Mixed Effects Envelope Models*

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Abstract

When multiple measures are collected repeatedly over time, redundancy typically exists among responses. The envelope method was recently proposed to reduce the dimension of responses without loss of information in regression with multivariate responses. It can gain substantial efficiency over the standard least squares estimator. In this paper, we generalize the envelope method to mixed effects models for longitudinal data with possibly unbalanced design and time-varying predictors. We show that our model provides more efficient estimators than the standard estimators in mixed effects models. Improved accuracy and efficiency of the proposed method over the standard mixed effects model estimator are observed in both the simulations and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.

Keywords: Envelope method, mixed effects model, sufficient dimension reduction, efficiency gain.

1 Introduction

1.1 Literature review

Over the past three decades, an increasing amount of literature has emerged on the topic of sufficient dimension reduction (SDR). Li (1991) proposed the sliced inverse regression to reduce the dimension of the predictors. That is, assuming the response only depends on a linear combination of the predictors, one regresses the predictors $X$ against the response $Y$ to circumvent any model-fitting process. Cook (1998) defined the central subspace as the

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subspace with the minimal dimension such that the response is independent of the predictors given the projection of the predictors onto the space. Other SDR methods include but not limited to sliced average variance estimation (Cook and Weisberg 1991), principal Hessian direction (Li 1992), contour regression (Li et al. 2005), inverse regression estimation (Cook and Ni 2005), directional regression (Li and Wang 2007), likelihood-acquired directions (Cook and Forzani 2009), discretization-expectation estimation (Zhu et al. 2010a), non-elliptically distributed predictors (Li and Dong 2009; Dong and Li 2010), dimension reduction based on canonical correlation (Fung et al. 2002; Zhou and He 2008), and average partial mean estimation (Zhu et al. 2010b). However, the aforementioned methods all focus on the dimension reduction of predictors with univariate response.

Recently, Cook et al. (2010) proposed a new sufficient dimension reduction method called the envelope method to reduce the dimension of responses in multivariate regression. Specifically, Cook et al. (2010) considered the following multivariate linear regression model

\[ Y_i = \alpha + \beta X_i + \epsilon_i, \tag{1} \]

where \( i \) indicates the \( i^{th} \) individual, \( Y_i, \epsilon_i \in \mathbb{R}^r, X_i \in \mathbb{R}^p \) and the parameter of interest is \( \beta \).

The key idea of the envelope method is to assume the existence of redundancy in responses that do not contribute to the estimation of \( \beta \) in model (1), so that the estimation of \( \beta \) is more efficient by leveraging this condition. Cook et al. (2010) assumes that there exists an orthogonal matrix \( (\Gamma, \Gamma_0) \in \mathbb{R}^{r \times r} \), where \( \Gamma \in \mathbb{R}^{r \times u} \) and \( \Gamma_0 \in \mathbb{R}^{r \times (r-u)} \), with \( 0 \leq u \leq r \) satisfying the following conditions:

**Condition 1.** \( \Gamma_0^T Y_i \perp \perp X_i; \)

**Condition 2.** \( \Gamma^T Y_i \perp \perp \Gamma_0^T Y_i | X_i; \)

where \( \perp \perp \) indicates independence. Under Conditions 1 and 2, \( \Gamma_0^T Y_i \) is redundant for a fixed effect regression (Cook et al. 2010). The \( \Sigma_\epsilon \)-envelope is uniquely defined to be the smallest subspace satisfying these conditions. Once the basis \( \hat{\Gamma} \) is obtained, the envelope estimator is obtained by projecting the ordinary least square estimator onto the estimated envelope space. Cook et al. (2010) showed that the envelope estimator can achieve efficiency gain over the OLS estimator. Following the definition in their paper, we define the variance of \( \Gamma_0^T Y_i | X_i \) as the material part variance, and \( \Gamma_0^T Y_i \) as the immaterial part variance. The efficiency gain will be substantial if the variation of the immaterial part is relatively large as compared with that of the material part.

The envelope methods have been developed in different settings, including response envelope (Cook et al. 2010), partial envelope (Su and Cook 2011), inner envelope (Su and Cook 2012), scaled envelope (Cook and Su 2013), predictor envelope (Cook et al. 2013), reduced rank envelope (Cook et al. 2015), simultaneous envelope (Cook and Zhang 2015b), model-free envelope (Cook and Zhang 2015a), and tensor envelope (Li and Zhang 2017).
Longitudinal data, also known as panel data, collects repeated measurements of the same subjects over time. As a distinctive feature of longitudinal data, measures that are collected repeatedly over time are typically correlated and redundancy typically exists among responses. Hence, reducing data to lower dimensions can improve efficiency while still preserving all relevant information on regression. Additionally, data may be unbalanced in the sense that subjects are not measured at the same time points. Moreover, the predictors may depend on time and may have different trajectories over time across individuals. For example, in a study of the effect of smoking on body weight, the number of cigarettes smoked per day may stay the same for some individuals but not for others. These features distinguish the longitudinal data from the cross-sectional data in terms of appropriate analyses. However, the study of sufficient dimension reduction for longitudinal data is quite limited. Pfeiffer et al. (2012) developed first-moment sufficient dimension reduction techniques to replace the original predictors with longitudinal nature. Bi and Qu (2015) applied the quadratic inference function to longitudinal data sufficient dimension reduction. The literature is even more scarce on dimension reduction in mixed effects models with high-dimensional response. Some early work has been done by Zhou et al. (2010) using a reduced rank model for spatially correlated hierarchical functional data and by Hughes and Haran (2013) using sparse reparameterization to reduce spatial confounding.

In this paper, we propose a mixed effects envelope model. Similar to the standard mixed effects model, the variability of each observation are composed of the within-individual variability and the between-individual variability. The mixed effects envelope model recovers the distribution of the unobserved between-individual random coefficient and reduces noises in the within-individual variation. The mixed effects envelope model inherits both the efficiency gain of the standard envelope model and the flexibility of the standard mixed effects model. Specifically, our methods result in more efficient estimators than those from the standard mixed effects models and can be used for unbalanced data as well as with time-varying predictors.

1.2 Notation

Consider a study with \( n \) individuals with each individual being measured at a total of \( J_i \) time points, where \( i = 1, \ldots, n \) and \( j = 1, \ldots, J_i \). Let \( J = \sum_{i=1}^n J_i \) denote the total number of the observations across time. For an individual \( i \) at time \( j \), let \( Y_{ij} \in \mathbb{R}^r \) denote the responses of length \( r \), let \( X_{ij} \in \mathbb{R}^p \) denote the vector of predictors of length \( p \), and let \( Z_{ij} \in \mathbb{R}^q \) denote the vector of predictors of length \( q \). Predictors \( X_{ij} \) and \( Z_{ij} \) can either be stochastic or nonstochastic. Let \( Y_i = (Y_{i1}, \ldots, Y_{iJ_i}) \) denote the responses, and \( X_i = (X_{i1}, \ldots, X_{iJ_i}) \), \( Z_i = (Z_{i1}, \ldots, Z_{iJ_i}) \) denote the predictors for one individual at all time points. Let \( \mathbb{R}^{r \times p} \) denote the class of all matrices with size \( r \times p \). Let \( \mathbb{S}^{r \times r} \) denote the class of all symmetric positive definite matrices of size \( r \). Let \( I_r \) denote the identity matrix of size \( r \). Let vec(·) denote the vectorization of a matrix by stacking the columns of the matrix on top of one another, and let vech(·) denote the vectorization of the unique part of each column that lies
on or below the diagonal. Let † denote the Moore-Penrose inverse. Also, let \( E_r \in \mathbb{R}^{r^2 \times r(r+1)/2} \) to be the expansion matrix such that vec(\( \cdot \)) = \( E_r \text{vech}(\cdot) \) and \( C_r \in \mathbb{R}^{r(r+1)/2 \times r^2} \) to be the contraction matrix such that vech(\( \cdot \)) = \( C_r \text{vec}(\cdot) \). Let \( \tilde{Y}_i = \text{vec}(Y_i) \) denote the vectorized responses. Let \( A \otimes B \) denote the kronecker product between \( A \) and \( B \). All the population covariance matrices in this paper are positive definite. We use \( \text{span}(A) \) to denote the span of the column vectors of \( A \).

1.3 Organization of the paper

We organize this paper as follows. In Section 2, we give the standard mixed effects model and discuss a special case where classic envelope can be directly applied. In Section 3, we propose the mixed effects envelope model as well as provide a graphical illustration of our method. We further illustrate our proposed method in the simulations in Section 4 and data analysis in Section 5. We conclude with a brief discussion in Section 6.

2 Preliminary

2.1 Mixed effects model

Consider the mixed effects model

\[
Y_{ij} = \alpha + \beta X_{ij} + b_i Z_{ij} + \varepsilon_{ij},
\]

where \( \alpha \in \mathbb{R}^r \) is the intercept, \( \beta \in \mathbb{R}^{r \times p} \) denotes the coefficient for the fixed effects and \( b_i \in \mathbb{R}^{r \times q} \) denotes the random coefficients. Assume vec(\( b_i \)) identically and independently follows \( N(0, \Sigma_b) \), where \( \Sigma_b \in S^{qr \times qr} \). The residual error \( \varepsilon_{ij} \) identically and independently follows \( N(0, \Sigma_\varepsilon) \) for \( i = 1, \ldots, n \) and \( j = 1, \ldots, J_i \), where \( \Sigma_\varepsilon \in S^{r \times r} \). The normality of random effect and error are assumed here for simplicity. We extend our result when they have finite \((4 + \delta)\)-th moment in Section 3. The random effect \( b_i \) is assumed to be independent from the residual error \( \varepsilon_{ij} \), i.e., \( b_i \perp \varepsilon_{ij} \). The variance due to random coefficient \( \Sigma_b \) is the between-subject variability and the variance due to the error \( \Sigma_\varepsilon \) is the within-subject variability. Let \( A_{ij} = Z_{ij}^T \otimes I_r \), then \( b_i Z_{ij} = (Z_{ij}^T \otimes I_r) \text{vec}(b_i) = A_{ij} \text{vec}(b_i) \). The covariance of responses across time for the same individual is correlated \( \text{Cov}(Y_{ij}, Y_{ij'} | X_{ij}, X_{ij'}, Z_{ij}, Z_{ij'}) = A_{ij} \Sigma_b A_{ij'}^T \) if \( j \neq j' \), and \( \text{Var}(Y_{ij} | X_{ij}, Z_{ij}) = A_{ij} \Sigma_b A_{ij}^T + \Sigma_\varepsilon \). Let \( \varepsilon_i = (\varepsilon_{i1}, \ldots, \varepsilon_{iJ_i}) \), we can rewrite the model above in a matrix form as

\[
Y_i = \alpha \otimes 1_{J_i}^T + \beta X_i + b_i Z_i + \varepsilon_i.
\]

Model (1) is a special case of model (2) when \( \Sigma_b = 0 \), and \( J_i = 1 \) for \( i = 1, \ldots, n \).
2.2 Classic envelope model for a special case of longitudinal data

The classic envelope method can be applied to longitudinal data in a special case: when the data is balanced, the predictors do not vary with time, and random slopes are not included in the model (random intercepts are included). We will show that under this setting, the mixed effects model naturally contains an envelope structure over the observations across time. Under this setting, $J_i = J$ for any $i$. Also, if we assume $X_i$ does not vary with time, then (2) can be written as

$$\tilde{Y}_i = 1_J \otimes \alpha + (1_J \otimes \beta)X_i + \tilde{\varepsilon}_i,$$

where $\tilde{\varepsilon}_i \in \mathbb{R}^{rJ}$ i.i.d follows $\mathcal{N}(0, \tilde{\Sigma}_e)$ and $\tilde{\Sigma}_e = I_J \otimes \Sigma_b + \Sigma_e$. This model is a standard multivariate model, hence we can impose an envelope model on it. Let $\mathcal{E}_{\Sigma_b}(\tilde{B})$ denote the $\tilde{\Sigma}_e$-envelope for $\tilde{B}$, where $\tilde{B} = \text{span}(1_J \otimes \beta)$. The structure of $\mathcal{E}_{\Sigma_b}(\tilde{B})$ is given in the following proposition and corollary.

