The Estimation of a Regression Curve by Using Mixed Truncated Spline and Fourier Series Models for Longitudinal Data

Made Ayu Dwi Octavanny, I Nyoman Budiantara, Heri Kuswanto, and Dyah Putri Rahmawati

Abstract— **There has been increasing interest in mixed estimators in nonparametric regression, although so far these have only been used for cross-sectional data. This paper proposes a new method to estimate nonparametric regression curves for longitudinal data. It uses two estimators: a truncated spline and Fourier series. The estimation of the regression curve is completed by minimizing the penalized weighted least squares and weighted least squares. This article also includes the properties of the new mixed estimator, which is biased and linear in the observations. This study selects the model with the smallest generalized cross-validation value. The performance of the new method is demonstrated by a simulation study with different subjects and numbers of time points. We also apply the proposed approach to a dataset of stroke patients. This study proves that the mixed estimator provides better results than a single estimator.**

Index Terms— **Fourier series, longitudinal data, mixed estimator, nonparametric regression, truncated spline**

I. Introduction

Regression analysis aims to determine the relations between the response and the predictors. A method used when the pattern of the regression curve for the data is unknown is nonparametric regression [1]. The strength of this method lies in its great flexibility, since it is necessary to find a way to estimate the regression curve only using the data, without being influenced by subjective opinions of the researcher [2]. Some of the estimators used for this are splines, Fourier series, kernels, and polynomials.

A truncated spline is a function capable of defining the change in the pattern in certain sub-intervals. This function can also, by the use of knot points, capture a pattern of the data that changes drastically from one interval to another. Splines are popular estimators in nonparametric regression because they provide an excellent visual interpretation. Several studies using splines have been carried out, including a simulation study to compare knot selection methods in a penalized regression spline model a geographically weighted nonparametric regression with a truncated spline approach [4], and a B-spline curve interpolation model [5]. The Fourier series is a much used function to describe curves that describe sine and cosine waves. This estimator is commonly used when there is some kind of periodicity. Bilodeau [6] estimated additive components with functions consisting of a truncated Fourier cosine series, using penalized least squares (PLS) to obtain the coefficients. In addition, [7] developed a Fourier series estimator for bi-response nonparametric regression.

Nonparametric regression often uses a single estimator, but this does not limit its ability to develop a mixed estimator. There are many cases where each predictor variable has a different pattern. Several studies using mixed estimators have been published, including [8] with a mixed estimator of a truncated spline and Fourier series in multivariable nonparametric regression, and [9] and [10] estimated the regression curve by using a mixed smoothing spline and kernel model. Besides, [11] developed a mixed estimator of smoothing spline and Fourier series.

Previous studies of mixed estimators have been limited to cross-sectional data. To remedy this, we here develop a longitudinal data model. The longitudinal data are obtained from observations on n independent subjects repeatedly observed over a certain period of time; this has the advantage of being able to observe changes over time [12]. In the previous study [13], the mixed estimator has a limited sample size. The present study extends the use of a mixed truncated spline and Fourier series (MTSFS) model to variety number of subjects and varied time point designs. Some properties of the new mixed estimator will also be provided. We use generalized cross-validation (GCV) to determine the best model from among various numbers of knots, oscillations, and values of the smoothing parameters. Simulation studies and real data are provided to demonstrate the performance of the proposed method. The case study used in this study includes the four factors that affect the Glasgow Coma Scale (GCS) in stroke patients, i.e., systolic blood pressure, diastolic blood pressure, body temperature, and pulse rate.

The rest of this paper is organized as follows. In Section

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2, we present the details of the new mixed estimator, its properties, and how to select the optimum number of knot points, oscillation parameter, and smoothing parameter. In Section 3, we present the results of a simulation study based on the proposed method. This is followed by an application to the data in Section 4. Section 5 is the Conclusion.

II. MTSFS MODEL FOR LONGITUDINAL DATA

A. The Estimators of the MTSFS Model for Longitudinal Data

Suppose y_{it} is the response variable and x_{it} and z_{it} are the predictor variables with sample size n subjects $(i=1,2,\ldots,n)$, each subject with T observations $(t=1,2,\ldots,T)$. The relationship between the response and predictors is assumed to follow the nonparametric regression model for longitudinal data, as follows:

$$y_{it}=\mu\left(x_{1it},\ldots,x_{pit},z_{1it},\ldots,z_{qit}\right)+\varepsilon_{it} \tag{1}$$

where μ is the regression curve and ε_{it} is the random error. Assume that the form of the regression curve μ is unknown and additive, so that

$$\mu\left(x_{1it},\ldots,x_{pit},z_{1it},\ldots,z_{qit}\right)=\sum_{j=1}^{p}f_{ji}\left(x_{jit}\right)+\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right) \tag{2}$$

where $\sum_{j=1}^{p}f_{ji}\left(x_{jit}\right)$ is the truncated spline component and $\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right)$ is the Fourier series component. The functions $f_{ji},\ j=1,2,\ldots p$ are approximations using truncated spline functions and the $g_{ki},\ k=1,2,\ldots,q$ are from Fourier series. The estimator μ is obtained through a two-stage optimization, i.e., penalized weighted least squares (PWLS) and weighted least squares (WLS). Some lemmas and a theorem are provided to obtain an MTSFS model for longitudinal data.

Lemma 1. *If the Fourier series component in Equation (2) is given by* $\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right)$*, then the goodness of fit is*

$$N^{-1}\left(\mathbf{y}^{*}-\mathbf{Zc}\right)'\mathbf{W}\left(\mathbf{y}^{*}-\mathbf{Zc}\right).$$

Proof of Lemma 1. The function g_{ki} is assumed to be unknown and contained in $C(0,\pi)$, the space of continuous functions on the interval $(0,\pi)$. The function is then approximated using Fourier series with trend, modified from Bilodeau [6]:

$$g_{ki}\left(z_{kit}\right)=d_{ki}z_{kit}+\frac{1}{2}c_{0ki}+\sum_{h=1}^{H}c_{hki}\cos hz_{kit} \tag{3}$$

