{B}_{c,i}^{**} = \hat{B}_{c,i}^* + \eta_{c,i}^{**}$.
- Step 3: Increase c by 1. Go back to Step 1 if $c < n_c$ and go to Step 4 if $c > n_c$. Here n_c is a pre-determined positive integer.
- Step 4: Compute S^* and S^{**} as the sample covariance matrices of $\{\hat{\boldsymbol{\beta}}_c^*(h) - \hat{\boldsymbol{\beta}}(h)\}_{c=1}^{n_c}$ and $\{\hat{\boldsymbol{\beta}}_c^{**}(h) - \hat{\boldsymbol{\beta}}^*(h)\}_{c=1}^{n_c}$, respectively.

- Step 5: Obtain $\hat{h}_{1,n} = \operatorname{argmin}_h \in \mathcal{H}_n M_{1,n}(h)$ and $\hat{h}_{2,n} = \operatorname{argmin}_h \in \mathcal{H}_n M_{2,n}(h)$, where
- $$M_{1,n}(h) = n_c^{-1} \sum_{c=1}^{n_c} \{\beta_c^*(h) - \hat{\beta}(h)\}^T (S^*)^{-1} \{\beta_c^*(h) - \hat{\beta}(h)\} \text{ and}$$
- $$M_{2,n}(h) = n_c^{-1} \sum_{c=1}^{n_c} \{\beta_c^{**}(h) - \beta^*(h)\}^T (S^{**})^{-1} \{\beta_c^{**}(h) - \beta^*(h)\}.$$
- Step 6: Calculate the second-order approximation to $h_{0,n}$ as $\hat{h}_{0,n} = \hat{h}_{1,n}^2 / \hat{h}_{2,n}$.

In Step 5, since $\hat{B}_{c,i}^{**}$ measures $\hat{B}_{c,i}^*$ in the same way that $\hat{B}_{c,i}^*$ measures B_j , it is reasonable to expect that the relationship between $\hat{h}_{2,n}$ and $\hat{h}_{1,n}$ is similar to that between $\hat{h}_{1,n}$ and $h_{0,n}$. Therefore, back extrapolation can be used to approximate h_0 . In Step 6, we apply the linear extrapolation from the pair $(\log \hat{h}_{1,n}, \log \hat{h}_{2,n})$ to obtain the second-order approximation to $h_{0,n}$, $\hat{h}_{0,n} = \hat{h}_{1,n}^2 / \hat{h}_{2,n}$.

3.5. Computational considerations

The proposed estimator of $\beta_0(\tau)$ is obtained through minimizing $\sum_{i=1}^n \rho_{\tau, h_n}^*(\mathcal{O}_i, \beta, \sigma^2)$ (if σ^2 is known) or $\sum_{i=1}^n \rho_{\tau, h_n}^*(\mathcal{O}_i, \beta, \hat{\sigma}^2)$ (if σ^2 is unknown). In either case, the objective function (multiplied by $1/n$) is smooth and converges to $E\{D_i^{-1/2} \rho(B_i - X_i^T \beta)\}$, a convex function of β , as $n \rightarrow \infty$. This means, when n is large, the corrected objective function, $\sum_{i=1}^n \rho_{\tau, h_n}^*(\mathcal{O}_i, \beta, \sigma^2)$, should be close to a smooth convex function, and thus usual optimization algorithms can work adequately for finding $\hat{\beta}(\tau)$. A pseudo algorithm for the case with unknown σ^2 is described as follows.

- Step 1. Calculate $\hat{\sigma}^2$ and $\hat{B}_i$ for $i = 1, \dots, n$.
- Step 2. Obtain $\hat{\beta}_{naive}(\tau)$ by applying the *rq()* function in R package *quantreg* with responses, $\{\hat{B}_i\}_{i=1}^n$, and covariates, $\{\hat{X}_i\}_{i=1}^n$.
- Step 3. Apply the *optim()* function to the objective function $\sum_{i=1}^n \rho_{\tau, h_n}^*(\mathcal{O}_i, \beta, \hat{\sigma}^2)$ with the initial value set as $\hat{\beta}_{naive}(\tau)$. Follow the procedure outlined in Section 3.4 to determine the optimal smoothing parameter $\hat{h}_{0,n}$.
- Step 4. The proposed estimator is obtained $\hat{\beta}_n, \hat{h}_{0,n}(\tau)$.

