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Identifying multiple change-points in a linear mixed effects model

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Abstract

Although change-point analysis methods for longitudinal data have been developed, it is often of interest to detect multiple change-points in longitudinal data. In this paper, we propose a linear mixed effects modeling framework for identifying multiple change-points in longitudinal Gaussian data. Specifically, we develop a novel statistical and computational framework that integrates the Expectation-Maximization (E-M) and the Dynamic Programming (DP) algorithms. We conduct a comprehensive simulation study to demonstrate the performance of our method. Our method is illustrated with an analysis of data from a trial evaluating a behavioral intervention for the control of type I diabetes in adolescents with HbA1c as the longitudinal response variable.

Keywords

Change-point; Longitudinal data; Linear mixed effects model; Expectation-Maximization algorithm; Dynamic programming algorithm

1. Introduction

In biomedical studies, it is common to collect data with repeated measurements (or longitudinal data). When the response variable is continuous, linear mixed effects models are widely used to analyze longitudinal data [1]. When observations are collected along a time course, it is often of interest to identify possible change-points that partition the whole time course into intervals [2, 3, 4]. For a change-point analysis, we assume that the response variable follows a common distribution within an interval but its distributions are different between two adjacent intervals. For data without repeated measurements, statistical methods for change-point analysis have been well developed [5, 6]. For longitudinal data, statistical methods for detecting a single change-point have also been well studied [7, 8]. Some related Bayesian approaches have also been studied [9, 10, 11, 12, 13]. However, the issue of detecting multiple change-points in longitudinal studies has not been well addressed.

The motivation for this work came from a longitudinal clinical trial that examined the effect of a behavior intervention on HbA1c, a biomarker of sugar level, over time in adolescents with type 1 diabetes [14]. The treatment effect might not be constant and the study interest

was on identifying regions of maximal treatment effect that could be reported to the diabetes research and practice community. A multiple change-point approach would help pediatricians in identifying these regions. Furthermore, we would like to detect change-points such that statistically significant differences could be shown for adjacent regions. This cannot be achieved by the method developed recently by Picard et al. [15]. Then, we would need a novel method to achieve this goal.

To describe our method, we first briefly review the basic linear mixed effects model and then we propose a model with a multiple change-point structure. For the model estimation, we develop a novel statistical and computational framework that integrates the Expectation-Maximization (E-M) algorithm [16] and the Dynamic Programming (DP) algorithm [17]. We conduct a comprehensive simulation study to demonstrate the performance of our method. Our methodology is illustrated by an analysis of diabetes study data with HbA1c as the longitudinal response variable.

2. Methods

2.1. A basic linear mixed effects model

Suppose there are n subjects with Gaussian response $\{y_i : i = 1, 2, \dots, n\}$. The repeated measurements $\{y_{ij} : j = 1, 2, \dots, n_i\}$ for each subject i are associated with a time variable $\{t_{ij} : j = 1, 2, \dots, n_i\}$. We assume all $\{t_{ij} : i = 1, 2, \dots, n; j = 1, 2, \dots, n_i\}$ take values from a finite set of m time points $\{s_1, s_2, \dots, s_m\}$. Some important covariates $X = (x_1, x_2, \dots, x_p)$ are also considered for the fixed effects. Denote $Z = (z_1, z_2, \dots, z_q)$ as a set of random effect covariates that represent individual departure from the fixed effect and induce correlations among the repeated measurements. Then, a basic mixed effects model is:

$$y_i = X_i \beta + Z_i b_i + e_i, \quad (1)$$

where X_i and Z_i are $n_i \times p$ and $n_i \times q$ matrices, respectively; and y_i , β , b_i and e_i are $n_i \times 1$, $p \times 1$, $q \times 1$ and $n_i \times 1$ vectors. In the above model, β represents the fixed effects, b_i represents the random effects and e_i represents observation errors. We assume that e_i is normally distributed as $N(0, \sigma^2 R_i)$ with R_i being a $n_i \times n_i$ identity matrix, and b_i is normally distributed as $N(0, D)$ with D being a $q \times q$ positive definite matrix. Furthermore, we assume that e_i is independent of b_i and also the error terms and random effects are all independent across individuals.

The above linear mixed effects model has been well studied in the statistical literature [18]. The related E-M algorithm has also been well described in the books of Verbeke and Molenberghs [1] and McLachlan and Krishnan [16].

2.2. Multiple change-points

Our method for the detection of multiple change-points is developed based on the extension of the model specified by Equation (1). The change-points considered in this study are those time points where any elements of β changes at a given significance level α_C . (This can be flexibly modified in practice. We will explain the detail in the section *Partitioning: test for change-point detection*.) Suppose that we know the number g change-points and their locations $\{s_{m_1}, s_{m_2}, \dots, s_{m_g}\}$ ($1 = m_0 < m_1 < m_2 < \dots < m_g < m_{g+1} = m$), then the set of time points can be partitioned into $g + 1$ consecutive non-overlapped blocks $\{B_k : k = 1, 2, \dots, g + 1\}$ with $B_k = [s_{m_{k-1}}, s_{m_k})$ for $k = 1, 2, \dots, g$ and $B_{g+1} = [s_{m_g}, s_{m_{g+1}}]$.

For the observation on subject i at time t_{ij} , let $\mathbf{x}_{i,j}$ and $\mathbf{z}_{i,j}$ be the $1 \times p$ covariate vector for the fixed effects and $1 \times q$ covariate vector for the random effects, respectively. The extended model can be written as:

$$y_{ij} = \sum_{k=1}^{g+1} \mathbf{x}_{i,j} \beta_{B_k} I(t_{ij} \in B_k) + \mathbf{z}_{i,j} b_i + e_{ij}, \quad (2)$$

where $I(\cdot)$ is the indicator function and β_{B_k} is the block-specific fixed effects for the k -th block, $k = 1, 2, \dots, g + 1$. It is clear that model (2) is a special case of the general model specified by Equation (1).

