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A Three-step Estimation Procedure Using Local Polynomial Smoothing for Inconsistently Sampled Longitudinal Data

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Abstract

Parametric mixed-effects models are useful in longitudinal data analysis when the sampling frequencies of a response variable and the associated covariates are the same. We propose a three-step estimation procedure using local polynomial smoothing and demonstrate with data where the variables to be assessed are repeatedly sampled with different frequencies within the same time frame. We first insert pseudo data for the less frequently sampled variable based on the observed measurements to create a new dataset. Then standard simple linear regressions are fitted at each time point to obtain raw estimates of the association between dependent and independent variables. Lastly, local polynomial smoothing is applied to smooth the raw estimates. Rather than use a kernel function to assign weights, only analytical weights that reflect the importance of each raw estimate are used. The standard errors of the raw estimates and the distance between the pseudo data and the observed data are considered as the measure of the importance of the raw estimates. We applied the proposed method to a weight loss clinical trial, and it efficiently estimated the correlation between the inconsistently sampled longitudinal data. Our approach was also evaluated via simulations. The results showed that the proposed method works better when the residual variances of the standard linear regressions are small and the within-subjects correlations are high. Also, using analytic weights instead of kernel function during local polynomial smoothing is important when raw estimates have extreme values, or the association between the dependent and independent variable is nonlinear.

Keywords

Analytical weight; Inconsistent sampling; Local polynomial smoothing; Longitudinal data; Repeated measures

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1. Introduction

Longitudinal data are frequently used in biomedical research where information is collected repeatedly on the same subjects over time. Because the multiple observations of each subject are correlated, the within-subjects correlation must be taken into account during analysis to draw valid inferences. Parametric mixed-effects models, including linear and nonlinear mixed-effects models, are powerful tools for analyzing longitudinal data. Comprehensive reviews on these methods have been performed [1].

If the longitudinal response variable is continuous and subjects are independent from each other, a linear mixed-effects model may be used when the relationship between the response variable and its covariates is linear [2]. For a response variable that has a nonlinear relationship with its covariates, a nonlinear mixed-effects model may be used [3]. The mixed-effects model contains both fixed and random components, and the correlations among repeated measures are introduced through the between- and within-subject variations. Longitudinal data can also be analyzed using the marginal model. Here, the correlations are specified through the variance-covariance matrix directly [4].

Parameters of the mixed-effects model are estimated using Maximum Likelihood Estimation (MLE) or Restricted Maximum Likelihood Estimation (REML) [5]. The Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC) can be used as model selection criteria [6]. However, successful implementation of a parametric mixed-effects model also depends on meeting the assumptions of the model.

In some applications, nonparametric or semiparametric mixed-effects models are used because parametric mixed-effects models are too restrictive. The basic idea is to let the data determine the most suitable functional form using smoothing techniques like local polynomial smoothing or splines [7]. However, these methods are computationally intensive especially when the number of covariates is large.

A two-step estimation of functional linear models has been proposed to overcome the computational disadvantage of using nonparametric or semiparametric mixed-effects models [8]. Fan and Zhang proposed to first compute raw estimates of the regression coefficients by fitting standard linear regression models at each time point, and then smooth the raw estimates using one of the existing smoothing techniques. The smoothing procedure pulls information from neighboring raw estimates to improve the efficiency of the final estimates and was shown to be accurate and effective.

Mixed-effects models and two-step estimation procedure are only suitable for the type of longitudinal data where the response variable and its covariates are measured at the same scheduled time points for all subjects. However, the sampling frequencies of the variables may be different. Many researchers use diary-based methods such as paper diaries, personal digital assistants (PDA) or smartphones to collect data, and this type of longitudinal data is usually intensively measured and has complicated patterns. Also there are other types of longitudinal data that cannot be collected frequently because the processes are invasive or take extensive time, for example lab tests or questionnaires. As a result, problems in existing

methodology arise when we examine the association between intensively repeated measured variables and less intensively repeated measured variables.