4. Inferences

Inferences about $\hat{\beta}(\tau)$ are important in applications. In the Supplementary Materials, we present the large sample properties of the proposed estimator, including uniform consistency and weak convergence to a Gaussian process; see Section S1 of the Supplementary Materials. By our theory, the limiting variance of $n^{1/2}\{\hat{\beta}(\tau) - \beta_0(\tau)\}$ involves complex quantities, estimation of which may be unstable with small or moderate sample sizes. In this subsection, we propose to use a simple resampling approach to estimating the asymptotic variance. Our procedure adapts the perturbing technique proposed by [24] to the estimation setting considered here.

Let $\omega_1, \omega_2, \dots, \omega_n$ be independent variates following a nonnegative known distribution with mean 1 and variance 1, for example, *Exponential*(1). With the data fixed at the observed

values, we repeatedly generate $\{\omega_1, \omega_2, \dots, \omega_n\}$ and obtain a large number of realizations of

$$\sigma_*^2 = \frac{(N - qn)^{-1} \sum_{i=1}^n \text{RSS}_i}{n^{-1} \sum_{i=1}^n \omega_i}, \text{ and } \boldsymbol{\beta}^*(\tau) = \underset{\boldsymbol{\beta} \in \mathcal{B}}{\text{argmin}} \sum_{i=1}^n \omega_i \rho_{\tau, h}(\mathcal{O}_i, \boldsymbol{\beta}, \sigma_*^2), \text{ denoted by}$$

$\{\boldsymbol{\beta}_r^*(\tau)\}_{r=1}^{n_b}$. Here n_b is a pre-determined positive integer indicating how many times the resampling is repeated. In the Supplementary Materials, we show that the conditional distribution of $n^{1/2}\{\boldsymbol{\beta}^*(\tau) - \hat{\boldsymbol{\beta}}(\tau)\}$ given the observed data is asymptotically the same as the unconditional distribution of $n^{1/2}\{\hat{\boldsymbol{\beta}}(\tau) - \boldsymbol{\beta}_0(\tau)\}$. Hence, the variance of $\hat{\boldsymbol{\beta}}(\tau)$ can be estimated by the sample variance of $\{\boldsymbol{\beta}_r^*(\tau)\}_{r=1}^{n_b}$. The confidence intervals for $\boldsymbol{\beta}(\tau)$ can be constructed using the normal approximation or by referring to the empirical percentiles of $\boldsymbol{\beta}^*(\tau)$.

When σ^2 is known, we can skip the resampling step for σ_*^2 and simply replace the σ_*^2 in obtaining $\boldsymbol{\beta}^*(\tau)$ by σ^2 . The justification of the presented resampling-based inference procedure is provided in the Supplementary Materials (see Section S2).