Remark. In practice, the set of time points $\{t_{ij}\}$ can be these at which observations are collected. They can also be a set of pre-specified time points so that the analysis can be simplified and also the computing time can be reduced. If a set of pre-specified time points is used, then the observations are assigned to their corresponding time intervals accordingly.

2.3. Random effects

In this paper, we consider a relatively simple random effects model. In addition to a random intercept, it is reasonable to incorporate block-specific random effects into the statistical modeling framework. Therefore, we are interested in the following specific model:

$$y_{ij} = \sum_{k=1}^{g+1} \mathbf{x}_{i,j} \beta_{B_k} I(t_{ij} \in B_k) + b_{i,0} + \sum_{k=1}^{g+1} b_{i,B_k} I(t_{ij} \in B_k) + e_{ij}, \quad (3)$$

where $b_{i,0}$ is the subject-specific random effect and b_{i,B_k} is the subject/block-specific random effect. Clearly, model (3) fits in to the framework of a traditional multi-level random effects model. For this model, we have $\mathbf{z}_{i,j} = (1, I(t_{ij} \in B_1), I(t_{ij} \in B_2), \dots, I(t_{ij} \in B_{g+1}))$ and $b_i = (b_{i,0}, b_{i,B_1}, b_{i,B_2}, \dots, b_{i,B_{g+1}})$. Furthermore, we assume a simple structure for $D = \text{diag}\{d_0, d_1, d_1, \dots, d_1\}$ (a $(g+2) \times (g+2)$ diagonal matrix). This random effect structure allows for an overall subject-specific shift in the mean structure ($b_{i,0}$) along with individual block-specific departure (b_{i,B_k}). Furthermore, one could allow for correlations among the random effects, e.g. $\text{cor}(b_{i,0}, b_{i,B_k}) = \rho_1$ and $\text{cor}(b_{i,B_k}, b_{i,B_l}) = \rho_2$ for $k \neq l$. Note that the change-points of the random effects are assumed to be the same as the change-points of the fixed effects in model (3).

When the change-points are given, these models can be estimated with standard methods that have been implemented in R with the lme procedure [19]. In this study, our goal is to develop a novel method to integrate the detection of multiple change-points within the class of linear mixed effects models.

2.4. Partitioning: test for change-point detection

We use a simple test for detecting possible single change-point. To check whether a time point s_k is a feasible change-point for two blocks $B_1 = [s_h, s_k)$ and $B_2 = [s_k, s_l)$ (or $B_2 = [s_k, s_m]$ if the right boundary is included), we propose to use a test that is based on a linear mixed effects model consistent with model (3). The data are the subset of data restricted to $\{t_{ij} \in B_1 \cup B_2\}$. For single change-point detection, we consider the following corresponding linear mixed effects model and test the fixed effect:

$$y_{ij} = \mathbf{x}_{i,j} \beta + \mathbf{x}_{i,j} \gamma I(t_{ij} \in B_2) + b_{i,0} + \sum_{k=1}^2 b_{i,B_k} I(t_{ij} \in B_k) + e_{ij}, \quad (4)$$

Where both β and γ can be vectors. The time point s_k will be considered as a feasible change-point between B_1 and B_2 if any individual p -values of the estimated elements in γ are lower than the given α_C . (Then, $\{B_1, B_2\}$ can be considered as a feasible partition.) Fitting

Equation (4) (with a partition given) can be performed by the standard statistical software (e.g. the lme procedure in R) for fitting linear mixed models [19]. Then, we compare α_C to the corresponding individual p -values (reported in the “tTable” returned by the lme function) for γ .

In our study, α_C can be considered as a smoothing parameter as well as a p -value threshold. If the statistical significance of our identified change-points is the major concern, then α_C must be set to address the issue of multiple hypothesis testing. However, we are also interested in the prediction performance of our linear mixed effects model. Therefore, we suggested a cross-validation procedure for selecting α_C from a predefined set of α_C , in which the multiple comparison issue may be partially considered.

Remark. In practice, different test setting may be considered. For example, we may be only interested in a specific effect, such as the interaction coefficient γ_1 in the following model:

$$y_{ij} = \beta_0 + \beta_1 z + (\gamma_0 + \gamma_1 z) I(t_{ij} \in B_2) + b_{i,0} + \sum_{k=1}^2 b_{i,B_k} I(t_{ij} \in B_k) + e_{ij},$$

where z can be a treatment effect. With an appropriate parameter setting, we can also test on both fixed and random effects changes. Therefore, the test setting can be flexibly modified to accommodate many different analysis scenarios.

2.5. Change-point detection and parameter estimation

When there is no detection of change-points, the E-M algorithm has been well described in the books of Verbeke and Molenberghs [1] and McLachlan and Krishnan [16]. When the change-point detection is required, the maximum likelihood estimation procedure is more complicated. (As we have described before, the change-points considered in this study are those time points where any elements of β change at a given significance level α_C .) However, given the random effects, we can detect change-points through our modified dynamic programming algorithm [6]; then the random effects can be updated based on the current partition of time-course and parameter estimates. (Although our algorithm optimizes model fitting in a constrained parameter space, the E-M algorithm still holds since the likelihood is non-decreasing.) In summary, with the initialization of random effects, we repeat the following M-step and E-step until convergence is achieved.

M-step With the given random effects, use a modified dynamic programming algorithm based procedure to choose the optimized change-points and also obtain the related parameter estimates;

E-step With the detected change-points and estimated parameters, re-estimate the posterior means of functions of the random effects.

The convergence is numerically defined by a given tolerance value that is larger than the maximum of the absolute difference values of the estimated parameters from two consecutive runs. (For the tolerance value, we use 0.01 for the cross-validation based selection of α_C and 0.001 for the final estimates with α_C determined.) The details are described as below.

M-step Our M-step is an extension of the M-step in the traditional E-M algorithm. This is briefly described as follows. If the partition of time course is given (or the change-points are given), then the mathematical formulas have been well studied for the parameter estimation conditional on the given random effects. The globally optimized change-points can be identified by a modified dynamic programming algorithm.

