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Multi-responses Model in Patients Suffering from Decubitus Wound Using Generalized Penalized Spline

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Abstract : Longitudinal data are derived from observations conducted to *n* subjects that are independent, observed repeatedly (repeated measurement) within a certain time. In longitudinal data of health sector, it is frequently found more than one response variable of repeated observations results on subjects that are similar, so that the proper data analysis is the analysis of biresponse longitudinal data. The purpose of this study is to establish the longitudinal equation with Generalized Penalized Spline (GPS) approach. The data were obtained from a study conducted by Fernandes and Wardhani, that was the data of patients suffering *Decubitus Wound* with the response of wound extent on hands and wound extent on body. The longitudinal data equation using the approach of GPS biresponse results in the best estimator when using knot at 1 with polynomial of degree 2 (quadratic) with GCV = 1983,417 and R^2 equal to 97.829% and 98.119%.
Keywords:Longitudinal Data, GPS, biresponse, Decubitus Wound.

Introduction

In some studies in the field of health, it is frequently found more than one response variables that are interconnected and one predictor variable derived from patients studied in some period of time in which the response is quantitative. The example of research in the field of health was observation on patients with *Decubitus wound* (Fernandes and Wardani[1]), that was the response of wound extent on hands and body of the same patients. Both responses could correlate to each other because both responses were observed in the same patients' body. In this case, it is less appropriate if the study on the patients with *Decubitus wound* only considers one response variable. Therefore, it needs to include other response variables in order to obtain more informative information.

A study often produces longitudinal data. According to Wu and Zhang[2], longitudinal data is the data obtained through observations made on *n* subjects that are independent, in which each subject is observed repeatedly (*repeated measurement*) within a certain time thereby having advantages of the ability in recognizing the influence of measurement time on response.Several studies have investigated nonparametric regression, such as the one conducted by Guo[3] by applying nonparametric regression to cross section of biresponse. This study showed several advantages of nonparametric regression that were more flexible than parametric regression. Nonparametric equation gave relationship equation estimator of predictor variables on response variables in the flexible form and closely related to the regression curve and it was not required assumptions regarding the parametric form[4].

For this reason, the researcher discusses nonparametric regression equation estimator for biresponse longitudinal based on Generalized and Penalized Spline estimators and applies these methods to the data of

Decubitus Wound patients.The research problem is: How to obtain nonparametric regression equation of Generalized Penalized Spline approach for biresponse longitudinal in patients with *Decubitus Wound* with the response of wound extent on hands and body? Based on the formulation of problem, the purpose of this study is: to obtain nonparametric regression equation of Generalized Penalized Spline for biresponse longitudinal in patients with *Decubitus Wound* with the response of wound extent on hands and body.

Material and Methods

1. Data

The data were obtained from a study conducted by Fernandes and Wardhani[1], that was the data of patients suffering *Decubitus Wound* with the response of wound extent on hands and wound extent on body. *Decubitus Wound* or pressure sore is localized tissue damage caused by soft tissue compression above bony prominence and external pressure in the long term. Tissue compression network will cause disturbance in the blood supply at the depressed area. If it lasts for a long time, this can lead to insufficiency of blood flow, tissue anoxia or ischemia and eventually can lead to cell death[4].

According to Hamza[5], every part of the body can be affected, but it generally occurs in areas of pressure and bony prominence. Likewise on hands and body as a result of soft tissue compression above bony prominence and external pressure for a long time can cause *Decubitus* disease. *Decubitus Wound* can occur at any stage of age, but this is the problem specific in the elderly, particularly in clients with immobility.

2. Methods

a. Longitudinal Data

Through the incorporation of cross-sectional data and time series data, the use of longitudinal data is more informative, varied and superior in studying the dynamic changes[6].Data generated from each unit of the same cross-sectional is called balanced longitudinal data[7]. Framework of a balanced longitudinal data shows same (fixed) measurement unit and the number of observations for same cross-sectional units (subjects) in all subjects observed. In longitudinal data, it is assumed that between objects are to be independent, but between observations in the same objects, correlation tends to be found.

The purpose of doing longitudinal data analysis is to know how the response changes from time to time are. According Hedeker and Gibbons[6], the advantage of longitudinal data analysis is the available information of response variable value changes upon time on each subject. The weaknesses of longitudinal data analysis are: Response between time units is correlated, thus requiring more sophisticated methods to analyze the data, and The existence of missing data that is often caused by a diminishing number of subjects with increasing observation time.