In addition, we may conduct second-stage inference procedures to render useful summaries of $\boldsymbol{\beta}_0(\tau)$ and explore the varying patterns of $\boldsymbol{\beta}_0(\tau)$ over τ , following the lines of [40]. For example, to evaluate whether a certain covariate is constant over τ , we can formulate the problem as testing $H_0: \boldsymbol{\beta}_0^{(l)}(\tau) = \eta_0$ for $\tau \in [\tau_L, \tau_U]$, where η_0 is an unspecified constant and $[\tau_L, \tau_U]$ is a pre-specified interval within $(0, 1)$. Here and hereafter $\boldsymbol{v}^{(l)}$ denotes the l th component of vector $\boldsymbol{v}$. To test H_0 , we may consider a test statistic taking the form $\mathcal{T} = n^{1/2} \int_{\tau_L}^{\tau_U} \Xi(\tau) \{\hat{\boldsymbol{\beta}}^{(l)}(\tau) - \hat{\boldsymbol{q}}^{(l)}\} d\tau$, where $\Xi(\tau)$ is a nonconstant nonnegative weight function, and $\hat{\boldsymbol{q}} = \{\int_{\tau_L}^{\tau_U} \hat{\boldsymbol{\beta}}(\tau) d\tau\} / (\tau_U - \tau_L)$. Inference on $\mathcal{T}$ can be conducted using the empirical distribution of $\mathcal{T}^* = n^{1/2} \int_{\tau_L}^{\tau_U} \Xi(\tau) [\{\boldsymbol{\beta}^{*(l)}(\tau) - \hat{\boldsymbol{\beta}}^{(l)}(\tau)\} - \{\boldsymbol{q}^{*(l)} - \hat{\boldsymbol{q}}^{(l)}\}] d\tau$, where $\boldsymbol{q}^* = \{\int_{\tau_L}^{\tau_U} \boldsymbol{\beta}^*(\tau) d\tau\} / (\tau_U - \tau_L)$. Specifically, we may reject H_0 if $\mathcal{T} < d_{\alpha/2}$ or $\mathcal{T} > d_{1-\alpha/2}$, where $d_{\alpha/2}$ and $d_{1-\alpha/2}$ are the $(\alpha/2)$ th and $(1 - \alpha/2)$ th empirical quantiles of $\mathcal{T}^*$ respectively. This procedure can be justified based on arguments similar to those of [40].

5. Simulation Studies

We conduct extensive simulations to investigate the performance of the proposed method with finite samples. First, we generate the longitudinal observations Y_{ij} as $Y_{ij} = a_i + b_i t_{ij} + \epsilon_{ij}$, $j = 1, \dots, m_i$, $i = 1, \dots, n$, where a_i is the random intercept, following the exponential distribution, $\text{Exp}(0.8)$, b_i is the random slope generated from the following linear model with heteroscedastic errors, $b_i = 2 + X_{1i} + X_{2i} + (0.1 + X_{1i} + X_{2i})e_i$. We generate observation time points, $\{t_{ij}, j = 1, \dots, m_i\}$, from a Poisson process with intensity 0.8 (i.e. t_{ij} is the sum of j independent exponential variables $\text{Exp}(0.8)$). We specify $\{m_i, i = 1, \dots, n\}$ as i.i.d. random variables generated from the uniform distribution, $\text{Unif}(4, 10)$. We generate X_{1i} from the uniform distribution, $\text{Unif}(0, 0.5)$, X_{2i} from the Binomial distribution, $\text{Ber}(0.5)$, and e_i from the standard Normal distribution, $N(0, 1)$. With the trajectory feature of interest B_i being the random slope b_i , it is easy to see that model (3) holds and $Q_{B_i}(\tau | X_i) = \beta_0(\tau) + \beta_1(\tau) X_{1i} +$

$\beta_2(\tau)X_{2i}$ with $\beta_0(\tau) = 2 + 0.1Q_\epsilon(\tau)$ and $\beta_1(\tau) = \beta_2(\tau) = 1 + Q_\epsilon(\tau)$, where $Q_\epsilon(\tau)$ is the τ th quantile of e_i .

We consider four different configurations for the error term in the trajectory model, ϵ_{ij} . We examine the cases with heavy-tailed trajectory errors and the cases where the trajectory errors depend on the covariates X_i . The specific configurations are listed as follows:

Case 1: $Y_{ij} = a_i + b_i t_{ij} + \epsilon_{ij}$ with $\epsilon_{ij} \sim N(0,1)$, the standard normal distribution;

Case 2: $Y_{ij} = a_i + b_i t_{ij} + \epsilon_{ij}$ with $\epsilon_{ij} \sim L(0,1)$, the standard Laplace distribution;

Case 3: $Y_{ij} = a_i + b_i t_{ij} + \epsilon_{ij}$ with $\epsilon_{ij} = \epsilon_{ij}^* / (1 + X_{i1})$ and $\epsilon_{ij}^* \sim N(0, 1)$;

Case 4: $Y_{ij} = a_i + b_i t_{ij} + \epsilon_{ij}$ with $\epsilon_{ij} = \epsilon_{ij}^* / (1 + X_{i1})$ and $\epsilon_{ij}^* \sim L(0, 1)$.

