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Spline Estimator for Bi-Responses and Multi-Predictors Nonparametric Regression Model in Case of Longitudinal Data

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Abstract: Nonparametric regression approach is used when the shape of the curve regression is unknown. The spline estimator approach for longitudinal data can accommodate the correlation between observations within the same subject, which is not found in the cross-section data, so that the autocorrelation assumption problem can be resolved. On the other hand, with bi-responses approach, it will accommodate any correlation between each response variables. The purposes of this study are (1) to obtain the function form of the nonparametric bi-responses and multi-predictorsregression on longitudinal data, (2) to obtain the spline estimator in estimating the nonparametric bi-responses and multi-predictorsregression curve on longitudinal data and (3) to apply the spline estimator in estimating the curve of nonparametric bi-responses and multi-predictorsregression on longitudinal data. Bi-responses and multi-predictors nonparametric regression of the spline estimator on longitudinal data which meet the criteria of minimizing Penalized Weighted Least Square (PWLS). Application of data set (Patient in Pulmonary Tuberculosis) result shows that the spline estimator can be applied which gives the value of R^2 of 97.77%.

Keywords: Spline, Bi-Responses, Multi-Predictors, Longitudinal, PWLS

Introduction

Spline estimator of Nonparametric Regression can be used to estimate functions which represent association of two responses variables are observed at several values of multi-predicors variable. One of the uses of Spline Estimator is in the analysis of longitudinal data, which is a combination of cross-section data and time-series, that is the observations which are made as many as r mutually independent subjects (cross-section) with each subject is repeatedly observed in *n* period of time (time-series) and between observations within the same subjectswhich are correlated (Diggle *et al.*, 2013).

In the applications in various fields, problems involving more than one correlated response variables are often encountered, so the regression model developed is bi-responses and multi-predictors as follows:

$$y_{kit} = \sum_{\ell=1}^{p} f_{ki}(x_{\ell it}) + \varepsilon_{kit},$$

$$k = 1, 2; \ell = 1, 2, .., p; i = 1, 2, ..., r; t = 1, 2, ..., n \tag{1}$$

The first predictor variable x_{1it} as the observation time (design time points) (Wu and Zhang, 2006) and f is the regression curve relationship between the predictor variables with the response variable y for to-i subject. The curve f in nonparametric regression approach is used when the shape of the curve f is unknown (Eubank, 1999).

Nonparametric regression is a regression approach suitable for the data patterns of unknown shape, or there is not complete information about previous data patterns (Budiantara *et al.*, 1997; Eubank, 1999). In nonparametric regression approach, the estimation modelshape of the curve regression is determined based on the pattern of existing data. Some nonparametric

regression approaches are: the kernel (Hardle, 1990), spline (Budiantara *et al.*, 1997; Wahba, 1990) and wavelets (Antoniadis and Sapatinas, 2007). Spline estimator is one of the most commonly used estimator in nonparametric regression because it has a good visual interpretation, high flexibility and able to handle smooth function characters (Eubank, 1999). Regression curve *f* in spline estimator for longitudinal data used is assumed smooth, meaning that it is contained in a certain function space, especially Sobolev space or as written (Wu and Zhang, 2006).

Spline estimator in the bi-responses and multi-predictors nonparametric regression model for longitudinal data is the generalization of the spline estimator in single-response nonparametric regression model for longitudinal data (Chen and Wang, 2011; Lin *et al.*, 2006), as well as spline estimator in the multi-response nonparametric regression model for cross-section data (Lestari *et al.*, 2010; Wang *et al.*, 2000). The spline estimator approach for longitudinal data can accommodate the correlation between observations within the same subject, which is not found in the cross-section data, so that the autocorrelation assumption problem can be resolved. On the other hand, with bi-responses approach, it will accommodate any correlation between each response variable. Fernandes *et al.* (2014a) has been solved the RKHS for bi-responses and Fernandes *et al.* (2014b) for multi-predictors.

Reproducing Kernel Hilbert Space (RKHS) play a central role in Penalized Regression as a form and estimator function of the model. Hilbert spaces that display certain properties on certain linear operators are RKHS. The function *f* the unknown function and assumed smooth in the sense of being contained in the space *H*. (Wahba, 1990). For the purposes of $\hat{f}$ estimation, RKHS approach with completes the Penalized Weighted Least Square (PWLS). Based on the above background, the purposes of this study are (1) to obtain the function form of the nonparametric bi-responses and multi-predictors regression on longitudinal data, (2) to obtain the spline estimator in estimating the nonparametric bi-responses and multi-predictors regression curve on longitudinal data, (3) to apply the spline estimator in estimating the curve of nonparametric bi-responses and multi-predictors regression on longitudinal, applicationin data with patient of Pulmonary Tuberculosis from Chozin (2009).

Materials and Methods

Suppose we want to find a function f_{ki} in equation (1), that interpolates between the points $(x_{\ell it}, \eta_{\ell it}), \ell = 1, 2, ..., p; i = 1, 2, ..., r; t = 1, 2, ..., n,$ and the boundary value of $a_{ki} = x_{\ell i1} < x_{\ell i2} < .... < x_{\ell in} = b_{ki}.$

The functions $f_{ki} \in W_2^m$ where:

$$W_2^m = \{f_{ki} : f_{ki} \text{ is absolutely continuous on } [a_{ki}, b_{ki}], f_{ki}' \in L^2[0,1]\} \tag{2}$$

And we called in Sobolev Space (Wahba, 1990).