During treatment, the response of patients observed was not only on hands, but also on body. Both responses were correlated as they were observed on the same subject, so that the appropriate data analysis was using biresponse longitudinal analysis that provided better estimators than using a single response. According to Semiati[8], biresponse data are the results of observation in the form of two response variables with the same predictor variables for each individual.

b. Generalized Penalized Spline (GPS) Biresponse

Regression is used to determine the equation of relationship pattern between predictor variables and response variable[9]. If the data pattern is known, the equation is called parametric regression equation. If the data pattern tends to follow linear/ quadratic/ cubic equations, the regression appropriate to the data is linear/ quadratic/ cubic parametric regression. Not all form of the data pattern is known, such as in longitudinal data, so that, as an alternative, it is used nonparametric regression approach.Nonparametric regression is a statistical method used to determine the relationship between response variable and predictor variable when the relationship pattern between the two of them is not patterned or following polynomial of degree m[10].

Look at the data pair (t_{IJ}, y_{ij}). The relationship between t_{ij} and y_{ij} follows biresponse regression equation.

$$y_{1ij} = f_1(t_{ij}) + \varepsilon_{1i}$$

$$y_{2ij} = f_2(t_{ij}) + \varepsilon_{2i}$$

The form of f_1 and f_2 regression curve is not known and assumed to be smooth in the sense that it is contained in continuous equation space. If there is a correlation between the first and second responses, the Spline equation will use weight. The following is variance covariance matrix structure as weighting in the Spline equation:

$$W^{-1} = \begin{bmatrix} 1/s_{11}^2 & 0 & \cdots & 0 & 1/s_{11}s_{21} & 1/s_{11}s_{22} & \cdots & 1/s_{11}s_{2i} \\ 0 & 1/s_{12}^2 & \cdots & 0 & 1/s_{12}s_{21} & 1/s_{12}s_{22} & \cdots & 1/s_{12}s_{2i} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1/s_{1i}^2 & 1/s_{1i}s_{21} & 1/s_{1i}s_{22} & \cdots & 1/s_{1i}s_{2i} \\ 1/s_{11}s_{21} & 1/s_{12}s_{21} & \cdots & 1/s_{1i}s_{21} & 1/s_{21}^2 & 0 & \cdots & 0 \\ 1/s_{11}s_{22} & 1/s_{12}s_{22} & \cdots & 1/s_{1i}s_{22} & 0 & 1/s_{22}^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 1/s_{11}s_{2i} & 1/s_{12}s_{2i} & \cdots & 1/s_{1i}s_{2i} & 0 & 0 & \cdots & 1/s_{2i}^2 \end{bmatrix}$$

Spline regression is polynomial pieces in which different polynomial segments are combined with knots in a way that ensures certain continuity property. Knot is a point in Spline equation segmented so that it is resulted segmented curve at that point.Nonparametric regression equation for biresponse longitudinal:

$$y_{1ij} = \eta_1(t_{ij}) + \varepsilon_{1i}$$,i =1,2,...,S; j=1,2,…T

$$y_{2ij} = \eta_2(t_{ij}) + \varepsilon_{2i}$$,i =1,2,...,S; j=1,2,…T

The estimator of $\eta_1(t_{ij})$ and $\eta_2(t_{ij})$ equations is based on *truncated power basis* $\Phi_p(t_{ij})$:

$$\phi_p(t_{ij})' = \left[1, t_{ij}, t_{ij}^2, \ldots, t_{ij}^m, (t_{ij}-\tau_1)_+^m, (t_{ij}-\tau_2)_+^m, \ldots, (t_{ij}-\tau_k)_+^m,\right.$$

$$\left. 1D, Dt_{ij}, Dt_{ij}^2, \ldots, Dt_{ij}^m, D(t_{ij}-\tau_1)_+^m, D(t_{ij}-\tau_2)_+^m, \ldots, D(t_{ij}-\tau_k)_+^m\right]$$

of which

D : is a dummy variable with 0 indicating the first response variable (Y_1) and 1 indicating the second response variable (Y_2).