In Case 3 and Case 4, $(1 + X_{i1})$ serves as the $\delta(X_i, Z_i)$ in the trajectory error distributions discussed in Sections 3.1 and 3.2.

Under each configuration, we simulate 1000 datasets of sample size 200 or 500. We apply the proposed method to each simulated dataset, examining the covariate effects on the 10th, 20th, ..., 90th quantiles of B_i . We compare the proposed estimator with the naive estimator, which is obtained by performing quantile regression of $\{B_i\}_{i=1}^n$ on $\{X_i = (X_{1i}, X_{2i})^T\}_{i=1}^n$.

As suggested by the Associate Editor, we also consider fitting data with the linear mixed effect (LME) model implied by our data generation scheme: $Y_{ij} = a_0 + a_1 t_{ij} + a_2 X_{1i} t_{ij} + a_3 X_{2i} t_{ij} + u_{1i} + u_{2i} t_{ij} + u_{3i} Z_{ij} + \epsilon_{ij}$, where $u_{1i} = a_i - a_0$, $u_{2i} = 0.1 e_i$, $u_{3i} = e_i$, $Z_{ij} = (X_{1i} + X_{2i}) t_{ij}$, $a_1 = 2$, $a_2 = a_3 = 1$. Ignoring the fact that ϵ_{ij} may not be normally distributed and may be covariate-dependent (e.g. Cases 3-4), we fit this model using the *lmer()* function in R package *lme4* with diagonal variance-covariance matrix assumed for $(u_{1i}, u_{2i}, u_{3i})'$. Our proposed estimator is obtained through the *optim()* function in R with the initial value set as the naive estimate. The bandwidth h_n is chosen as 0.8 and the smoothing function $K(\cdot)$ is chosen as the standard normal distribution function. We use the resampling method presented in Section 4 to estimate the asymptotic variance of the proposed estimator, choosing $n_b = 200$ and generating $\{\omega_1, \dots, \omega_n\}$ from the exponential distribution $Exp(1)$.

We only present simulation results for $n = 500$ because the results for $n = 200$ deliver very similar messages and thus are omitted. In Figure 2, we present the empirical biases of the proposed estimator, the naive estimator, and the LME estimator. It is clear that the proposed estimator yields considerable bias reductions compared to the naive estimator. The bias reductions are most prominent at τ 's close to 0 or 1. The LME estimator is generally less biased compared to the naive estimator but has larger biases than the proposed estimator. We also observe that the bias of the proposed estimator decreases towards 0 as n increases (results not shown). Figure 3 depicts the estimated standard errors (ESE) and empirical standard deviations (SD) for Cases 1–4. We can see that the estimated standard error (ESE) well match the empirical SDs. We also observe that ESEs and empirical SDs decrease with the sample size at the expected rate (results not shown). The empirical coverage probabilities of 95% confidence intervals (CI) for Cases 1–4 are presented in Figure S1 of the

Supplementary Materials. It is shown that the empirical coverage probabilities are close to the nominal level for all τ 's.

Next, we consider settings where the longitudinal trajectory model is not linear over time t (i.e. $f(t, \boldsymbol{\alpha}_i)$ is not a linear function of t). Specifically, we generate longitudinal observations from the following models:

Case 5: $Y_{ij} = a_i + b_{it_{ij}} + c_{it_{ij}}^2 + \epsilon_{ij}$ with $\epsilon_{ij} = \epsilon_{ij}^* / (1 + X_{i1})$ and $\epsilon_{ij}^* \sim N(0, 1)$;