**Proposition 1.** Under model (3), the basis for $\mathcal{E}_{\Sigma_b}(\tilde{B})$ is $1_J \otimes \Phi$, where $\Phi$ is the basis for $\mathcal{E}(\Sigma_{e/J} + \Sigma_b)(B)$.

**Corollary.** Under model (3), the dimension of $\mathcal{E}_{\Sigma_b}(\tilde{B}) \subseteq \mathbb{R}^{rJ}$ cannot exceed $r$.

Intuitively, although the repeated measures from the same individual are correlated, because neither the fixed effects nor the random effects change over time, we can reduce the dimension of responses by averaging each individual over different time points. That is, model (2) naturally results in combinations of the responses of dimension $r(J-1)$ that do not contribute to the regression. This results in a $\tilde{\Sigma}_e$-envelope $\mathcal{E}_{\Sigma_b}(\tilde{B})$ with envelope dimension no greater than $r$ rather than $rJ$.

Proposition 1 presents a simple but important observation: if the true model is a mixed effects model but instead we fit a standard multivariate linear regression, even we have a reduced dimension from $rJ$ to $r$ by the envelope method, we do not gain additional efficiency. This is because the failure to leverage the mixed effects model structure creates redundancy. Such an observation naturally leads us to explore an envelope model that can incorporate the mixed effects model structure to gain further efficiency.

3 The mixed effects envelope model

3.1 Conditions

Now, we propose the mixed effects envelope model. The key requirement of the classic envelope method is the existence of some linear combination of the responses that do not
contribute to the regression. With longitudinal data, because both \( X_i \) and \( Z_i \) are observed predictors, it may seem natural to extend Conditions 1 and 2 by replacing \( X_i \) with \( (X_i, Z_i) \) as

**Condition 1°.** \( \Gamma_0^T Y_i \perp (X_i, Z_i) \);  

**Condition 2°.** \( \Gamma^T Y_i \perp \Gamma_0^T Y_i \mid X_i, Z_i \).

It has been shown that the standard envelope Conditions 1 and 2 are equivalent to the reparameterization \( \text{span}(\beta) \subseteq \text{span}(\Gamma) \) and \( \Sigma_\varepsilon = \Gamma \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T \), where \( \Omega = \Gamma \Sigma_\varepsilon \Gamma \), and \( \Omega_0 = \Gamma_0 \Sigma_\varepsilon \Gamma_0 \). Unlike Conditions 1 and 2 which impose conditions on population parameters, Conditions 1° and 2° are equivalent to requiring certain relationships between \( Z_i \) and parameters as shown in the proposition below. In general, Conditions 1° and 2° are hard to satisfy because their validity is contingent on the observed value of \( Z_i \) in the sample.

**Proposition 2.** Conditions 1° and 2° hold under model (2) if and only if \( \Gamma_0^T \beta = 0 \), \( Z_i \otimes \Gamma_0 = 0 \), and \( I_{J_i} \otimes (\Gamma^T \Sigma_\varepsilon \Gamma_0) + (Z_i^T \otimes \Gamma^T) \Sigma_b (Z_i \otimes \Gamma_0) = 0 \).

To modify Condition 1°, we want to find a condition that reduces to Condition 1 when there is no random effect. Recall under (1), \( \text{vec}(\Gamma_0^T Y_i) \) only depends on predictors through \( \beta X_i \) in the mean and to have its distribution free of \( \beta \) is the same as to have \( \Gamma_0^T Y_i \perp X_i \). In other words, Condition 1 can be equivalently expressed as \( E(\Gamma_0^T Y_i \mid X_i) = E(\Gamma_0^T Y_i) \) under linear model. However, under model (2), \( \text{vec}(\Gamma_0^T Y_i) \) depends on the predictors \( (X_i, Z_i) \) through both mean and variance. Notice that the parameter of interest \( \beta \) only involves in the mean of \( \text{vec}(\Gamma_0^T Y_i) \). Thus, this motivates us to relax the distributional independence between \( \Gamma_0^T Y_i \) and \( (X_i, Z_i) \) to be just mean independence, i.e., \( E(\Gamma_0^T Y_i \mid X_i, Z_i) = E(\Gamma_0^T Y_i) \) so that this condition reduces to Condition 1 when there is no random effect.

To modify Condition 2°, we also want to find a condition that reduces to Condition 2 in the absence of the random effect. Note \( \text{vec}(\Gamma^T Y_i) \mid \text{vec}(\Gamma_0^T Y), X_i, Z_i, b_i \sim N(\mu^*, \Sigma^*) \), where

\[
\mu^* = \text{vec}(\Gamma^T \beta X_i + \Gamma^T b_i Z_i) + I_{J_i} \otimes \left\{ \Gamma^T \Sigma_\varepsilon \Gamma_0 \Gamma_0^T \Sigma_\varepsilon^{-1} \Gamma \right\} \left\{ \text{vec}(\Gamma_0^T Y_i) - \text{vec}(\Gamma_0^T \beta X_i + \Gamma_0^T b_i Z_i) \right\},
\]

and \( \Sigma^* = I_{J_i} \otimes (\Gamma^T \Sigma_\varepsilon^{-1} \Gamma)^{-1} \). That is, if we conditional on both predictors and random effects, the conditional independence between \( \Gamma^T Y_i \) and \( \Gamma_0^T Y_i \) is equivalent to \( \Gamma^T \Sigma_\varepsilon \Gamma_0 = 0 \), i.e., \( \Gamma \) reduces \( \Sigma_\varepsilon \). This condition reduces to Condition 2 when there is no random effect.

Thus, to develop the mixed effects envelope model, we assume

**Condition 1*.** \( E(\Gamma_0^T Y_i \mid X_i, Z_i) = E(\Gamma_0^T Y_i) \),

**Condition 2*.** \( \Gamma^T Y_i \perp \Gamma_0^T Y_i \mid X_i, Z_i, b_i \).

As mentioned, in the absence of random effects, Condition 1* and 2* will reduce to Condition 1 and 2 under the linear model. Conditions 1* and 2* can be viewed as extensions of
Conditions 1* and 2* for longitudinal data. However, unlike the classic envelope condition \((\text{Cook et al.}, 2010)\), Condition 1* only requires the expectation of \(\Gamma_0^T Y_i \mid X_i, Z_i\) and \(\Gamma_0^T Y_i\) to be the same. The motivation of Condition 1* is that instead of imposing the redundancy of \(\Gamma_0^T Y_i\) on its entire distribution, we just assume the redundancy on its mean, which is easier to satisfy.

Condition 2* assumes the independence between \(\Gamma^T Y_i\) and \(\Gamma_0^T Y_i\) conditional on predictors \((X_i, Z_i)\), as well as on the unobservable \(b_i\). Equivalently, the redundancy of responses is within individuals rather than across. In other words, Condition 2* excludes the possibility of \(\Gamma_0^T Y_i\) contributing to the regression through a correlation with \(\Gamma^T Y_i\) given any individual, although such correlation may be present in the population. Here, different from the original envelope model, under model (2), \(\Sigma_e\) is the variance of outcomes given predictors and random effects, which is only the within-subject variation not including the between-subject variation. Thus, when the study is balanced, even when the classic envelope model does not have much efficiency gain, the mixed effects envelope may achieve substantial efficiency gain: decomposing part of the variability into material and immaterial variability may be possible even when decomposing the total variability may not be possible. The idea of using part of parameters to form an envelope was also adopted in the development of partial envelope (\(\text{Su and Cook}, 2011\)), where part of parameters in the mean model are used.

Other than having clear interpretations, Conditions 1* and 2* also facilitate the reparameterization of the original parameters in (2). Under Condition 1*, \(\mathbb{E}(\Gamma_0^T Y_i \mid X_i, Z_i)\) is free of \(\beta\), which indicates \(\text{span}(\beta) \subseteq \text{span}(\Gamma)\). Additionally, since Condition 2* conditions on the random effects, we have \(\Sigma_e = \Gamma_0 \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T\). We define the smallest reducing subspace that satisfies Conditions 1* and 2* as the mixed effects envelope, or \(\Sigma_e\)-mean envelope and write it as \(\hat{\mathcal{E}}_{\Sigma_e}(B)\). Under Conditions 1* and 2*, model (2) can be written as:

\[
Y_{ij} = \alpha + \Gamma_0 \eta X_{ij} + b_i Z_{ij} + \varepsilon_{ij},
\]

where \(\varepsilon_{ij}\) identically and independently follows \(N(0, \Sigma_e)\), and \(\Sigma_e = \Gamma_0 \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T\).

Under the mixed effects envelope model (4), the number of variational independent parameters changes from \(r + rp + r(r + 1)/2 + qr(qr + 1)/2\) to \(r + up + r(r + 1)/2 + qr(qr + 1)/2\). Since \(u \leq r\), the number of parameters of mixed effects envelope model is no more than the standard mixed effects model. When \(J\) is large, the number of parameters in the mixed effects envelope model (4) can be substantially fewer than those in the standard envelope model, but there is no general relationship between the number of parameters in these two envelope models.