Using mixed-effects models or the two-step estimation procedure to estimate the correlation between intensively and less intensively repeated measured variables involves reducing the dimension of the intensively measured variable. However, the advantages of collecting detailed longitudinal data are not fully utilized in this way. We propose a three-step modelling approach to address the problem of modeling inconsistently sampled longitudinal data. This new method is based on the two-step estimation procedure proposed by Fan and Zhang. We will extend their method by using local polynomial smoothing with only analytical weights and apply the proposed method to the Self-Monitoring And Recording using Technology (SMART) Trial where data are inconsistently sampled. A simulation study will be used to assess the performance of our new approach.

2. Local Polynomial Smoothing Method

Let (t_i, y_i) , $i = 1, 2, \dots, n$, be an independent and identical distributed sample from a population, where t_i is the designed time point and y_i is an observation at t_i . In local polynomial smoothing, we want to estimate the conditional expectation of y_i in the form of $f(t) = E(y_i | t_i = t)$, $i = 1, 2, \dots, n$. The idea is to locally approximate $f(t)$ using Taylor series expansion. Assuming that the $(p+1)^{\text{th}}$ derivative of $f(t)$ at the time point t_0 exists, for t in the local neighborhood of t_0 , a Taylor series expansion gives the approximation

$$f(t) \approx f(t_0) + f'(t_0)(t - t_0) + \frac{f''(t_0)}{2!}(t - t_0)^2 + \dots + \frac{f^{(p)}(t_0)}{p!}(t - t_0)^p.$$

At t_0 the estimator $\hat{f}(t)$ is obtained by fitting the polynomial

$$\beta_0 + \beta_1(t - t_0) + \dots + \beta_p(t - t_0)^p$$

to the points (t_i, y_i) in the local neighborhood of t_0 using weighted least squares. The value of $\hat{f}(t)$ is obtained by minimizing

$$\sum_{i=1}^n \{y_i - \sum_{j=0}^p \beta_j(t_i - t_0)^j\}^2 K_h(t_i - t_0),$$

where K_h is a kernel function re-scaled by a constant h ($h > 0$), called the bandwidth, that controls the size of the local neighborhood $I_h(t_0) = [t_0 - h, t_0 + h]$ where the local smoothing is conducted.

The kernel function K in the local polynomial smoothing is usually a symmetric probability density function used to decide how much the observations in the local neighborhood contribute to the fit at t_0 by assigning weights to each observation. Usually the shorter the distance between t_i and t_0 , the bigger the contribution will be, and the data outside the bandwidth are assigned zero weights. The choice of a kernel function is not crucial, but the Epanechnikov has been shown to be the ideal kernel function [9]. Analytical weights that

reflect the importance of the data in the neighborhood can also be used along with the kernel function. Using analytical weights will be the focus of our new method.

The bandwidth h influences both the bias and the variance of the local polynomial smoother [10]. An ideal bandwidth can be selected using cross-validation methods [11]. For a given bandwidth, a low odd order value of p has been recommended [11]. Because local polynomial smoothing has only two smoothing parameters h and p , computation time is short in comparison to other smoothing methods.

Locally Weighted Scatterplot Smoothing (LOWESS) is a special type of local polynomial smoothing which is robust against extreme observations [12]. During the fitting of LOWESS, robust weights are assigned to residuals of a local polynomial smoother, with large residuals given small robust weights. Then the local polynomial smoothing is fitted again with new weights that are the product of the kernel weights at the first fit and the robust weights. The procedure is done iteratively.

The local neighborhoods of LOWESS are defined by a nearest neighbor bandwidth a ($0 < a \leq 1$). Each local fit uses $n \times a$ observations that are closest to the point where the response is being smoothed. Reasonable values of the smoothing parameter a lie between 0.2 and 0.8 for most applications [12].