Case 6: $Y_{ij} = a_i + b_{it_{ij}} + c_{it_{ij}}^2 + \epsilon_{ij}$ with $\epsilon_{ij} = \epsilon_{ij}^* / (1 + X_{i1})$ and $\epsilon_{ij}^* \sim L(0, 1)$,

and let the trajectory feature of interest be the changing rate of $Y_{ij}(t)$ at a given time point t_* , which satisfies $B_i \doteq b_i + 2c_{it_*} = 2 + X_{1i} + X_{2i} + (0.1 + X_{1i} + X_{2i})e_i$. Here we let $a_i \sim \text{Exp}(0.15)$, $c_i \sim \text{Exp}(0.15)$, and $t_* = 1$. We generate $\{t_{ij}, j = 1, \dots, m_i\}$, from a Poisson process with intensity 0.15, and generate X_i and e_i in the same way as before. The empirical biases, estimated standard errors, empirical standard deviations, and empirical coverage probabilities of 95% confidence intervals are plotted in Figures S2-S4 in the same manner as in Figures 1-2 and Figure S1. Similar to the results for Cases 1–4, the results for Cases 5–6 suggest substantial bias reduction resulted from the proposed method as compared to the naive ones. The coverage probabilities match quite well with the nominal value. The empirical standard errors and the estimated ones agree well and decrease with the sample size as expected. Overall, the performance of the proposed method are comparable between the cases with nonlinear and linear trajectory models.

We further examine the robustness of the proposed method to the misspecification of the polynomial trajectory model. First, we generate data in the same way as in Case 2, except for letting ϵ_{ij} follow the uniform distribution, $\text{Unif}(-\sqrt{3}/2, \sqrt{3}/2)$. Then we assess the performance of $\hat{\boldsymbol{\beta}}(\tau)$ which is obtained by assuming a linear trajectory model with normal or Laplace random errors. The simulation results about such obtained $\hat{\boldsymbol{\beta}}(\tau)$, including empirical biases, estimated standard errors, empirical SDs, and empirical coverage probabilities of 95% confidence intervals, are presented in Figure S5 of the Supplementary Materials. Next, we generate data based on the linear trajectory model specified in Case 3 but with $\epsilon_{ij} \sim \text{Unif}(-\sqrt{3}/2, \sqrt{3}/2)$. In this case, we obtain the proposed estimator assuming a quadratic trajectory model with normal or Laplace random errors. The simulation results for this situation are presented in Figure S6 of the Supplementary Materials.

By comparing the results for Case 2, given in Figures 2, 3, and Figure S1, with the results in Figure S5, we observe that the estimator that does not assume the correct trajectory error distribution (uniform versus normal or Laplace) still yields negligible empirical biases. The impact of misspecifying the error distribution on the variance estimation and coverage probabilities also seems minimal. The results in Figures S5 suggest quite robust performance of the proposed estimator to the misspecification of the trajectory error distribution in model (1).

Figure S6 corresponds to a scenario where the trajectory error distribution is not correctly specified and the polynomial order is specified as a value larger than the true one. In

Figure S6, we observe that the proposed estimator produces mildly to moderately elevated empirical biases, while still yielding notable bias reductions as compared to the naive estimator. Estimated standard errors remain to well match empirical standard deviations. The empirical coverage probabilities are within a reasonable range from the nominal level; the departures from the nominal level are bigger for τ closer to 0 or 1. On the other hand, some of our unreported simulation results show that taking a polynomial order smaller than the true one can lead to quite substantial biases in estimating covariate effects on trajectory features. Based on these numerical experiences, in practice, we recommend being aggressive toward “over-estimating” the polynomial order from examining the observed within-subject longitudinal data.

6. Analysis of the DURABLE Study

Diabetes is a chronic disease in which there are high blood sugar levels over a prolonged period. It is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation and is the 7th leading cause of death affecting 422 million people worldwide [42]. Insulins are important treatments for diabetes. The DURABLE [1] trial was designed to study the efficacy, safety, and durability of two common insulin initiation regimens: twice-daily insulin lispro mixture 75/25 (LM75/25) versus once-daily insulin glargine (GL) added to oral antihyperglycemic drugs (OADs) to achieve and maintain hemoglobin A1c (HbA1c) goals. This randomized, open label, parallel study enrolled 2187 insulin-naïve patients with type 2 diabetes from 11 countries, aged 30 to 80 years, with HbA1c > 7.0% on at least two oral antihyperglycemic agents. The HbA1c level was collected every 6 weeks during 24 weeks.