For convenience, Equation (3) can be written in following matrix form:

$$\mathbf{g}=\mathbf{Zc} \tag{4}$$

where

$$\mathbf{Z}=\begin{bmatrix}\mathbf{Z}_1 & \mathbf{0} & \ldots & \mathbf{0}\\ \mathbf{0} & \mathbf{Z}_2 & \ldots & \mathbf{0}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \ldots & \mathbf{Z}_n\end{bmatrix},$$

$$\mathbf{Z}_i=\begin{bmatrix} z_{1i1} & 1/2 & \cos z_{1i1} & \ldots & \cos Hz_{1i1} & \ldots & z_{qi1} & 1/2 & \cos z_{qi1} & \ldots & \cos Hz_{qi1}\\ z_{1i2} & 1/2 & \cos z_{1i2} & \ldots & \cos Hz_{1i2} & \ldots & z_{qi2} & 1/2 & \cos z_{qi2} & \ldots & \cos Hz_{qi2}\\ \vdots & \vdots & \vdots & \ddots & \vdots & \ldots & \vdots & \vdots & \vdots & \ddots & \vdots\\ z_{1iT} & 1/2 & \cos z_{1i2} & \ldots & \cos Hz_{1iT} & \ldots & z_{qiT} & 1/2 & \cos z_{qi2} & \ldots & \cos Hz_{qiT}\end{bmatrix}$$

$$\mathbf{c}=\begin{bmatrix}\mathbf{c}_1\\ \mathbf{c}_2\\ \vdots\\ \mathbf{c}_n\end{bmatrix}, \text{ and}$$

$$\mathbf{c}_i=\begin{bmatrix}d_{1i} & c_{01i} & c_{11i} & \ldots & c_{H1i} & \ldots & d_{qi} & c_{0qi} & c_{1qi} & \ldots & c_{Hqi}\end{bmatrix}'.$$

If the regression model follow the Equation (1), then we can modify it as shown below:

$$\begin{aligned} y_{it}-\sum_{j=1}^{p}f_{ji}\left(x_{jit}\right)&=\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right)+\varepsilon_{it}\\ y_{it}^{*}&=\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right)+\varepsilon_{it},\ i=1,2,\ldots,n,\ t=1,2,\ldots,T \end{aligned} \tag{5}$$

The goodness of fit for Equation (5) can be written as

$$\begin{aligned} &N^{-1}\sum_{i=1}^{n}\sum_{t=1}^{T}w_{it}\left(y_{it}^{*}-\sum_{k=1}^{q}\sum_{t=1}^{T}g_{ki}\left(z_{kit}\right)\right)^{2}\\ &=N^{-1}\sum_{i=1}^{n}\sum_{t=1}^{T}w_{it}\left(y_{it}^{*}-\sum_{k=1}^{q}\sum_{t=1}^{T}\left(d_{ki}z_{kit}+\frac{1}{2}c_{0ki}+\sum_{h=1}^{H}c_{hki}\cos hz_{kit}\right)\right)^{2} \end{aligned} \tag{6}$$

As a result, the goodness of fit component in Equation (6) can be drawn in the following matrix form:

$$N^{-1}\mathbf{W}\left(\mathbf{y}^{*}-\mathbf{Zc}\right)^{2}=N^{-1}\left(\mathbf{y}^{*}-\mathbf{Zc}\right)'\mathbf{W}\left(\mathbf{y}^{*}-\mathbf{Zc}\right)\quad\square$$

Lemma 2. *If the penalty component is given by*

$$\sum_{k=1}^{q}\lambda_k\int_0^{\pi}\frac{2}{\pi}\left(g_{ki}''\left(z_k\right)\right)^2 dz_k\ ,$$

then

$$\sum_{k=1}^{q}\lambda_k\int_0^{\pi}\frac{2}{\pi}\left(g_{ki}''\left(z_k\right)\right)^2 dz_k=\mathbf{c}'\mathbf{D}(\lambda)\mathbf{c}\ .$$

Proof of Lemma 2. Regarding Equation (3), we define

$$\begin{aligned} g_{ki}''\left(z_k\right)&=\frac{d}{dz_k}\left[\frac{d}{dz_k}\left(d_{ki}z_{kit}+\frac{1}{2}c_{0ki}+\sum_{h=1}^{H}c_{hki}\cos hz_{kit}\right)\right]\\ &=-\sum_{h=1}^{H}h^2c_{hki}\cos hz_{kit} \end{aligned}$$

Consequently,

$$\begin{aligned} P_k\left(g_k\right)&=\int_0^{\pi}\frac{2}{\pi}\left(\sum_{h=1}^{H}h^2c_{hki}\cos hz_{kit}\right)^2 dz_k\\ &=\frac{2}{\pi}\int_0^{\pi}\left[\left(\sum_{h=1}^{H}h^2c_{hki}\cos hz_{kit}\right)^2+2\sum_{h<m}^{H}\left(h^2c_{hki}\cos hz_{kit}\right)\left(m^2c_{mki}\cos mz_{kit}\right)\right]dz_k \end{aligned}$$

Let

$$A=\frac{2}{\pi}\sum_{h=1}^{H}\int_0^{\pi}\left(h^2c_{hki}\cos hz_{kit}\right)^2 dz_k$$

$$B=\frac{2}{\pi}2\sum_{h<l}^{H}\int_{0}^{\pi}\left(h^2c_{hki}\cos hz_{kit}\right)\left(l^2c_{lki}\cos lz_{kit}\right)dz_k$$

Thus,

$$P_k\left(g_k\right)=A+B=\sum_{h=1}^{H}h^4c_{hki}^2 \qquad (7)$$

After obtaining the result of penalty in Equation (7), it can be rewritten in matrix form:

$$\mathbf{c}'\mathbf{D}(\lambda)\mathbf{c}$$

where

$$\mathbf{D}(\lambda)=\begin{bmatrix}\mathbf{D}_1(\lambda) & \mathbf{0} & \dots & \mathbf{0}\\ \mathbf{0} & \mathbf{D}_2(\lambda) & \dots & \mathbf{0}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \dots & \mathbf{D}_n(\lambda)\end{bmatrix},$$

$\mathbf{I}_k=\left[\lambda_k 1^4 \quad \lambda_k 2^4 \quad \dots \quad \lambda_k H^4\right]$, $\mathbf{d}_k=diag\left(0,0,\mathbf{I}_k\right)$, $k=1,2,...,q$,

and $\mathbf{D}_i(\lambda)=\begin{bmatrix}\mathbf{d}_1 & \mathbf{0} & \dots & \mathbf{0}\\ \mathbf{0} & \mathbf{d}_2 & \dots & \mathbf{0}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \dots & \mathbf{d}_q\end{bmatrix}$.