Under Conditions 1* and 2* and model (2), the covariance \(\text{Var}(\tilde{Y}_i \mid X_i, Z_i)\) has a specific heteroscedastic error structure \(\text{Var}(\tilde{Y}_i \mid X_i, Z_i) = A_i \Sigma_e A_i^T + I_J \otimes \Sigma_e\), where \(A_i = Z_i^T \otimes I_r\). Another heteroscedastic error model was considered in \(\text{Su and Cook}, 2013\), where the predictors are only indicators for the subpopulation and individuals in the same subpopulation have the same distribution. Following \(\text{Su and Cook}, 2013, \text{Park et al.}, 2017\) generalized the multivariate envelope mean model to groupwise envelope regression models with
heteroscedastic error. In their setting, the envelope is assumed to be the intersection of subspaces that contains columns of all the coefficients across populations. Under model (2), it is possible that $Z_i$ is different for all individuals, then we have $n$ single individual subpopulations. This situation cannot be directly handled in their framework.

### 3.2 Graphical illustration

Before diving into the estimation details of the mixed effects envelope model, we first provide a graphical illustration of the classic envelope, the standard mixed effects estimator and our mixed effects envelope estimator, under the mixed effects model. We generate the outcomes $Y_i$ from (1) with $Z_{ij} = 1$. To compare the classic envelope with the mixed effects envelope, we only consider the setting where data is balanced and the predictors are time-invariant.

Consider two groups of individuals with $X_i = 0$ and 1 respectively. We generate $n = 2000$ individuals with $J_i = 5$ observation for each group. For individual $i$ at time point $j$, we generate a bivariate response $Y_{ij} = (Y_{ij1}, Y_{ij2})^T$ from the mixed effects model (1) with $\alpha = 0$ and $\beta = (-7.07, 7.07)^T$. We are interested in examining the mean group difference.

Figure 1a presents the raw data, where we directly implement the OLS method and the classic envelope model. The OLS estimator is $(-7.54, 6.38, -7.17, 6.83, -7.23, 6.66, -7.81, 6.28, -7.68, 6.27)^T$ with the MSE 1.10. Model (3) ignores the fact that some responses are repeated measures over time and does not distinguish them from different measures collected at the same time point. As a result, the OLS estimator of model (3) is relatively inefficient.

By applying the classic envelope method, the estimated envelope dimension is $\hat{u} = 2$. The envelope estimate for the group difference is $(-7.46, 6.52, -7.49, 6.49, -7.41, 6.53, -7.50, 6.49, -7.57, 6.39)^T$ with the MSE 0.93. The classic envelope removes some redundancy in the responses as compared with the OLS estimator from model (3). However, as we show below, such redundancy can easily be removed by incorporating the mixed effects model structure.

Figure 1b shows the performance of the estimator under model (1) using the expectation-maximization (EM) algorithm, a standard mixed effects model estimator. For comparison, we keep the OLS estimate of $Y_{ij} - b_i$ in two groups when $b$ is assumed observed (dashed curve in Figure 1b) as a benchmark. The solid curves denote the estimated distribution of $Y_{ij} - b_i$ using the standard EM. The density curves related to the EM algorithm are not simply projections of scattered points obtained by subtracting $b$, and the scatter points just provide intuitions. The EM algorithm separates the between-subject variability from the within-subject variability when calculating the point estimates, hence, the solid and dashed density curves almost overlap completely. The group difference using the standard EM is $(-7.48, 6.48)^T$ with the MSE 0.95. The MSE is similar to that of the classic envelope in (5), which confirms that incorporating the mixed effects model already eliminates some noise in the repeated measures.
Figure 1. Graphical illustration of the standard mixed effects estimator and the mixed effects envelope estimator, with a random intercept. Individuals of the two groups are represented by cross dots ($X = 0$) and triangles ($X = 1$). The scatter points in Figure 1a demonstrate the original data, whereas Figure 1b and 1c demonstrate the data of $Y - b$ as if $b$ is observed. Solid curves are from the EM-type estimates, and the dashed curves are from the estimates when $b$ is given.

Figure 1c illustrates the performance of our mixed effects envelope method. The solid curves at the bottom are obtained by applying our method on the data set in Figure 1a. Unlike the standard EM algorithm which only recovers the between-subject variability, our method additionally reduces the within-subject variability. The estimated envelope dimension $\hat{u} = 1$. The group difference estimated from our method is $(-6.97, 6.99)^T$ with the MSE 0.40. The solid and dashed curves are similar, indicating that our method provides a similar point estimate as the standard envelope estimator with random effects subtracted. While the classic envelope estimator has almost no efficiency gain over the standard EM estimator (similar MSEs), our mixed effects envelope method achieves substantial efficiency gain over the standard EM estimator (the MSE ratio is only about 0.4) and even more efficiency gain over the OLS estimator from model (4) (the MSE ratio is about 0.36). This shows that by leveraging both the mixed effects model and the envelope structure, our method may achieve a much greater amount of efficiency gain as compared with either method.
3.3 Maximum likelihood estimation

Under the reparameterization implied by Conditions 1* and 2*, we first investigate the likelihood function given the observed data. Recall that \( A_i = Z_i^T \otimes I_r \). We have

\[
L(\theta; Y; X, Z) \propto n \prod_{i=1}^{n} \left| I_{J_i} \otimes \Sigma_\varepsilon + A_i \Sigma_b A_i^T \right|^{-1/2} \exp \left\{ -\frac{1}{2} \{ \text{vec}(Y_i) - \alpha \otimes 1_{J_i} - \text{vec}(\beta X_i) \}^T (I_{J_i} \otimes \Sigma_\varepsilon + A_i \Sigma_b A_i^T)^{-1} \{ \text{vec}(Y_i) - \alpha \otimes 1_{J_i} - \text{vec}(\beta X_i) \} \right\},
\]

(5)

where \( \theta = (\alpha, \Gamma, \eta, \Omega, \Omega_0, \Sigma_b) \), \( \beta = \Gamma \eta \), \( \Sigma_\varepsilon = \Gamma \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T \) and \( \propto \) denotes proportional to. The formula above is obtained by square completion and the Woodbury matrix identity. As the likelihood function \( L(\theta; Y; X, Z) \) have a complicated form in \( \theta \), the MLE of model (4) does not have a closed form in general.

In order to obtain the maximum likelihood estimate, we combine the EM-algorithm and the envelope structure. The resulting algorithm is not trivial since the parameters are not element-wise identifiable and random effects are not observable. Due to space constraints, we only briefly describe the steps here and relegate the technical details of the algorithm in the Supplementary Materials. For any predetermined envelope dimension \( u \), we start with an initial value for all parameters. We calculate the E-step and then, during the M-step, we decompose the expectations from the E-step such that all the other parameters can be optimized individually given \( \Gamma \), and then we optimize over \( \Gamma \). We iterate such EM process till convergence.

We adapt the BIC in the classic envelope models (Eck and Cook, 2017) to estimate \( u \) in the mixed effects envelope model. Under model (4), BIC is \(-2l(\hat{\theta}; Y \mid X, Z) + \log(J_u)pu\), where \( l(\hat{\theta}; Y \mid X, Z) \) is the log of the likelihood \( L(\theta; Y; X, Z) \) given in (5). The penalty coefficient in BIC is \( \log(J_u) \) rather than \( \log(n) \) to take the longitudinal feature of data into consideration (Jones, 2011). Also, the likelihood in BIC is the observed data likelihood rather than the full data one. We summarize the mixed effects envelope algorithm in the appendix.

3.4 Efficiency Gain

We discuss the asymptotic variance of the mixed effects envelope estimator. The parameters of the envelope model is vector \( \phi = (\eta, \Gamma, \Omega, \Omega_0, \Sigma_b) \). A more rigorous notation is \( \phi = (\text{vec}(\eta), \text{vec}(\Gamma), \text{vech}(\Omega), \text{vech}(\Omega_0), \text{vech}(\Sigma_b)) \). We omit the vectorization notations here. We are interested in the property of the parameter \( \beta, \Sigma_\varepsilon \) and \( \Sigma_b \), which can be viewed as functions of \( \phi \). Generally, we have \( h(\phi) = (\beta, \Sigma_\varepsilon, \Sigma_b) = (\Gamma \eta, \Gamma \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T, \Sigma_b) = (h_1(\phi), h_2(\phi), h_3(\phi)) \). Let \( \theta = h(\phi), \hat{\theta}_{\text{mix-env}} \) and \( \hat{\theta}_{\text{mix-em}} \) denote the mixed effects envelope and standard EM estimates under (2). The asymptotic variance of our estimator can be
calculated using Shapiro (1986).

**Proposition 3.** Under model (2) and assume envelope conditions (i) and (ii) hold, then \( \sqrt{n}(\hat{\theta}_{mix-em} - \theta) \xrightarrow{d} N(0, V) \), and \( \sqrt{n}(\hat{\theta}_{mix-env} - \theta) \xrightarrow{d} N(0, V_{mix-env}) \) where \( V_{mix-env} = G(G^T VG)^\dagger G \), the form of \( V \) is given in the appendix, and \( G \) is given by

\[
\begin{pmatrix}
    I_p \otimes I & \eta^T \otimes I_r & 0 & 0 & 0 \\
    0 & 2C_r(\Gamma \Omega \otimes I_r - \Gamma \otimes \Gamma_0 \Omega_0^T) & C_r(\Gamma \otimes \Gamma)E_u & C_r(\Gamma_0 \otimes \Gamma_0)E_{r-u} & 0 \\
    0 & 0 & 0 & 0 & I_{qr(qr+1)/2}
\end{pmatrix},
\]

Moreover, \( V^{-\frac{1}{2}}(V - V_0)V^{-\frac{1}{2}} = I - V^{-\frac{1}{2}}G(G^T V^{-1} G)^\dagger G^T V^{-\frac{1}{2}} \geq 0 \), so the mixed effects envelope always has no larger asymptotic variance.