HbA1c level is an important index of glycemic control. To assess the efficacy of different treatments, we analyze the longitudinal measurements of HbA1c under the proposed quantile regression framework. Specifically, let Y_{ij} represent the j -th HbA1c measurements of the i th individual recorded in the t_{ij} th week since the study enrollment ($j = 1, \dots, m_i$). After examining the observed data, we assume a quadratic trajectory model for within-subject HbA1c measurements during the 24 week follow-up period. That is,

$$Y_{ij} = \alpha_{i0} + \alpha_{i1}t_{ij} + \alpha_{i2}t_{ij}^2 + \epsilon_{ij}.$$

Under this model, the random intercept α_{i0} denotes the subject-specific baseline HbA1c measurement, and the subject-specific decreasing rate of HbA1c at a specified time point t^* is given by $-\alpha_{i1} - 2\alpha_{i2}t^*$. In our analysis, we take $t^* = 3$ (corresponding to 12 weeks) and set $B_i \doteq -\alpha_{i1} - 2\alpha_{i2}t^*$, a meaningful trajectory feature which is not directly observed. Under this setup, we exploit how treatments and other risk factors influence the HbA1c reduction rate at 12 weeks after the initiation of the assigned insulin treatment. By adopting the quantile regression modeling, we can further delineate whether and how their associations with B_i vary across diabetes patients.

The covariate of our main interest is *therapy*, coded as 1 if the subject took the LM75/25 regimen and 0 if GL regimen. We consider three other covariates according to our exploratory analysis: *sulfouse*, 1 if the subject uses the sulfonylurea (SU) and 0 otherwise;

basfglu, baseline fasting plasma glucose; and *basfins*, baseline fasting insulin. Here we standardize *basfglu* and *basfins* by subtracting their means and then dividing by their standard deviations. Because the two regimes are added to OADs, we also include the interaction term, *therapy*sulfuse*, in our model to examine if the treatment effect (i.e. LM75/25 versus GL) on the HbA1c decreasing rate is modified by the use of SU. We exclude 107 subjects who have missing covariates in the analysis. We also exclude 263 subjects who have less than three measurements of HbA1c, because they do not contribute information to studying B_i . There are 1,717 subjects in our analysis; 71 subjects are in GL group without SU, 800 subjects are in GL group with SU, 65 subjects are in LM75/25 group without SU, and 781 subjects are in LM75/25 group with SU. More detailed summary statistics for this dataset are provided in Table 1.

We apply the proposed method to perform quantile regression for B_i on the covariates specified above at quantile levels equally spaced between 0.1 and 0.8 with step size 0.02. For selecting the smoothing parameter h_n , we employ the procedure introduced in Subsection 3.4 on a h -grid between 0.8 and 1.5 with step size 0.1. In Figure 4, we plot the proposed coefficient estimates (solid line) along with the 95% pointwise confidence intervals (dashed lines) for $\tau \in [0.1, 0.8]$ based on 200 resampling samples. In Figure 4, the estimated intercept coefficients represent the estimated quantiles of HbA1c decreasing rate for subjects receiving GL therapy, no SU use, with baseline fasting glucose and baseline fasting insulin set as 10.98mmol/L and 10.06 units (which are their observed average values in this dataset). For example, Figure 4 shows that the estimated median rate of HbA1c decreasing is about 0.34(%) per month.

To interpret the covariate coefficients in Figure 4, note that positive covariate coefficients indicate quicker HbA1c decreasing over time given one unit increase in the corresponding covariate. We observe that the coefficients for baseline fasting glucose and baseline fasting insulin are significantly different from 0 for all τ 's considered. These results suggest that a higher baseline fasting glucose and a lower baseline fasting insulin are significantly associated to faster decreasing of HbA1c. More specifically, 1 mg/dl increase in baseline fasting glucose (or 1 μ U/mL increase in baseline fasting insulin) is associated with 0.08(%) per month higher (or 0.04(%) per month lower) A1c decreasing rate. These are sensible findings that can be explained as follows. First, a higher baseline glucose generally implicates a higher baseline HbA1c. It is reasonable to expect a more rapid HbA1c reduction for those with high baseline HbA1c values compared to those with low baseline HbA1c values. Secondly, a lower baseline insulin may imply less insulin resistance. Consequently, it is associated with a stronger response to an insulin treatment that is manifested by a quicker HbA1c decreasing.