Considering the goodness of fit in Lemma 1 and penalty component in Lemma 2, we obtain the PWLS optimization as

$$N^{-1}\sum_{i=1}^{n}\sum_{t=1}^{T}w_{it}\left(y_{it}^*-\sum_{k=1}^{q}g_{ki}\left(z_{kit}\right)\right)^2+\sum_{k=1}^{q}\lambda_k\int_{0}^{\pi}\frac{2}{\pi}\left(g_{ki}''\left(z_k\right)\right)^2dz_k, 0<\lambda_k<\infty \qquad (8)$$

For simplification, Equation (8) can be rewritten in matrix form:

$$N^{-1}\left(\mathbf{y}^*-\mathbf{Zc}\right)'\mathbf{W}\left(\mathbf{y}^*-\mathbf{Zc}\right)+\mathbf{c}'\mathbf{D}(\lambda)\mathbf{c} \qquad (9)$$

Theorem 1. *If the goodness of fit is given in Lemma 1 and penalty component is given in Lemma 2, then the Fourier series component obtained by minimizing PWLS in Equation (8) is*

$$\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)=\mathbf{Ly}^*$$

where $\mathbf{y}^*=\mathbf{y}-\mathbf{f}$ *and* $\mathbf{L}=\mathbf{Z}\left[\mathbf{Z}'\mathbf{WZ}+N\mathbf{D}(\lambda)\right]^{-1}\mathbf{Z}'\mathbf{W}$.

Proof of Theorem 1. The optimization in Equation (8) can be written as

$$\underset{g_k\in C(0,\pi)}{Min}\left\{N^{-1}\sum_{i=1}^{n}\sum_{t=1}^{T}w_{it}\left(y_{it}^*-\sum_{k=1}^{q}\sum_{t=1}^{T}g_{ki}\left(z_{kit}\right)\right)^2+\sum_{k=1}^{q}\lambda_k\int_{0}^{\pi}\frac{2}{\pi}\left(g_k''\left(z_k\right)\right)^2dz_k\right\} \qquad (10)$$

Equation (10) can be rewritten in matrix form:

$$\underset{\mathbf{c}\in C(0,\pi)}{Min}\left\{N^{-1}\left(\mathbf{y}^*-\mathbf{Zc}\right)'\mathbf{W}\left(\mathbf{y}^*-\mathbf{Zc}\right)+\mathbf{c}'\mathbf{D}(\lambda)\mathbf{c}\right\} = \underset{\mathbf{c}\in C(0,\pi)}{Min}\left\{Q(\mathbf{c})\right\} \qquad (11)$$

We obtain

$$Q(\mathbf{c})=N^{-1}\mathbf{y}^{*\prime}\mathbf{Wy}^*-2N^{-1}\mathbf{c}'\mathbf{Z}'\mathbf{Wy}^*+N^{-1}\mathbf{c}'\mathbf{Z}'\mathbf{WZc}+\mathbf{c}'\mathbf{D}(\lambda)\mathbf{c}$$

The completion of the optimization (11) is obtained by taking the partial derivatives of $Q(\mathbf{c})$ at $\mathbf{c}$ and setting them to zero,

$$\frac{\partial Q(\mathbf{c})}{\partial \mathbf{c}}=\mathbf{0}$$

giving the result

$$\hat{\mathbf{c}}=\left[\mathbf{Z}'\mathbf{WZ}+N\mathbf{D}(\lambda)\right]^{-1}\mathbf{Z}'\mathbf{Wy}^*. \qquad (12)$$

By substituting Equation (12) into Equation (4), we obtain

$$\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)=\mathbf{Z}\hat{\mathbf{c}}=\mathbf{Z}\left[\mathbf{Z}'\mathbf{WZ}+N\mathbf{D}(\lambda)\right]^{-1}\mathbf{Z}'\mathbf{Wy}^*=\mathbf{Ly}^* \qquad (13)$$

Hence, the nonparametric regression model in Equation (5) can be written as

$$\mathbf{y}^*=\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)=\mathbf{Ly}^*,$$

where $\mathbf{y}^*=\mathbf{y}-\mathbf{f}$ and $\mathbf{L}=\mathbf{Z}\left[\mathbf{Z}'\mathbf{WZ}+N\mathbf{D}(\lambda)\right]^{-1}\mathbf{Z}'\mathbf{W}$. □

Lemma 4. *If the truncated spline component in Equation (2) is given by* $\sum_{j=1}^{p}f_{ji}\left(x_{jit}\right)$, *then the WLS is*

$$\left[(\mathbf{I}-\mathbf{L})\mathbf{y}-(\mathbf{I}-\mathbf{L})\mathbf{M}\boldsymbol{\gamma}\right]'\mathbf{W}\left[(\mathbf{I}-\mathbf{L})\mathbf{y}-(\mathbf{I}-\mathbf{L})\mathbf{M}\boldsymbol{\gamma}\right].$$

Proof of Lemma 4. The function f_{ji} is a linear truncated spline function with s knot for each x_j, $j=1,2,...,p$

$$f_{ji}\left(x_{jit}\right)=\alpha_{ji}x_{jit}+\sum_{u=1}^{s}\beta_{uji}\left(x_{jit}-K_{uji}\right)_+ \quad □ \qquad (14)$$

where $\left(x_{jit}-K_{uji}\right)_+=\begin{cases}\left(x_{jit}-K_{uji}\right) & , x_{jit}\geq K_{uji}\\ 0 & , x_{jit}<K_{uji}\end{cases}$.

