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Predicting Blood Pressures and Heart Rate Associated with Stress Level Using Spline Estimator: A Theoretically Discussion

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Abstract: *Hypertension has become a serious health problem in Indonesia because of its prevalence, however, the causative factors could not be ascertained for about ninety percent of the patients. Various studies have found several risk factors causing hypertension to be obesity, family history, stress levels, heart rate, and an unhealthy lifestyle. In this case, the variables are considered influential on hypertension through a regression function without a specific pattern, i.e., a regression function of multi-response nonparametric regression model. The basic idea of multi-response nonparametric regression where there are correlations between responses is to let the data decide which regression function fits the best without imposing any specific form on it. In this paper we present a theoretically discussion in predicting blood pressures and heart rate affected by stress level that can be used for early detection of hypertension by using spline estimator in multi-response nonparametric regression. The estimated regression function that draws association between blood pressures, heart rate, and stress level can be obtained by taking solution of penalized weighted least square optimization by using reproducing kernel Hilbert space approach. Next, we can get the optimal smoothing parameter by minimizing generalized cross validation function. In this paper we obtain predicted model of blood pressures and heart rate associated with stress level which can be used for early prediction of hypertension.*

Keywords — Blood Pressures, Heart Rate, Multi-response Nonparametric Regression, Smoothing Parameter, Stress Level.

1. INTRODUCTION

Hypertension is often referred to as the silent killer because it takes the life of affected individuals without showing symptoms. However, the factors causing the disease (around 90%) are still unknown. The number of people living with hypertension is predicted to become 1.56 billion worldwide by the year 2025 [1]. The sickness is associated with cardiovascular diseases (CVD) risk factors, incidence, and mortality [2]. It is also found to be prevalent among people of 35 years of age and above, currently smoking, and obese [3]. The Seventh Report on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure created a category called "pre-hypertension" which was defined as a systolic blood pressure (SBP) of 120-139 millimeters of mercury (mmHg) and a diastolic blood pressure (DBP) of 80-89 mmHg [1]. Pre-hypertension, even in the low range (SBP: 120-130 mmHg or DBP: 80-85 mmHg), has been confirmed to have a higher risk of developing into hypertension [4]. Hypertension has been associated with increased risk of coronary artery and cardiovascular and cerebrovascular diseases [5-6]. A meta-analysis also reported that lower blood pressure could also lead to cardiovascular and chronic kidney diseases [7-8]. This situation is critical in the Southeast Asian region with studies reporting in [9-10] as an important risk factor for the attributable burden. Several studies have found different risk factors for hypertension such as obesity, family history, stress levels, heart rate, and an unhealthy lifestyle. In [11], researchers used penalized spline to model hypertension risk factors for preventing hypertension in Indonesia.

In statistical modeling, we frequently use estimators to estimate models which are expressed as parametric regression model or nonparametric regression model not only for uni-response but also for multi-response. Local polynomial estimator has been used by [12] for improving classification accuracy of cyst and tumor. Next, [13] identified glaucoma on fundus retinal images by using local linear estimator. Also, [14] used local linear estimator to classify choroidal neovascularisation on fundus retinal images. Lung tumor classification on human chest X-ray by using local linear estimator has been discussed by [15]. Image enhancement sputum containing mycobacterium tuberculosis using a spatial domain filter has been studied by [16]. Further, [17] used local linear estimator for modeling maternal mortality and infant mortality cases in East Kalimantan. Estimation of dissolved oxygen using spatial analysis based on ordinary kriging method as effort to improve the quality of Surabaya's river water has been studied by [18]. Spline estimator of nonparametric regression was used by [19] to predict suspended and attached process behavior in anaerobic batch reactor. Truncated spline estimator of nonparametric regression was used by [20] for modeling the percentage of aids sufferers in East Java province. Least squared spline estimator has been used by [21] for modeling poverty percentage of non-food per capita expenditures in Indonesia. Multi-response nonparametric regression model provides powerful tools to model the functions which represent association between two or more dependent variables and independent variables. There are many researchers who have considered nonparametric models for modeling medical data. In [22] researchers used local linear of bi-variate longitudinal data to model the admission test of State Islamic College in Indonesia. Truncated spline estimator in multi-response semiparametric regression was used by [23] for modeling computer based national examination in West Nusa Tenggara, Indonesa. Standard growth chart of weight for height to determine wasting nutritional status in East Java based on semiparametric least square spline estimator has been studied by [24]. Modeling of HIV and AIDS in Indonesia by using bivariate negative binomial regression have been discussed by [25]. Penalized spline estimator has been used by [26] to estimate median growth charts for height of children in East Java province of Indonesia. Penalized spline estimator with multi-smoothing parameters in bi-response multi-predictor nonparametric regression model for longitudinal data has been discussed by [27]. Spline for estimating nonparametric functions from bivariate data with the same correlation of errors has been studied by [28]. Methods for estimating nonparametric regression model with spatially correlated errors were proposed by [29]. Next, [30] and [31] have studied spline estimators in multi-response nonparametric regression model with equal correlation of errors and unequal correlation of errors, respectively. Multi-response nonparametric regression model approach to design child growth chart has been used by [32]. A mathematical statistics method for estimating regression curve of the multi-response nonparametric regression model in case of heteroscedasticity of variance was proposed by [33]. Estimating regression function of the homoscedastic multi-response nonparametric regression in which the number of observations were unbalance has been discussed by [34]. Next, [35-37] proposed smoothing spline estimator for estimating of the multi-response nonparametric regression model by using reproducing kernel Hilbert space (RKHS). In addition, [38] discussed construction of covariance matrix in case of homoscedasticity of variances of errors. Also, [39] discussed estimating of both covariance matrix and optimal smoothing parameter. Further, [40] used spline to show ability of covariance matrix. But, these researchers have not discussed estimating of smoothing parameter in multi-response nonparametric regression model when the variances of errors are not the same for cross-section data. In addition, all these researchers have not theoretically discussed application of the estimated model on the real case data.