P : k+m+1 is the number of base equation

s : 0, 1, 2,... m, m = degree of polynomial from *truncated power basis*; m: 0 (constant), 1 (linear), 2 (quadratic) and 3 (cubic)

τ_r : knot at point r (r = 1, 2,..., k), k = number of knot point

This equation can be written in the form of matrix form as follows:

[█(▪(y↓111@y↓112@⋮)@y↓█(1ST@⋮)@y↓221@y↓222@⋮@y↓2ST)]↓ = [█(η↓1 (t↓11)@η↓1 (t↓12)@⋮@η↓1 (t↓ST)@⋮@η↓2 (t↓11)@η↓2 (t↓12)@⋮@η↓2

Estimation of $\eta_1(t_{ij})$ and $\eta_2(t_{ij})$ equation is performed with spline regression approach based on *truncated power basis*:

$$\eta(t_{ij}) = \sum_{s=0}^{m} \beta_{s_1} t_{ij}^s + \sum_{r=0}^{k} \beta_{(m+r)_1} (t_{ij}-\tau_r)_+^m + \sum_{s=0}^{m} \beta_{s_2} D t_{ij}^s + \sum_{r=0}^{k} \beta_{(m+r)_2} D(t_{ij}-\tau_r)_+^m$$

With:

$$\beta_s = (\beta_0, \beta_1, \dots, \beta_m);\ \beta_{m+r} = (\beta_{m+1}, \dots, \beta_{m+k})$$

$$(t_{ij} - \tau_r)_+^m = \left[(t_{ij} - \tau_r)_+\right]^m ; (t_{ij} - \tau_r)_+ = \max[0, (t_{ij} - \tau_r)] \text{ atau}$$

$$(t_{ij} - \tau_r)_+^m = \begin{cases} (t_{ij} - \tau_r)_+^m & , t_{ij} \geq \tau_r \\ 0 & , t_{ij} < \tau_r \end{cases}$$

Wu and Zhang[2] describe the estimator of Penalized Spline of m degree and τ_r knot points is:

$$\eta(t_{ij}) = \Phi_p(t_{ij})'\beta = \sum_{s=0}^{m} \beta_{s_1} t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_1} (t_{ij} - \tau_r)_+^m + \sum_{s=0}^{m} \beta_{s_2} D t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_2} D (t_{ij} - \tau_r)_+^m$$

$$\Phi_p(t_{ij})' = \left[1, t_{ij}, t_{ij}^2, \dots, t_{ij}^m, (t_{ij} - \tau_1)_+^m, (t_{ij} - \tau_2)_+^m, \dots, (t_{ij} - \tau_k)_+^m,\right.$$

$$\left. 1D, Dt_{ij}, Dt_{ij}^2, \dots, Dt_{ij}^m, D(t_{ij} - \tau_1)_+^m, D(t_{ij} - \tau_2)_+^m, \dots, D(t_{ij} - \tau_k)_+^m\right]$$

$$\beta' = [\beta_s, \beta_{m+r}] \text{ atau } \beta' = [\beta_0, \beta_1, \beta_2, \dots, \beta_m, \beta_{m+1}, \cdots, \beta_{m+k}]$$

The Penalized Spline equation for each response:

$$\eta_1(t_{ij}) = \Phi_p(t_{ij})'\beta = \sum_{s=0}^{m} \beta_{s_1} t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_1} (t_{ij} - \tau_r)_+^m + \sum_{s=0}^{m} \beta_{s_2} D t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_2} D (t_{ij} - \tau_r)_+^m$$

$$\eta_2(t_{ij}) = \Phi_p(t_{ij})'\beta = \sum_{s=0}^{m} \beta_{s_1} t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_1} (t_{ij} - \tau_r)_+^m + \sum_{s=0}^{m} \beta_{s_2} D t_{ij}^s + \sum_{s=0}^{m} \beta_{(m+r)_2} D (t_{ij} - \tau_r)_+^m$$

In the form of matrix, Penalized Spline equation is written as:

$$\begin{bmatrix} \eta_1(t_{11}) \\ \eta_1(t_{12}) \\ \vdots \\ \eta_1(t_{ST}) \\ \eta_2(t_{11}) \\ \eta_2(t_{12}) \\ \vdots \\ \eta_2(t_{ST}) \end{bmatrix} = \begin{bmatrix} 1 & t_{11} & t_{11}^2 & \cdots & t_{11}^m & (t_{11}-\tau_1)_+^m & \cdots & (t_{11}-\tau_k)_+^m & 1D & \cdots & Dt_{11}^m & \cdots D(t_{11}-\tau_k)_+^m \\ 1 & t_{12} & t_{12}^2 & \cdots & t_{12}^m & (t_{12}-\tau_1)_+^m & \cdots & (t_{12}-\tau_k)_+^m & 1D & \cdots & Dt_{12}^m & \cdots D(t_{12}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{1T} & t_{1T}^2 & \cdots & t_{1T}^m & (t_{1T}-\tau_1)_+^m & \cdots & (t_{1T}-\tau_k)_+^m & 1D & \cdots & Dt_{1T}^m & \cdots D(t_{1T}-\tau_k)_+^m \\ 1 & t_{21} & t_{21}^2 & \cdots & t_{21}^m & (t_{21}-\tau_1)_+^m & \cdots & (t_{21}-\tau_k)_+^m & 1D & \cdots & Dt_{21}^m & \cdots D(t_{21}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{2T} & t_{2T}^2 & \cdots & t_{2T}^m & (t_{2T}-\tau_1)_+^m & \cdots & (t_{2T}-\tau_k)_+^m & 1D & \cdots & Dt_{2T}^m & \cdots D(t_{2T}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{ST} & t_{ST}^2 & \cdots & t_{ST}^m & (t_{ST}-\tau_1)_+^m & \cdots & (t_{ST}-\tau_k)_+^m & 1D & \cdots & Dt_{ST}^m & \cdots D(t_{ST}-\tau_k)_+^m \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \vdots \\ \beta_m \\ \beta_{m+1} \\ \vdots \\ \beta_{m+k} \end{bmatrix}$$

$$\eta(t) = \Phi_p(t)\beta = t\beta$$

Or

$$\eta(t) = \begin{bmatrix} \eta_1(t_{11}) \\ \eta_1(t_{12}) \\ \vdots \\ \eta_1(t_{ST}) \\ \eta_2(t_{11}) \\ \eta_2(t_{12}) \\ \vdots \\ \eta_2(t_{ST}) \end{bmatrix}; \beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \vdots \\ \beta_m \\ \beta_{m+1} \\ \vdots \\ \beta_{m+k} \end{bmatrix}; t = \begin{bmatrix} 1 & t_{11} & t_{11}^2 & \cdots & t_{11}^m & (t_{11}-\tau_1)_+^m & \cdots & (t_{11}-\tau_k)_+^m & 1D & \cdots & Dt_{11}^m & \cdots D(t_{11}-\tau_k)_+^m \\ 1 & t_{12} & t_{12}^2 & \cdots & t_{12}^m & (t_{12}-\tau_1)_+^m & \cdots & (t_{12}-\tau_k)_+^m & 1D & \cdots & Dt_{12}^m & \cdots D(t_{12}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{1T} & t_{1T}^2 & \cdots & t_{1T}^m & (t_{1T}-\tau_1)_+^m & \cdots & (t_{1T}-\tau_k)_+^m & 1D & \cdots & Dt_{1T}^m & \cdots D(t_{1T}-\tau_k)_+^m \\ 1 & t_{21} & t_{21}^2 & \cdots & t_{21}^m & (t_{21}-\tau_1)_+^m & \cdots & (t_{21}-\tau_k)_+^m & 1D & \cdots & Dt_{21}^m & \cdots D(t_{21}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{2T} & t_{2T}^2 & \cdots & t_{2T}^m & (t_{2T}-\tau_1)_+^m & \cdots & (t_{2T}-\tau_k)_+^m & 1D & \cdots & Dt_{2T}^m & \cdots D(t_{2T}-\tau_k)_+^m \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & t_{ST} & t_{ST}^2 & \cdots & t_{ST}^m & (t_{ST}-\tau_1)_+^m & \cdots & (t_{ST}-\tau_k)_+^m & 1D & \cdots & Dt_{ST}^m & \cdots D(t_{ST}-\tau_k)_+^m \end{bmatrix}$$

Estimator for $\boldsymbol{\eta}(\mathbf{t})$:

$$\hat{\eta}(t) = t\hat{\beta}$$

is obtained through *Penalized Least Square (PLS)* as the completion of equation optimization[4]:

$$\min_{f\in W_2^m}\left\{\sum_{i=1}^{s}\sum_{j=1}^{T}(y_{ij}-\eta(t_{ij}))^2+\lambda\beta' G\beta\right\}$$

$$G_{2x(k+m+1)}=\begin{bmatrix} 0_{m+1} & {}_{m+1}0_k & 0_{m+1} & {}_{m+1}0_k \\ {}_k0_{m+1} & I_k & {}_k0_{m+1} & 0_k \\ 0_{m+1} & {}_{m+1}0_k & 0_{m+1} & {}_{m+1}0_k \\ {}_k0_{m+1} & 0_k & {}_k0_{m+1} & I_k \end{bmatrix}$$

I_k = identity matrix with k degree

$\sum_{i=1}^{s}\sum_{j=1}^{T}(y_{ij}-\eta(t_{ij}))^2$: Function of goodness of fit of equation, λ : weight value that measures the balance between the equation of data conformity appropriateness and curve smoothness, $\beta' G\beta$: size of curve smoothness.