To evaluate the treatment effect, we examine the coefficient plots for *therapy*, *sulfuse*, and *therapy*sulfuse* simultaneously. In the presence of the interaction term *therapy*sulfuse*, the coefficients for *therapy* can be interpreted as the treatment effect for subjects without SU use. The estimated coefficients for *therapy* suggest that the therapy LM75/25 may offer some significant advantage over GL in terms of lowering HbA1c more quickly among the “strong” responders of the insulin treatments (corresponding to the large τ 's) when SU is not used. For the subjects with sustained HbA1c, either due to low baseline HbA1c or weak

response to the insulin treatment, the GL and LM75/25 therapies demonstrate little difference in the decreasing rate of HbA1c. The estimated coefficients for *sulfouse* suggest some negative impact of using SU on the treatment efficacy in lowering HbA1c. The negative impact seems diminished in “strong” responders of the insulin treatment.

In Figure 5, we plot the estimates for *therapy* coefficient + *therapy*sulfouse* coefficient and *sulfouse* coefficient + *therapy*sulfouse* coefficient, which represent the treatment effect for subjects with SU use and the effect of SU use for subjects receiving LM75/25. Comparing Figure 5 with the plots for *therapy* and *sulfouse* in Figure 4, we see that for subjects with SU, choosing LM75/25 versus GL has little impact on the HbA1c decreasing rate, while LM75/25 demonstrates some moderate advantage over GL for subjects without SU use. This may be due to the fact that SU is a treatment for lowering postprandial blood glucose level, GL is a basal insulin to lower the overall glucose level, and LM75/25 targets both basal and postprandial. Therefore, when SU is added, both GL and LM75/25 will cover basal and postprandial blood glucose, thereby resulting in similar glycemic control, and hence similar HbA1c decreasing rates. Without SU, LM75/25 can cover postprandial glucose, while GL cannot; therefore LM75/25 demonstrates some moderate benefit over GL. It is also shown by comparing Figure 5 with Figure 4 that for subjects treated with LM75/25, using SU may be associated with slower HbA1c reduction; its effect has a consistent direction with but a smaller magnitude than that in subjects treated with GL, particularly for τ 's less than 0.5. The overall negative impact of SU may associate with hypoglycemic events, as SU is a known significant factor to cause hypoglycemic events, which limits titrating insulin [9] and then lead to worse glycemic control. The smaller impact of SU use under LM75/25 (versus that under GL) may be explained by the bigger overlap in glucose control coverage between SU and LM75/25. Despite these sensible observations regarding the interaction between *therapy* and *sulfouse*, the confidence intervals for the coefficient for *therapy*sulfouse* (see Figure 4) do not suggest statistical significance. This is likely due to the small size of the group without SU use. A larger future study may help provide a more confirmative conclusion.

Finally, we employ the proposed test $\mathcal{T}$ to assess whether or not the effects of *therapy* and other covariates are constant over τ . We set $\tau_L = 0.1$ and $\tau_U = 0.8$ and adopt $\Xi(v) = I\{v > (\tau_L + \tau_U)/2\}$. For the coefficient for *therapy*, we obtain $\mathcal{T} = 0.589$, which falls into the rejection region $(-\infty, -0.259) \cup (0.291, \infty)$ at level 0.05. This suggests that the difference between LM75/25 and GL may vary across type II diabetes patients. For example, it may differ by the status of SU use as suggested by Figure 4 and Figure 5. We also reject the constancy of the effect of *basfglu*. This is consistent with our observation in Figure 4, which is, baseline fasting glucose has a bigger influence on the upper quantiles of the HbA1c decreasing rate. Our constancy tests suggest that the location-shift effects may be adequate for *sulfouse* and *basfins*.