Therefore, in this paper, we discuss theoretically methods to estimate regression function and optimum smoothing parameter of the multi-response nonparametric regression model if it is applied to blood pressures and heart rate affected by stress level.

2. MATERIAL AND METHODS

We consider multi-response nonparametric regression model as follows:

$$y_{ki} = f_k(t_{ki}) + \varepsilon_{ki}, \quad k = 1, 2, ..., p, \quad i = 1, 2, ..., n_k \qquad (1)$$

where $Var(\varepsilon_{ki}) = \sigma_{ki}^2$ [33, 35-36, 39, 41]. Next, suppose that we apply the model in (1) to data of blood pressures and heart rate that are affected by stress level such that we have the blood pressures and heart rate model as follows:

$$y_{ki} = f_k(t_{ki}) + \varepsilon_{ki}; \; k = 1, 2, 3; \; i = 1, 2, ..., n_k \qquad (2)$$

where $Var(\varepsilon_{ki}) = \sigma_{ki}^2$, y_{1i}, y_{2i} and y_{3i} are response variables that represent the first response (i.e., systolic blood pressure), the second response (i.e., diastolic blood pressure), and the third response (i.e., heart rate), respectively; and $f_k(t_{ki})$ are unknown regression functions which represent function of predictor variable (i.e., stress level).

The estimated regression function can be obtained by taking solution of penalized weighted least square optimization by using reproducing kernel Hilbert space approach. Next, we can get the optimal smoothing parameter by minimizing generalized cross validation function. Finally, we apply the estimated model that we have obtained to the real case data, i.e., blood pressures and heart rate affected by stress level. In this case, the estimated systolic and diastolic blood pressures, and heart rate that we have obtained can be used for early prediction of hypertension.

3. RESULTS AND DISCUSSION

In this section, we present results and discussion about theoretically methods for both estimating regression function and estimating optimal smoothing parameter of the model of blood pressures and heart rate affected by stress level by using spline estimator in multi-response nonparametric regression.

3.1 Estimation of Regression Function of Blood Pressures and Heart Rate Model

Firstly, we consider a paired data set that follows the blood pressures and heart rate model as given in (2), i.e.,:

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$$y_{ki} = f_k(t_{ki}) + \varepsilon_{ki}\ ;\ i = 1,2,...,n_k\ ;\ a_k \le t_k \le b_k\ ; \qquad (3)$$