According to Equation (14), the trunvated spline function for nonparametric regression for longitudinal data can be expressed in matrix form

$$\mathbf{f}=\left[\mathbf{X}|\mathbf{S}\right]\begin{bmatrix}\boldsymbol{\alpha}\\ \boldsymbol{\beta}\end{bmatrix}=\mathbf{M}\boldsymbol{\gamma} \qquad (15)$$

where

$$\mathbf{X}=\begin{bmatrix}\mathbf{X}_1 & \mathbf{0} & \cdots & \mathbf{0}\\ \mathbf{0} & \mathbf{X}_2 & \cdots & \mathbf{0}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \cdots & \mathbf{X}_n\end{bmatrix}, \mathbf{S}=\begin{bmatrix}\mathbf{S}_1 & \mathbf{0} & \cdots & \mathbf{0}\\ \mathbf{0} & \mathbf{S}_2 & \cdots & \mathbf{0}\\ \vdots & \vdots & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \cdots & \mathbf{S}_n\end{bmatrix}, \boldsymbol{\alpha}=\begin{bmatrix}\boldsymbol{\alpha}_1\\ \boldsymbol{\alpha}_2\\ \vdots\\ \boldsymbol{\alpha}_n\end{bmatrix},$$

$$\boldsymbol{\beta}=\begin{bmatrix}\boldsymbol{\beta}_1\\ \boldsymbol{\beta}_2\\ \vdots\\ \boldsymbol{\beta}_n\end{bmatrix}, \mathbf{X}_i=\begin{bmatrix}x_{1i1} & x_{2i1} & \dots & x_{pi1}\\ x_{1i2} & x_{2i2} & \dots & x_{pi2}\\ \vdots & \vdots & \ddots & \vdots\\ x_{1iT} & x_{2iT} & \dots & x_{piT}\end{bmatrix}, \boldsymbol{\alpha}_i=\begin{bmatrix}\alpha_{1i}\\ \alpha_{2i}\\ \vdots\\ \alpha_{pi}\end{bmatrix},$$

$$\mathbf{S}_i=\begin{bmatrix}\left(x_{1i1}-K_{11i}\right)_+^1 & \dots & \left(x_{1i1}-K_{s1i}\right)_+^1 & \dots & \left(x_{pi1}-K_{1pi}\right)_+^1 & \dots & \left(x_{pi1}-K_{spi}\right)_+^1\\ \left(x_{1i2}-K_{11i}\right)_+^1 & \dots & \left(x_{1i2}-K_{s1i}\right)_+^1 & \dots & \left(x_{pi2}-K_{1pi}\right)_+^1 & \dots & \left(x_{pi2}-K_{spi}\right)_+^1\\ \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots\\ \left(x_{1iT}-K_{11i}\right)_+^1 & \dots & \left(x_{1iT}-K_{s1i}\right)_+^1 & \dots & \left(x_{piT}-K_{1pi}\right)_+^1 & \dots & \left(x_{piT}-K_{spi}\right)_+^1\end{bmatrix}$$

and $\boldsymbol{\beta}_i=\left[\beta_{11i} \quad \dots \quad \beta_{s1i} \quad \dots \quad \beta_{1pi} \quad \dots \quad \beta_{spi}\right]^T$.

Hence, the MTSFS model for longitudinal data in Equation (1) can be written in the form

$$\mathbf{y}=\mathbf{f}+\mathbf{g}+\boldsymbol{\varepsilon}. \qquad (16)$$

By substituting Equation (13) into Equation (16), we obtain

$$\mathbf{y}=\mathbf{f}+\mathbf{Ly}^*+\boldsymbol{\varepsilon}. \qquad (17)$$

To obtain the estimator of truncated spline component, Equation (17) can be written as

$$\begin{aligned}\mathbf{y}-\mathbf{Ly}^*&=\mathbf{f}+\boldsymbol{\varepsilon}\\ \mathbf{y}-\mathbf{L}\left(\mathbf{y}-\mathbf{f}\right)&=\mathbf{f}+\boldsymbol{\varepsilon}\\ (\mathbf{I}-\mathbf{L})\mathbf{y}&=(\mathbf{I}-\mathbf{L})\mathbf{f}+\boldsymbol{\varepsilon}\end{aligned} \qquad (18)$$

Equation (18) can be rewritten as

$$\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}=\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}+\boldsymbol{\varepsilon}\,. \tag{19}$$

Thus,

$$\boldsymbol{\varepsilon}=\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}-\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}\,.$$

As a consequence, the WLS is given by

$$\boldsymbol{\varepsilon}'\boldsymbol{\varepsilon}=\left[\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}-\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}\right]'\mathbf{W}\left[\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}-\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}\right].\square$$

Theorem 2. *Suppose the WLS is given by Lemma 4. Then the mixed estimator obtained by minimizing WLS is*

$$\hat{\mathbf{f}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)=\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\mathbf{y}$$

where $\mathbf{J}=\left(2-\mathbf{L}'\right)\mathbf{WLM}-\mathbf{WM}$ *and* $\mathbf{K}=\left[\left(\mathbf{L}'-\mathbf{I}\right)\mathbf{W}\left(\mathbf{I}-\mathbf{L}\right)\right]$.

Proof of Theorem 2. The WLS optimization in Lemma 4 can be written as

$$\begin{aligned}&\underset{\boldsymbol{\gamma}}{Min}\left\{\left[\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}-\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}\right]'\mathbf{W}\left[\left(\mathbf{I}-\mathbf{L}\right)\mathbf{y}-\left(\mathbf{I}-\mathbf{L}\right)\mathbf{M}\boldsymbol{\gamma}\right]\right\}\\&=\underset{\boldsymbol{\gamma}}{Min}\left\{Q\left(\boldsymbol{\gamma}\right)\right\}\end{aligned} \tag{20}$$

We obtain

$$\begin{aligned}Q(\boldsymbol{\gamma})=\{&\mathbf{y}'\mathbf{W}\mathbf{y}+\mathbf{y}'\mathbf{L}'\mathbf{W}\mathbf{L}\mathbf{y}+\boldsymbol{\gamma}'\mathbf{M}'\mathbf{L}'\mathbf{W}\mathbf{L}\mathbf{M}\boldsymbol{\gamma}+\boldsymbol{\gamma}'\mathbf{M}'\mathbf{W}\mathbf{M}\boldsymbol{\gamma}-2\mathbf{y}'\mathbf{L}'\mathbf{W}\mathbf{y}+2\boldsymbol{\gamma}'\mathbf{M}'\mathbf{L}'\mathbf{W}\mathbf{y}+\\&-2N^{-1}\boldsymbol{\gamma}'\mathbf{M}'\mathbf{W}\mathbf{y}-2N^{-1}\boldsymbol{\gamma}'\mathbf{M}'\mathbf{L}'\mathbf{W}\mathbf{L}\mathbf{y}+2N^{-1}\boldsymbol{\gamma}'\mathbf{M}'\mathbf{W}\mathbf{L}\mathbf{y}-2N^{-1}\boldsymbol{\gamma}'\mathbf{M}'\mathbf{W}\mathbf{L}\mathbf{M}\boldsymbol{\gamma}\}\end{aligned}$$