It is worth mentioning that we also apply the proposed method assuming the linear trajectory model for within-subject HbA1c. We obtain quite similar results regarding the covariate effects on the decreasing rate of HbA1c at the 12 weeks follow-up. The counterparts of Figure 4 and Figure 5 are presented in the Supplementary Materials; see Figures S7 and S8.

This suggests the robustness of the proposed trajectory quantile regression method to the specification of the underlying trajectory model.

7. Discussion

This work, to the best of our knowledge, is the first effort to utilize the device of quantile regression to explore the associates of longitudinal outcome trajectory which may follow heterogeneous patterns. As a proof of concept, we assume polynomial outcome trajectories in the present paper, while the methodology can readily be extended to accommodate nonparametric trajectories, for example, through B-Spline. The details with such extensions will be spelled out in separate work. Exploring extensions to other more flexible trajectory models, such as hidden Markov models [36, 38] merits future research.

In this paper, we derive the regression quantiles of the latent trajectory feature when the error term in the trajectory model follows the Normal or Laplace distribution. Appealingly, they take the same practical form, as pointed out at the end of Section 3.2, and are shown to have robust performance when the trajectory errors follow a different distribution. It is worth noting that the bias correction strategy adopted in the proposed estimation procedure can be further extended to a wider class of distribution families, as long as their characteristic functions are proportional to the inverse of a polynomial; see [22] and [51] for related discussions. This entails broader applicability and enhanced usefulness of the proposed trajectory quantile regression framework.

As raised by one referee, estimating extreme quantiles may be of great interest in many real applications. Our simulation studies indicate more substantial bias reduction for τ closer to 0 or 1. However, the proposed methods are not tailored to estimating extreme quantiles (e.g. $\tau = 0.01, 0.99$); hence issues like excessive estimation variability may occur in those situations. Addressing such a problem often requires additional modeling of the tail response distribution, which is beyond the scope of this work. Based on our numerical experiences, the proposed method can have reasonable performance when τ is as small as 0.1 or as large as 0.9 with moderate to large sample sizes. In practice, unusually large estimated standard errors may be an indication of τ being too close to 0 or 1 for the proposed methods to produce reliable estimates. This may serve as a useful practical rule for determining the τ -range to make inference based on the proposed methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. DURABLE trial: HbA1c values over time. The solid black lines depict the 25th, 50th, and 75th quantiles of HbA1c at different time points; the dashed lines exemplify the HbA1c trajectories of 5 subjects.

Figure 2. Empirical biases of the proposed estimator (solid lines), the naive estimator (dashed lines), and the LME estimator (dash-dotted lines) for Cases 1–4.

Figure 3. Estimated standard errors (solid lines) and empirical standard deviations (dashed lines) of the proposed estimator for Cases 1–4.

Figure 4.

The DURABLE data example: the proposed coefficient estimates (solid lines) and the 95% point-wise confidence intervals (dash-dotted lines).

Figure 5.

The DURABLE data example: the estimates for *therapy* coefficient plus *therapy*sulfouse* coefficient and *sulfouse* coefficient plus *therapy*sulfouse* coefficient (solid lines), and the corresponding 95% pointwise confidence intervals (dash-dotted lines).

Table 1.

Summary statistics for the DURABLE data (SD: standard deviation).

Therapy \ Sulfouse	with SU	without SU
	n(%)	n(%)
LM75/25	781(45.49%)	65 (3.79%)
GL	800 (46.59%)	71 (4.14%)
	Range	Mean ± SD
Baseline fasting glucose	(1.036, 25.96)	10.98 ± 3.586
baseline fasting insulin	(0, 142.68)	10.06 ± 8.987
HbA1c at 0 week	(5.61, 13.84)	9.01 ± 1.338
HbA1c at 6 weeks	(6.89, 9.74)	7.96 ± 1.064
HbA1c at 12 weeks	(4.42, 15.45)	7.33 ± 1.086
HbA1c at 18 weeks	(5.97, 9.45)	7.28 ± 0.953
HbA1c at 24 weeks	(3.63, 13.02)	7.23 ± 1.155