If we restrict the boundary value in [0, 1] with transformation, then the value of $f_{ki}(0)=0$ is not really necessary, but simplifies the presentation of derivative values of f_{ki}' or f_{ki}''. Defining an inner product of W_2^m by:

$$\langle f_{ki}, g_{ki} \rangle = \int_0^1 f_{ki}'(x_{\ell it}) g_{ki}'(x_{\ell it}) dx_{\ell i} \tag{3}$$

Implies a norm over the space W_m^2 that is small for "smooth" functions (Wahba, 1990). To address the interpolation problem, is given:

$$\langle f_{ki}, R_{kit} \rangle = \int_0^1 f_{ki}'(x_{\ell it}) R'_{kit}(x_{\ell it}) dx_{\ell it}$$
$$= f_{ki}(x_{\ell it}) - f_{ki}(0) = f_{ki}(x_{\ell it}) \tag{4}$$

Thus interpolator f_{ki} satisfies a system of equation (5), namely:

$$f_{ki}(x_{\ell it}) = \langle R_{kit}, f_{ki} \rangle = \eta_{kit} \tag{5}$$

And the smoothest function f_{ki} satisfies an equation (6):

$$f_{ki}(x_{\ell it}) = \sum_{k=1}^2 \sum_{i=1}^r \sum_{t=1}^n \xi_{kit} R_{kit}(x_{\ell it}) \tag{6}$$

The ξ_{kit}'s are the solutions to the system of real linear equations obtained by substituting of $\hat{f}_{ki}$ satisfies into (5):

$$\sum_{k=1}^2 \sum_{i=1}^r \sum_{t=1}^n \langle R_{kit}, R_{kis} \rangle \xi_{kit} = \eta_{kit} \tag{7}$$

Note that:

$$\langle R_{kit}, R_{kis} \rangle = R_{kis}(x_{\ell it}) = R_{kit}(x_{\ell is}) = min(x_{\ell is}, x_{\ell it}) \tag{8}$$

And define the function $R_{x_{kis}}(x_{kit}) = min(x_{kis}, x_{kit})$ which turns out to be a reproducing kernel.

Bi-responses and multi-predictors nonparametric regression model for longitudinal data which involves *r* subject on *n* observation in each subject in Equation (1). The error random variable ε_{kit} assumed to be normally distributed to N-variat ($N = 2rn$), with zero mean and covariance matrix W^{-1} is follows:

$$W^{-1} = \begin{bmatrix} \Sigma_{11} & 0 & \cdots & 0 & \Psi_{11} & \Psi_{12} & \cdots & \Psi_{1r} \\ 0 & \Sigma_{12} & \cdots & 0 & \Psi_{21} & \Psi_{22} & \cdots & \Psi_{2r} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \Sigma_{1r} & \Psi_{r1} & \Psi_{r2} & \cdots & \Psi_{rr} \\ \Psi_{11} & \Psi_{21} & \cdots & \Psi_{r1} & \Sigma_{21} & 0 & \cdots & 0 \\ \Psi_{12} & \Psi_{22} & \cdots & \Psi_{r1} & 0 & \Sigma_{22} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \Psi_{1r} & \Psi_{21} & \cdots & \Psi_{rr} & 0 & 0 & \cdots & \Sigma_{2r} \end{bmatrix} \quad (9)$$

The spline approach generally defines f_{ki} in equation (1) in form of an unknown regression curve, but f_{ki} is only assumed as smooth, in a sense of being contained in a specified function space, especially Sobolev space or written as $f_{ki} \in W_2^m [a_{ki}, b_{ki}]$, with:

$$W_2^m[a_{ki}, b_{ki}] = \left\{ f_{ki} : \int_{a_{ki}}^{b_{ki}} [f_{ki}^{(m)}(x_{\ell i})]^2 dx_{\ell i} < \infty \right\} \quad (10)$$

For a positive integer m (polynomial order, $m=2$ linear, $m=3$ quadratic, $m=4$ cubic). Optimization Penalized Weighted Least Square (PWLS) involves weighting in form of random error variance-covariance matrix as has been described in equation (9). To obtain the estimate of the regression curve f_{ki} using optimization PWLS that is the completion of optimization as follows (Eubank, 1999):

$$\underset{f_{ki} \in W_2^m[a_{ki}, b_{ki}], k=1,2; i=1,2,...,r}{Min}$$
$$\left\{ N^{-1}(\underset{\sim}{y} - \underset{\sim}{f})' W(\underset{\sim}{y} - \underset{\sim}{f}) + \sum_{k=1}^{2}\sum_{i=1}^{r} \lambda_{ki} \int_{a_{ki}}^{b_{ki}} (f_{ki}^{(m)}(x_{\ell i}))^2 dx_{\ell i} \right\} \quad (11)$$

The PWLS optimization in equation (11) in addition to considering the weight, also considers the use of *2r* smoothing parameter λ_{ki} as a controller between the goodness of fit (the first segment) and the roughness penalty (second segment). The covariance matrix in (9) is the weighted in PWLS (11), which accommodate (1) the correlation between observations within the same subject and (2) accommodate any correlation between each response variable.

Result

Assume that the data follow the bi-responses and multi-predictors nonparametric regression models for longitudinal data:

$$\underset{\sim}{y}_t = L_x \underset{\sim}{f} + \underset{\sim}{\varepsilon}_t \quad (12)$$

With $\underset{\sim}{y}_t = (y_{11t}, y_{12t}, ..., y_{1rt}, y_{21t}, y_{22t}, ... y_{2rt})'$ as the response variable, L_x limited linear function and

$\underset{\sim}{f} = (f_{11}, f_{12}, ..., f_{1r}, f_{21}, f_{22}, ..., f_{2r})'$ is the inknown function and is assumed smooth in a sense of contained in space *H*. In order to obtain the function (12), Theorem 1 is presented in the following.