The complete optimization is obtained by setting the partial derivatives of $Q\left(\boldsymbol{\gamma}\right)$ at $\boldsymbol{\gamma}$ to zero. This yields the result

$$\hat{\boldsymbol{\gamma}}=\left[\left(2-\mathbf{L}'\right)\mathbf{WLM}-\mathbf{WM}\right]^{-1}\left[\left(\mathbf{L}'-\mathbf{I}\right)\mathbf{W}\left(\mathbf{I}-\mathbf{L}\right)\right]\mathbf{y}=\mathbf{J}^{-1}\mathbf{K}\mathbf{y}\,. \tag{21}$$

By substituting $\hat{\boldsymbol{\gamma}}$ into Equation (15), we obtain

$$\hat{\mathbf{f}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)=\mathbf{M}\hat{\boldsymbol{\gamma}}=\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\mathbf{y}=\mathbf{A}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\,. \tag{22}$$

We obtain $\hat{\mathbf{c}}$ by substituting Equation (22) into Equation (12):

$$\begin{aligned}\hat{\mathbf{c}}&=\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\mathbf{y}^{*}\\&=\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\left(\mathbf{y}-\hat{\mathbf{f}}\right)\\&=\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\left(\mathbf{y}-\mathbf{M}\hat{\boldsymbol{\gamma}}\right)\\&=\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\left(\mathbf{y}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\mathbf{y}\right)\\&=\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\left(\mathbf{I}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\right)\mathbf{y}\end{aligned} \tag{23}$$

As a consequence,

$$\begin{aligned}\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)&=\mathbf{Z}\hat{\mathbf{c}}\\&=\mathbf{Z}\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}\left(\mathbf{I}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\right)\mathbf{y}\\&=\mathbf{L}\left(\mathbf{I}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\right)\mathbf{y}\\&=\mathbf{B}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\end{aligned} \tag{24}$$

By substituting $\hat{\boldsymbol{\gamma}}$ and $\hat{\mathbf{c}}$ into MTSFS model for longitudinal data, we obtain

$$\begin{aligned}\hat{\mathbf{y}}=\hat{\boldsymbol{\mu}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)&=\hat{\mathbf{f}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)+\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\\&=\mathbf{M}\hat{\boldsymbol{\gamma}}+\mathbf{Z}\hat{\mathbf{c}}\\&=\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\mathbf{y}+\mathbf{L}\left(\mathbf{I}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\right)\mathbf{y}\\&=\left[\mathbf{M}\mathbf{J}^{-1}\mathbf{K}+\mathbf{L}\left(\mathbf{I}-\mathbf{M}\mathbf{J}^{-1}\mathbf{K}\right)\right]\mathbf{y}\\&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\end{aligned} \tag{25}$$

where $\mathbf{J}=\left(2-\mathbf{L}'\right)\mathbf{WLM}-\mathbf{WM}$, $\mathbf{K}=\left[\left(\mathbf{L}'-\mathbf{I}\right)\mathbf{W}\left(\mathbf{I}-\mathbf{L}\right)\right]$, $\mathbf{L}=\mathbf{Z}\left[\mathbf{Z}'\mathbf{W}\mathbf{Z}+N\mathbf{D}\left(\lambda\right)\right]^{-1}\mathbf{Z}'\mathbf{W}$.

B. The Properties of MTSFS Model for Longitudinal Data

This section proves two properties of the MTSFS model for longitudinal data: it is biased and linear in the observations. It is biased, as proved by

$$\begin{aligned}E\left[\hat{\boldsymbol{\mu}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\right]&=E\left[\hat{\mathbf{f}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)+\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\right]\\&=E\left[\mathbf{A}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}+\mathbf{B}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\right]\\&=E\left[\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\right]\\&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)E\left(\mathbf{y}\right)\end{aligned}$$

considering $\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\neq\mathbf{I}$, so that

$$\begin{aligned}E\left[\hat{\boldsymbol{\mu}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\right]&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)E\left(\mathbf{y}\right)\\&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\left(\mathbf{f}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)+\mathbf{g}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\right)\\&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\boldsymbol{\mu}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\end{aligned} \tag{26}$$

The result in Equation (26) showed that the mixed estimator is biased, because $E\left[\hat{\boldsymbol{\mu}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\right]\neq\boldsymbol{\mu}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)$. Even though the mixed estimator is biased, it is linear in the observations, as proved by Equation (27) below.

$$\begin{aligned}\hat{\boldsymbol{\mu}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)&=\hat{\mathbf{f}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)+\hat{\mathbf{g}}_{(\mathbf{k},\mathbf{h},\lambda)}\left(\mathbf{x},\mathbf{z}\right)\\&=\mathbf{A}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}+\mathbf{B}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\\&=\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\mathbf{y}\end{aligned} \tag{27}$$

C. The Selection of the Optimal Number of Knot Points, Oscillation Parameter, and Smoothing Parameter

One of the most important steps in nonparametric regression modeling is choosing the optimal number of knot points, oscillation parameter, and smoothing parameter. The GCV value is a criterion that can be used to determine the best model from a variety of knots, oscillation, and smoothing parameters. The criteria for choosing the best model include taking the model with the lowest value of the GCV. The modified GCV function of the MTSFS model for longitudinal is stated as follows.

$$GCV\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)=\frac{N^{-1}\left\|\left(\mathbf{I}-\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\right)\mathbf{y}\right\|^{2}}{\left[N^{-1}trace\left(\mathbf{I}-\mathbf{C}\left(\mathbf{k},\mathbf{h},\boldsymbol{\lambda}\right)\right)\right]^{2}} \tag{28}$$

III. Simulation Study

In this section, the results of applying the MTSFS model to simulated data are presented, to see the performance of the obtained estimators. The simulation was carried out with four different sample sizes $n=5$, 10, 20, 40 and two different numbers of time points $T=7$, 14. We created models for each subject generated from the formula that discribes two different functions that represent the truncated spline and Fourier series pattern. A polynomial function is used to represent the truncated spline, while a trigonometric series is used to represent the Fourier series. The predictors are generated from $U\left(0,1\right)$ and random errors ε_{it} are generated from a multivariate normal distribution.