Estimation of population mean **η(t)** equation in the longitudinal data with Penalized Spline estimator ignores the correlation of each subject and it is assumed that the variety within subjects is equal or *Homoscedasticity*, while the variety between subjects is not equal or *Heteroscedasticity*. Wu and Zhang[2] defines GPS as Penalized Spline which uses variance covariance matrix weight and GPS estimator as the population mean **η(t)** equation predictor that is better, because it can overcome population *heteroscedasticity*. H Statistics as *Penalized Generalized Least Square* estimator is:

$$H=(y-t\beta)'W^{-1}(y-t\beta)+\lambda\beta' G\beta$$

$$y'=[y_1',y_2',\ldots,y_1'] ; W^{-1}=diag[W_{11},W_{12},\ldots,W_{1s},W_{21},W_{22},\ldots,W_{2s},];$$

$W_{Ki}=diag\left[V_{i1},V_{i2},\ldots,V_{iT_i}\right]$ is weight matrix with K=1,2

The weight depends on the information and accuracy of observations results and is the inverse variance, that is $V_{ij}=\sigma_i^{-2}$ as the weight for (i,j) response, because $\hat{\sigma}_i^{-2}=s_i^{-2}$, then:

$$V_{ij}=s_i^{-2}=\left(\frac{\sum_{j=1}^{T}(y_{ij}-\bar{y}_i)^2}{T-1}\right)$$

Generalized Cross Validation (GCV) method is used for the selection of optimal knot point. Wu and Zhang[2] state that the GCV is a modification of Cross-Validation (CV), obtained by minimizing CV equation:

$$\mathrm{GCV_{gps}}=\frac{(\mathrm{y}-\hat{\mathrm{y}}_{\mathrm{gps}})'\mathrm{W}^{-1}(\mathrm{y}-\hat{\mathrm{y}}_{\mathrm{gps}})}{\left(1-\frac{\mathrm{tr}(\mathrm{A_{gps}})}{\mathrm{n}}\right)^2}$$

According to Wahba[10], pairing smoother parameter that is very small or large will give the form of equation that is very rough or smooth. Budiantara (2006) explains that the form of spline estimator is strongly influenced by λ smoother parameter, so that whether spline approach matches or not, it depends on optimal λ smoother parameter. Being similar with the selection of knot point, GCV approach is used to select the optimal smoother parameter.

The role of Spline estimator with optimal smoother parameter developed by Wahba[10], is visually difficult to see to distinguish behaviour changes of data pattern at different intervals so that it is important to choose the optimal λ smoother parameter.According to Eubank[4], λ is smoother parameter that controls the curve balance and equation ability to map phenomena. A good equation is expected to have λ that is optimal, because the larger the λ is, the smoother the curve is, otherwise the equation ability to map data is poor and on the contrary if λ is small. The optimum λ value is associated with minimum GCV (λ) value.

Nonparametric regression analysis in longitudinal data aims to estimate population mean equation with the unknown form of curve using penalized generalized least square method.

Population mean equation estimator is:

$$\widehat{\eta_1}(t) = \Phi_P(t)'\widehat{\beta}$$
$$= \Phi_P(t)'\left(t'W^{-1}t + \lambda G\right)^{-1}t'W^{-1}y$$
$$\widehat{\eta_2}(t) = \Phi_P(t)'\widehat{\beta}$$

Equation y estimator using GPS biresponse:

$$\widehat{Y_1}_{gps} = t\widehat{\beta}$$
$$= t\left(t'W^{-1}t + \lambda G\right)^{-1}t'W^{-1}y$$
$$= A_{gps}y$$
$$\widehat{Y_2}_{gps} = t\widehat{\beta}$$

$A_{gps}y = t\left(t'W^{-1}t + \lambda G\right)^{-1}t'W^{-1}$ is smoother matrix.

Results and Discussion

1. Data exploration

Figure 1 is the wound extent on hands of 4 patients for 6 months measured every 2 weeks. It can be that seen the changes of wound extent on hands are different in the four subjects observed. Individual profile of wound extent on hands formed in patient 1 is increased over time, whereas in patient 2, patient 3, and patient 4, it experiences a decrease over time. The profile results of each individual in Figure 1, and The profile results of each individual in Figure 2.