where k represents the number of response, $n_k = n$ for $k = 1,2,3$ and f_1, f_2, f_3 are unknown regression functions assumed to be smooth in Sobolev space $W_2^m[a_k, b_k]$, and ε_{ki} are zero-mean independent random errors with variance σ_{ki}^2. The main objective of nonparametric regression analysis is estimate unknown regression functions $f_k \in W_2^m[a_k, b_k]$ in model (3). Next, suppose that $\underset{\sim}{y} = (\underset{\sim}{y}_1, \underset{\sim}{y}_2, \underset{\sim}{y}_3)'$, $\underset{\sim}{f} = (\underset{\sim}{f}_1, \underset{\sim}{f}_2, \underset{\sim}{f}_3)'$, $\underset{\sim}{\varepsilon} = (\underset{\sim}{\varepsilon}_1, \underset{\sim}{\varepsilon}_2, \underset{\sim}{\varepsilon}_3)'$, and $\underset{\sim}{t} = (\underset{\sim}{t}_1, \underset{\sim}{t}_2, \underset{\sim}{t}_3)'$ where $\underset{\sim}{y}_k = (y_{k1}, ..., y_{kn})'$, $\underset{\sim}{f}_k = (f_k(t_{k1}), ..., f_k(t_{kn}))'$, $\underset{\sim}{\varepsilon}_k = (\varepsilon_{k1}, \varepsilon_{k2}, ..., \varepsilon_{kn})'$, $\underset{\sim}{t}_k = (t_{k1}, t_{k2}, ..., t_{kn})'$. Therefore, for $i = 1,2,...,n$ and $k = 1,2,3$ we can write equation (3) in the following equation:

$$\underset{\sim}{y} = \underset{\sim}{f} + \underset{\sim}{\varepsilon} \qquad (4)$$

where $E(\underset{\sim}{\varepsilon}) = \underset{\sim}{0}$ (zero mean), and $Cov(\underset{\sim}{\varepsilon}) = [W(\underset{\sim}{\sigma}^2)]^{-1}$ $= diag(W_1(\underset{\sim}{\sigma}_1^2), W_2(\underset{\sim}{\sigma}_2^2), W_3(\underset{\sim}{\sigma}_3^2))$. Estimating of the functions $\underset{\sim}{f}$ in (4) by using smoothing spline estimator appears as a solution to the penalized weighted least-square (PWLS) minimization problem, i.e., determine $\hat{\underset{\sim}{f}}$ that can make the following PWLS minimum:

$$\underset{f_1, f_2, f_3 \in W_2^m}{Min} \{ (\sum_{k=1}^{3} n_k)^{-1} (\underset{\sim}{y}_1 - \underset{\sim}{f}_1)' W_1 (\underset{\sim}{y}_1 - \underset{\sim}{f}_1) + ... + (\underset{\sim}{y}_3 - \underset{\sim}{f}_3)' W_3 (\underset{\sim}{y}_3 - \underset{\sim}{f}_3) +$$
$$\lambda_1 \int_{a_1}^{b_1} (f_1^{(2)}(t))^2 dt + ... + \lambda_3 \int_{a_3}^{b_3} (f_3^{(2)}(t))^2 dt \} \qquad (5)$$

for pre-specified value $\underset{\sim}{\lambda} = (\lambda_1, \lambda_2, \lambda_3)'$. Note that, in equation (5), the first term represents the sum squares of errors and it penalizes the lack of fit. While, the second term which is weighted by $\underset{\sim}{\lambda}$ represents the roughness penalty and it imposes a penalty on roughness. It means that the curvature of $\underset{\sim}{f}$ is penalized by it. In equation (5), λ_k $(k = 1,2,3)$ is called as the smoothing parameter. The solution will be vary from interpolation to a linear model, if λ_k varies from 0 to $+\infty$. So that, if $\lambda_k \to +\infty$, the roughness penalty will dominate in (5), and the smoothing spline estimate will be forced to be a constant. If $\lambda_k \to 0$, the roughness penalty will disappear in (5), and the spline estimate will interpolate the data. Thus, the trade-off between the goodness of fit given by:

$$(\sum_{k=1}^{3} n_k)^{-1} (\underset{\sim}{y}_1 - \underset{\sim}{f}_1)' W_1 (\underset{\sim}{y}_1 - \underset{\sim}{f}_1) + ... + (\underset{\sim}{y}_3 - \underset{\sim}{f}_3)' W_3 (\underset{\sim}{y}_3 - \underset{\sim}{f}_3)$$

and smoothness of the estimate given by:

$$\lambda_1 \int_{a_1}^{b_1} (f_1^{(2)}(t))^2 dt + \lambda_2 \int_{a_2}^{b_2} (f_2^{(2)}(t))^2 dt + \lambda_3 \int_{a_3}^{b_3} (f_3^{(2)}(t))^2 dt$$