In order to provide some insights on occasions where our estimator can be efficient as compared with the standard method, we compare \( \text{avar}[\sqrt{n}\text{vec}(\hat{\beta})] \) using the mixed envelope model with the standard model under a relatively simple setting. Specifically, we set \( r = 2, \ J = 2, \ p = 1, \ Z_{i,j} = 1 \) for all \( i, j \), \( \Sigma_e = \begin{pmatrix} \sigma^2_1 & 0 \\ 0 & \sigma^2_0 \end{pmatrix} \), \( \Sigma_b = \begin{pmatrix} \sigma^2_b & 0 \\ 0 & \sigma^2_b \end{pmatrix} \), \( \Gamma = (1, 0)^T, \Gamma_0 = (0, 1)^T \) and \( \eta = 1 \). In this specific case, we have the close form formula

\[
\text{avar}[\sqrt{n}\text{vec}(\hat{\beta}_{mix-em})] = \begin{pmatrix}
    \frac{\sigma^2_0(\sigma^2_1 + 2\sigma^2_b)}{\sigma^2_0\sigma^2_{x_1} + \sigma^2_1\sigma^2_{x_2}} & 0 \\
    0 & \frac{\sigma^2_0(\sigma^2_0 + 2\sigma^2_b)}{\sigma^2_0\sigma^2_{x_1} + \sigma^2_0\sigma^2_{x_2}}
\end{pmatrix},
\]

and

\[
\text{avar}[\sqrt{n}\text{vec}(\hat{\beta}_{mix-env})] = \begin{pmatrix}
    \frac{\sigma^2_0(\sigma^2_1 + 2\sigma^2_b)}{\sigma^2_0\sigma^2_{x_1} + \sigma^2_1\sigma^2_{x_2}} & 0 \\
    0 & \sigma^2_{b_2}
\end{pmatrix},
\]

where \( \sigma^2_{b_2} = \left[ \frac{\sigma^2_0\sigma^2_{x_1} + \sigma^2_0\sigma^2_{x_2} + 4(\sigma^2_1 - \sigma^2_0)(\sigma^2_1\sigma^2_0 + 2\sigma^2_1\sigma^2_b + 2\sigma^2_0\sigma^2_b + 2\sigma^2_b)}{\sigma^2_1\sigma^2_0 + 2\sigma^2_b} \right]^{-1} \), \( \sigma^2_{x_1} = \sum^n_{i=1}(x_{i1} - \bar{x}_{i2})^2/n \) and \( \sigma^2_{x_2} = \sum^n_{i=1}(x_{i1}^2 + x_{i2}^2)/n \). As long as \( \sigma^2_1 \neq \sigma^2_0 \) and \( \sigma^2_0 > 0 \),

\[
\sigma^2_{b_2} < \frac{\sigma^2_0(\sigma^2_0 + 2\sigma^2_b)}{\sigma^2_0\sigma^2_{x_1} + \sigma^2_0\sigma^2_{x_2}}.
\]

The ratio

\[
\frac{\text{avar}[\sqrt{n}\text{vec}(\hat{\beta}^{(2)}_{mix-em})]}{\text{avar}[\sqrt{n}\text{vec}(\hat{\beta}^{(2)}_{mix-env})]} = 1 + \frac{4(\sigma^2_1 - \sigma^2_0)^2(\sigma^2_1\sigma^2_0 + 2\sigma^2_1\sigma^2_b + 2\sigma^2_0\sigma^2_b + 2\sigma^2_b)}{\sigma^2_1(\sigma^2_1 + 2\sigma^2_b)(\sigma^2_0\sigma^2_{x_1} + \sigma^2_0\sigma^2_{x_2})}
\]

tends to \( +\infty \) as \( \sigma^2_0 \to +\infty \). Therefore, the efficiency gain is large when \( \sigma^2_0 \) is large relative to \( \sigma^2_1 \). Consequently, in this case, fewer samples are needed to detect the same effect size for our method as compared with the standard EM.
The consistency and efficiency gain of the mixed effects envelope estimator in Proposition 3 is derived based on the normality of the error and random effect. In the next proposition, we justify the \(\sqrt{n}\)-consistency of \(\hat{\theta}_{\text{mix-env}}\) without the normality conditions on the error and random effect.

**Proposition 4.** If the error \(\varepsilon_{ij}\) and random effect \(b_i\) have finite \((4+\delta)\)-th moments for some \(\delta > 0\), and the regularity conditions in the appendix hold, then \(\sqrt{n}(\hat{\theta}_{\text{mix-env}} - \theta) \xrightarrow{d} N(0, \tilde{V})\), and \(\sqrt{n}(\hat{\theta}_{\text{mix-env}} - \theta) \xrightarrow{d} N(0, \tilde{V}_{\text{mix-env}})\) for some covariance matrices \(\tilde{V}\) and \(\tilde{V}_{\text{mix-env}}\). In addition, we have \(\tilde{V}_{\text{mix-env}} = G(G^TJG)^\dagger G^TJ\tilde{V}G(G^TJG)^\dagger G^T\). The definition of \(J\) is given in the Appendix.

### 4 Simulations

In this section, we carry out simulations to compare the finite sample efficiency of our estimator with the standard EM method, the response envelope method and the response PLS method using the SIMPLS algorithm. The response PLS is a counterpart algorithm of the standard PLS algorithm but to reduce the dimension reduction rather than that for predictors. A detailed algorithm can be found in [Cook (2018)](https://www.jstatsoft.org/v84/i02/paper). The response envelope and the response PLS methods do not take the time dependency among responses into consideration, but still provide consistent estimators. Although envelopes and PLS are asymptotically equivalent as [Cook et al. (2013)](https://dx.doi.org/10.1177/0027064413510814) suggested, their finite sample properties are different. We first consider a balanced case by generating a population of \(n = 50\) individuals, and each has \(r = 10\) responses measured at each of the 5 time points \((J_i = J = 5, i = 1, \ldots, 50)\). We set \(p = 6\) and \(q = 2\) for the fixed and random effects.

We generate parameters \(\Gamma\) and \(\beta_0\) of size \(r \times u\) and \(r \times p\), where \(u = 1\). The elements of \(\Gamma\) and \(\beta_0\) are from \(U(0, 1)\) and \(U(-10, 10)\). Let \(\beta = P\Gamma\beta_0\). We generate a matrix \(\mathbf{B}\) of dimension \(qr \times qr\) with each element from \(U(-10, 10)\) and let \(\Sigma_b = \mathbf{B}\mathbf{B}^T\). Let \(\Omega = 0.01I_u\) and \(\Omega_0 = 100I_{(r-u)}\) and let \(\Sigma_\varepsilon = \Gamma\Omega\Gamma^T + \Gamma_0\Omega_0\Gamma_0^T\). For each individual, \(X_{i1}, X_{i2}, X_{i3}\) vary with time, and \(X_{i4}, X_{i5}, X_{i6}\) stay fixed for all the time points, where each predictor (time varying or fixed over time) is independently generated from \(U(-10, 10)\). Then, generate \(Z_i = (Z_{i1}^T, Z_{i2}^T)^T\), where \(Z_{i1} = 1_{1 \times J}\), and each element of \(Z_{i2}\) follows \(U(-10, 10)\). Generate vector \(\varepsilon_{ij} \in \mathbb{R}^r\), where each column follows \(N(0, \Sigma_\varepsilon)\). Also generate \(b_i \in \mathbb{R}^{r \times q}\), where \(\text{vec}(b_i)\) is from the normal distribution \(N(0, \Sigma_b)\). Set \(Y_{ij} = \beta X_{ij} + b_i Z_{ij} + \varepsilon_{ij}\). We then calculate \(\hat{\beta}_{\text{mix-env}}, \hat{\beta}_{\text{mix-env}}^\dagger, \hat{\beta}_{\text{env}}\) and \(\hat{\beta}_{\text{pls}}\), and repeat the above procedure for 100 times.

We compute the square of \(l_2\) norm \(||\hat{\beta} - \beta||_2^2\) for each simulation. The boxplot of \(l_2^2\) error across 100 simulations is given in Figure 2a, where we suppress the outliers to make the figure clean. The mixed envelope estimates are significantly better in terms of both bias and variance than the standard EM estimates. For example, the mean \(l_2^2\) error of the mixed envelope estimate for \(\beta\) is 12.12, while that is 104.77, 79.40 and 105.99 for the standard
Figure 2. Empirical distribution of $\|\hat{\beta} - \beta\|_2^2$

EM, response envelope and response PLS estimates respectively. Also, 99 out of 100 of our method selected the correct envelope dimension $u = 1$.

Then, we examine the results where $J_i$ is uniformly generated from $\{5, 6, 7, 8, 9\}$. Other steps in the previous simulation remain unchanged. The mean $l_2^2$ error of $\hat{\beta}_{\text{mix-env}}$ is 9.30, while that is 69.11, 79.05 and 72.16 for $\hat{\beta}_{\text{mix-em}}, \hat{\beta}_{\text{env}}$ and $\hat{\beta}_{\text{pls}}$. Also, the envelope dimension is always correctly estimated as $\hat{u} = 1$. The empirical distribution of $l_2^2$ error is shown in Figure 2b. Our proposed mixed effects envelope estimator has much smaller MSE than the standard EM estimator even in relatively small samples.

5 Data Analysis

In this section, we apply our proposed method to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. The ACCORD randomized-control trial aimed at determining whether cardiovascular disease (CVD) event rates can be reduced in people with diabetes. Participants are between the ages of 40 and 82. All participants have Type 2 diabetes and an especially high risk for heart attack and stroke.

We are interested in the treatment effect on the quality of life and changes in health outcomes. The responses were collected at four time points, which are 12, 24, 36, 48 months after the beginning of the trial. We consider 2054 participants who responded to the survey, among whom 1156 individuals responded to all surveys. In our analysis, the response variables were treatment satisfaction, depression scale, aggregate physical activity score, aggregate mental score, aggregate interference score, symptom and distress score, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. The predictors were age and treatment, where we consider the intensive glycemia treatment ($T = 1$) and the standard glycemia treatment ($T = 0$).

We first assessed the difference in the quality of life versus glycemia level and age for people
Figure 3. The empirical cumulative distribution of the ratio between the estimated standard errors of the standard EM and that of our method for ACCORD data.

who attended all four surveys ($J_i = 4$). All responses except systolic blood pressure and diastolic blood pressure had a missing rate less than 1.5%. Since the missing rate is low, we imputed the missing data using its mean value. We assume there is only random intercept in our model. The mixed effects envelope method reduced the dimension of the response variable from $r = 9$ to $\hat{u} = 4$. The point estimates, bootstrap standard errors, and $p$-values for the regression parameter is given in Table 1 in the Supplementary Material. The magnitude of the point estimates of our method is in general slightly smaller than those of the standard EM. For example, the coefficient for treatment satisfaction with respect to treatment is 0.46 using our method and 0.69 using the standard EM. As the envelope estimate is obtained by projecting the standard estimates onto the envelope direction, the reduction in the magnitude can be interpreted as the noise subtracted from the original estimates. As mentioned in Section 3.3, the closed form of the standard errors of our method are difficult to obtain. Therefore, we used the nonparametric bootstrap. Figure 3a shows the empirical cumulative density distributions of the estimated standard errors of the standard EM versus that of our method. The estimated standard errors are in general smaller (on the right hand side of 1 in Figure 3a) using our method than using the standard EM, which indicates the efficiency gain of our method. The mean ratio of the coefficient standard error using our method over the standard EM is 1.33. That is, to achieve the same mean power among all predictors, our methods require 75.2% of the original sample.