The weight matrix is specified by the user [12], and in this simulation study we use weight matrix type 2, $\mathbf{W} = n^{-1}\mathbf{I}$, so that each of the measurements in the same subject is treated equally. In this study, we use two numbers of knots ($K = 1$ and $K = 2$) and also two number of the oscillation parameter ($H = 1$ and $H = 2$). The GCV results of the simulation studies are shown in Table 1.

Table 1 shows that the model with $n = 5$ and using one knot appears to have smaller GCV value. The same can be seen at $n = 10$, $n = 20$ and $n = 40$ as well. We can conclude that the lower number of knots, the lower the GCV. The smallest GCV occurs when number of time points $T = 14$ for all subjects, except $n = 20$. Also, the greater number of time points, the lower the GCV for all subjects, except $n = 20$. Other results show that the larger values of the oscillation parameter are not guaranteed to produce large or small values of the GCV. Therefore, it is necessary to choose the optimal value of H, namely, the one that produces the smallest GCV.

TABLE I
COMPARISON OF GCV VARYING THE NUMBER OF SUBJECTS AND TIME POINTS

Number of Subjects	Number of Time Points	Number of Knots	Number of Oscillations	Smoothing Parameter	GCV
5	7	1	1	0.033	4.709
			2	0.500	4.683
		2	1	1.000	5.193
			2	0.300	5.182
	14	1	1	0.033	3.735
			2	1.000	3.739
		2	1	0.010	3.818
			2	0.267	3.817
10	7	1	1	1.000	4.599
			2	0.133	4.435
		2	1	1.000	4.847
			2	0.067	4.840
	14	1	1	0.010	4.413
			2	0.033	4.404
		2	1	0.010	4.611
			2	0.067	4.558
20	7	1	1	1.000	3.509
			2	0.800	3.522
		2	1	1.000	3.856
			2	0.033	3.853
	14	1	1	0.033	3.791
			2	1.000	3.798
		2	1	0.033	3.945
			2	1.000	3.954
40	7	1	1	1.000	5.215
			2	0.967	5.216
		2	1	1.000	5.924
			2	0.967	5.923
	14	1	1	0.010	3.940
			2	0.867	3.953
		2	1	0.033	4.043
			2	0.867	4.045

IV. DATA APPLICATION

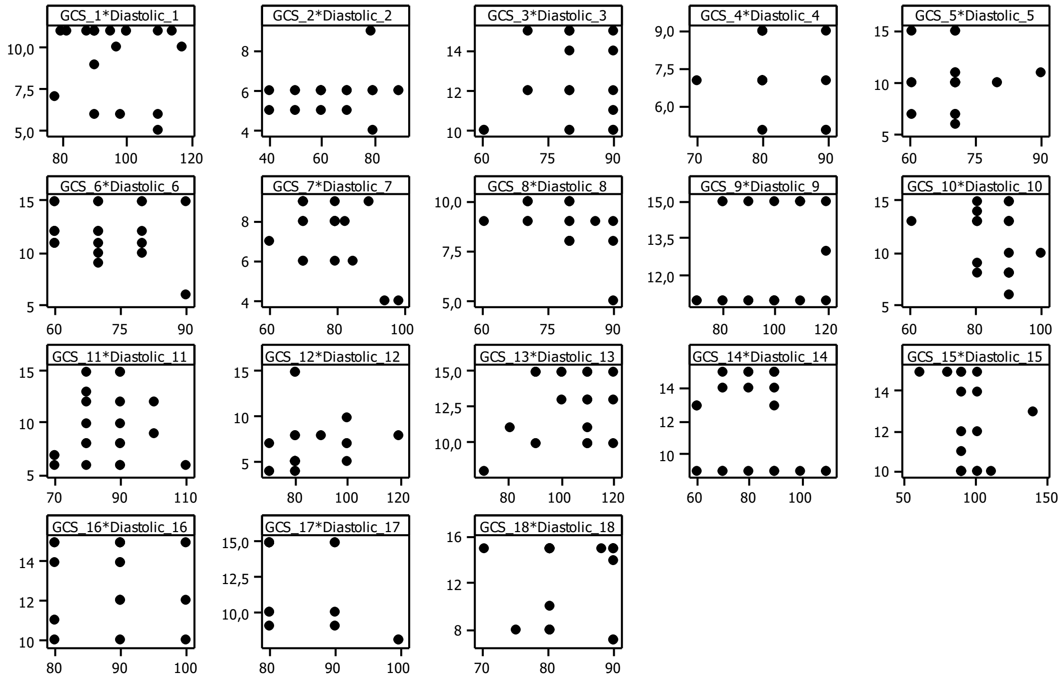
The MTSFS model for the longitudinal data obtained is applied to the stroke patient data set. Stroke is a non-communicable disease with an increasing number of sufferers around the world. In 2013, stroke was the second leading cause of death worldwide (11.8% of all deaths) after ischemic heart disease (14.8% of all deaths). Furthermore, stroke is the third leading cause of disability, which is 4.5% of all causes of disability [14]. Based on the 2016 Global Burden of Disease (GBD), the estimated global lifetime risk of stroke for people 25 years and older reached almost 25% [15]. The global prevalence of stroke in 2017 was 104.2 million people. Indonesia is one of the countries with the highest death rates from stroke. According to the 2007 Indonesian Basic Health Survey report, stroke was the leading cause of death (15.4%) [16]. The prevalence of stroke in Indonesia was 7% in 2013 and increased to 10.9%, according to the 2018 Indonesia Basic Health Survey report.

Stroke patients often suffer head injuries from falls. Trauma or head injury requires vigilance to ensure further medical treatment. The GCS was originally used to assess consciousness after head injuries and is now used in the medical field for both acute and trauma patients. The data were applied after an initial study of GCS in stroke patients and the four factors that influenced them. The pattern of the relations between the predictors and response followed the characteristics of a truncated spline and Fourier series. Under the characteristic curve of the truncated spline there is a predictor that changes in certain subintervals. The other predictors have the characteristics of a Fourier series, which has a repeating pattern.