is controlled by the smoothing parameter λ_k. The solution for minimization problem in (5) is a smoothing spline estimator where its function basis is a "natural cubic spline" with $t_1, t_2, ..., t_{n_k}$ $(k = 1,2,3)$ as its knots. Based on this concept, a particular structured spline interpolation that depends on selection of the smoothing parameter λ_k value becomes a appropriate approach of the functions f_k $(k = 1,2,3)$ in model (1). Let $\underset{\sim}{f} = (\underset{\sim}{f}_1, \underset{\sim}{f}_2, \underset{\sim}{f}_3)'$ where $\underset{\sim}{f}_k = (f_k(t_{k1}), f_k(t_{k2}), ..., f_k(t_{kn}))'$, $k = 1,2,3$, be the vector of values of function f_k $(k = 1,2,3)$ at the knot points $t_1, t_2, ..., t_{n_k}$ $(k = 1,2,3)$. If we express the model of paired data set into a general smoothing spline regression model, we will get the following expression:

$$y_{ki} = L_{t_k} f_k + \varepsilon_{ki}\ ,\ i = 1,2,...,n_k\ ;\ k = 1,2,3 \qquad (6)$$

where $f_k \in \mathrm{H}_k$ (H_k represents Hilbert space) is an unknown smooth function, and $L_{t_k} \in \mathrm{H}_k$ is a bounded linear functional.

Suppose H_k can be decomposed into two subspaces U_k and W_k as follows:

$$\mathrm{H}_k = \mathrm{U}_k \oplus \mathrm{W}_k$$

where U_k is orthogonal to W_k, $k = 1,2,3$. Suppose that $\{u_{k1}, u_{k2}, ..., u_{km_k}\}$ and $\{\omega_{k1}, \omega_{k2}, ..., \omega_{kn_k}\}$ are bases of spaces U_k and W_k, respectively. Then, we can express every function $f_k \in \mathrm{H}_k$ ($k = 1,2,3$) into the following expression:

$$f_k = g_k + h_k$$

where $g_k \in \mathrm{U}_k$ and $h_k \in \mathrm{W}_k$. Since $\{u_{k1}, u_{k2}, ..., u_{km_k}\}$ is basis of space U_k and $\{\omega_{k1}, \omega_{k2}, ..., \omega_{kn_k}\}$ is basis of space W_k, then for every $f_k \in \mathrm{H}_k$ ($k = 1,2,3$) follows:

$$f_k = \sum_{j=1}^{m_k} d_{kj} u_{kj} + \sum_{i=1}^{n_k} c_{ki} \omega_{ki} = \underset{\sim}{u}_k' \underset{\sim}{d}_k + \underset{\sim}{\omega}_k' \underset{\sim}{c}_k\ ; \qquad (7)$$

where $d_{kj} \in \mathrm{R}$; $c_{ki} \in \mathrm{R}$; $\underset{\sim}{u}_k = (u_{k1}, u_{k2}, ..., u_{km_k})'$, $\underset{\sim}{d}_k = (d_{k1}, d_{k2}, ..., d_{km_k})'$, $\underset{\sim}{\omega}_k = (\omega_{k1}, \omega_{k2}, ..., \omega_{kn_k})'$, and $\underset{\sim}{c}_k = (c_{k1}, c_{k2}, ..., c_{kn_k})'$. Furthermore, since $L_{t_{ki}}$ is a function which is bounded and linear in H_k, and $f_k \in \mathrm{H}_k$, $k = 1,2,3$ then we have

$$L_{t_{ki}} f_k = L_{t_{ki}}(g_k + h_k) = g_k(t_{ki}) + h_k(t_{ki}) = f_k(t_{ki})\ . \qquad (8)$$

Based on model (3), and by applying the Riesz representation theorem [42-43], and because of $L_{t_{ki}} \in \mathrm{H}_k$ is bounded linear

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functional, then according to [42-43] there is a representer $\xi_{ki} \in \mathrm{H}_k$ of $L_{t_{ki}}$ which follows:

$$L_{t_{ki}} f_k = \langle \xi_{ki}, f_k \rangle = f_k(t_{ki}), \; f_k \in \mathrm{H}_k \tag{9}$$

where $\langle \cdot, \cdot \rangle$ denotes an inner product. Based on (6) and by applying the properties of the inner product, we get:

$$\begin{aligned} f_k(t_{ki}) &= \langle \xi_{ki}, \underset{\sim}{u}_k' \underset{\sim}{d}_k + \underset{\sim}{\omega}_k' \underset{\sim}{c}_k \rangle \\ &= \langle \xi_{ki}, \underset{\sim}{u}_k' \underset{\sim}{d}_k \rangle + \langle \xi_{ki}, \underset{\sim}{\omega}_k' \underset{\sim}{c}_k \rangle . \end{aligned} \tag{10}$$