Then, we repeated the analysis by including people with less than four surveys, thus $J_i$ varies across each person. In this case, the total number of observations $J$ increases from 1156 to 2054. The missing rate is about the same, so we imputed them using their mean again. The estimated envelope dimension is $\hat{u} = 1$. The point estimate, bootstrap standard errors and $p$-values for the regression coefficients are given in Table 2 in the Supplementary Material. It is worth noticing that our method found SBP and DBP corresponding to age significant, whereas the standard method found physical score corresponding to age significant. Figure 3b shows the empirical distribution of the ratio between the estimated standard errors of the two methods. The mean ratio of the coefficient standard error using our method over the standard EM is 4.07. That is, to achieve the same mean power among all predictors, our
Methods require 24.6% of the original sample. All the regression coefficients except symptom and distress score corresponding to age have a smaller standard error, which again shows that our method is more efficient.

6 Discussion

In this paper, we proposed the mixed effects envelope method to achieve a more efficient estimation than the traditional EM in longitudinal studies. Although this paper is motivated by the repeated measures problem, the mixed effects envelope model can also be used in clustered data to achieve efficiency gain. For example, patients are nested in physicians, who are in turn nested in clinics. Such clustered data also features in correlations between observations.

The mixed effects model is closely related to the missing data problem since the random effects can be viewed as missing for all observations. Moreover, the missing data techniques may be combined with the mixed effects model to further relax conditions. [Ma et al. (2019)] discussed the envelope method under the ignorable missingness of predictors and covariates.

In this paper, we assume that the measures collected at each visit are balanced and repeated measures may be collected at different time points across individuals. Such a condition may be violated when a different number of measures are collected every time. One possible solution is to use the union of responses as the balanced response and frame this into a missing data problem. The extension of the mixed effects models with missing data is left as a future research avenue.

In this paper, we considered a heteroscedastic error induced by the mixed effects model. [Su and Cook (2013)] proposed an alternative method for another heteroscedastic error covariance structure under the multivariate regression. Both covariance structures allow us to formulate the regression with heteroscedastic variance as a variation of the original envelope model and thus we can use the original computation to obtain the MLE of the likelihood. How to generalize the model with a general heteroscedastic variance structure is left for future research.

In many contemporary studies and applications, the dimension of data can be much larger than the number of observations. Under such high-dimensional settings, more refined variants of the envelope method are desired. Many studies have adapted the envelope method to high-dimensional settings under sparsity conditions. [Su et al. (2016)] proposed the envelope model for response variable selection under high-dimensional settings. [Zhu and Su (2020)] incorporated the envelope model with partial least squares for high-dimensional regression. We leave the extension of our mixed effects model for high-dimensional data as a future research topic.
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Supporting Information

Additional information for this article, including the proof of Proposition 1, 2, 3, 4, graphical illustration of the response envelope, EM-algorithm for the mixed effects envelope model, derivation of $\mu_{b_i,t}$ and $\Sigma_{b_i,t}$, the 1-D algorithm, the mixed effects envelope algorithm, and Tables 1 and 2 for the data analysis are available in the supplementary materials.

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Supplementary Material

The Supplementary Material contains the proof of Proposition 1, 2, 3, 4, graphical illustration of the response envelope, EM-algorithm for the mixed effects envelope model, derivation of \( \mu_{bi,t} \) and \( \Sigma_{bi,t} \), the 1-D algorithm, the mixed effects envelope algorithm, and Tables 1 and 2 for the data analysis.

Proof of Proposition 1

Under model \((3)\),

\[
\tilde{Y}_i = 1_J \otimes \alpha + (1_J \otimes \beta)X_i + \tilde{\varepsilon}_i,
\]

Let

\[
\tilde{\Gamma} = \frac{1}{\sqrt{J}} \begin{bmatrix} I_r \\ \vdots \\ I_r \end{bmatrix}, \quad \tilde{\Gamma}_0 = \frac{1}{\sqrt{J}} \begin{bmatrix} I_r & I_r & \cdots & I_r \\ -I_r & 0 & \cdots & 0 \\ 0 & -I_r & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & -I_r \end{bmatrix}.
\]

Notice that, \( \tilde{\Gamma}_0^T \tilde{Y}_i = (\varepsilon_{i1} - \varepsilon_{i2}, \ldots, \varepsilon_{i1} - \varepsilon_{ij})^T \), and \( \tilde{\Gamma}^T \tilde{Y}_i = \sqrt{J}(\alpha + \beta X_i + \varepsilon_i) \), where \( \varepsilon_i = b_i + \sum_{j=1}^J \varepsilon_{ij}/J \). We have \( \tilde{\Gamma}_0^T \tilde{Y}_i \perp \perp X_i \) and

\[
\text{Cov}(\tilde{\Gamma}_0^T \tilde{Y}_i, \tilde{\Gamma}^T \tilde{Y}_i) = \text{Cov}(J \varepsilon_i^T, (\varepsilon_{i1}^T - \varepsilon_{i2}^T, \ldots, \varepsilon_{i1}^T - \varepsilon_{ij}^T)^T) = 0,
\]

which indicates \( \tilde{\Gamma}_0^T \tilde{Y}_i \perp \perp \tilde{\Gamma}^T \tilde{Y}_i|X_i \). Hence, Conditions 1 and 2 are satisfied with \((\tilde{\Gamma}, \tilde{\Gamma}_0)\).

The envelope must be contained in \( \text{span}(\tilde{\Gamma}) \), i.e., \( \tilde{u} \leq r \). Hence we proved Corollary 1. We can further find a semi-orthogonal matrix \( \Phi \) with maximum dimension such that \( \Phi_0^T \tilde{\Gamma}^T Y_i \perp \perp (\Phi^T \tilde{\Gamma}^T Y_i, X_i) \). Thus, by definition, \( \tilde{\Gamma} \Phi = 1_J \otimes \Phi \) is the basis matrix for \( \mathcal{E}_{\mathcal{X}}(\mathcal{B}) \).

Proof of Proposition 2

Under model \((1)\), it is easy to verify that

\[
\text{vec}(\Gamma_0^T Y_i)|X_i, Z_i \sim N(\text{vec}(\Gamma_0^T \beta X_i), M_{22}),
\]

\[
\text{vec}(\Gamma^T Y_i)|\text{vec}(\Gamma_0^T Y_i), X_i, Z_i \sim N(\mu^{**}, \Sigma^{**}),
\]
where \( \mathbf{M}_{11} = \mathbf{I}_L \otimes (\Gamma^T \Sigma_\varepsilon \Gamma) + (\mathbf{Z}_i^T \otimes \Gamma^T) \Sigma_b(\mathbf{Z}_i \otimes \Gamma), \) \( \mathbf{M}_{12} = \mathbf{I}_L \otimes (\Gamma^T \Sigma_\varepsilon \Gamma_0) + (\mathbf{Z}_i^T \otimes \Gamma^T) \Sigma_b(\mathbf{Z}_i \otimes \Gamma_0), \) \( \mathbf{M}_{22} = \mathbf{I}_L \otimes (\Gamma_0^T \Sigma_\varepsilon \Gamma_0) + (\mathbf{Z}_i^T \otimes \Gamma_0^T) \Sigma_b(\mathbf{Z}_i \otimes \Gamma_0), \) \( \mathbf{M}_{12} = \mathbf{M}_{22}^{-1}(\{\text{vec}(\Gamma_0^T \mathbf{Y}_i) - \text{vec}(\Gamma_0^T \beta \mathbf{X}_i)\}), \) and \( \Sigma^{**} = \mathbf{M}_{11} - \mathbf{M}_{12} \mathbf{M}_{22}^{-1} \mathbf{M}_{12}. \)

Condition 1° holds if and only if the distribution of \( \Gamma_0^T \mathbf{Y}_i | \mathbf{X}_i, \mathbf{Z}_i \) is free of \( \mathbf{X}_i \) and \( \mathbf{Z}_i \), that is, \( \Gamma_0^T \mathbf{Y}_i = \mathbf{0}, \mathbf{Z}_i \otimes \Gamma_0 = \mathbf{0} \). Condition 2° holds if and only \( \mathbf{M}_{12} = \mathbf{0} \), that is, \( \mathbf{I}_L \otimes (\Gamma^T \Sigma_\varepsilon \Gamma_0) + (\mathbf{Z}_i^T \otimes \Gamma^T) \Sigma_b(\mathbf{Z}_i \otimes \Gamma_0) = \mathbf{0} \).

### Proof of Proposition 3

Let \( \hat{\theta}_{\text{obs-em}} \) denote the maximizer of \( \beta, \Sigma_\varepsilon \) and \( \Sigma_b \) in the observed data likelihood in (5). Similarly, let \( \hat{\theta}_{\text{obs-em}} \) denote the maximizer of \( \beta, \Sigma_\varepsilon \) and \( \Sigma_b \) in (5) under additional conditions (i)* and (ii)*. Let \( \mathbf{V}_0 = \text{avar}(\hat{\theta}_{\text{obs-em}}) \) and \( \mathbf{V} = \text{avar}(\hat{\theta}_{\text{obs-em}}) \) denote the asymptotic covariance matrices of the estimators obtained by directly maximizing (5) instead of using EM algorithm. Also, let \( \phi = (\eta, \Gamma, \Omega, \Omega_0, \Sigma_b) \) and \( \theta = (\beta, \Sigma_\varepsilon, \Sigma_b) \) denote the parameter under the envelope model and the standard model. Let \( \{\phi_t\} \) and \( \{\theta_t\} \) denote the EM sequences, i.e., the parameters sequences we obtain from each EM iteration, of the envelope model and the standard model. By Corollary 1 of [Wu (1983)], the two EM sequences \( \{\phi_t\} \) and \( \{\theta_t\} \) converge to their unique maximizer of \( L_{\text{obs}} \). Hence, in order to prove \( \mathbf{V}_{\text{mix-em}} \leq \mathbf{V}_{\text{mix-em}} \), it suffices to prove \( \mathbf{V}_0 \leq \mathbf{V} \). We found function \( h(\phi) \) such that \( h(\phi) = (h_1(\phi), h_2(\phi), h_3(\phi)) \).