Based on our modeling assumptions, given the random effects $\{\hat{b}_i\}$ for the 1st conditional moment and $\{\hat{\Gamma}_i\}$ for the 2nd conditional moment ($\hat{b}_i = \mathbf{E}(b_i | y_i)$ and $\hat{\Gamma}_i = \mathbf{E}(b_i b_i^T | y_i)$), the maximum likelihood estimation is equivalent to the estimation by minimizing the sum of squared errors (SSE). For a block of time points $B = \{s_j, s_{j+1}, \dots, s_i\}$, the associated SSE is simply

$$SSE(j, j+1, \dots, i) = \sum_{k=1}^n \sum_{l=1}^{n_k} \left(y_{kl} I(t_{kl} \in B) - \mathbf{x}_{k,l} \hat{\beta}_B I(t_{kl} \in B) - \mathbf{z}_{k,l} \hat{b}_i \right)^2,$$

where $\hat{\beta}_B$ is calculated by the well-known formulas [16] based on the subset of data $\{(\tilde{y}_i, \tilde{X}_i, \tilde{Z}_i)\}$ restricted to $\{t_{ij} \in B\}$:

$$\hat{\beta}_B = \left(\sum_{i=1}^n \tilde{X}_i^T \tilde{R}_i^{-1} \tilde{X}_i \right)^{-1} \sum_{i=1}^n \tilde{X}_i^T \tilde{R}_i^{-1} (\tilde{y}_i - \tilde{Z}_i \hat{b}_i),$$

where $\tilde{R}_i$ is an identity matrix. Notice that the SSE of several blocks is simply the sum of SSEs of individual blocks. According to this “optimal substructure”, we have developed a modified dynamic programming algorithm for the change-point analysis of binary or normal type of response data [6]. This modified dynamic programming algorithm can also be extended for the Gaussian random effect models. The algorithm details are given in the Appendix. Essentially, the algorithm minimizes the SSE sequentially. From the first time point to the last time point, each time point is considered as an ending time point and a list of eligible solutions are calculated. Furthermore, the solution history is always saved. Then, for a next time point, we can use the solution history and reduce the number of possible partitions. Based on this strategy, the search space for the global optimization is much reduced from the whole power set to a subset with polynomial order. In more mathematical detail, assume that we have sequentially optimized the time points from 1 to i . For time point $i + 1$, to optimize $SSE(1, \dots, i + 1)$, we check each possible change-point j (from 2 to $i + 1$) such that the time points $(j, \dots, i + 1)$ are included in one block. Notice that $SSE(1, \dots, i + 1) = SSE(1, \dots, j - 1) + SSE(j, \dots, i + 1)$ and all the $\{SSE(1, \dots, j - 1)\}$ have been already optimized. Then, it is time-efficient to identify the best j that optimizes $SSE(1, \dots, i + 1)$. (Notice that the optimized time course partition is determined by the observed data and also a given α_C as described in *Partitioning: test for change-point detection*. If $\alpha_C \rightarrow 1$, then each time point will be a partitioned block; if $\alpha_C \rightarrow 0$, then there will be no partition of time course.)

With our modified dynamic programming algorithm, we can obtain

$\hat{g}, \{\hat{B}_k : k=1, 2, \dots, \hat{g}+1\}$ as well as $\{\hat{\beta}_{\hat{B}_k}\}$. According to the books of Verbeke and Molenberghs [1] and MacLachlan and Krishnan [16], we can estimate σ^2 as:

$$\hat{\sigma}^2 = \frac{1}{n} \left[SSE(1, \dots, m) + \sum_{i=1}^n \text{tr} \left[R_i^{-1} Z_i \left(\mathbf{E}(b_i b_i^T | y_i) - \mathbf{E}(b_i | y_i) \mathbf{E}(b_i | y_i)^T \right) Z_i^T \right] \right].$$

The estimation of D is simple and we do not need any complicated algorithm. Notice that D is a special diagonal matrix with only d_0 and d_1 to be estimated. We first calculate a related $\tilde{D}$ as:

$$\tilde{D} = \frac{1}{n} \sum_{i=1}^n \{\hat{\Gamma}_i\}.$$

Its elements are denoted as $\{\tilde{d}_{ij}\}$ and its dimension is denoted as $(K+1) \times (K+1)$. (Since $\hat{\Gamma}$ is from the previous E-step, K can be different from the estimated $\hat{g}$ in the current M-step.) Then, we estimate d_0 and d_1 as follows:

$$\begin{aligned} \hat{d}_0 &= \tilde{d}_{11}; \\ \hat{d}_1 &= \frac{1}{K} \sum_{i=2}^{K+1} \tilde{d}_{ii}. \end{aligned}$$

For this model, it is also necessary to update the dimension of $\hat{D}$ and $\{Z_i\}$ accordingly for the next iteration of E-step and M-step: $D = \text{diag}\{\hat{d}_0, \hat{d}_1, \hat{d}_1, \dots, \hat{d}_1\}$ (a $(\hat{g}+2) \times (\hat{g}+2)$ diagonal matrix); and $\mathbf{z}_{i,j} = (1, I(t_{ij} \in \hat{B}_1), I(t_{ij} \in \hat{B}_2), \dots, I(t_{ij} \in \hat{B}_{\hat{g}+1}))$.