3. Proposed Method

Let there be N subjects observed during time 0 to T . Y_{ij} is the outcome measured for the i^{th} subject at time t_{ij} ($0 \leq t_{ij} \leq T$), and X_{ik} is its covariate vector measured for the i^{th} subject at time t_{ik} ($0 \leq t_{ik} \leq T$). We assume that the outcome is repeatedly measured less frequently than its covariates. However, when the covariates are repeatedly measured less frequently than the outcome, the proposed method is also applicable. For each subject, when $k = j$, both the outcome and its covariates are measured, and when there are no matching j for k , only covariates are measured. Neither parametric nor nonparametric mixed models can be applied to inconsistently sampled longitudinal data directly. Consequently, we introduce a three-step estimation procedure to explore this type of data that can use all available data with no information loss instead of reducing the dimension of the more frequently measured covariate.

3.1. Step One – Insert Pseudo Data

When only the covariates are measured, pseudo data for the outcome are inserted for every subject to create a new dataset. At any two adjacent times points t_{iv} and t_{iu} ($0 \leq v < u \leq T$) both outcome and covariate are measured and between these two time points t_{ik} ($v < k < u$) only covariate are measured. We assume that the change of outcome from time t_{iv} to t_{iu} is linear, because with only the inconsistently sampled outcome and its covariates, the information is too limited to generate pseudo data in a more complicated way. By solving for a_i and b_i in function (1a) below we can get a straight line that connects Y_{iv} and Y_{iu} for the i^{th} subject.

$$\begin{cases} Y_{iv} = a_i t_{iv} + b_i \\ Y_{iu} = a_i t_{iu} + b_i \end{cases} \quad (1a)$$

$$Y_{ik} = a_i t_{ik} + b_i \quad (1b)$$

Then by substituting t_{ik} ($v < k < u$) repeatedly into the function (1b) above, we will get pseudo data Y_{ik} ($v < k < u$) that match for the real measurements X_{ik} between times t_{iv} and t_{iu} ($0 < v < u < T$) for the i^{th} subject. This procedure is done repeatedly in the same way between all of the adjacent sampling time points of the outcome to insert pseudo data of the outcome at the time points where only covariates are measured. After this step, a new dataset (t_{ik}, Y_{ik}, X_{ik}) is created.

Missing data due to subjects skipping assessments or withdrawing from a trial is common in longitudinal studies. If an outcome is missing for the i^{th} subject at time t_{iv} or t_{iu} ($0 < v < u < T$), there is no way to insert data between these two adjacent time points using functions (1a) and (1b) for the outcome. Missing data are inserted as pseudo data for the outcome under this situation.

3.2. Step Two – Raw Estimates

For the n_k ($n_k < N$) subjects who have full data at time t_k ($0 < k < T$), a standard linear regression model (2) is fitted to get the raw estimate and standard error of β .

$$Y(t_k) = \beta_0(t_k) + X(t_k)\beta(t_k) + e(t_k) \quad (2)$$

where $e(t_k)$ is the error term, and β_0 and β are regression coefficients to be estimated. Here, sample sizes of the local linear regressions may vary due to subjects skipping assessments or withdrawing from a trial. Because the regression coefficients are the raw estimates to be smoothed in the next step, when the covariates are repeatedly measured less frequently than the outcome in a trial, pseudo data can be inserted for the covariates using the method described in step one. Subsequently, standard linear regression models can be fitted accordingly to obtain the raw estimates.

3.3. Step Three – Smooth Raw Estimates

Local polynomial smoothing is used to smooth the raw estimates from step two. Rather than using a kernel function to assign weights, only analytical weights that indicate the importance of the raw estimates are used. Let p be the degree of the polynomial being fit. At time t_k ($0 < k < T$), the smoothed estimates $\beta_{\text{smooth}(k)}$ are obtained by smoothing the raw estimates in the local neighborhood $I_h(t_k) = [t_k - h, t_k + h]$. By using analytical weights, the smoothed estimate $\beta_{\text{smooth}(k)}$ at time t_k is the value of estimated $\hat{\beta}_0$, where $\hat{\beta} = (\hat{\beta}_0, \dots, \hat{\beta}_p)$ minimizes

$$\sum_{k=0}^N \{\beta_{\text{raw}(k)} - \beta_0 - \beta_1(t_k - t) - \cdots - \beta_p(t_k - t)^p\}^2 W_k.$$