Because of the over-parameterization of \( \theta \), the gradient matrix \( \mathbf{G} = \frac{\partial h(\phi)}{\partial \phi^T} \) is not of full rank. By Proposition 4.1 in [Shapiro (1986)], we have

\[
\mathbf{V}_0 = \mathbf{G}(\Gamma^T \mathbf{V}^{-1} \Gamma)^{\dagger} \Gamma^T.
\]

\[
\mathbf{V} - \mathbf{V}_0 = \mathbf{V} - \mathbf{G}(\Gamma^T \mathbf{V}^{-1} \Gamma)^{\dagger} \Gamma^T = \mathbf{V}^{\frac{1}{2}} \left[ \mathbf{I} - \mathbf{V}^{-\frac{1}{2}} \mathbf{G}(\Gamma^T \mathbf{V}^{-1} \Gamma)^{\dagger} \Gamma^T \mathbf{V}^{-\frac{1}{2}} \right] \mathbf{V}^{\frac{1}{2}}.
\]

Since \( \mathbf{I} - \mathbf{V}^{-\frac{1}{2}} \mathbf{G}(\Gamma^T \mathbf{V}^{-1} \Gamma)^{\dagger} \Gamma^T \mathbf{V}^{-\frac{1}{2}} \) is the projection matrix onto the orthogonal complement of \( \text{span}(\mathbf{V}^{-\frac{1}{2}} \mathbf{G}) \), it is positive semi-definite. Hence, \( \mathbf{V}_0 \leq \mathbf{V} \). In order to find out the close form of \( \mathbf{V}_0 \). Because \( \hat{\theta}_{\text{obs-em}} \) is MLE, we can obtain \( \mathbf{V}_0 \) by inverting its Fisher information matrix.

The log-likelihood is

\[
l(\theta; \mathbf{Y}, \mathbf{X}, \mathbf{Z}) = C - \frac{1}{2} \sum_{i=1}^{n} \left[ \log \det(\mathbf{I}_L \otimes \Sigma_\varepsilon + \mathbf{A}_i \Sigma_b \mathbf{A}_i^T) - \{\text{vec}(\mathbf{Y}_i) - \text{vec}(\mathbf{1}^T \mathbf{1}_r) - \text{vec}(\beta \mathbf{X}_i)\}^T \right.
\]

\[
(\mathbf{I}_L \otimes \Sigma_\varepsilon + \mathbf{A}_i \Sigma_b \mathbf{A}_i^T)^{-1}\{\text{vec}(\mathbf{Y}_i) - \text{vec}(\mathbf{1}^T \mathbf{1}_r) - \text{vec}(\beta \mathbf{X}_i)\}.
\]

(7)

For calculating Fisher, we need the following result in [Magus and Neudecker (1984)]:
Lemma 1. Let \( U \in \mathbb{R}^{m \times p}, V \in \mathbb{R}^{r \times s} \) and \( X \in \mathbb{R}^{n \times q} \), then
\[
\frac{\partial \text{vec}(U \otimes V)}{\partial \text{vec}^T(X)} = (I_p \otimes G)(\frac{\partial \text{vec}(U)}{\partial \text{vec}^T(X)}) + (H \otimes I_r)(\frac{\partial \text{vec}(V)}{\partial \text{vec}^T(X)}),
\]
where \( G = (K_{sm} \otimes I_r)(I_m \otimes \text{vec}V) \), \( H = (I_p \otimes K_{sm})(\text{vec}(U) \otimes I_s) \), with \( K_{sm} \) being the commutation matrix in \( \mathbb{R}^{sm \times sm} \), such that for any \( A \in \mathbb{R}^{sm} \), \( K_{sm} \text{vec}(A) = \text{vec}(A^T) \).

Let \( l_i \) denote the log-likelihood for individual \( i \) and \( \psi_i(Y_i, \theta) = \frac{\partial l_i}{\partial \theta} \). Denote \( \Sigma_i = I_i \otimes \Sigma_\epsilon + A_i \Sigma_b A_i^T \in \mathbb{R}^{J_i \times J_i}, D_i = \text{vec}(Y_i) - \alpha \otimes 1_i - \text{vec}(\beta X_i) \in \mathbb{R}^{J_i \times r} \). We have \( C_r E_r = I_{r(r+1)/2} \).

Also, denote \( M_{i1} = \frac{\partial \text{vech}(\Sigma_i)}{\partial \text{vech}^T(\Sigma_\epsilon)} \), and \( M_{i2} = \frac{\partial \text{vech}(\Sigma_i)}{\partial \text{vech}^T(\Sigma_b)} \). By using Lemma 1, we can also obtain the closed form for \( M_{i1} \):
\[
M_{i1} = C_{J_i, \epsilon} \frac{\partial \text{vech}(\Sigma_i)}{\partial \text{vech}^T(\Sigma_\epsilon)} E_r = C_{J_i, \epsilon} \{(I_{J_i} \otimes K_{r,J_i})(\text{vec}(I_{J_i}) \otimes I_r) \otimes I_r\} E_r,
\]
Also, the matrix \( M_{i2} = C_{J_i, \epsilon}(A_i \otimes A_i) E_{qr} \).

Using the notation above, we have
\[
l_i(\beta, Y_i; X_i, Z_i) = - \frac{1}{2} \log \det(\Sigma_i) - \frac{1}{2} D_i^T \Sigma_i^{-1} D_i.
\]

By matrix calculus, we have
\[
\frac{\partial l_i}{\partial \text{vec}^T(\beta)} = -D_i^T \Sigma_i^{-1} \frac{\partial D_i}{\partial \text{vec}^T(\beta)} = D_i^T \Sigma_i^{-1} (X_i^T \otimes I_r),
\]
\[
\frac{\partial l_i}{\partial \text{vech}^T(\Sigma_\epsilon)} = -\frac{1}{2} \text{vec}^T(\Sigma_i^{-1}) E_{J_i, r} M_{i1} + \frac{1}{2} (D_i^T \otimes D_i^T)(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i1},
\]
\[
\frac{\partial l_i}{\partial \text{vech}^T(\Sigma_b)} = -\frac{1}{2} \text{vec}^T(\Sigma_i^{-1}) E_{J_i, r} M_{i2} + \frac{1}{2} (D_i^T \otimes D_i^T)(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i2},
\]
and
\[
\psi_i(Y_i, \theta) = (\psi_{i1}, \psi_{i2}, \psi_{i3})^T = (\frac{\partial l_i}{\partial \text{vec}^T(\beta)}, \frac{\partial l_i}{\partial \text{vech}^T(\Sigma_\epsilon)}, \frac{\partial l_i}{\partial \text{vech}^T(\Sigma_b)})^T.
\]

Then, we can calculate the expression for \( \frac{\partial \psi_i}{\partial \theta^T} \):
\[
\frac{\partial \psi_{i1}}{\partial \text{vec}^T(\beta)} = -(X_i \otimes I_r) \Sigma_i^{-1} (X_i^T \otimes I_r),
\]
\[
\frac{\partial \psi_{i1}}{\partial \text{vech}^T(\Sigma_\epsilon)} = \{D_i^T \otimes (X_i \otimes I_r)\} \frac{\partial \text{vec}(\Sigma_i^{-1})}{\partial \text{vech}^T(\Sigma_\epsilon)} = -\{D_i^T \otimes (X_i \otimes I_r)\}(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i1}.
\]
\[
\frac{\partial \psi_{i1}}{\partial \text{vech}^T(\Sigma_b)} = -\{D_i^T \otimes (X_i \otimes I_r)\}(\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{J,r}M_{i2},
\]
\[
\frac{\partial \psi_{i2}}{\partial \text{vech}^T(\beta)} = -\frac{1}{2}M_{i1}^T E_{J,r}^T (\Sigma_i^{-1} \otimes \Sigma_i^{-1})(D_i \otimes D_i),
\]
\[
\frac{\partial \psi_{i3}}{\partial \text{vech}^T(\beta)} = -\frac{1}{2}M_{i2}^T E_{J,r}^T (\Sigma_i^{-1} \otimes \Sigma_i^{-1})(I_{r,J} \otimes D_i + D_i \otimes I_{r,J})(X_i^T \otimes I_r).
\]

In order to calculate \( \frac{\partial \psi_{i2}}{\partial \text{vech}^T(\Sigma_e)} \),
\[
\frac{\partial \psi_{i2}}{\partial \text{vech}^T(\Sigma_e)} = \frac{1}{2}M_{i1}^T E_{J,r}^T (\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{J,r}M_{i1} + \frac{1}{2}\{D_i^T \otimes D_i^T \otimes (M_{i1}^T E_{J,r}^T)\} \frac{\partial}{\partial \text{vech}^T(\Sigma_e)} \text{vech}(\Sigma_i^{-1} \otimes \Sigma_i^{-1}).
\]

By Lemma \( \Pi \) we have
\[
\frac{\partial}{\partial \text{vech}^T(\Sigma_e)} \text{vech}(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) = [I_{r,J} \otimes \{(K_{r,J,r,J} \otimes I_{r,J})(I_{r,J} \otimes \text{vec}(\Sigma_i^{-1}))\} + \{(I_{r,J} \otimes K_{r,J,r,J})(\text{vec}(\Sigma_i^{-1}) \otimes I_{r,J})\}(-I_{r,J} \otimes I_{r,J})](\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{r,J}M_{i1},
\]

Hence,
\[
\frac{\partial \psi_{i2}}{\partial \text{vech}^T(\Sigma_e)} = \frac{1}{2}M_{i1}^T E_{J,r}^T (\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{J,r}M_{i1} - \frac{1}{2}\{D_i^T \otimes D_i^T \otimes (M_{i1}^T E_{J,r}^T)\} [I_{r,J} \otimes \{(K_{r,J,r,J} \otimes I_{r,J})(I_{r,J} \otimes \text{vec}(\Sigma_i^{-1}))\} + \{(I_{r,J} \otimes K_{r,J,r,J})(\text{vec}(\Sigma_i^{-1}) \otimes I_{r,J})\}(-I_{r,J} \otimes I_{r,J})](\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{r,J}M_{i1},
\]

Similarly,
\[
\frac{\partial \psi_{i3}}{\partial \text{vech}^T(\Sigma_b)} = \frac{1}{2}M_{i2}^T E_{J,r}^T (\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{J,r}M_{i2} - \frac{1}{2}\{D_i^T \otimes D_i^T \otimes (M_{i2}^T E_{J,r}^T)\} [I_{r,J} \otimes \{(K_{r,J,r,J} \otimes I_{r,J})(I_{r,J} \otimes \text{vec}(\Sigma_i^{-1}))\} + \{(I_{r,J} \otimes K_{r,J,r,J})(\text{vec}(\Sigma_i^{-1}) \otimes I_{r,J})\}(-I_{r,J} \otimes I_{r,J})](\Sigma_i^{-1} \otimes \Sigma_i^{-1})E_{r,J}M_{i1},
\]