E-step In the E-step, we update the first two moments of the random effects. Since the details have been described in the books of Verbeke and Molenberghs [1] and McLachlan and Krishnan [16] for the general model, we only provide the necessary formulas below. We first calculate $w_i = (w_{i1}, w_{i2}, \dots, w_{in_i})$ as follows:

$$w_{ij} = y_{ij} - \sum_{k=1}^{\hat{g}+1} \mathbf{x}_{i,j} \hat{\beta}_{\hat{B}_k} I(t_{ij} \in \hat{B}_k);$$

Then, we have

$$\begin{aligned} \hat{b}_i &= \mathbf{E}(b_i | y_i) = (Z_i^T R_i^{-1} Z_i + \hat{\sigma}^2 \hat{D}^{-1})^{-1} Z_i^T R_i^{-1} w_i; \\ \hat{\Gamma}_i &= \mathbf{E}(b_i b_i^T | y_i) = \mathbf{E}(b_i | y_i) \mathbf{E}(b_i | y_i)^T + (\hat{D}^{-1} + Z_i^T R_i^{-1} Z_i / \hat{\sigma}^2)^{-1}. \end{aligned}$$

Notice that $\hat{\beta}$, $\hat{\sigma}^2$ and $\hat{D}$ are the estimated parameters, and $\hat{g}$ and $\{\hat{B}_k: k=1, 2, \dots, \hat{g}+1\}$ are the estimated partitions for change-points from the M-step.

2.6. Initializing random effects

An appropriate initialization of the random effects is important since it can reduce a considerable amount of computing time. We consider a two-step approach: the random effects are initialized after a preliminary time-course partition. For the preliminary time-course partition, we only consider a random intercept for our linear mixed effects model. The initial values for this simplified model are the estimated random intercepts from a standard linear mixed model (that can be estimated using the **lme** procedure in R) based on a saturated partition structure for the fixed effects (but with only one random intercept, i.e. no partition for the random effects). [For the saturated partition structure, each time point is a

partitioned block (then there are m blocks).] With these estimated random intercepts as the starting values, the simplified model can be estimated by our proposed method and then a preliminary time-course partition can be obtained as initial change-points. As we have explained in the early sections, when the change-points are given, our linear mixed effects model can be estimated again using the R procedure **lme**. This allows us to obtain the initialized random effects.

3. Likelihood ratio test and permutation p -value

According to our model specification, the likelihood can be calculated after the convergence of the E-M algorithm. Then, we can calculate a likelihood ratio test score T by comparing the likelihood based on the change-point model (Equation 3) to the likelihood based on a specified null model. The null model is specified according to our null hypothesis. A typical test situation is whether there is any time effect, i.e. whether the detected change-points are statistically significant. For this test situation, the null model is that there is no change-point. Since it is difficult to study the theoretical null distribution for this likelihood ratio test statistic (our algorithm optimizes model fitting in a constrained parameter space), we can perform the following permutation procedure for generating an empirical null distribution.

1. For the i -th subject, $i = 1, 2, \dots, n$, generate $\{t_{ij}^*: j=1, 2, \dots, n_i\}$ as a random sample (without replacement) from $\{t_{ij}\}$;
2. Run the EM-DP algorithm with $\{t_{ij}^*\}$ as the set of observation time points and calculate the associated likelihood ratio test score T^* ;
3. Repeat steps 1&2 B times to obtain a collection of permuted likelihood ratio test scores, which can be considered as an empirical null distribution.

The above procedure essentially breaks the association between the response and time. In this way, the null hypothesis can be simulated with the observed data and the null distribution of the likelihood ratio test can be approximated after many permutations [20].

In many analysis situations, we may focus on the effect of an important variable $\tilde{x}$. For example, the treatment effect in a clinical study. For this test situation, the null model is that the β coefficient for the variable of interest is zero. We can also run a permutation procedure for generating an empirical distribution for this likelihood ratio test.

1. Generate $\{\tilde{x}_{ij}^*: i=1, 2, \dots, n, j=1, 2, \dots, n_i\}$ as a random sample (without replacement) from $\{\tilde{x}_{ij}\}$;
2. Run the EM-DP algorithm with $\{\tilde{x}_{ij}\}$ replaced by $\{\tilde{x}_{ij}^*\}$ (but all the rest variables unchanged) and calculate the associated likelihood ratio test score T^* ;
3. Repeat steps 1&2 B times to obtain a collection of permuted likelihood ratio test scores, which can be considered as an empirical null distribution.

This procedure essentially breaks the association between the response and $\tilde{x}$. The p -value of an observed likelihood ratio test score can be computed as: $(\text{number of } T^* \leq T)/B$.

4. Bootstrap confidence intervals

For the parameters estimated by the EM-DP algorithm, it is also difficult to develop the theoretical formulas for constructing the confidence intervals (our algorithm optimizes model fitting in a constrained parameter space). Instead, we consider a bootstrap procedure.

1. Generate $\{k_i : i = 1, 2, \dots, n\}$ as a random sample (with replacement) from $\{i : i = 1, 2, \dots, n\}$;
2. Run the EM-DP algorithm with $\{(x_{ij}, y_{ij})\}$ replaced by $\{(x_{ki,j}, y_{kij})\}$ to obtain the resampled parameter estimates;
3. Repeat steps 1&2 B times to obtain a collection of resampled estimates.

The procedure applies the “plug-in principle” so that a resampled distribution can be generated [21]. A pair of empirical percentiles (e.g. 2.5% and 97.5%) can be used to construct a confidence interval for each parameter estimated by the EM-DP algorithm.

Remark. The uncertainty of change-point detection is considered in our statistical inference. In both the permutation test procedure and the bootstrap procedure, we do not assume any fixed number or locations of change-points.