Theorem 1

If given the data pairs following $(x_{1it}, ..., x_{pit}, y_{1it}, y_{2it})$, the bi-responses and multi-predictors nonparametric regression model for longitudinal data as given in the equation (1), then the form of the bi-responses and multi-predictors nonparametric regression function for longitudinal data is: $f(x) = T\underset{\sim}{d} + V\underset{\sim}{c}$, with $\underset{\sim}{d}$ and $\underset{\sim}{c}$ coefficient of estimation and $T = \begin{pmatrix} T_{11} & 0 & \cdots & 0 \\ 0 & T_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & T_{2r} \end{pmatrix}$ and

$$V = \begin{pmatrix} V_{11} & 0 & \cdots & 0 \\ 0 & V_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & V_{2r} \end{pmatrix}.$$

Proof of Theorem 1:

Hilbert spaces that display certain properties on certain linear operators are RKHS. The function $\underset{\sim}{f} = (f_{11}, f_{12}, ..., f_{1r}, f_{21}, f_{22}, ..., f_{2r})'$ the unknown function and assumed smooth in the sense of being contained in the space *H*. Then the space *H* is decomposed into a direct sum of two spaces H_0 and H_1, that is $H = H_0 \oplus H_1$, with $H_0 = H_1^\perp$. Suppose the basis for the space H_0 is $\{\phi_{ki1}, \phi_{ki2}, \cdots, \phi_{kim}\}$ and the basis for the space H_1 is $\{\xi_{ki1}, \xi_{ki2}, \cdots, \xi_{kin}\}$, then for each function $f_{ki} \in H$ can be presented individually as:

$$f_{ki} = g_{ki} + h_{ki} \quad (13)$$

Furthermore, for each function $f_{ki} \in H$ can be presented individually as:

$$f_{ki} = g_{ki} + h_{ki} = \sum_{j=1}^{m} d_{kij}\phi_{kij} + \sum_{t=1}^{n} c_{kit}\xi_{kit} = \underset{\sim}{\phi}_{ki}' \underset{\sim}{d}_{ki} + \underset{\sim}{\xi}_{ki}' \underset{\sim}{c}_{ki} \quad (14)$$

is a limited linear function in the space *H* and function $f_{ki} \in H$, obtained:

$$L_{x_{\ell it}} f_{ki} = L_{x_{\ell it}} (g_{ki} + h_{ki}) = f_{ki}(x_{\ell it}) \quad (15)$$

$f_{ki}(x_{\ell it})$ in the equation (15) can be expressed as:

$$f_{ki}(x_{\ell it}) = \left\langle \eta_{kit}, \underset{\sim}{\phi}'_{ki} \underset{\sim}{d}_{ki} \right\rangle + \left\langle \eta_{kit}, \underset{\sim}{\xi}'_{ki} \underset{\sim}{c}_{ki} \right\rangle \quad (16)$$

The description of the Equation (16) for $\ell = 1, k = 1, i = 1$ obtained:

$$f_{11}(x_{11t}) = \left\langle \eta_{11t}, \phi'_{11}\, \underset{\sim}{d}_{11} \right\rangle + \left\langle \eta_{11t}, \xi'_{11}\, \underset{\sim}{c}_{11} \right\rangle, \ t = 1, 2, \ldots, n$$

$$\underset{\sim}{f}_{11}(x_{11}) = \begin{pmatrix} f_{11}(x_{111}) \\ f_{11}(x_{112}) \\ \vdots \\ f_{11}(x_{11n}) \end{pmatrix}$$

$$\underset{\sim}{f}_{11}(x_{11}) = \begin{pmatrix} d_{111}\langle \eta_{111},\phi_{111}\rangle + \ldots + d_{11m}\langle \eta_{111},\phi_{11m}\rangle \\ + c_{111}\langle \eta_{111},\xi_{111}\rangle + \ldots + c_{11n}\langle \eta_{111},\xi_{11n}\rangle \\ d_{111}\langle \eta_{112},\phi_{111}\rangle + \ldots + d_{11m}\langle \eta_{112},\phi_{11m}\rangle \\ + c_{111}\langle \eta_{112},\xi_{111}\rangle + \ldots + c_{11n}\langle \eta_{112},\xi_{11n}\rangle \\ \vdots \\ d_{111}\langle \eta_{11n},\phi_{111}\rangle + \ldots + d_{11m}\langle \eta_{11n},\phi_{11m}\rangle \\ + c_{111}\langle \eta_{11n},\xi_{111}\rangle + \ldots + c_{11n_1}\langle \eta_{11n},\xi_{11n}\rangle \end{pmatrix}$$

$$= \begin{pmatrix} \langle \eta_{111},\phi_{111}\rangle & \langle \eta_{111},\phi_{112}\rangle & \cdots & \langle \eta_{111},\phi_{11m}\rangle \\ \langle \eta_{112},\phi_{111}\rangle & \langle \eta_{112},\phi_{112}\rangle & \cdots & \langle \eta_{112},\phi_{11m}\rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \eta_{11n},\phi_{111}\rangle & \langle \eta_{11n},\phi_{112}\rangle & \cdots & \langle \eta_{11n},\phi_{11m}\rangle \end{pmatrix} \begin{pmatrix} d_{111} \\ d_{112} \\ \vdots \\ d_{11m} \end{pmatrix}$$

$$+ \begin{pmatrix} \langle \eta_{111},\xi_{111}\rangle & \langle \eta_{111},\xi_{112}\rangle & \cdots & \langle \eta_{111},\xi_{11n}\rangle \\ \langle \eta_{112},\xi_{111}\rangle & \langle \eta_{112},\xi_{112}\rangle & \cdots & \langle \eta_{112},\xi_{11n}\rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \eta_{11n},\xi_{111}\rangle & \langle \eta_{11n},\xi_{112}\rangle & \cdots & \langle \eta_{11n},\xi_{11n}\rangle \end{pmatrix} \begin{pmatrix} c_{111} \\ c_{112} \\ \vdots \\ c_{11n} \end{pmatrix} \quad (17)$$

$$\underset{\sim}{f}_{11}(x_{11}) = \mathbf{T}_{11}\underset{\sim}{d}_{11} + \mathbf{V}_{11}\underset{\sim}{c}_{11}$$