Weighted least squares theory leads to the solution

$$\hat{\beta} = (\mathbf{t}^T \mathbf{W} \mathbf{t})^{-1} \mathbf{t}^T \mathbf{W} \boldsymbol{\beta}_{\text{raw}},$$

Where $\boldsymbol{\beta}_{\text{raw}}$ is a vector of raw estimates from step two, and

$$\mathbf{t} = \begin{bmatrix} 1 & t_1 - t_k & \cdots & (t_1 - t_k)^p \\ \vdots & \vdots & \ddots & \vdots \\ 1 & t_n - t_k & \cdots & (t_n - t_k)^p \end{bmatrix}$$

is an $n \times (p + 1)$ design matrix. $\mathbf{W}$ is an $n \times n$ diagonal matrix of analytical weights given by

$$\mathbf{W} = \text{diag}\{w_1, \dots, w_n\}.$$

Because pseudo data were inserted in step one, the raw estimates $\beta_{\text{raw}(k)}$ do not have the same accuracy. The most accurate raw estimators will be the ones from local linear regressions fitted at t_k ($0 \leq k \leq T$) where both the outcome and its covariates were measured. The highest analytical weights are given to these raw estimates during smoothing. The raw estimates from the local linear regressions fitted at t_k^* ($0 \leq k \leq T$) that use pseudo data for the outcome but are close to the time of the real measurement are also given higher analytical weights than the raw estimates that are far from the time of real measurement. The measure of the time distance between a raw estimate at time t_k^* using pseudo data of the outcome and the adjacent raw estimate at time t_k using real measurements of the outcome is defined as

$$D_k = \min(|t_k - t_{\text{last real measure}}| + 1, |t_k - t_{\text{next real measure}}| + 1).$$

For example, at any two adjacent time points t_{iv} and t_{iu} ($0 \leq v < u \leq T$) both the outcome and its covariates are measured and between these two time points at t_{ik} ($v < k < u$) only covariates are measured. D_v and D_u will equal 1 and D_k will be calculated as

$$D_k = \min(|t_k - t_v| + 1, |t_k - t_u| + 1).$$

We define the analytical weights in four different ways using D_k and the standard error (*se*) of the raw estimates obtained in step two to reflect the importance of the raw estimates.

$$\text{Type 1: } w_k = \frac{1}{\sqrt{D_k}}$$

$$\text{Type 2: } w_k = \frac{1}{D_k}$$

$$\text{Type 3: } w_k = \frac{1}{\sqrt{D_k}} + \frac{1}{\sqrt{se_k}}$$

$$\text{Type 4: } w_k = \frac{1}{D_k} + \frac{1}{se_k}$$

The performance of the local polynomial smoothing also depends on the values chosen for the bandwidth h and the fitting order p . The choice of p is not as critical as the choice of h . However, a small odd p is better for the following reasons. Even order approximations have the same asymptotic variance as their consecutive odd order approximations, but the asymptotic variances are smaller for odd order approximations as compared to their consecutive even order approximations [9]. As the order of the approximation increases, the bias decreases, but the asymptotic variance and computational time increases [9]. For example, if you were to choose the order 2, order 3 in fact, will be better, because the asymptotic variances are the same but the bias is smaller for order 3. The focus of this paper is not how to choose the best h and p for the proposed model so we will use the value $p = 3$ as recommended by Wand and Jones [11] as this has been shown to be adequate for local polynomial smoothing. For the example data whose sampling time periods are not equally spaced, choosing a fixed bandwidth h results in less data falling into the local neighborhood where the data are sparser. In this situation, we will use a certain proportion of the data in the nearest neighborhood to which a local polynomial smoothing with analytical weights is fitted, which is the same as LOWESS. Besides using cross-validation methods to find an ideal bandwidth, it is also appropriate to choose the bandwidth subjectively by looking at several smoothed lines with different bandwidths. We used $a = 0.3$ in our example because with smaller bandwidth the line was too jagged to see a trend, while with larger bandwidth the line was too smooth to capture all of the useful information.