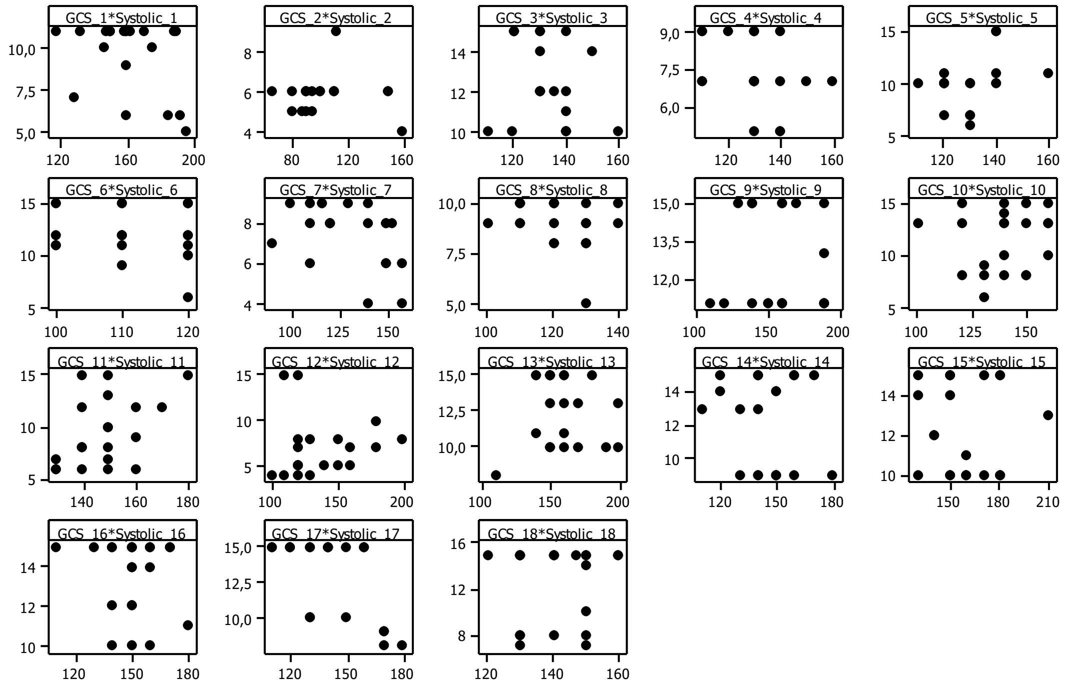
This paper uses GCS as the response in 18 stroke patients ($n = 18$) with 21 measurements ($T = 21$) for each person. The predictor variables are systolic blood pressure, diastolic blood pressure, body temperature, and pulse rate. The partial relations between GCS and each predictor variable are shown in Figure 1. It can be seen from the data in Table 1 that the plot shows a different pattern for each predictor. Diastolic blood pressure is approximated by a truncated spline estimator, while the systolic blood pressure, body temperature, and pulse rate are approximated by a Fourier series estimator.

To obtain the best model, in this case study we will try to use multiple combinations of the mixed estimator model. A single estimator is also tried. Due to computational limitations, this study is limited to the use of one knot point, three oscillation parameters, and multiple types of smoothing parameters. Unlike the simulation study, this case study uses three types of weights that correspond to [12]. Next, the best model with the lowest GCV is selected. The results of modeling with different types of combination are shown in Table 2.

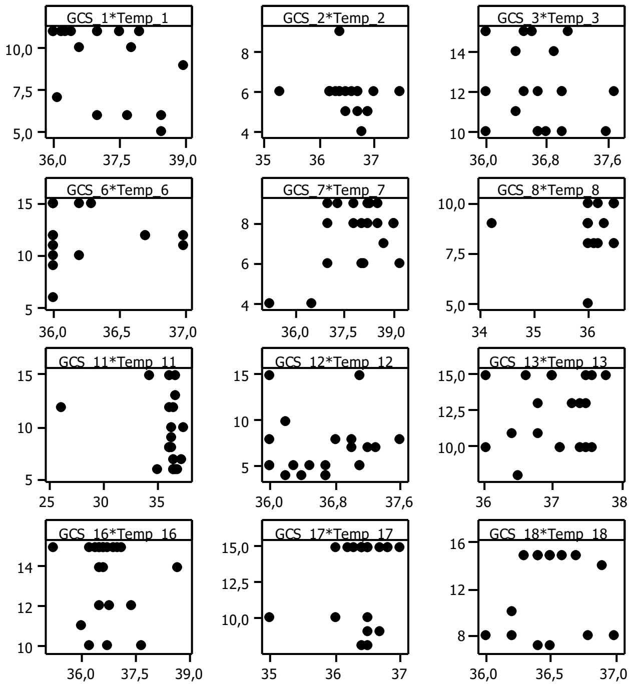
As can be seen from Table 2, we attempted to model GCS in stroke patients with the MTSFS model on longitudinal data with different types of model combinations. The mixed estimator model was tested with one knot, three oscillation parameters, and several smoothing parameters ($\lambda = 0.1$, $\lambda = 0.3$, $\lambda = 0.5$, $\lambda = 0.7$, and $\lambda = 0.9$). Using the $H = 1$, the lowest GCV was obtained at 1462.374 with a second weight, giving the same treatment of observations on the same subject. The model uses a combination of smoothing parameters, namely $\lambda_1 = 0.9$, $\lambda_2 = 0.9$, and $\lambda_3 = 0.5$. In the models with $H = 2$ and $H = 3$, the best model is obtained with the first weight, which treats all observations equally. The lowest GCVs in the model are 1462.321 and 1462.314, respectively. Both models use a combination of smoothing parameters, namely $\lambda_1 = 0.9$, $\lambda_2 = 0.9$, and $\lambda_3 = 0.1$.