With:

$$T_{11} = \begin{pmatrix} \langle \eta_{111},\phi_{111}\rangle & \langle \eta_{111},\phi_{112}\rangle & \cdots & \langle \eta_{111},\phi_{11m}\rangle \\ \langle \eta_{112},\phi_{111}\rangle & \langle \eta_{112},\phi_{112}\rangle & \cdots & \langle \eta_{112},\phi_{11m}\rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \eta_{11n},\phi_{111}\rangle & \langle \eta_{11n},\phi_{112}\rangle & \cdots & \langle \eta_{11n},\phi_{11m}\rangle \end{pmatrix},$$

$$V_{11} = \begin{pmatrix} \langle \xi_{111},\xi_{111}\rangle & \langle \xi_{111},\xi_{112}\rangle & \cdots & \langle \xi_{111},\xi_{11n}\rangle \\ \langle \xi_{112},\xi_{111}\rangle & \langle \xi_{112},\xi_{112}\rangle & \cdots & \langle \xi_{112},\xi_{11n}\rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{11n},\xi_{111}\rangle & \langle \xi_{11n},\xi_{112}\rangle & \cdots & \langle \xi_{11n},\xi_{11n}\rangle \end{pmatrix}$$

For longitudinal, each observations in same subject are time ordered. The t-observation only depend on (t-1), (t-2), ..., (t-n+1) and not depend on (t+1), (t+2), ..., (t+n-1), then V_{11} is

$$V_{11} = \begin{pmatrix} \langle \xi_{111},\xi_{111}\rangle & 0 & \cdots & 0 \\ \langle \xi_{112},\xi_{111}\rangle & \langle \xi_{112},\xi_{112}\rangle & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{11n},\xi_{111}\rangle & \langle \xi_{11n},\xi_{112}\rangle & \cdots & \langle \xi_{11n},\xi_{11n}\rangle \end{pmatrix}.$$

Then from the same way, it was obtained the result for:

$$\ell = 1, 2, \ldots, p, k = 1, 2, i = 1, 2, \ldots, r$$
$$\underset{\sim}{f}_{ki}(x_{\ell i}) = T_{ki}\underset{\sim}{d}_{ki} + V_{ki}\underset{\sim}{c}_{ki} \quad (18)$$

Thus, the form of spline estimator $\underset{\sim}{f}(x)$ is as follows:

$$\underset{\sim}{f}(x) = T\underset{\sim}{d} + V\underset{\sim}{c} \quad (19)$$

$\underset{\sim}{d}$ is the vector of order $2rm$ and $\underset{\sim}{c}$ is the vector of order $2rn$ as follow:

$$\underset{\sim}{d}_{ki} = \begin{pmatrix} d_{ki1} \\ d_{ki2} \\ \vdots \\ d_{kim} \end{pmatrix} and \ \underset{\sim}{c}_{ki} = \begin{pmatrix} c_{ki1} \\ c_{ki2} \\ \vdots \\ c_{kin} \end{pmatrix}$$

T is the matrix of order $(2rn) \times (2rm)$ and V is the matrix of order $(2rn) \times (2rn)$ as follows:

$$T = \begin{pmatrix} T_{11} & 0 & \cdots & 0 \\ 0 & T_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & T_{2r} \end{pmatrix} and \ V = \begin{pmatrix} V_{11} & 0 & \cdots & 0 \\ 0 & V_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & V_{2r} \end{pmatrix}$$

Vector $\underset{\sim}{d}$ and $\underset{\sim}{c}$ are coefficients of estimation and matrix T and V are given. Matrix T_{ki} as reproducing kernel in H_0 as follow:

$$T_{ki} = \begin{pmatrix} \langle \eta_{ki1},\phi_{ki1}\rangle & \langle \eta_{ki1},\phi_{ki2}\rangle & \cdots & \langle \eta_{ki1},\phi_{kim}\rangle \\ \langle \eta_{ki2},\phi_{ki1}\rangle & \langle \eta_{ki2},\phi_{ki2}\rangle & \cdots & \langle \eta_{ki2},\phi_{kim}\rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \eta_{kin},\phi_{ki1}\rangle & \langle \eta_{kin},\phi_{ki2}\rangle & \cdots & \langle \eta_{kin},\phi_{kim}\rangle \end{pmatrix}$$

With

$$\langle \eta_{kit},\phi_{kij}\rangle = L_{kit}\phi_{kij} = \frac{x_{kit}^{\,j-1}}{(j-1)!}, j = 1, 2, \ldots, m \quad (20)$$

Matrix V_{ki} as reproducing kernel in H_1 as follow:

$$V_{ki} = \begin{pmatrix} \langle \xi_{ki1},\xi_{ki1}\rangle & 0 & \cdots & 0 \\ \langle \xi_{ki2},\xi_{ki1}\rangle & \langle \xi_{ki2},\xi_{ki2}\rangle & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{kin},\xi_{ki1}\rangle & \langle \xi_{kin},\xi_{ki2}\rangle & \cdots & \langle \xi_{kin},\xi_{kin}\rangle \end{pmatrix},$$

$$\langle \xi_{kit},\xi_{kis}\rangle = L_{kit}\xi_{kis} = R_1(x_{\ell it}, x_{\ell is}) = \int_{a_{ki}}^{b_{ki}} \frac{(x_{\ell it}-u)_+^{m-1}(x_{\ell is}-u)_+^{m-1}}{((m-1)!)^2} du \quad (21)$$

With $(x_{\ell it}-u)_+^{m-1} = (x_{\ell it}-u)^{m-1}$ if $x_{\ell it}-u \geq 0$ or $x_{\ell it} \geq u$ and $(x_{\ell it}-u)_+^{m-1} = 0$ if $x_{\ell it}-u < 0$ or $x_{\ell it} < u$.