5. A simulation study

Simulation configuration

We performed a comprehensive simulation study to evaluate the performance of our proposed method. We simulated data according to the model given by Equation (3). The number of subjects was set to $n = 80$ or 120 (we also tried some other sample size values and observed similar results). We set $\sigma = 0.5$, $d_0 = 0.8$ and $d_1 = 0.6$. We considered a time course with 9 time points $\{1, 2, \dots, 9\}$ and 2 change-points: one between time points 3 and 4, the other between time points 6 and 7. The number of repeated measurements for each subject was set to $n_i = 6$ or 9 . For $n_i = 6$, we random chose 6 time points without replacement from the total 9 time points; for $n_i = 9$, all the total 9 time points were assigned to each subject. We set $p = 2$ and then set $x = (1, 0)$ for the first $n/2$ subjects (sample 1) and $x = (1, 1)$ for the remaining $n/2$ subjects (sample 2). There were $g = 3$ blocks of time points $\{B_1, B_2, B_3\}$ separated by the two change-points. We set the model coefficients $\beta_{B_1} = (\beta_{01}, \beta_{11}) = (\beta_{02}, \beta_{12}) = (\beta_{03}, \beta_{13}) = (0.3, 0.4)^T$, $\beta_{B_2} = (\beta_{04}, \beta_{14}) = (\beta_{05}, \beta_{15}) = (\beta_{06}, \beta_{16}) = (0.7, -0.6)^T$ and $\beta_{B_3} = (\beta_{07}, \beta_{17}) = (\beta_{08}, \beta_{18}) = (\beta_{09}, \beta_{19}) = (0.1, 0.2)^T$. (Then, the block mean values were 0.3, 0.7 and 0.1 for sample 1 and these values were 0.7, 0.1 and 0.3 for sample 2. Since the number and locations of change-points are assumed unknown in our estimation procedure, we present the estimation performance results for all the parameters including 18 β 's as described above.)

An appropriately selected α_C can improve our analysis results. In our simulation study, we simply considered three different values: 0.05, 0.005 and 0.0005. (Since our simulation study was comprehensive and time-consuming, we limited the number of α_C values so that we could afford the computing burden. However, more choices of α_C values should be feasible in a near future due to the advance of parallel computing power. Our main purpose was to demonstrate a satisfactory performance of our method when α_C could be appropriately selected.) We considered a cross-validation (CV) procedure for the choice of α_C . Due to the time complexity of our analysis procedure, we used the two-fold CV procedure to reduce the computing time. (We could not afford the ten-fold CV or leave-one-out CV with our current computing power.) We chose α_C to minimize the sum of square of prediction errors. Then, we re-run our analysis procedure with the selected α_C for the whole data to identify the change-points and to estimate the parameters.

Change-point detection results

For each simulated data set, a detection of multiple change-points partitions the time course $\{1, 2, \dots, 9\}$ into several blocks of time points. If there are $\hat{g}$ change-points detected, then the time course is partitioned into $\hat{g}+1$ blocks. The true number of change-points for our

simulation study is two. Table 1 shows that we estimate two change-points in between 65.4% and 82.0% of simulated data sets with the proportion increasing as we increase the number of subjects and/or the number of repeated measurements per subject. Furthermore, the proportion of zero as the number of estimated change-points is clearly decreased from 9.2% to 0.1% as we increase either the number of subjects or repeated measurements. We also obtain three as the number of estimated change-points in between 13.7% and 19.1% of our simulated data sets. The maximum number of estimated change-points can be six, but there are only very few of such simulation results.

We also evaluate whether the change-point locations can be correctly detected. Our two true locations are one change-point between the third and fourth time points (3|4) and the other change-point between the sixth and seventh time points (6|7). Table 2 shows that the first change-point can be correctly detected in between 88.5% and 93.5% of our simulated data sets, and the second change-point can be correctly detected in between 78.4% and 88.0% of our simulation results. As we increase the number subjects and/or the number of repeated measurements per subject, these two proportions are clearly increased. According to our observation from Table 1, it is quite possible to detect three change-points. Table 1 shows that the proportion of identifying 6|7 (a true change-point) as the third change-point ranges between 45.7% and 60.7%.

In summary, although we have set relatively weak change-point signals for our simulation study, we can still detect the correct number of change-points and the correct change-points locations among the majority of our simulation results. Therefore, our method shows an overall satisfactory performance on the change-point detection.

Remark. Notice that the reported numbers in these two tables are not directly related. For each simulation scenario, Table 1 reports the distribution of total number of detected change-points; while Table 2 reports the distribution of change-point locations given they were detected. For a simple example, as reported in Table 1, there were totally 5 change-points identified among 6 out of 1000 simulation repetitions for the simulation scheme (c). Furthermore, the maximum number of total change-points was 5 for this scheme. Then, as reported in Table 2, 4 were located on 6|7, one on 7|8 and one on 8|9.

Parameter estimation results

Since the detection of change-points and the estimation of model parameters are closely connected, it is also necessary to evaluate the estimation performance from our method. Overall, Figure 1 shows that the estimated model coefficients are unbiased and the related estimation variances are reduced when n_i is increased from 6 to 9 or n is increased from 80 to 120. For the model variance parameter σ^2 , the estimation results are overall unbiased and the related estimation variances are clearly reduced when either n or n_i is increased. For d_0 and d_1 , the estimation results are visibly biased when n is 80. However, the bias and the estimated variance are reduced when n is increased from 80 to 120 (see Table 3 for details).

6. An application

In a recent study by Nansel, Iannotti, Simons-Morton et al. [14], adolescents (11–16 years old) with type 1 diabetes were randomized to either usual care or a behavioral intervention involving self-motivating, goal setting, and problem-solving sessions. The scientific interest was to examine changes in the treatment effect over the study time course, and possibly to identify period of maximum treatment effect.

This analysis includes a total of eighty adolescents (40 in each of the intervention and control groups, respectively) followed for up to five years after randomization. The range

and median of follow-up time are [231, 1764] and 1072 days. The range and median of the number of repeated measurements per subject are [2, 19] and 9. For the illustration purpose of our proposed method, we considered a relatively simple model to analyze these data. The model was also a special case of Equation (3), in which we only considered two coefficients for each β_k : $\beta_{k,0}$ for the baseline effect (control group specific parameter) and $\beta_{k,1}$ for the treatment effect. Then, the treatment group specific parameter was $\beta_{k,0} + \beta_{k,1}$.