4. Application Using Real Longitudinal Data

The SMART trial was a 2-year clinical weight loss trial where the data were inconsistently sampled [13]. Two hundred and ten participants were randomized to 3 different methods of self-monitoring: paper diary or personal digital assistant with or without feedback. All of the participants were asked to self-monitor their daily food intake. Adherence to self-monitoring was a binary variable (yes/no) and was measured weekly for the first 4 months, biweekly for 8 months and then monthly for 12 months. The primary outcome was subject weight (kg), and was measured objectively using a digital scale at the 5 clinical visits: baseline, 6-, 12-, 18-, and 24-months. Subjects' weight was assessed less frequently than their adherence to self-monitoring during the two years, and one of the research interests was to examine the effect of adherence to self-monitoring on the participants' weight.

Using a parametric mixed-effects model to explore the association between the participants' weight and adherence to self-monitoring involves reducing the dimension of the adherence data [14]. In the published primary outcome paper, the adherence data were modified by taking average values between baseline and the 6th month, the 6th month and the 12th month, the 12th month and the 18th month, and the 18th month and the 24th month for each subject. After the data modification every subject had both weight data and proportion of time adherent to self-monitoring data at baseline, 6th, 12th, 18th and 24th month, so the parametric mixed-effects model could be easily applied to this modified dataset. The drawback of this approach is that the detailed information on the changes in adherence to self-monitoring among the 5 time points was lost. Also using the term of 'proportion of the time subjects were adherent to self-monitoring during a period of 6 months' is too general and harder to understand than a binary (yes/no) adherence variable.

To apply the proposed method to the SMART data we first inserted pseudo data for subjects' weight between baseline and 6th month, 6th and 12th month, 12th and 18th month, and 18th and 24th month according to the sampling schedule of adherence to self-monitoring. After this step, every subject had both weight data and adherence to self-monitoring data at all 43 time points. Standard simple linear regressions were fitted at each of the 43 time points. The dependent variable was subjects' weight in kilogram which is continuous. The independent variable was adherence to self-monitoring and was binary (yes group was the reference group). The regression coefficients of adherence to self-monitoring indicated the weight differences between subjects who were not adherent to self-monitoring and subjects who were adherent to self-monitoring.

Local polynomial smoothing using only analytical weights was applied to smooth the raw estimates (regression coefficients) from the standard simple linear regressions. The degree of the polynomial was chosen to be 3, and about one third of the raw estimates were used in each local fit. Four types of analytical weights defined earlier that reflected the importance of the raw estimators were used. Results from using local polynomial kernel smoothing on the same set of raw estimates with Epanechnikov kernel were compared with the results from the proposed method. Results are shown in Figures 1.a and 1.b.

Because the distributions and standard errors of the smoothed regression coefficients are unknown, we cannot test on these estimates. However by smoothing the standard errors of the raw regression coefficients with the same type of analytical weights and plot them together with the smoothed regression coefficients, it gives a general idea of whether the smoothed regression coefficients are statistically significant. Using the SMART data, the standard errors of the regression coefficients from the standard simple linear regressions

were smoothed using analytical weight type 1 ($w_k = \frac{1}{\sqrt{D_k}}$). In Figures 1.c and 1.d, at each time point, the smoothed regression coefficients using analytical weight type 1 were shown within the range of one unit of smoothed standard error.

In Figure 1, we can see that the intercepts and regression coefficients of adherence to self-monitoring were not constant over time. The intercept was generally decreasing while the regression coefficients of adherence to self-monitoring were generally increasing over time.