In this case, $a_{ki} \leq u \leq b_{ki}$ and $a_{ki} = min(x_{\ell it})$, then $x_{\ell it} \geq u$, so it always $(x_{\ell it} - u)_{+}^{m-1} = (x_{\ell it} - u)^{m-1}$.

If $m = 2$ (linear), then:

$$\langle \xi_{kit}, \xi_{kis} \rangle = \int_{a_{ki}}^{b_{ki}} (x_{\ell it} - u)(x_{\ell is} - u) du$$

$$\langle \xi_{kit}, \xi_{kis} \rangle = \int_{a_{ki}}^{b_{ki}} \left[x_{\ell it} x_{\ell is} - x_{\ell it} u - x_{\ell is} + u^2 \right] du \qquad (22)$$

$$\langle \xi_{kit}, \xi_{kis} \rangle = x_{\ell it} x_{\ell is} u - \tfrac{1}{2} x_{\ell it} u^2 - \tfrac{1}{2} x_{\ell is} u^2 + \tfrac{1}{3} u^3 \Big|_{a_{ki}}^{b_{ki}}$$

For $x \in [0,1]$, solving this Equation (22) as:

$$\langle \xi_{kit}, \xi_{kis} \rangle = x_{\ell it} x_{\ell is} - \tfrac{1}{2}(x_{\ell it} + x_{\ell is}) + \tfrac{1}{3}$$

Based on the Theorem 1, it was used as the basis to obtain estimates of the spline as shown in the following theorem 2:

Theorem 2:

The spline estimator in the bi-responses and multi-predictors nonparametric regression for longitudinal data. If given the data pairs following the bi-responses nonparametric regression models involving a multi-predictor variable on longitudinal data that meets the functional form of bi-responsesand multi-predictors nonparametric regression for longitudinal data as presented in the Theorem 1 and with the assumption $E(\varepsilon_t) = 0$ and $Var(\varepsilon_t) = W^{-1}$ (presented in the equation (9) so the spline estimator minimizing PWLS in the equation (11) is $\hat{f}_\lambda = A(\underset{\sim}{\lambda})\underset{\sim}{y}$ with:

$$A(\underset{\sim}{\lambda}) = T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W + VM^{-1}W[I - T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W]$$

Proof of Theorem 2:

Given the equation (19), then regression curve estimator $\underset{\sim}{f}$ will be obtained if T and V are given in Equation (20) and (21), respectively and estimate the coefficients $\underset{\sim}{d}$ and $\underset{\sim}{c}$. For the purposes of this estimation, RKHS approach will be used if we want to meet the estimation $\underset{\sim}{f}$ which completes the PWLS estimation:

$$\underset{\substack{f_{ki}\in H \\ k=1,2; i=1,2,..,r}}{Min} \left\{ \| W\underset{\sim}{\varepsilon} \|^2 \right\} = \underset{\substack{f_{ki}\in H \\ k=1,2; i=1,2,..,r}}{Min} \left\{ \| W(\underset{\sim}{y} - f) \|^2 \right\} \qquad (23)$$

With constrain: $\| f_{ki} \|^2 < \gamma_{ki}, \quad \gamma_{ki} \geq 0$.

Then function $H = W_2^m[a_{ki}, b_{ki}]$ used was Sobolev order-2 space which is defined as follows:

$$W_2^m[a_{ki}, b_{kl}] = \left\{ f ; \int_{a_{ki}}^{b_{ki}} [f_{ki}^{(m)}(x_{\ell i})]^2 dx_{\ell i} < \omega \right\}, \qquad \text{with}$$

$x_{\ell i} \in [a_{ki}, b_{ki}]$. Based on that space, Norm for each function $f_{ki} \in W_2^m[a_{ki}, b_{ki}]$, defined is $\| f_{ki} \|^2 = \int_{a_{ki}}^{b_{ki}} [f_{ki}^{(m)}(x_{\ell i})]^2 dx_{\ell i}$.

Optimization with constrain on the equation (23) can be written as:

$$\underset{\substack{f_{ki}\in W_2^m[a_{ki}] \\ k=1,2; i=1,2,..,r}}{Min} \left\{ \| W\underset{\sim}{\varepsilon} \|^2 \right\} = \underset{\substack{f_{ki}\in W_2^m[a_{ki}] \\ k=1,2; i=1,2,..,r}}{Min} \left\{ \| W(\underset{\sim}{y} - \underset{\sim}{f}) \|^2 \right\} \qquad (24)$$

With constrain $\int_{a_{ki}}^{b_{ki}} [f_{ki}^{(m)}(x_{\ell i})]^2 dx_{\ell i} < \gamma_{ki}, \quad \gamma_{ki} \geq 0$.

Weighed optimization with constrain (24) is equivalent to completing PWLS optimization with the equation (11). To complete the optimization, first penalty component must be described:

$$\lambda_{ki} \int_{a_{12}}^{b_{12}} \left[f_{ki}^{(m)}\left(x_{\ell i}\right) \right]^2 dx_{\ell i} = \lambda_{ki} \underset{\sim}{c}_{ki}' V_{ki} \underset{\sim}{c}_{ki}. \qquad (25)$$

Based on the equation (25), penaltyvalue gained:

$$\sum_{k=1}^{2} \sum_{i=1}^{r} \lambda_{ki} \int_{a_{ki}}^{b_{ki}} \left[f_{ki}^{(m)}\left(x_{\ell i}\right) \right]^2 dx_{\ell i} = \underset{\sim}{c}' \lambda V \underset{\sim}{c} \qquad (26)$$

with $\underset{\sim}{\lambda} = diag(\lambda_{11} I_n, \lambda_{12} I_n, \cdots, \lambda_{2r} I_n)$.