Since our computing power was limited, we considered the following time points: 180, 360, 540, 720, 900, 1080, 1260 and 1800 days. Then, in our application analysis, the number of possible change-points was $m = 7$. (The time complexity for our dynamic programming algorithm was $O(m^3)$, where m was the number of possible change-points.) The right boundary of a sub-interval was considered as the observation time point for any data observed within that interval (left-open and right-closed). The length of the last time interval was specified before our analysis to ensure that there were adequate observations in each time interval. The response variable of interest was the difference between HbA1c measurement after randomization and the measurement before randomization (HbA1c difference).

The choice of α_C was crucial in our analysis. For our application analysis, we considered three different values: 0.05, $0.05/m$ and $0.05/c(m)$, where $c(m)$ was the maximum number of change-point tests possibly conducted during each round of DP algorithm run. (Notice that $c(m)$ could be simply programmed and calculated by a computer. In many situations, this number was not reached but $0.05/c(m)$ was still considered for a conservative purpose. See *dynamic programming algorithm* in the Appendix for more details.) The motivation for our consideration of these three values was as follows: 0.05 was the traditional α -level for declaring a significance without any adjustment for multiple hypothesis testing; $0.05/m$ was α -level after a simple adjustment of the number of possible change-points; and $0.05/c(m)$ was α -level with a conservative adjustment of the maximum number of possible change-point tests. (Notice that the set of these three α_C choice values were not the same from those used in our simulation study, in which the issue of multiple comparisons was not considered. We understood that an appropriate adjustment should be a value between α/m and $\alpha/c(m)$. However, it was difficult to theoretically determine this value.) We considered a cross-validation (CV) procedure for the choice of α_C . Due to the time complexity of our analysis procedure, we used the two-fold CV procedure to reduce the computing time. We chose α_C to minimize the sum of square of prediction errors. Then, we re-run our analysis procedure with the selected α_C for the whole data to identify the change-points and to estimate the parameters.

The aforementioned bootstrap procedure was used to generate the point-wise confidence intervals. For each round of bootstrap, we also first used the two-fold CV procedure to choose α_C and then used the selected α_C in our method. This strategy could prevent the over-fitting due to choosing α_C based on the same data that was used in evaluating this choice. For the placebo group, treatment group and time-point-wise treatment effect, Figure 2 shows the estimated time-point-wise mean values of HbA1c difference. The time-point-wise $100(1 - 0.05)\%$ and $100(1 - 0.05/8)\%$ confidence intervals are also presented in Figure 2. According to Figure 2(a), HbA1c difference was clearly increasing in the placebo group and this increasing trend was especially significant at very late time-points. According to Figure 2(c), the treatment effect was overall insignificant although there was likely an increasing trend of treatment effect over the study period with the region from 1260 days to the end of follow-up showing a marked treatment effect. (Interestingly, the treatment effect decreased during the region between 540 and 900 days but began to increase afterwards.) However, according to Figure 2(b), HbA1c difference was stabilized over all the study

period since the horizontal line was always included in any time-point-wise confidence interval. (Notice that $-\beta_{B_k,1}$ was actually reported for the treatment effect in Figure 2.)

The aforementioned permutation procedure was used to evaluate the significance of treatment effect, which was the main focus of the study. Again, for each round of permutation, we first used the aforementioned two-fold CV procedure to choose α_C and then used the selected α_C in our method. Our permutation p -value for the likelihood ratio test was 0.387. Therefore, the treatment effect was not overall significant. This was consistent with our bootstrap analysis result as shown in Figure 2(c).

The estimated variance components are $\hat{d}_0=1.402$, $\hat{d}_1=0.337$, and $\hat{\sigma}^2=0.835$. Therefore, the overall between-subject variation (d_0 and d_1) is modest relative to the within-subject variation (σ^2).

7. Discussion

In this work, we have proposed a novel method for detecting multiple change-points in the analysis of data with repeated measurements. Our method has been developed based on the Expectation-Maximization (E-M) algorithm and the Dynamic Programming (DP) algorithm. We have conducted a simulation study as well as an application analysis for this method.

The random effects variance structure is completely consistent with the change-point structure. Our algorithm has been designed to achieve an optimization within a constrained parameter space. All the feasible change-points define the constrained parameter space. Our feasibility criterion specifies all the possible partitions (they are fixed when data are given) before our model estimation. The feasibility criterion defined in Section 2.4 is actually not related to our estimation of model parameters and random effects described in Equation (3). For each feasible partition of time points, there is a specific linear mixed effects model. When the number of time points is small, we can simply enumerate and compare these linear mixed effects models to select the best one. However, this is not practically feasible when the number of time points is large. Therefore, to make our proposed model practically useful, we have proposed a procedure that is based on our modified dynamic programming algorithm and the traditional E-M algorithm. First, the E-M algorithm iterates between an M-step where parameters are estimated based on the complete data likelihood and an E-step where the expectations of the random effects are computed based on the observed data and current parameter estimates. In this algorithm, we consider the partition as a set of parameters that are optimized in the M-step. Within this framework, we are able to show through a comprehensive simulation study and an application that the algorithm converges and has good operating characteristics. Second, we do recognize that the model does stipulate that change points identified for the fixed effects are the same as those for the random effects. This is explicit in Equation (3).

To illustrate the constrained parameter space for our analysis, let us first consider the related unconstrained parameter space. It can be described based on the completely saturated partition structure that each time point is a partitioned block. Then, there are m β 's. Furthermore, the random effects variance matrix D is a $(m+1) \times (m+1)$ matrix with $\{d_0, d_1, d_1, \dots, d_1\}$ as diagonal elements. Notice that these m d_1 are structurally related to m β 's. Now, let us consider a feasible change-point structure that partitions m β 's into g groups. Then, these β 's in the same group are forced to be the same and there are g β -groups. At the same time, the random effects matrix D is forced to be a special matrix that each group-structurally related sub-matrix is actually $d_1 E$ (where E is a square matrix with unit value on all of its elements) and the number of these special sub-matrices is also g . This is an expanded description for our linear mixed effects model with a change-point structure. As

described by Dempster et al. [22], E-step is to compute $Q(\phi'|\phi(p))$ and M-step is to choose $\phi(p+1)$ to be a value of ϕ' which maximizes $Q(\phi'|\phi(p))$, where $Q(\phi'|\phi) = E(\log f(x|\phi')|y, \phi)$. Then, it is clear that our algorithm is an extension of E-M algorithm designed for a constrained parameter space.