Next, by applying equation (10), for $k=1$ we have:
$f_1(t_{1i}) = \langle \xi_{1i}, \underset{\sim}{u}_1' \underset{\sim}{d}_1 \rangle + \langle \xi_{1i}, \underset{\sim}{\omega}_1' \underset{\sim}{c}_1 \rangle$, $i = 1, 2, ..., n_1$;
and for $i = 1, 2, 3, ..., n_1$ we have:

$$\begin{aligned} \underset{\sim}{f}_1(t_1) &= (f_1(t_{11}), f_1(t_{12}), ..., f_1(t_{1n_1}))' \\ &= K_1 \underset{\sim}{d}_1 + \Sigma_1 \underset{\sim}{c}_1 , \end{aligned} \tag{11}$$

where:

$$K_1 = \begin{bmatrix} \langle \xi_{11}, u_{11} \rangle & \langle \xi_{11}, u_{12} \rangle & \cdots & \langle \xi_{11}, u_{1m_1} \rangle \\ \langle \xi_{12}, u_{11} \rangle & \langle \xi_{12}, u_{12} \rangle & \cdots & \langle \xi_{12}, u_{1m_1} \rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{1n_1}, u_{11} \rangle & \langle \xi_{1n_1}, u_{12} \rangle & \cdots & \langle \xi_{1n_1}, u_{1m_1} \rangle \end{bmatrix},$$

$$\Sigma_1 = \begin{bmatrix} \langle \xi_{11}, \omega_{11} \rangle & \langle \xi_{11}, \omega_{12} \rangle & \cdots & \langle \xi_{11}, \omega_{1n_1} \rangle \\ \langle \xi_{12}, \omega_{11} \rangle & \langle \xi_{12}, \omega_{12} \rangle & \cdots & \langle \xi_{12}, \omega_{1n_1} \rangle \\ \vdots & \vdots & \vdots & \vdots \\ \langle \xi_{1n_1}, \omega_{11} \rangle & \langle \xi_{1n_1}, \omega_{12} \rangle & \cdots & \langle \xi_{1n_1}, \omega_{1n_1} \rangle \end{bmatrix},$$

$\underset{\sim}{d}_1 = (d_{11}, d_{12}, ..., d_{1m_1})'$, and $\underset{\sim}{c}_1 = (c_{11}, c_{12}, ..., c_{1n_1})'$. In the similar process, we obtain: $\underset{\sim}{f}_2(t_2) = K_2 \underset{\sim}{d}_2 + \Sigma_2 \underset{\sim}{c}_2$; $\underset{\sim}{f}_3(t_3) = K_3 \underset{\sim}{d}_3 + \Sigma_3 \underset{\sim}{c}_3$. Therefore, the regression function $\underset{\sim}{f}(t)$ can be expressed as:

$$\begin{aligned} \underset{\sim}{f}(t) &= (\underset{\sim}{f}_1(t_1), \underset{\sim}{f}_2(t), \underset{\sim}{f}_3(t))' \\ &= (K_1 \underset{\sim}{d}_1, K_2 \underset{\sim}{d}_2, K_3 \underset{\sim}{d}_3)' + (\Sigma_1 \underset{\sim}{c}_1, \Sigma_2 \underset{\sim}{c}_2, \Sigma_3 \underset{\sim}{c}_3)' \\ &= diag(K_1, K_2, K_3)(\underset{\sim}{d}_1, \underset{\sim}{d}_2, \underset{\sim}{d}_3)' + \\ &\quad diag(\Sigma_1, \Sigma_2, \Sigma_3)(\underset{\sim}{c}_1, \underset{\sim}{c}_2, \underset{\sim}{c}_3)' \\ &= K \underset{\sim}{d} + \Sigma \underset{\sim}{c} . \end{aligned} \tag{12}$$

In equation (12), K is a $(N \times M)$-matrix and $\underset{\sim}{d}$ is a vector of parameters with dimension $(M \times 1)$ (where $N = \sum_{k=1}^{3} n_k = 3n$, $M = \sum_{k=1}^{3} m_k = 3m$) that are expressed as: $K = diag(K_1, K_2, K_3)$, and $\underset{\sim}{d} = (\underset{\sim}{d}_1', \underset{\sim}{d}_2', \underset{\sim}{d}_3')'$, respectively. Also, Σ is a $(N \times N)$-matrix, and $\underset{\sim}{c}$ is a $(N \times 1)$-vector of parameters which are expressed as:
$\Sigma = diag(\Sigma_1, \Sigma_2, \Sigma_3)$, and $\underset{\sim}{c} = (\underset{\sim}{c}_1', \underset{\sim}{c}_2', \underset{\sim}{c}_3')'$, respectively.