To be specific, the effect of adherence to self-monitoring on subjects' weight started with negative values, but from Figure 1.d it appears that the effect was not statistically significant at least for the first 10 weeks. After about 10 weeks the subjects who were not adherent to self-monitoring had higher weight compared to subjects who were adherent to self-monitoring as the smoothed coefficients of adherence to self-monitoring became positive, and this weight difference kept increasing and peaked around the 50th week. After about 50 weeks, the effect of adherence to self-monitoring was weaker until around the 70th week and increased slightly afterwards. Because the standard errors were very large after about 90 weeks, the effect of adherence to self-monitoring appeared not to be statistically significant (Figure 1.d).

Comparing the smoothing results from using the four different types of analytical weights (Figures 1.a and 1.b), before the 50th week, the four smoothed lines cannot be distinguished. After the 50th week, the lines became more separated. One possible reason for the phenomenon is that the values of the raw estimates at the 48th, 52nd and 76th week were more extreme compared to the data around them. Also, the raw estimates at the 48th week were very close to the time where the real measurement of subject's weight was taken and the raw estimates at the 52nd and the 76th weeks were from standard simple linear regressions using real measurement data. As a result, these two raw estimates were given higher analytical weights and based on the scale of the weights, the fitted lines were different. Another possible reason is that the association between subjects' weights and adherence to self-monitoring was linear before the 50th week, and became nonlinear afterwards.

The results from using local polynomial kernel smoothing with Epanechnikov kernel are also shown in Figures 1.a and 1.b. The smoothed lines using the kernel function were the same as the other 4 smoothed lines before the 50th week. However, after the 50th week the smoothed line using the kernel function had a w shape which mirrors the data flow. For example, between the 58th and 70th weeks, the estimates of the kernel smoothing were not very different from the raw estimates. However, because these raw estimates are far from the 52nd and the 76th week where real measures of subjects' weight were taken these values should be adjusted up like the other four smoothed lines.

There are differences when comparing the SMART trial results from using the proposed method to the results using a parametric mixed-effects model. The first difference is that more detailed results can be obtained from using the proposed method. Because pseudo data were inserted, we estimated the correlation between weight and self-monitoring at 43 time points. However, the mixed-effects model was used after reducing the dimension of self-monitoring data to 4 time points, so the correlation was estimated at 4 time points [14]. Second, the interpretations of the results are different. By using the proposed method the results were weight differences between subjects who were adherent to self-monitoring and subjects who were not at each time point. In the mixed-effects model, because the adherence data were modified to be 'proportion of the time subjects were adherent to self-monitoring during a period of 6 months', the result was the correlation between weight and the frequencies of self-monitoring during each period of 6 months [14]. Finally, the conclusions were different. The proposed method showed that the correlation between weight and self-

monitoring were conservatively not statistically significant in the beginning and end of the trial. The possible reasons are that the self-monitoring took time to become effective in the beginning, and in the end fewer and fewer subjects were adherent to self-monitoring. However the mixed-effects model showed that the correlation between weight and the frequencies of self-monitoring were significant at all 4 time points. This might be because the self-monitoring data were aggregated for every 6 months in the mixed-effects model [14].

5. Simulation Study

A simulation study was conducted to examine the performance and features of the proposed method. The data used in our simulation study attempted to mimic the SMART trial data and was designed as follows. We chose $N=200$ subjects, and the two true coefficient functions were given as modelled after the SMART trial:

$$\beta_0^{\text{true}} = 90.5 - 0.2t_j$$

$$\beta_1^{\text{true}} = -1.1 + 0.4t_j - 0.003t_j^2$$

The t_j in weeks ($1 \leq t_j \leq 96$, $1 \leq j \leq 43$) were defined as the time points where measures were taken, and the measures were taken weekly for the first 4 months, biweekly for 8 weeks, then monthly for 12 months. The intercept was a straight decreasing line, and the coefficient of the covariate was a curve over the 43 time points.