GCS_1*Diastolic_1
GCS_2*Diastolic_2
GCS_3*Diastolic_3
GCS_4*Diastolic_4
GCS_5*Diastolic_5
GCS_6*Diastolic_6
GCS_7*Diastolic_7
GCS_8*Diastolic_8
GCS_9*Diastolic_9
GCS_10*Diastolic_10
GCS_11*Diastolic_11
GCS_12*Diastolic_12
GCS_13*Diastolic_13
GCS_14*Diastolic_14
GCS_15*Diastolic_15
GCS_16*Diastolic_16
GCS_17*Diastolic_17
GCS_18*Diastolic_18

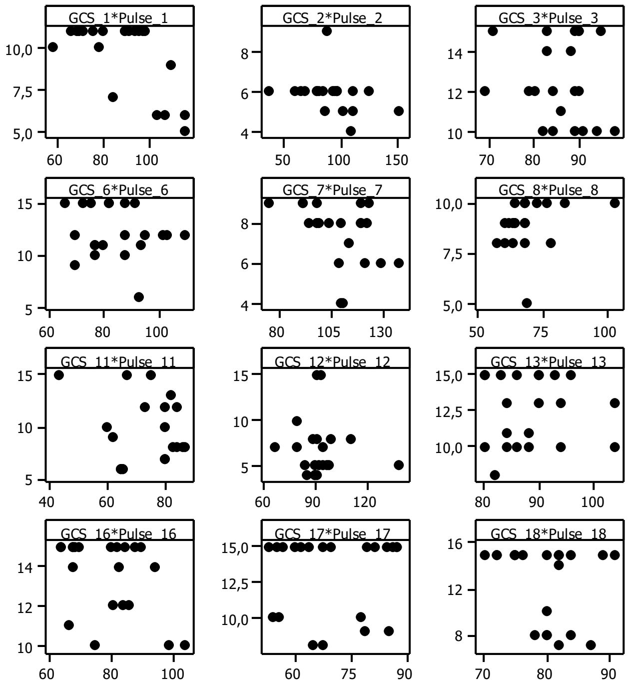
(a)


GCS_1*Systolic_1
GCS_2*Systolic_2
GCS_3*Systolic_3
GCS_4*Systolic_4
GCS_5*Systolic_5
GCS_6*Systolic_6
GCS_7*Systolic_7
GCS_8*Systolic_8
GCS_9*Systolic_9
GCS_10*Systolic_10
GCS_11*Systolic_11
GCS_12*Systolic_12
GCS_13*Systolic_13
GCS_14*Systolic_14
GCS_15*Systolic_15
GCS_16*Systolic_16
GCS_17*Systolic_17
GCS_18*Systolic_18

(b)



(c)



(d)

Fig. 1. Scatterplot of 18 stroke patients between: (a) GCS and diastolic blood pressure; (b) GCS and systolic blood pressure; (c) GCS and body temperature; (d) GCS and pulse rate.

When comparing various types of weights, the third type of weight, which takes into account the correlation between observations on the same subject, yields a model with a high GCV, greater than 1900. The first and second weights give almost the same value of GCV in any combination of models. One of the important things about Table 2 is that the model using a single estimator produces a fairly large GCV. The GCV value obtained is very different from the mixed estimator. What is striking in the table is that the results of the case studies are in line with the results of the simulation study. In both cases, the lowest GCV value was obtained using the oscillation parameter $H = 3$. Taken together, these results suggest that the performance of the mixed estimator exceeds that of the single estimator in the GCS modeling in stroke patients.

TABLE II

SUMMARY OF GCS MODELING USING MODEL COMBINATIONS

Number of Knots	Number of Oscillations	Smoothing Parameter			GCV		
		1	2	3	Weight 1	Weight 2	Weight 3
Truncated Spline Model							
1	-		-		361817.8	297849.1	428343.9
Fourier Series Model							
	1				350463	289807.2	417041.6
-	2		-		143203.5	131242.5	137519.1
	3				93563.96	88905.9	116303.6
Mixed Truncated Spline and Fourier Series Model							
1	1	0.1	0.1	0.1	1463.113	1462.405	1913.382
1	1	0.3	0.1	0.1	1462.864	1462.394	1911.442
1	1	0.5	0.1	0.1	1462.814	1462.391	1911.028
1	1	0.7	0.1	0.1	1462.793	1462.39	1910.848
1	1	0.9	0.1	0.1	1462.781	1462.39	1910.747
...	...	...	...	...	...	...	...
1	1	0.9	0.9	0.5	1462.460	**1462.374**	1911.324
...	...	...	...	...	...	...	...
1	2	0.9	0.9	0.9	1462.453	1462.374	1911.206
1	2	0.1	0.1	0.1	1462.946	1462.398	1911.313
1	2	0.3	0.1	0.1	1462.693	1462.385	1909.613
1	2	0.5	0.1	0.1	1462.642	1462.383	1909.25
1	2	0.7	0.1	0.1	1462.62	1462.382	1909.091
1	2	0.9	0.1	0.1	1462.608	1475.991	1909.002
...	...	...	...	...	...	...	...
1	2	0.9	0.9	0.1	**1462.321**	1475.979	1911.401
...	...	...	...	...	...	...	...
1	2	0.9	0.9	0.9	1462.435	1475.982	1910.968
1	3	0.1	0.1	0.1	1462.947	1462.398	1911.235
1	3	0.3	0.1	0.1	1462.688	1465.174	1909.532
1	3	0.5	0.1	0.1	1462.636	1465.171	1909.167
1	3	0.7	0.1	0.1	1462.614	1465.17	1909.008
1	3	0.9	0.1	0.1	1462.602	1465.17	1908.919
...	...	...	...	...	...	...	...
1	3	0.9	0.9	0.1	**1462.314**	1465.158	1911.387
...	...	...	...	...	...	...	...
1	3	0.9	0.9	0.9	1462.435	1465.161	1910.959

V. CONCLUSION

The main goal of the current study was to introduce a new mixed estimator in a nonparametric regression model for longitudinal data. We also presented a new two-stage method to estimate the parameters, i.e., PWLS and WLS. We combined the truncated spline estimator and the Fourier series to obtain better estimation results when different data patterns are found between each predictor. Next, we modified this method to choose the best model based on the proposed model.

In this paper, GCV criterion was employed to select the best model for the simulation study, as well as the case study. The simulation study identified that a larger oscillation parameter does not necessarily produce a low GCV. Therefore, we must try various combinations of these to determine the best model. One of the most significant findings to emerge from the case study is that the best model (from among those using one knot) is achieved by using three oscillations and a combination of smoothing parameters, namely $\lambda_1 = 0.9$, $\lambda_2 = 0.9$, and $\lambda_3 = 0.1$. The results of this research support the idea that the mixed estimator is better than a single estimator in modeling GCS in stroke patients.

The major limitation of this study is the constraint of the smoothing parameters. Further studies are needed with higher number of knots and different smoothing parameters so that researchers can compare results to improve model performance. Another possible topic for further research is using another function to validate the performance of the proposed model. In spite of its limitations, the study certainly contributes to our understanding of a new alternative for estimating nonparametric regression curves for longitudinal data.

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