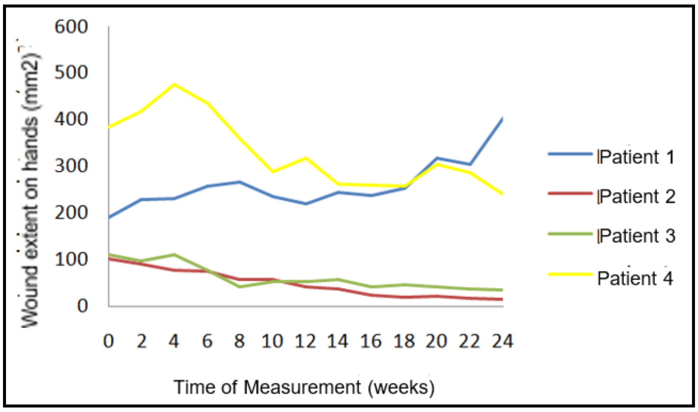

Figure 1: Plot of wound extent on hands (mm^2) on time measurement (weeks)

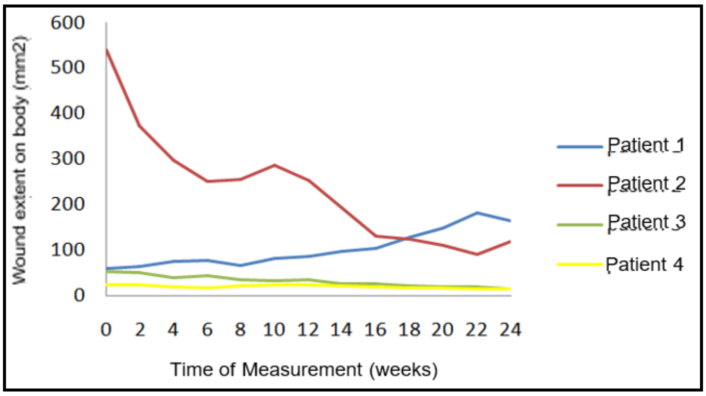

Figure 2: Plot of wound extent on body (mm^2) on time measurement

Figure 2, shows the individual profiles of patient 2 and patient 3, of which the wound extent on body is decreased over time, whereas patient 1 experiences an increase over time. Patient 4 is constant over time.The results of exploration on the mean structure are presented in Figure 3, showing the effect of time changes (every 2 weeks) on the wound extent mean on hands and body. The wound extent mean on hands and body is decreased over time so that the structure of quadratic fixed effect needs to be considered in the formation of equations.

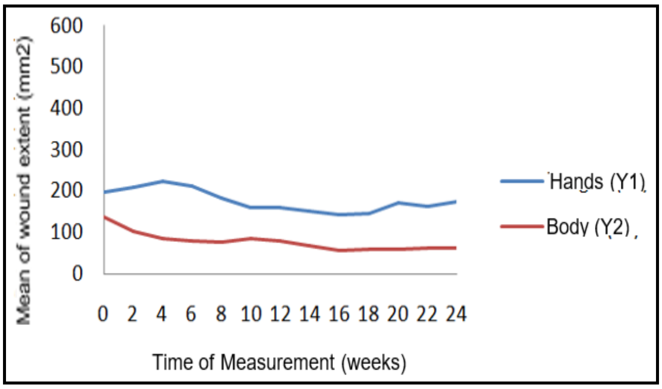

Figure 3: Mean Structure

Exploration to the variance structures is presented in Figure 4, showing the overall variance structures in subject in which there is variety changes of wound extent on hands and body on time so that it is necessary to include random effects on the formation of the equation.

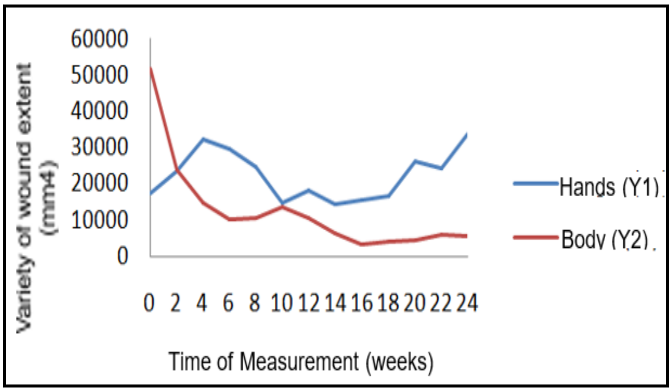

Figure 4: Structure of variance

Correlation testing between the response variable (Y_1) and the response variable (Y_2) was conducted to determine how high the relationship between the two variables. This correlation coefficient shows that between the two response variables (Y_1 and Y_2), there is a very strong correlation, indicating that it needs to consider the equation which includes both responses simultaneously, in other words, using GPS biresponse. The following is presented W^{-1} variance-covariance matrix:

$$W^{-1} = \begin{bmatrix} 0.00033 & 0.00000 & \cdots & 0.00000 & 0.00050 & 0.00010 & \cdots & 0.00540 \\ 0.00000 & 0.00115 & \cdots & 0.00000 & 0.00080 & 0.00030 & \cdots & 0.01010 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0.00000 & 0.00000 & \cdots & 0.00017 & 0.00030 & 0.00010 & \cdots & 0.00390 \\ 0.00050 & 0.00080 & \cdots & 0.00030 & 0.00061 & 0.00000 & \cdots & 0.00000 \\ 0.00010 & 0.00030 & \cdots & 0.00010 & 0.00000 & 0.00006 & \cdots & 0.00000 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0.00540 & 0.01010 & \cdots & 0.00390 & 0.00000 & 0.00000 & \cdots & 0.08855 \end{bmatrix}$$

Matrix W^{-1} is used as initial input of the equation of Generalized Penalized Spline (GPS) biresponse. Of the results of GPS1Bires program on Appendix 6 with various knots and degree polynomial, it is obtained GCV values as follows:

Table 1: GCV at various knots and degree polynomial (Y_1 and Y_2)

GCV Knot	Location of knot point		Degree Polynomial 1	2	3
1	3.5		2212.257	1983.417	2467.872
	4.5		2220.043	1990.876	2487.406
	5.5		2224.763	2010.693	2498.507
	6.5		2224.848	2010.693	2499.186
	7.5		2221.15	2009.267	2480.773
	8.5		2212.758	1991.233	2454.358
2	3.5	6.5	2299.405	2045.589	2605.681
	3.5	7.5	2304.432	2043.715	2611.086
	3.5	8.5	2301.729	2029.752	2594.751
	4.5	7.5	2304.736	2042.137	2621.278
	4.5	8.5	2303.972	2036.277	2611.146
	5.5	8.5	2297.884	2039.773	2620.949

Based on the results of Table, it is obtained minimum GCV value equal to 1983.417 achieved at knots 1 ($\tau_1 = 3.5$) with polynomial of degree 2 (quadratic).The controller of balance between curve suitability on data and curves smoothness is shown by smoother parameter. It is similar with the selection of knot point, λ selection is approached with GCV approach. Based on the output of GPS2Bires program (Appendix 7), the value of GCV at various lambda (λ) are presented in Appendix 8. Figure 5 shows GCV graph at various values of λ, in which optimum lambda is the minimum GCV value.

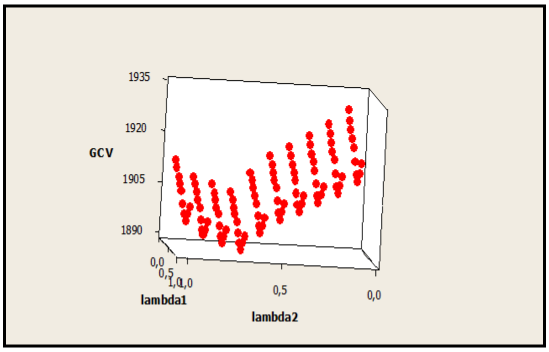

Figure 5: Plot of lambda (λ_1 and λ_2) value on GCV

Based on Figure 5, it is obtained minimum GCV value equal to 1890.877 achieved in knot at 1 with polynomial of degree 2 (quadratic) with the optimal value of λ_1 = 0.8 and λ_2 = 0.6. Next, it is conducted the testing coefficient β partially to determine whether each parameter has significant influence on the equation based on t-test statistic. Based on GPS1Bires program, the results of testing on each parameter are presented in Table 2.