Therefore, we can write model in (3) as follows:

$$\underset{\sim}{y} = K \underset{\sim}{d} + \Sigma \underset{\sim}{c} + \underset{\sim}{\varepsilon} .$$

We use the RKHS method to obtain the estimation of $\underset{\sim}{f}$, by solving the following optimization:

$$\underset{\substack{f_k \in \mathcal{H}_k \\ k=1,2,3}}{Min} \left\{ \left\| W^{\frac{1}{2}}(\underset{\sim}{\sigma}^2) \underset{\sim}{\varepsilon} \right\|^2 \right\} = \underset{\substack{f_k \in \mathcal{H}_k \\ k=1,2,3}}{Min} \left\{ \left\| W^{\frac{1}{2}}(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - \underset{\sim}{f}) \right\|^2 \right\}, \tag{13}$$

with constraint:

$$\int_{a_k}^{b_k} [f_k^{(m)}(t_k)]^2 dt_k < \gamma_k \;, \; \gamma_k \geq 0 . \tag{14}$$

To solve the optimization (13) with constraint (14) is equivalent to solve the optimization PWLS:

$$\underset{\substack{f_k \in W_2^m[a_k, b_k] \\ k=1,2,3}}{Min} \left\{ N^{-1}(\underset{\sim}{y} - \underset{\sim}{f})' W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - \underset{\sim}{f}) + \sum_{k=1}^{3} \lambda_k \int_{a_k}^{b_k} [f_k^{(m)}(t_k)]^2 dt_k \right\}, \tag{15}$$

where λ_k, $k = 1, 2, 3$ are smoothing parameters that control trade-off between goodness of fit represented by:

$$N^{-1}(\underset{\sim}{y} - \underset{\sim}{f})' W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - \underset{\sim}{f})$$

and the roughness penalty measured by:

$$\lambda_1 \int_{a_1}^{b_1} [f_1^{(m)}(t_1)]^2 dt_1 + ... + \lambda_3 \int_{a_3}^{b_3} [f_3^{(m)}(t_3)]^2 dt_3 .$$

To get the solution to (15), we first decompose the roughness penalty as follows:

$$\begin{aligned} \int_{a_1}^{b_1} [f_1^{(m)}(t_1)]^2 dt_1 &= \| P f_1 \|^2 = \langle P f_1, P f_1 \rangle \\ &= \langle \underset{\sim}{\omega}_1' \underset{\sim}{c}_1, \underset{\sim}{\omega}_1' \underset{\sim}{c}_1 \rangle = \underset{\sim}{c}_1' (\underset{\sim}{\omega}_1 \underset{\sim}{\omega}_1') \underset{\sim}{c}_1 = \underset{\sim}{c}_1' \Sigma_1 \underset{\sim}{c}_1 \end{aligned}$$

It implies:

$$\lambda_1 \int_{a_1}^{b_1} [f_1^{(m)}(t_1)]^2 dt_1 = \lambda_1 \underset{\sim}{c}_1' \Sigma_1 \underset{\sim}{c}_1 . \tag{16}$$

Next, by similar way, we get:

$$\lambda_2 \int_{a_2}^{b_2} [f_2^{(m)}(t_2)]^2 dt_2 = \lambda_2 \underset{\sim}{c}_2' \Sigma_2 \underset{\sim}{c}_2 ,$$

$$\lambda_3 \int_{a_3}^{b_3} [f_3^{(m)}(t_3)]^2 dt_3 = \lambda_3 \underset{\sim}{c}_3' \Sigma_3 \underset{\sim}{c}_3 . \tag{17}$$

Based on (16) and (17), we have penalty:

$$\sum_{k=1}^{3} \lambda_k \int_{a_k}^{b_k} [f_k^{(m)}(t_k)]^2 dt_k \} = \underset{\sim}{c}' \lambda \Sigma \underset{\sim}{c} \tag{18}$$

where $\Lambda = diag(\lambda_1 I_{n_1}, \lambda_2 I_{n_2}, \lambda_3 I_{n_3})$. We can express the goodness of fit in (15) as follows:

$$N^{-1}(\underset{\sim}{y} - \underset{\sim}{f})' W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - \underset{\sim}{f}) =$$

$$N^{-1}(\underset{\sim}{y} - K \underset{\sim}{d} - \Sigma \underset{\sim}{c})' W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - K \underset{\sim}{d} - \Sigma \underset{\sim}{c}) .$$