Hence,
\[
\frac{\partial \psi_i}{\partial \theta^T} = \begin{pmatrix}
\frac{\partial \psi_{i1}}{\partial \text{vech}^T(\beta)} & \frac{\partial \psi_{i1}}{\partial \text{vech}^T(\Sigma_e)} & \frac{\partial \psi_{i1}}{\partial \text{vech}^T(\Sigma_b)} \\
\frac{\partial \psi_{i2}}{\partial \text{vech}^T(\beta)} & \frac{\partial \psi_{i2}}{\partial \text{vech}^T(\Sigma_e)} & \frac{\partial \psi_{i2}}{\partial \text{vech}^T(\Sigma_b)} \\
\frac{\partial \psi_{i3}}{\partial \text{vech}^T(\beta)} & \frac{\partial \psi_{i3}}{\partial \text{vech}^T(\Sigma_e)} & \frac{\partial \psi_{i3}}{\partial \text{vech}^T(\Sigma_b)}
\end{pmatrix}.
\]
We can obtain the Fisher information of \( \theta \) by taking expectation of \( \frac{\partial \psi_i}{\partial \theta^T} \) with respective to \( Y_i \)

\[
I_i(\theta) = \begin{pmatrix}
I_{11}^i & I_{12}^i & I_{13}^i \\
I_{21}^i & I_{22}^i & I_{23}^i \\
I_{31}^i & I_{32}^i & I_{33}^i
\end{pmatrix},
\]

where

\[
I_{11}^i = -\mathbb{E}\{(-X_i \otimes I_r)^T \Sigma_i^{-1} (X_i \otimes I_r) = (X_i \otimes I_r) \Sigma_i^{-1} (X_i^T \otimes I_r)\},
\]

\[
I_{12}^i = -\mathbb{E}\{-D_i^T \otimes (X_i \otimes I_r)\} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i} M_{i1} = 0,
\]

\[
I_{13}^i = -\mathbb{E}\{-D_i^T \otimes (X_i \otimes I_r)\} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i} M_{i2} = 0,
\]

By symmetry of \( I_i(\theta) \), \( I_{21}^i = I_{31}^i = 0 \).

\[
I_{22}^i = -\frac{1}{2} M_{11}^T E_{J_i, r} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i1} + \frac{1}{2} \{ \text{vec}(\Sigma_i) \otimes (M_{11}^T E_{J_i, r})\} [I_{rJ} \otimes \{(K_{rJ, rJ} \otimes I_r, J_i) (I_{rJ} \otimes \text{vec}(\Sigma_i^{-1}))\}] + \{(I_{rJ} \otimes K_{rJ, rJ}) (\text{vec}(\Sigma_i^{-1}) \otimes I_{rJ}) \otimes I_{rJ}\} \{(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{rJ} M_{i1}\},
\]

\[
I_{23}^i = -\frac{1}{2} M_{12}^T E_{J_i, r} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i2} + \frac{1}{2} \{ \text{vec}(\Sigma_i) \otimes (M_{12}^T E_{J_i, r})\} [I_{rJ} \otimes \{(K_{rJ, rJ} \otimes I_r, J_i) (I_{rJ} \otimes \text{vec}(\Sigma_i^{-1}))\}] + \{(I_{rJ} \otimes K_{rJ, rJ}) (\text{vec}(\Sigma_i^{-1}) \otimes I_{rJ}) \otimes I_{rJ}\} \{(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{rJ} M_{i2}\},
\]

\[
I_{32}^i = -\frac{1}{2} M_{21}^T E_{J_i, r} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i1} + \frac{1}{2} \{ \text{vec}(\Sigma_i) \otimes (M_{21}^T E_{J_i, r})\} [I_{rJ} \otimes \{(K_{rJ, rJ} \otimes I_r, J_i) (I_{rJ} \otimes \text{vec}(\Sigma_i^{-1}))\}] + \{(I_{rJ} \otimes K_{rJ, rJ}) (\text{vec}(\Sigma_i^{-1}) \otimes I_{rJ}) \otimes I_{rJ}\} \{(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{rJ} M_{i1}\},
\]

\[
I_{33}^i = -\frac{1}{2} M_{22}^T E_{J_i, r} (\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{J_i, r} M_{i2} + \frac{1}{2} \{ \text{vec}(\Sigma_i) \otimes (M_{22}^T E_{J_i, r})\} [I_{rJ} \otimes \{(K_{rJ, rJ} \otimes I_r, J_i) (I_{rJ} \otimes \text{vec}(\Sigma_i^{-1}))\}] + \{(I_{rJ} \otimes K_{rJ, rJ}) (\text{vec}(\Sigma_i^{-1}) \otimes I_{rJ}) \otimes I_{rJ}\} \{(\Sigma_i^{-1} \otimes \Sigma_i^{-1}) E_{rJ} M_{i2}\},
\]

this is because \( \mathbb{E}(D_i) = 0 \) and \( \mathbb{E}(D_i \otimes D_i) = \text{vec}(\Sigma_b) \).

The \( I_i(\theta) \) we obtained is when assuming \( X_i \) and \( Z_i \) are fixed. Since \( \hat{\theta}_{\text{mix-em}} \) is the MLE with regularity conditions satisfied, we have

\[
\text{Var}(\hat{\theta}_{\text{mix-em}}) = \left\{ \sum_{i=1}^n I_i(\theta) \right\}^{-1}.
\]

Let \( \phi = (\text{vec}^T(\eta), \text{vec}^T(\Gamma), \text{vech}^T(\Omega), \text{vech}^T(\Sigma_b))^T \), \( h(\phi) = (\text{vec}^T(\Gamma \eta), \text{vech}^T(\Gamma \Omega \Gamma^T + \Gamma_0 \Omega_0 \Gamma_0^T), \text{vech}^T(\Sigma_b))^T \), and \( G = \frac{\partial h(\phi)}{\partial \phi^T} \). Then, we have

\[
G = \begin{pmatrix}
I_\eta \otimes \Gamma \\
0 & 2C_r(\Gamma \Omega \otimes I_r - \Gamma \otimes \Gamma_0 \Omega_0 \Gamma_0^T) & C_r(\Gamma \otimes \Gamma) E_{ru} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \text{I}_{q(r+1)/2}
\end{pmatrix}.
\]

Hence, \( \text{Var}(\hat{\theta}_{\text{mix-em}}) = V_0 = G (G^T VG)^+ G^T \), where \( V = \sum_{i=1}^n I_i(\theta) \).
Proof of Proposition 4

Since the mixed effects envelope model is overparameterized, we will use Proposition 4.1 of Shapiro (1986) to prove Proposition 4. We will check their conditions. For convenience, we match Shapiro’s notations in our context. Shapiro’s $x$ in our context is $\hat{\theta}_{\text{mix-em}} = (\hat{\beta}_{\text{mix-em}}, \hat{\Sigma}_{\text{mix-em}}, \hat{\Sigma}_b_{\text{mix-em}})$. We need to show the $\sqrt{n}$-consistency and asymptotical normality of $x$. We assume the following regularity conditions: the error $\varepsilon_{ij}$ and random effect $b_i$ have finite $(4 + \delta)$-th moment, $\sup_i ||X_i|| < \infty$, $\sup_i ||Z_i|| < \infty$, $\sup_i J_i < \infty$, $\inf_i \det(I_j \otimes \Sigma_\varepsilon + A_i \Sigma_b A_i^T) \geq 0$, $\lim \sup_i \lambda_{n-1} \text{Var}(s_i(\theta)) > 0$ and $\lim \inf_i \lambda_{n} [-1 \text{Var}(s_n(\theta))] > 0$, where $\lambda_{\cdot}[A]$ denote the smallest eigenvalue of the matrix $A$, $M_n(\theta) = -E\left\{ \frac{\partial^2 l}{\partial \theta \partial \theta^T} \right\}$, and $l$ is the log-likelihood when the error is normally distributed.

The estimator $\hat{\theta}_{\text{mix-em}}$ is obtained by maximizing the following misspecified log-likelihood:

$$l(\theta, Y; X, Z) = C - \frac{1}{2} \sum_{i=1}^{n} \left[ \log \det(I_j \otimes \Sigma_\varepsilon + A_i \Sigma_b A_i^T) - \{\text{vec}(Y_i) - \alpha \otimes 1_{J_i} - \text{vec}(\beta X_i)\}^T \right]$$

$$\left(I_j \otimes \Sigma_\varepsilon + A_i \Sigma_b A_i^T\right)^{-1}\left[\text{vec}(Y_i) - \alpha \otimes 1_{J_i} - \text{vec}(\beta X_i)\right].$$

Thus $\hat{\theta}_{\text{mix-em}}$ is the solution to the generalized estimating equation (GEE)

$$\frac{\partial l}{\partial \theta^T} = \sum_{i=1}^{n} \frac{\partial l_i}{\partial \theta} = \sum_{i=1}^{n} \psi_i^T(Y_i, \theta) = 0,$$

where $l_i$ is the misspecified log-likelihood of each observation, and $\psi_i(Y_i, \theta) = \frac{\partial l_i}{\partial \theta}$. Because $Y_i$ has finite second moment, $E\{\psi_i(Y_i, \theta_0)\} = 0$, where the subscript 0 indicates the true parameter value. We apply Proposition 5.5 and Theorem 5.14 in Shao (2003) to prove consistency and asymptotical normality of $\hat{\theta}_{\text{mix-em}}$.

In order to use Proposition 5.5, we need to show the conditions in Lemma 5.3 in Shao (2003) holds for any compact subset of the parameter space. That is, for any $c > 0$ and sequence $\{y_i\}_{i=1}^\infty$ satisfying $||y_i|| < c$, the sequence of functions $\psi_i(y_i, \theta)$ is equicontinuous on any compact set of the parameter space. It is easy to see that $\frac{\partial \psi_i}{\partial \theta^T}$ (derived in the previous subsection) is uniformly bounded in any compact subset $\Theta$ of the parameter space when $||y_i|| < c$ if $\sup_i ||X_i|| < \infty$, $\sup_i ||Z_i|| < \infty$, $\sup_i J_i < \infty$ and $\sup_i ||\Sigma_i^{-1}||_{\text{inf}} < \infty$, where $||\cdot||_{\text{inf}}$ indicates matrix infinity norm. Since $\sup_i ||\Sigma_i^{-1}||_{\text{inf}} < \infty$ if and only if $\sup_i ||Z_i|| < \infty$ and $\inf_i \det(\Sigma_i) > 0$, the aforementioned conditions holds under the regularity conditions. Therefore, $\psi_i(y_i, \theta)$ is equicontinuous on $\Theta$. Moreover, since $Y_i$ has finite $(4 + \delta)$-th moment, $E\{\sup_{\theta \in \Theta} ||\psi_i(Y_i, \theta)||\}^2 < \infty$ and $\sup_i E||Y_i|| < \infty$, the conditions in Lemma 5.3 in Shao (2003) holds.