Table 2: The results of partial testing on the coefficient parameters of GPS biresponse

Parameter	Beta	Estimation	t_{stat}	p-value
Intercept	β_{01}	173.732	281.517	0.000*
t_{1ij}	β_{11}	-14.443	-48.069	0.000*
t_{1ij}^{2}	β_{21}	0.863	23.438	0.000*
$(t_{1ij}-\tau_1)^2$	β_{31}	-0.211	-5.725	0.000*
Intercept	β_{02}	-136.940	-218.749	0.000*
t_{1ij}	β_{12}	11.307	37.102	0.000*
t_{1ij}^{2}	β_{22}	-0.319	-8.568	0.000*
$(t_{1ij}-\tau_1)^2$	β_{32}	-0.519	-13.904	0.000*

*p-value < 0.05 (significant)

Based on Table 2, p-value < 0.05 indicate all parameters significantly influence both responses. It is concluded that time (t) provides influence on wound extent on hands (Y_1) and body (Y_2).Using the knot at point 1 ($\tau_1 = 3.5$) with polynomial of degree 2 (quadratic), it is obtained the equation of Generalized Penalized Spline (GPS) biresponse as follows:

$$\hat{y}_{1ij} = 173.732 - 14.4435 t_{ij} + 0.86326 t_{ij}^2 - 0.2115 (t_{ij} - 3.5)_+^2 + \varepsilon_{ij}$$

$$\hat{y}_{2ij} = (173.732 - 136.940) - (14{,}443 - 11{,}307) t_{ij} + (0.863 - 0.319) t_{1ij}^2 - [(0.211 + 0.519)(t_{ij} - 3.5)_+^2] + \varepsilon_{ij}$$

$$\hat{y}_{2ij} = 36.792 - 3.136 t_{ij} + 0.544 t_{ij}^2 - 0.730 (t_{ij} - 3.5)_+^2 + \varepsilon_{ij}$$

Here are presented the results of nonparametric equation estimation with the GPS approach on knot at 1 with polynomial of degree 2 (quadratic):

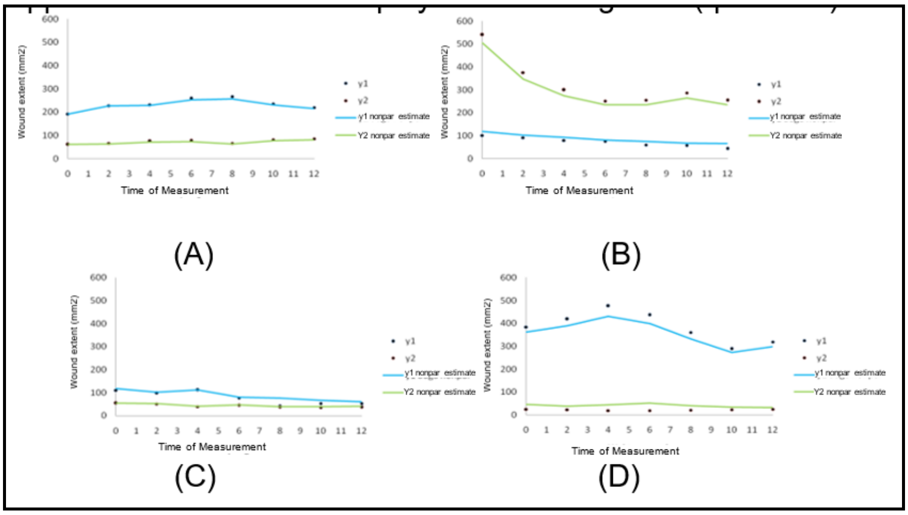

Figure 6: GPS biresponse approach for patient 1 (A), patient 2 (B), patient 3 (C), and patient 4 (D)

Figure 6 shows the nonparametric of form knot at 1 with polynomial of degree 2 (quadratic) on the equation of influence of time (t) on wound extent on hands (Y1) and body (Y2) of patients with *Decubitus Wound*. Coefficient R^2 (Y_1) indicates that equal to 97.829% (Y_1) is influenced by time (t) and 98.119% (Y_2) is influenced by time (t).

Conclusions and Suggestions

The conclusions of this research are as follows: The equation of GPS biresponse provides the best estimator at the time of knot at 1 with polynomial of degree 2 with GCV = 1983.417 and R^2 = 97.829% for response variable of wound extent on hands (Y_1). While the equation estimator of GPS biresponse with response variable of wound extent on body body (Y_2) results in R^2 = 98.119%, meaning that wound extent on hands and wound extent on hands body are influenced by time (t):

$$\hat{Y}_{1ij} = 173.732 - 14.4435 t_{ij} + 0.86326 t_{ij}^2 - 0.2115 (t_{ij} - 3.5)_+^2$$
$$\hat{Y}_{2ij} = 36.792 - 3.136 t_{ij} + 0.544 t_{ij}^2 - 0.730 (t_{ij} - 3.5)_+^2$$

Based on the conclusions, there are some suggestions given Modeling unbalanced longitudinal data, and Using Spline Multirespon approach.

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