Let $X_0(t)$ be a vector of 1's (200 by 1), and $X_1(t)$ be a vector of binomial random variable with a success rate of 0.5. We sampled the errors from a multivariate normal distribution with mean 0 and a compound symmetry covariance structure (43 by 43). Different variances with high correlation ($\rho = 0.7$), medium correlation ($\rho = 0.5$) or low correlation ($\rho = 0.3$) of the compound symmetry covariance structure were used and results from them were compared. The simulated full data were the sum of the errors and the underlying true coefficients at each time point.

$$Y_{ij} = X_{0i}\beta_0^{\text{true}}(t_{ij}) + X_{1i}\beta_1^{\text{true}}(t_{ij}) + \varepsilon_{ij}, \quad j=1, 2, \dots, T; i=1, 2, \dots, N$$

Using the simulated full data, we fitted standard simple linear regressions at each time point to get 43 estimated $\beta_1(\hat{\beta}_1^{\text{simulate}})$.

Using the proposed method, y_{ij}^{pseudo} was inserted between time points $t_{ij}=1$ and $t_{ij}=24$, $t_{ij}=24$ and $t_{ij}=48$, $t_{ij}=48$ and $t_{ij}=72$, $t_{ij}=72$ and $t_{ij}=96$ using functions (1a) and (1b) to create a new dataset. Standard simple linear regressions were fitted at each time point using the new dataset to obtain 43 raw estimates of $\beta_1(\hat{\beta}_1^{\text{raw}})$. Local polynomial smoothing using only analytical weights was applied to estimate smoothed β_1 's ($\hat{\beta}_1^{\text{smooth}}$). The degree of the

polynomial was set to be 3, and about one third of the raw estimators were used in each local fit. For each different covariance structure of the error term and each different analytical weight, the process was repeated with 5000 replications.

The performance of the proposed method was measured by the Averaged Deviation (AD) defined as

$$AD = \left\{ \frac{1}{5000} \sum_{q=1}^{5000} \sum_{j=1}^{43} (\hat{\beta}_1^{\text{simulate}} - \beta_{1jq}^{\text{true}})^2 \right\} - \left\{ \frac{1}{5000} \sum_{q=1}^{5000} \sum_{j=1}^{43} (\hat{\beta}_1^{\text{smooth}} - \beta_{1jq}^{\text{true}})^2 \right\}$$

The simulation results are shown in Table 1. Smaller absolute values of AD indicate a better fit. When the variance of the error term at each time point was small and the repeated measures were highly correlated to each other, the performance of our proposed model was better, and the different types of analytical weight did not make much difference.

Because the covariance matrix of a real longitudinal dataset typically does not have a compound symmetry structure, a more realistic covariance matrix was also used in the simulation study. The subjects in the SMART study self-reported their weight at the same scheduled time as adherence to self-monitoring. These data were not as accurate as the subjects' weight measured at clinical visits and more data were missing. However, by fitting a mixed model using self-reported weights and adherence to self-monitoring a residual covariance structure (R matrix) can be estimated. The variance and covariance in the estimated R matrix ranged from 430 to 570. The AD of the simulation study using different analytical weights and estimated R matrix were $AD_1 = 65.61$, $AD_2 = 65.17$, $AD_3 = 68.29$ and $AD_4 = 68.26$. The performance was good and each type of analytical weight produced similar results.

6. Discussion

We have demonstrated the application of a proposed three-step procedure using local polynomial smoothing for inconsistently sampled longitudinal data where the outcome was sampled less frequently than its covariates. This method also works when covariates are sampled less frequently than the outcome, because it involves smoothing coefficients of local linear regressions. For the same reason, any type of generalized linear regressions can be implemented at step two, and no matter how many covariates are modeled, the fitting process is fast.

Compared to applying parametric mixed-effects models to inconsistently sampled longitudinal data, the proposed method does not require reducing the dimension of the more frequently repeated sampled data. As a result less information will be lost during data analysis. Also the results of the proposed procedure have straightforward interpretations. Not only does this method show the association between the dependent and independent variables, it also displays the change of the association over time.