A more complex random effect structure (such as a structure with correlation in the random effects) only requires a small amount of additional computational time. However, the most time-consuming tasks are the recursive computations for the E-M algorithm and also the modified dynamic programming algorithm. More computing time is required if a cross-validation procedure is used to choose α_C . However, our suggested permutation and bootstrap procedures can be easily parallelized for faster computations. The recent technology advance of parallel computing will be greatly helpful for the use of our method. For the next generation of computers, it will be common to configure a multi-core and multi-CPU workstation. Therefore, although our statistical methodology is computationally intensive, we believe that it is an important contribution to the scientific community.

In a cross-validation procedure, the number of fold K is usually set as 5 or 10. It is well-known that both bias and variance in performance evaluation can be well balanced if an appropriate K can be selected. However, it is usually difficult to select this value theoretically. The widely suggested values (5 or 10) for K are actually based on the accumulated experience in data analysis practice. Since our data analyses required a significant amount of computing time, we decided to choose $K = 2$ for our cross-validation setting so that our analysis results could be obtained within a reasonable amount of time. However, our simulation results demonstrated a satisfactory performance when $K = 2$ was used for our cross-validation setting.

Although there is a large literature on analyzing longitudinal data, the methodology for identifying multiple change-points in this setting has not been well addressed. Our method provides a novel contribution toward this research area. This technique will help investigators identify regions where the mean structure is either inflated or deflated relatively to the longitudinal region. We assume that the locations of change-points are common across subjects. For our application, this is reasonable since we are interested in identifying regions of increased treatment effect across all subjects. When interest is on identifying subject-specific change-point, new methodology will need to be developed. This is an area of future research. This research focused on developing multiple change-point models in the context of linear mixed effects models. Future research will focus on adapting the DP algorithm to the Generalized Estimating Equations [23] for the marginal analysis of discrete and continuous longitudinal data with multiple change-points.

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Appendix: dynamic programming algorithm

We have recently proposed this modified dynamic programming algorithm [6]. It can achieve a global optimization in the detection of multiple change-points. With this algorithm, we can detect multiple change-points based on statistically significant distribution

changes. Based on the traditional dynamic algorithm, there is an additional back-search layer included in this algorithm so that the adjacent comparison testing criterion can be checked. Then, a global maximization of likelihood can be achieved within a constrained parameter space defined by the adjacent comparison testing criterion. The illustrative flow-chart, theoretical properties and simulation study results have been described in detail in our publication, which is open-access to the public. Therefore, we only provide the necessary computer pseudo-code here.

We define the term “triplet” as a vector containing (link, index, score) that are described in the following modified dynamic programming algorithm. (Notice that the symbol i and j are used here to represent the indices of time points, although they have been used before as the subject/measurement indices.)

```

link  $\leftarrow$  1; index  $\leftarrow$  0; score  $\leftarrow$  SSE(1)
Create  $V_1$  as a vector set with only one element with the above triplet
for  $i = 2$  to  $m$  do {
  link  $\leftarrow$  1; index  $\leftarrow$  0; score  $\leftarrow$  SSE(1, 2, ...,  $i$ )
  Create  $V_i$  as a vector set with only one element with the above triplet
  for  $j = 2$  to  $i$  do {
    Go through  $V_{j-1}$  as ordered until a feasible index can be found {
      link  $\leftarrow j - 1$ 
      index  $\leftarrow$  current position in  $V_{j-1}$ 
      score  $\leftarrow$  (current score in  $V_{j-1}$ ) + SSE( $j, j + 1, \dots, i$ )
      Include the above triplet as a new element in  $V_i$ 
    }
  }
  Sort  $V_i$  according to the increasing order of SSE scores
}

```

In the above algorithm, the term “feasible” is defined in the section *Partitioning: test for change-point detection*. When we finish screening the last time points, the overall optimized partition $S = \{s_{m_k} : k=0, 1, 2, \dots, \hat{g}, \hat{g}+1, m_0=1, m_{\hat{g}+1}=m\}$ can be obtained in a backward manner:

```

 $i \leftarrow m$ ;  $h \leftarrow 1$ 
Create the set  $S$  with an element  $s_m$ 
while  $h > 0$  do {
   $j \leftarrow i$ ;  $i \leftarrow V_j.link[h]$ ;  $h \leftarrow V_j.index[h]$ 
  Include  $s_j$  as a new element in the set  $S$ 
}

```

Notice $\hat{g}$ is determined after the above procedure is completed. Then, we obtain the estimated $\{\hat{B}_k : k=1, 2, \dots, \hat{g}+1\}$. Since $\{\hat{\beta}_{\hat{B}_k}\}$ have already been calculated in our dynamic algorithm, they can be simply retrieved from the computer memory.

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Figure 1.

The simulation based estimation performance evaluation of our method. The traditional boxplots are presented for the estimation results (y-axis) for different parameters (described on x-axis). The short gray solid horizontal lines represent the true values of β 's and variance parameters. The simulation results based on different simulation scenarios are presented: (a) 80 subjects and 6 repeated measurements per subject; (b) 80 subjects and 9 repeated measurements per subject; (c) 120 subjects and 6 repeated measurements per subject; (d) 120 subjects and 9 repeated measurements per subject.

Figure 2.

The change-point detection results for a diabetes study data set with HbA1c as the response variable. Three change-points detected by our method are illustrated in the plots for the estimated mean levels of HbA1c difference vs. the days since randomization. (a) The estimation results for the control group patients; (b) The estimation results for the treatment group patients; (c) The estimation results for the treatment effect. The time-point-wise $100(1 - 0.05/8)\%$ and $100(1 + 0.05/8)\%$ confidence intervals are also presented in each plot.