If we combine the goodness of fit and the roughness penalty, we will have optimization PWLS:

$$\underset{\substack{\underset{\sim}{c} \in R^{3n} \\ \underset{\sim}{d} \in R^{3m}}}{Min} \left\{ (\underset{\sim}{y} - K \underset{\sim}{d} - \Sigma \underset{\sim}{c})' W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y} - K \underset{\sim}{d} - \Sigma \underset{\sim}{c}) + \underset{\sim}{c}' N \Lambda \Sigma \underset{\sim}{c} \right\}$$

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$$= \underset{\substack{\underset{\sim}{c}\in R^{3n}\\ \underset{\sim}{d}\in R^{3m}}}{Min}\left\{Q(\underset{\sim}{c},\underset{\sim}{d})\right\}. \quad (19)$$

To get the solution to (19), firstly we must take the partially differential of $Q(\underset{\sim}{c},\underset{\sim}{d})$ and then their results are equaled to zeros as follows:

$$\frac{\partial Q(\underset{\sim}{c},\underset{\sim}{d})}{\partial \underset{\sim}{c}} = \underset{\sim}{0} \;\Leftrightarrow\; \hat{\underset{\sim}{c}} = M^{-1}W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y}-K\underset{\sim}{d}). \quad (20)$$

$$\frac{\partial Q(\underset{\sim}{c},\underset{\sim}{d})}{\partial \underset{\sim}{d}} = \underset{\sim}{0} \;\Leftrightarrow$$

$$\hat{\underset{\sim}{d}} = [K'M^{-1}W(\underset{\sim}{\sigma}^2)K]^{-1}K'M^{-1}W(\underset{\sim}{\sigma}^2)\underset{\sim}{y}. \quad (21)$$

Next, if we substitute (21) into (20) , we obtain:

$$\hat{\underset{\sim}{c}} = M^{-1}W(\underset{\sim}{\sigma}^2)[I-K(K'M^{-1}W(\underset{\sim}{\sigma}^2)K)^{-1}K'M^{-1}W(\underset{\sim}{\sigma}^2)]\underset{\sim}{y}. \quad (22)$$

Finally, based on (12), (21) and (22), we get the smoothing spline estimator which can be expressed as follows:

$$\hat{\underset{\sim}{f}}_\lambda(\underset{\sim}{t}) = \begin{pmatrix} \hat{\underset{\sim}{f}}_{1,\lambda_1}(\underset{\sim}{t}_1) \\ \hat{\underset{\sim}{f}}_{2,\lambda_2}(\underset{\sim}{t}_2) \\ \hat{\underset{\sim}{f}}_{3,\lambda_3}(\underset{\sim}{t}_3) \end{pmatrix} = K\hat{\underset{\sim}{d}} + \Sigma\hat{\underset{\sim}{c}} = H(\underset{\sim}{\lambda})\underset{\sim}{y} \quad (23)$$

where

$$H(\underset{\sim}{\lambda}) = K[K'M^{-1}W(\underset{\sim}{\sigma}^2)K]^{-1}K'M^{-1}W(\underset{\sim}{\sigma}^2) + \Sigma M^{-1}W(\underset{\sim}{\sigma}^2)$$
$$[I-K(K'M^{-1}W(\underset{\sim}{\sigma}^2)K)^{-1}K'M^{-1}W(\underset{\sim}{\sigma}^2)],$$

and $\hat{\underset{\sim}{f}}_\lambda(\underset{\sim}{t})$ is smoothing spline with a natural cubic spline as a basis function with knots at $t_1,t_2,...,t_{n_k}$ $(k=1,2,3)$, for a fixed smoothing parameter $\underset{\sim}{\lambda} > \underset{\sim}{0}$. $H(\underset{\sim}{\lambda})$ is a positive-definite (symmetrical) smoother matrix that depends on smoothing parameter $\underset{\sim}{\lambda}$ and the knot points $t_1,t_2,...,t_{n_k}$ $(k=1,2,3)$. Yet, it does not depend on $\underset{\sim}{y}$.

Based on estimated model we have in (23), we conclude that the estimated model is a linear function in observation. In addition, by taking expectation of equation (23), i.e., $E(\hat{\underset{\sim}{f}}_\lambda(t))$ we obtain that the estimated regression function in (23) is a biased estimator. Further discussion about this estimator can be obtained on [42-48].