The proposed method does have limitations. Because the distributions and standard errors of the smoothed regression coefficients are unknown, we cannot draw statistical inferences.

However, one can try to measure the variability of the smoothed regression coefficients by smoothing the standard errors of the raw estimated as what we did in the example or use a bootstrap method. When time distances and associated standard errors used for computing analytical weights do not have the same scale, further modifications are necessary. If the variations of errors from the standard simple linear regressions are big and the correlations among them are small, the proposed method is less accurate. During the standard simple linear regression fitting, although one can use as many covariates as needed, when there are interactions among these covariates, the final results will be hard to understand. Because subject withdrawing from the trial is a common situation in longitudinal studies, each standard simple linear regression may not have the same power due to missing data. Lastly, the proposed method cannot estimate profiles for individual subject.

As data collection techniques become increasingly better in scientific studies, participants' experiences can be recorded as they occur in real time. Such intensive longitudinal data provide detailed information to better understand the trajectory of human behavior. The method we propose in this paper will be a useful tool for exploring this type of data when they are to be correlated with other less intensively sampled longitudinal variables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Superimposed smoothed coefficients using three-step estimation procedure

In (a) and (b) black diamonds, raw coefficients using pseudo data. Blue oval, raw coefficients using real measurements. Dashed line, estimates using analytical weight type 1

$(\frac{1}{\sqrt{D_k}})$. Tight dotted line, estimates using analytical weight type 2 $(\frac{1}{D_k})$. Long dash dotted

line, estimators using analytical weight type 3 $(\frac{1}{\sqrt{D_k}} + \frac{1}{\sqrt{se_k}})$. Short dash dotted line,

estimates using analytical weight type 4 $(\frac{1}{D_k} + \frac{1}{se_k})$. Solid line, estimates using kernel function epanechnikov. In (c) and (d) solid line, estimates using analytical weight type 1.

Dashed line, estimates plus or minus smoothed standard errors using analytical weight type 1.

Table 1

Simulation results (Averaged Deviation) using analytical weight type 1, 2, 3 and 4

Averaged Deviation 1*	$\rho = 0.3$	$\rho = 0.5$	$\rho = 0.7$
Averaged Deviation 2**			
Averaged Deviation 3***			
Averaged Deviation 4****			
	0.18	-1.21	-2.27
	0.14	-0.65	-1.92
$\sigma^2 = 5^2$	-0.48	-1.27	-2.40
	-0.14	-0.88	-2.41
	11.13	7.08	3.42
$\sigma^2 = 10^2$	11.06	7.65	3.78
	11.57	7.67	2.70
	10.79	6.77	3.00
	30.93	22.31	10.63
$\sigma^2 = 15^2$	30.14	16.96	9.27
	32.91	20.09	10.91
	31.04	20.95	11.70
	55.05	42.35	20.16
$\sigma^2 = 20^2$	52.68	38.39	23.90
	61.17	44.37	22.77
	59.00	42.74	25.13
	91.87	63.29	38.57
$\sigma^2 = 25^2$	87.02	63.85	37.67
	91.44	61.67	36.47
	88.55	56.69	34.56
	132.10	98.36	53.40
$\sigma^2 = 30^2$	137.04	84.93	46.68
	140.47	98.70	62.38
	145.45	93.47	52.99
	191.54	123.05	67.91
$\sigma^2 = 35^2$	188.49	126.86	64.59
	173.83	123.67	77.23
	189.14	124.97	67.97
	237.17	171.99	106.66
$\sigma^2 = 40^2$	231.87	150.87	109.00
	238.47	180.84	100.38
	241.36	158.41	91.90

* Use analytical weight type 1: $\frac{1}{\sqrt{D_k}}$

** Use analytical weight type 2: $\frac{1}{D_k}$

Use analytical weight type 3: $\frac{1}{\sqrt{D_k}} + \frac{1}{\sqrt{se_k}}$

Use Analytical weight type 4: $\frac{1}{D_k} + \frac{1}{se_k}$

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