Table 1

The distribution (in percentage) of total number of detected change-points based on the simulation study with different sample size scenarios: (a) 80 subjects and 6 repeated measurements per subject; (b) 80 subjects and 9 repeated measurements per subject; (c) 120 subjects and 6 repeated measurements per subject; (d) 120 subjects and 9 repeated measurements per subject.

Scheme	Total number of change-points								
	0	1	2	3	4	5	6	7	8
(a)	9.2	4.3	65.4	16.6	4.2	0.3	0	0	0
(b)	4.3	3.6	69.0	19.1	2.9	0.9	0.2	0	0
(c)	1.3	1.1	75.5	16.6	4.9	0.6	0	0	0
(d)	0.1	0.7	82.0	13.7	2.5	0.9	0.1	0	0

Table 2

The distribution (in percentage) of detected change-point locations based on the simulation study with different sample size scenarios: (a) 80 subjects and 6 repeated measurements per subject; (b) 80 subjects and 9 repeated measurements per subject; (c) 120 subjects and 6 repeated measurements per subject; (d) 120 subjects and 9 repeated measurements per subject. In the table, “index” represents the index of each identified change-point.

Scheme	index	Change-point locations							
		1 2	2 3	3 4	4 5	5 6	6 7	7 8	8 9
(a)	1st	6.2	2.8	88.5	1.1	0.2	0.9	0.2	0.1
	2nd	0	0.7	7.6	6.1	6.1	78.4	1.0	0
	3rd	0	0	1.9	2.4	6.6	60.7	14.7	13.7
	4th	0	0	0	2.2	0	40.0	17.8	40.0
	5th	0	0	0	0	0	33.3	33.3	33.3
(b)	1st	5.4	4.1	89.1	0.5	0	0.7	0.1	0
	2nd	0	1.0	8.5	4.7	3.8	81.5	0.4	0.1
	3rd	0	0	3.9	1.7	3.9	57.6	19.0	13.9
	4th	0	0	0	5.0	10.0	40.0	15.0	30.0
	5th	0	0	0	0	9.1	45.5	9.1	36.4
	6th	0	0	0	0	0	50.0	50.0	0
(c)	1st	4.8	4.2	90.7	0.3	0	0.1	0	0
	2nd	0	0.9	7.5	4.0	5.3	81.6	0.6	0.1
	3rd	0	0	4.1	4.1	5.9	60.2	14.9	10.9
	4th	0	0	0	3.6	3.6	45.5	16.4	30.9
	5th	0	0	0	0	0	66.7	16.7	16.7
(d)	1st	3.2	3.1	93.5	0	0	0.2	0	0
	2nd	0	0.9	5.3	3.2	2.5	88.0	0	0
	3rd	0	0	5.2	0.6	5.8	56.4	17.4	14.5
	4th	0	0	0	5.7	5.7	45.7	17.1	25.7
	5th	0	0	0	0	0	40.0	30.0	30.0
	6th	0	0	0	0	0	0	0	100.0

Table 3

The simulation based estimation performance evaluation of our method. The bias and standard deviation are calculated for each of the model parameters. The simulation results based on different simulation scenarios are presented: (a) 80 subjects and 6 repeated measurements per subject; (b) 80 subjects and 9 repeated measurements per subject; (c) 120 subjects and 6 repeated measurements per subject; (d) 120 subjects and 9 repeated measurements per subject.

Parameter	Scheme							
	Bias			(d)	Standard deviation			(d)
	(a)	(b)	(c)		(a)	(b)	(c)	
β_{01}	0.0043	-0.0021	0.0022	0.0008	0.169	0.172	0.140	0.136
β_{02}	0.0059	-0.0035	0.0020	0.0003	0.164	0.168	0.138	0.136
β_{03}	0.0082	-0.0051	0.0038	0.0010	0.163	0.171	0.139	0.137
β_{04}	-0.0252	-0.0161	-0.0015	0.0002	0.206	0.185	0.150	0.139
β_{05}	-0.0198	-0.0135	-0.0015	0.0013	0.202	0.183	0.148	0.138
β_{06}	-0.0287	-0.0158	-0.0042	0.0007	0.211	0.190	0.152	0.139
β_{07}	0.0447	0.0187	0.0077	0.0007	0.201	0.185	0.152	0.143
β_{08}	0.0376	0.0190	0.0034	-0.0012	0.194	0.182	0.145	0.142
β_{09}	0.0320	0.0149	0.0047	-0.0001	0.198	0.184	0.147	0.140
β_{11}	-0.0364	-0.0102	-0.0109	-0.0017	0.270	0.243	0.196	0.183
β_{12}	-0.0405	-0.0084	-0.0105	-0.0009	0.265	0.243	0.193	0.185
β_{13}	-0.0461	-0.0079	-0.0124	-0.0015	0.264	0.249	0.202	0.189
β_{14}	0.0553	0.0298	0.0122	0.0047	0.309	0.275	0.211	0.186
β_{15}	0.0459	0.0241	0.0102	0.0018	0.295	0.266	0.204	0.185
β_{16}	0.0567	0.0274	0.0122	0.0027	0.308	0.275	0.213	0.189
β_{17}	-0.0514	-0.0197	-0.0085	0.0021	0.261	0.242	0.208	0.188
β_{18}	-0.0415	-0.0223	-0.0031	0.0042	0.249	0.239	0.199	0.187
β_{19}	-0.0373	-0.0171	-0.0036	0.0028	0.251	0.243	0.199	0.186
$\sqrt{d_0}$	-0.0212	-0.0167	-0.0084	-0.0072	0.090	0.086	0.067	0.067
$\sqrt{d_1}$	-0.0494	-0.0274	-0.0205	-0.0114	0.097	0.056	0.053	0.039
σ	0.0352	0.0170	0.0062	-0.0001	0.085	0.063	0.041	0.020