Based on the equation (26), the Goodness of fit on the PWL Soptimization (21) can be written as:

$$N^{-1} \left(\underset{\sim}{y} - f \right)' W \left(\underset{\sim}{y} - f \right) = \\ N^{-1} \left(\underset{\sim}{y} - T\underset{\sim}{d} - V\underset{\sim}{c} \right)^T W \left(\underset{\sim}{y} - T\underset{\sim}{d} - V\underset{\sim}{c} \right) \qquad (27)$$

By combining the Goodness of fit (26) and the penalty (25), the PWLS optimization can be presented in the form of:

$$\underset{\substack{c\in\mathfrak{R}^{2rn} \\ d\in\mathfrak{R}^{2rm}}}{Min} \left\{ N^{-1} \left(\underset{\sim}{y} - T\underset{\sim}{d} - V\underset{\sim}{c} \right)' W \left(\underset{\sim}{y} - T\underset{\sim}{d} - V\underset{\sim}{c} \right) + \underset{\sim}{c}' \lambda V \underset{\sim}{c} \right\}$$

$$= \underset{\substack{c\in\mathfrak{R}^{2rn} \\ d\in\mathfrak{R}^{2rm}}}{Min} \left\{ \begin{array}{l} (y'Wy - 2\underset{\sim}{d}'T'Wy - 2\underset{\sim}{c}'V'Wy + \underset{\sim}{d}'T'WT\underset{\sim}{d} \\ + \underset{\sim}{d}'T'WV\underset{\sim}{c} + \underset{\sim}{c}'V'WT\underset{\sim}{d} + \underset{\sim}{c}'\left(V'WV + N\lambda V \right)\underset{\sim}{c} \end{array} \right\} \qquad (28)$$

$$= \underset{\substack{c\in\mathfrak{R}^{2rn} \\ d\in\mathfrak{R}^{2rm}}}{Min} \left\{ Q(\underset{\sim}{c}, \underset{\sim}{d}) \right\}$$

The completion of the optimization (28), was obtained by partially derivating $Q(\underset{\sim}{c}, \underset{\sim}{d})$ against $\underset{\sim}{c}$ then the result was equated to zero and gave the result:

$$-2V'W\underset{\sim}{y} + 2V'WT\underset{\sim}{d} + 2\left(V'WV + N\lambda V \right)\underset{\sim}{c} = 0 \qquad (29)$$

Suppose given matrix $M = WV + N\lambda I$, then the Equation 29 can be written as:

$$M\underset{\sim}{c} = W(\underset{\sim}{y} - T\underset{\sim}{d}) \qquad (30)$$

The Equation 30 was multiply with M^{-1} it was obtained the equation:

$$\hat{\underset{\sim}{c}} = M^{-1}W(\underset{\sim}{y} - T\underset{\sim}{d}) \qquad (31)$$

Then partial derivatif against $\underset{\sim}{d}$ then the result was equated to zero, it gave the result of:

$$-T'W\underset{\sim}{y} + T'WT\underset{\sim}{d} + T'WV\underset{\sim}{c} = \underset{\sim}{0}$$

Because the Equation 28, it was obtained the equation:

$$-T'W\underset{\sim}{y} + T'WT\underset{\sim}{d} + T'[WVM^{-1}]W(\underset{\sim}{y} - T\underset{\sim}{d}) = \underset{\sim}{0}$$

As a result, it was obtained the equation:

$$VM^{-1} = W^{-1}(M - N\lambda I)M^{-1} = W^{-1}(I - N\lambda M^{-1})$$

The equation (26) was multiply with W it was obtained:

$$WVM^{-1} = I - N\lambda M^{-1}$$

This equation was substituted in the Equation 26 it was obtained the equation:

$$-T'W\underset{\sim}{y} + T'WT\underset{\sim}{d} + T'[I - N\lambda M^{-1}]W(\underset{\sim}{y} - T\underset{\sim}{d}) = \underset{\sim}{0}$$

Solve the equation above:

$$\hat{\underset{\sim}{d}} = \left(T'M^{-1}WT\right)^{-1}T'M^{-1}W \qquad (32)$$

$$\hat{\underset{\sim}{c}} = M^{-1}W[I - T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W]\underset{\sim}{y} \qquad (33)$$

Based on the Equation 32 and 33, it was obtained the estimator for bi-responses and multi-predictors nonparametric regression curve for longitudinal data involving a single predictor variable as follows:

$$
\begin{aligned}
\hat{\underset{\sim}{f}}_\lambda &= T\hat{\underset{\sim}{d}} + V\hat{\underset{\sim}{c}} \\
\hat{\underset{\sim}{f}}_\lambda &= T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W \\
&\quad + VM^{-1}W\left[I - T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W\right]\Bigg\}\underset{\sim}{y} \\
\hat{\underset{\sim}{f}}_\lambda &= A(\lambda)\underset{\sim}{y}
\end{aligned}
\qquad (34)
$$

with:

$$A(\underset{\sim}{\lambda}) = T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W + VM^{-1}W[I - T\left(T'M^{-1}WT\right)^{-1}T'M^{-1}W]$$

The application using data with patient of Pulmonary Tuberculosis from Chozin (2009). The data coming from 4 patients (s1,s2,s3,s4), with two response variables: suPAR (y_1) and Monocite (y_2) and predictor variables: Design time point (x_1). Figure 1 shows the plot of each responsesand shows that the correlation between the response variables.