3.2. Estimation of Optimal Smoothing Parameter

Researcher [43] has shown that in uniresponse spline nonparametric regression, if smoothing parameter (λ) value is very small $(\lambda \to 0)$ then it will give a very rought estimator of nonparametric regression function. In contrary, if smoothing parameter (λ) value is very large $(\lambda \to \infty)$ then it will give a very smooth estimator of nonparametric regression function. Therefore, we need to select optimal smoothing parameter (λ) in order to obtain estimator that is suitable with data. For this need, some researchers have proposed some selection methods, for instance [49] proposed cross validation (CV) method, [50] proposed unbiased risk (UBR) method, and [43] proposed generalized cross validation (GCV) method. Not only does uni-response spline nonparametric regression, but also multi-response spline nonparametric regression depends on smoothing parameter λ_k , $k=1,2,3$.

In this section we discuss selection method for selecting the optimal smoothing parameter in multi-response nonparametric regression model for data of blood pressures and heart rate affected by stress level. Regression function estimator of multi-response nonparametric regression model for data of blood pressures and heart rate as given in equation (23) can be expressed as follows:

$$\hat{\underset{\sim}{f}}_\lambda(t) = H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\underset{\sim}{y} \quad (24)$$

where $\underset{\sim}{\sigma}^2 = (\sigma_1^2,\sigma_2^2,\sigma_3^2)'$. MSE (Mean Square Error) of (24) can be determined as follows:

$$MSE(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2) = \frac{(\underset{\sim}{y}-\hat{\underset{\sim}{f}}_\lambda(t))'W(\underset{\sim}{\sigma}^2)(\underset{\sim}{y}-\hat{\underset{\sim}{f}}_\lambda(t))}{\sum_{k=1}^{3} n_k}$$

$$= \frac{\left(\underset{\sim}{y}-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\underset{\sim}{y}\right)' W(\underset{\sim}{\sigma}^2)\left(\underset{\sim}{y}-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\underset{\sim}{y}\right)}{\sum_{k=1}^{3} n_k}$$

$$= \frac{\left[\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\underset{\sim}{y}\right]' W(\underset{\sim}{\sigma}^2)\left[\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\underset{\sim}{y}\right]}{N}$$

$$= \frac{\left\|\left(W(\underset{\sim}{\sigma}^2)\right)^{\frac{1}{2}}\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\underset{\sim}{y}\right\|^2}{N}.$$

where $\left(W(\underset{\sim}{\sigma}^2)\right)^{\frac{1}{2}}$ is a diagonal matrix, and $N=\sum_{k=1}^{3} n_k$.

Next, we define a quantity (further it is called as GCV function) as follows:

$$G(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2) = \frac{N^{-1}\left\|\left(W(\underset{\sim}{\sigma}^2)\right)^{\frac{1}{2}}\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\underset{\sim}{y}\right\|^2}{\left[N^{-1}trace\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\right]^2}$$

The optimal smoothing parameter $\underset{\sim}{\lambda}_{opt}$ is obtained by taking the solution of the following optimization:

$$G_{opt}(\lambda_{1(opt)},\lambda_{2(opt)},\lambda_{3(opt)};\underset{\sim}{\sigma}^2)$$
$$= \underset{\lambda_1\in R^+,\lambda_2\in R^+,\lambda_3\in R^+}{Min}\left\{\frac{N^{-1}\left\|\left(W(\underset{\sim}{\sigma}^2)\right)^{\frac{1}{2}}\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\underset{\sim}{y}\right\|^2}{\left[N^{-1}trace\left(I_N-H(\lambda_1,\lambda_2,\lambda_3;\underset{\sim}{\sigma}^2)\right)\right]^2}\right\},$$

where $\|\underset{\sim}{v}\| = \sqrt{v_1^2 + v_2^2 + v_3^2}$ for $\underset{\sim}{v} = (v_1, v_2, v_3)'$, and $\underset{\sim}{\lambda}_{opt} = (\lambda_{1(opt)}, \lambda_{2(opt)}, \lambda_{3(opt)})'$.

4. CONCLUSION

In estimating of the regression function that draws the association between blood pressures, heart rate and stress level by using spline estimator in the multiresponse nonparametric regression model depends on the optimal smoothing parameter $\underset{\sim}{\lambda}_{opt} = (\lambda_{1(opt)}, \lambda_{2(opt)}, \lambda_{3(opt)})'$. In addition, by determining predicted values of blood pressures (systolic and diastolic blood pressures) and heart rate which are affected by stress level, we can predict and prevent from suffering of hypertension earlier.

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