The Plot of predictor and responses to be given in Fig. 2. From the plot in Fig. 2 shows that no form of a particular pattern (the pattern was less clear form) between the predictor variables x with response variabley each i subject. The results of the smoothing parameter λ_{ki} based on the minimum value of GCV. The optimizations results showed that the coefficient of determination 97.77%. Figure 3 shows the results of Spline Estimator for bi-response multi-predictor longitudinal data that provide the minimum value of GCV with m = 4 (quadratic spline). From data set given the optimal solution, the curve can describe 97.77% of the variance of the original data.
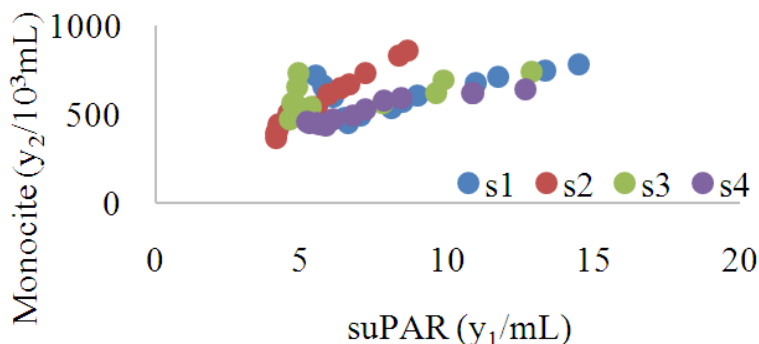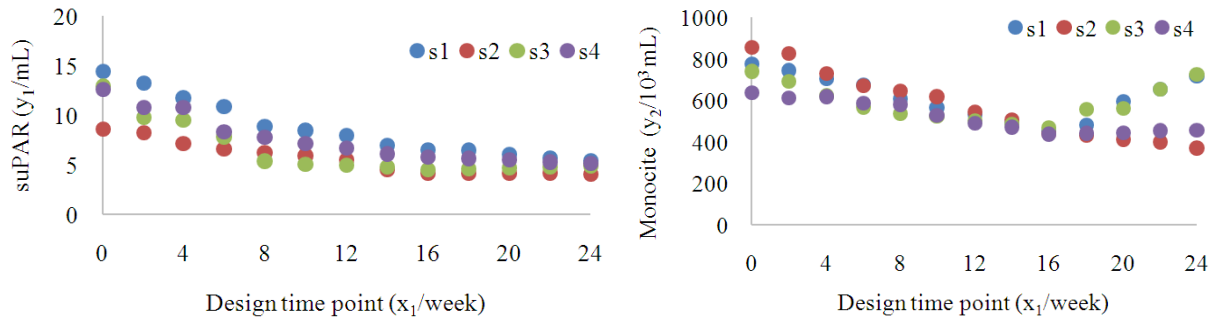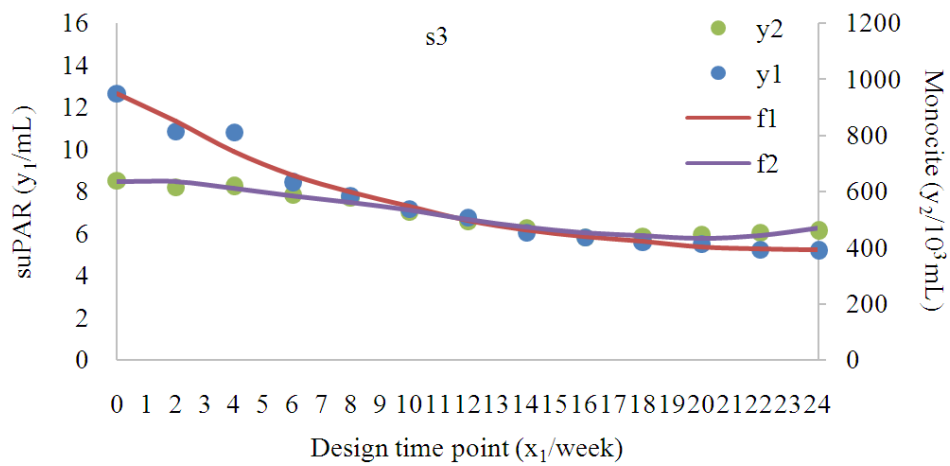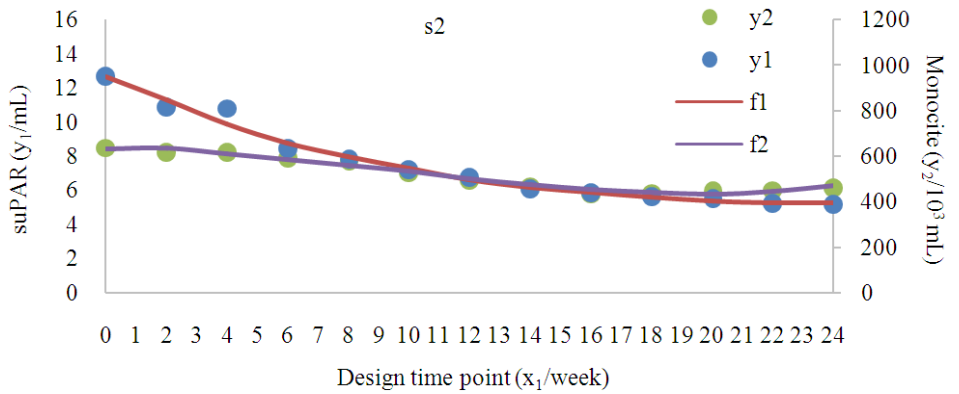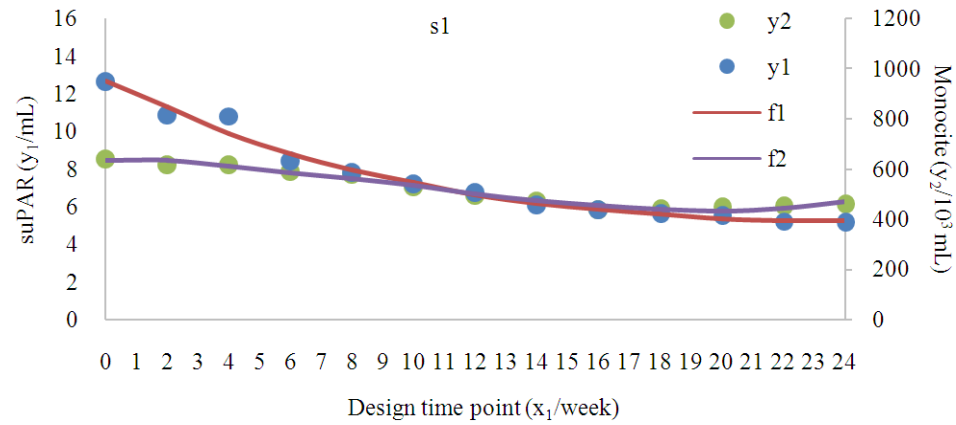

Fig. 1. Plot of each responses

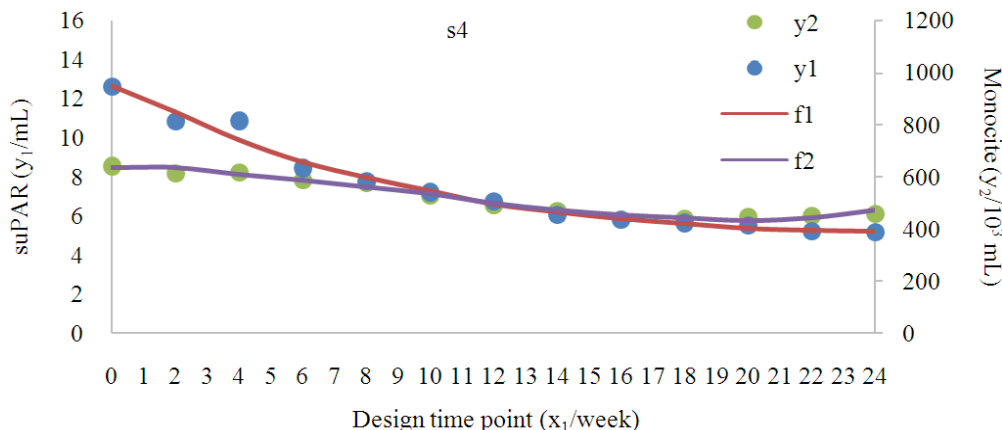Fig. 2. Plot of predictor Vs responses

Fig. 3. Result of spline estimator

Conclusion

Based on the results of the study presented on the previous part, several things can be concluded as follows: Bi-responses and multi-predictors nonparametric regression mdel on longitudinal data on the equation $y_{kit} = f_{ki}(x_{it}) + \varepsilon_{kit}$ has a function form $\underset{\sim}{f}(x) = T\underset{\sim}{d} + V\underset{\sim}{c}$, with

$$T = \begin{pmatrix} T_{11} & 0 & \cdots & 0 \\ 0 & T_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & T_{2r} \end{pmatrix},$$

$$T_{ki} = \begin{pmatrix} \langle \eta_{ki1}, \phi_{ki1} \rangle & \langle \eta_{ki1}, \phi_{ki2} \rangle & \cdots & \langle \eta_{ki1}, \phi_{kim} \rangle \\ \langle \eta_{ki2}, \phi_{ki1} \rangle & \langle \eta_{ki2}, \phi_{ki2} \rangle & \cdots & \langle \eta_{ki2}, \phi_{kim} \rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \eta_{kin}, \phi_{ki1} \rangle & \langle \eta_{kin}, \phi_{ki2} \rangle & \cdots & \langle \eta_{kin}, \phi_{kim} \rangle \end{pmatrix},$$

$$V = \begin{pmatrix} V_{11} & 0 & \cdots & 0 \\ 0 & V_{12} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & V_{2r} \end{pmatrix},$$

$$V_{11} = \begin{pmatrix} \langle \xi_{111}, \\ \xi_{111} \rangle & 0 & \cdots & 0 \\ \langle \xi_{112}, \xi_{111} \rangle & \langle \xi_{112}, \xi_{112} \rangle & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{11n}, \xi_{111} \rangle & \langle \xi_{11n}, \xi_{112} \rangle & \cdots & \langle \xi_{11n}, \xi_{11n} \rangle \end{pmatrix}.$$

Bi-responses and multi-predictors nonparametric regression of the spline estimator on longitudinal data which meet the criteria of minimizing PWLS

$$\underset{f_{ki} \in W_2^m [a_{ki}, b_{ki}], k=1,2; i=1,2,\ldots,r}{Min}$$

$$\left\{ N^{-1} (\underset{\sim}{y} - \underset{\sim}{f})' W (\underset{\sim}{y} - \underset{\sim}{f}) + \sum_{k=1}^{2} \sum_{i=1}^{r} \lambda_{ki} \int_{a_{ki}}^{b_{ki}} (f_{ki}^{(m)}(x_{\ell i}))^2 dx_{\ell i} \right\}$$

is $\hat{\underset{\sim}{f}}_\lambda = A(\underset{\sim}{\lambda}) \underset{\sim}{y}$, with

$$A(\underset{\sim}{\lambda}) = T\left(T'M^{-1}WT\right)^{-1} T'M^{-1}W + VM^{-1}W[I - T\left(T'M^{-1}WT\right)^{-1} T'M^{-1}W]$$

The aplication of data results show that the spline estimator given the optimal solution, the curve can describe 97.77% of the variance of the original data.

Author's Contributions

Adji Achmad Rinaldo Fernandes: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

I Nyoman Budiantara: Contributing the theoretical result and data-analysis.

Bambang Widjanarko Otok: Contributing the program for data-analysis.

Suhartono: Contributed to writing the manuscript.

Ethics

There are no financial or personal conflicts of interest involved in any aspect of this paper.

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