According to Proposition 5.5 of Shao (2003), we also need to prove $\lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{n} E\{\psi_i(Y_i, \theta)\} = 0$ implies $\theta = \theta_0$. Let $\theta_{10} = \beta_0, \theta_{20} = \Sigma_{\varepsilon 0}, \theta_{30} = \Sigma_{b0}$ denote the true parameter value, and
\[ \Sigma_{i0} = I_{j_i} \otimes \theta_{20} + A_i \theta_{30} \Lambda_i^T. \] Taking expectation of \( \psi_i(Y_i, \theta) \), we have
\[ \mathbb{E}\{ \psi_{i1}(Y_i, \theta) \} = \text{vec}^T \{ (\theta_{10} - \beta) X_i \} \Sigma_i^{-1} (X_i \otimes I_r), \]
\[ \mathbb{E}\{ \psi_{i2}(Y_i, \theta) \} = \frac{1}{2} \text{vec}^T (\Sigma_{i0}^{-1} \Sigma_i \Sigma_{i0}^{-1} - \Sigma_i^{-1}) \mathbb{E}_{j,r} \mathbb{M}_1, \]
\[ \mathbb{E}\{ \psi_{i3}(Y_i, \theta) \} = \frac{1}{2} \text{vec}^T (\Sigma_{i0}^{-1} \Sigma_i \Sigma_{i0}^{-1} - \Sigma_i^{-1}) \mathbb{E}_{j,r} \mathbb{M}_2. \]

Also,
\[ \text{vec}^T (\Sigma_{i0}^{-1} \Sigma_i \Sigma_{i0}^{-1} - \Sigma_i^{-1}) = 0 \text{ if and only if } \Sigma_i = \Sigma_{i0}. \]

Because \( X_i \) and \( Z_i \) can be arbitrary,
\[ \Sigma_i = \Sigma_{i0} \text{ if and only if } \Sigma_\epsilon = \theta_{20} \text{ and } \Sigma_b = \theta_{30}. \]
Therefore,
\[ \lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{\infty} \mathbb{E}\{ \psi_{i1}(Y_i, \theta) \} = 0 \text{ implies } \beta = \theta_{10}, \]
\[ \lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{\infty} \mathbb{E}\{ \psi_{i2}(Y_i, \theta) \} = 0 \text{ implies } \Sigma_\epsilon = \theta_{20}, \Sigma_b = \theta_{30}. \]

Hence
\[ \lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{\infty} \mathbb{E}\{ \psi_{i}(Y_i, \theta) \} = 0 \text{ implies } \theta = \theta_0. \] Since \( \hat{\theta}_{\text{mix-em}} \) is always \( O_p(1) \), by Proposition 5.5 in (Shao 2003), \( \hat{\theta}_{\text{mix-em}} \overset{p}{\to} \theta_0 \).

Then we prove asymptotic normality of \( \hat{\theta}_{\text{mix-em}} \) using Theorem 5.14 of (Shao 2003). Since \( Y_i \) has finite \((4 + \delta)\)-th moment, \( \sup_i \| \psi_i(Y_i, \theta) \|^{2 + \frac{\delta}{2}} < \infty \). Then, if conditions \( \lim \inf_n \lambda_- [n^{-1} \text{Var}(s_n(\theta))] > 0 \) and \( \lim \inf_n \lambda_- [n^{-1} \mathbb{M}_n(\theta)] > 0 \) holds, we have
\[ \sqrt{n} (\hat{\theta}_{\text{mix-em}} - \theta_0) \overset{d}{\to} N(0, \tilde{V}), \]
where \( \tilde{V} = \frac{1}{n} [\mathbb{M}_n(\theta_0)]^{-1} \text{Var}(s_n(\theta)) [\mathbb{M}_n(\theta_0)]^{-1}. \)

Shapiro’s \( \xi \) in our context is \( \xi = (\beta, \Sigma_\epsilon, \Sigma_b) \). Following the same technique in (Su and Cook 2012) and (Cook et al. 2015), we give the minimum discrepancy function as \( f_{MDF} = l_{\text{max}} - l \), where \( l \) is the misspecified log-likelihood function \( (7) \), and \( l_{\text{max}} \) is obtained by substituting \( \hat{\theta}_{\text{mix-em}} \) for \( \theta \) in \( (7) \). Although \( f_{MDF} \) is written in terms of \( \theta \) and \( \hat{\theta}_{\text{mix-em}} \), there must be one-to-one functions \( f_1 \) from \( \theta \) to \( \xi \) and \( f_2 \) from \( \hat{\theta}_{\text{mix-em}} \) to \( x \) so that \( \xi = f_1(\theta) \) and \( x = f_2(\hat{\theta}_{\text{mix-em}}) \). As \( f_{MDF} \) is constructed under the normal likelihood, it satisfies the four conditions required by (Shapiro 1986). Denote \( \phi = (\eta, \Gamma, \Omega, \Omega_0, \Sigma_b), \ \theta = h(\phi), \ \mathbb{G} = \partial h(\phi)/\partial \phi^T \) and \( \mathbb{J} = \frac{1}{2} \frac{\partial^2 f_{MDF}}{\partial \theta \partial \theta^T} \). Notice that \( \mathbb{J} \) equals the Fisher information matrix for \( \theta \) when \( \epsilon \) is normal.
Because $\hat{θ}_{\text{mix-em}}$ is obtained by minimizing $f_{MDF}$, by Proposition 4.1 of Shapiro (1986),
$$\sqrt{n}(\hat{θ}_{\text{mix-env}} - θ_0) \overset{d}{\rightarrow} N(0, \tilde{V}_{\text{mix-env}}),$$
where $\tilde{V}_{\text{mix-env}} = G(G^T J G)^\dagger G^T J \tilde{V} J G(G^T J G)^\dagger G^T$. If we define the inner product as
$$\langle x_1, x_2 \rangle_J = x_1^T J x_2,$$
then the projection onto $\text{span}(B)$ relative to $J$ has the matrix representation
$$P_B(J) = B(B^T J B)^\dagger B^T J.$$ Hence, $\tilde{V}_{\text{mix-env}} = P_G(J) \tilde{V} P_G(J) \leq \tilde{V}$.

**Graphical illustration of the fixed effects model**

We present a graphical illustration of the fixed effects model. Using the same data as Section 3.2 except that we assume the random effects $b_i$ are observed. In this case, we use $Y_i - b_i$ as response. That is, (1) holds for response $Y_i$ and observations are independent for different $i$. After subtracting $b_i$, (3) holds for response $Y_i - b_i$ and observations are independent for different $i$ and $j$.

Figure 4 demonstrates the intuition for the efficiency gain of the classic envelope method in standard multivariate regression with fixed effects only. In Figure 4a, the ordinary least square estimator (OLS) is obtained by projecting all the data onto the $Y_1 - b_1$ axis, ignoring $Y_2$ completely. The density curves of the two group distributions of $Y_{ij1} - b_{i1}$ are given at the bottom in Figure 4a and similar curves can be made for $Y_{ij2} - b_{i2}$. The two density curves are not well separated. The OLS of the group difference of $Y_{ij} - b_i$ is $(-7.67, 6.53)^T$ with standard error being $(0.60, 0.60)^T$ and mean square error (MSE) of the group difference being 0.69.

The idea of the envelope method is to reduce noise in the data by projecting each observation onto the direction that can best distinguish the groups. The two groups are well separated along the dashed black line. Also, they have almost the same distribution in the direction that is orthogonal to the black solid line. Therefore, discarding that part of variation does not sacrifice the information of group difference, but instead, it makes the estimation more efficient. The density curves of the two groups under the envelope estimation are shown at the bottom of Figure 4b and they have much smaller spreads than the OLS. The envelope estimate for the group difference of $Y_{ij} - b_i$ is $(-7.10, 7.10)^T$ with standard error $(0.04, 0.04)^T$ and MSE 0.0025.

**EM-algorithm for the mixed effects envelope model**

Recall the standard EM-algorithm iterates through the following two steps:

(a) E-step. Suppose we have the parameter $θ_i$ from the $t$-th iteration, then we compute the function $Q(θ|θ_t) = \int l(θ|X, Y, Z, b) \prod_{i=1}^n f(b_i|X_i, Y_i, Z_i, θ_i)db_i$, where $l$ is the
To calculate the function $Q$ of two parts, i.e.,

\[ Q(f_{\theta_1}|X, Y, Z, \theta_t) \]

where $C$ and $l$ follow a normal distribution $N(\mu, \Sigma)$, and $f_{\theta_1}$ is given later in the Supplementary Material. Therefore, $Q(\theta|\theta_t)$ can be decomposed as a summation of two parts, i.e., $Q(\theta|\theta_t) = Q_1(\Sigma_b|\theta_t) + Q_2(\alpha, \Sigma_\epsilon|\theta_t)$, where

\[
Q_1(\Sigma_b|\theta_t) = -\frac{n}{2} \log |\Sigma_b| + \frac{1}{2} \sum_{i=1}^{n} \{ \mu_{b,i}^T \Sigma_b^{-1} \mu_{b,i} + \text{tr}(\Sigma_\epsilon^{-1} \Sigma_b) \} - \frac{J}{2} \log |\Sigma_\epsilon| - \frac{n}{2} \log |\Sigma_b| + C,
\]

where $C$ is a constant.

Omitting the constant $C$, $Q(\theta|\theta_t)$ in the above equation can be decomposed as a summation of two parts, i.e., $Q(\theta|\theta_t) = Q_1(\Sigma_b|\theta_t) + Q_2(\alpha, \Sigma_\epsilon|\theta_t)$, where

\[
Q_1(\Sigma_b|\theta_t) = -\frac{n}{2} \log |\Sigma_b| + \frac{1}{2} \sum_{i=1}^{n} \{ \mu_{b,i}^T \Sigma_b^{-1} \mu_{b,i} + \text{tr}(\Sigma_\epsilon^{-1} \Sigma_b) \} ,
\]
\[ Q_2(\alpha, \beta, \Sigma_\varepsilon | \theta_t) = \sum_{i=1}^{n} \sum_{j=1}^{J_i} -\frac{1}{2} \left\{ (Y_{ij} - \alpha - \beta X_{ij} - A_{ij} \mu_{b,t})^T \Sigma_\varepsilon^{-1} (Y_{ij} - \alpha - \beta X_{ij} - A_{ij} \mu_{b,t}) 
right.
\]
\[ + \text{tr}(\Sigma_\varepsilon^{-1} A_{ij} \Sigma_{b,t} A_{ij}^T) \right\} - \frac{J}{2} \log |\Sigma_\varepsilon|. \]

Updates of parameters can be done separately for the two parts. Let \( \mu_{b,t} = (\mu_{b_{1,t}}, \ldots, \mu_{b_{n,t}}) \), then \( Q_1 \) can be written as
\[ Q_1(\Sigma_b | \theta_t) = -\frac{n}{2} \log |\Sigma_b| - \frac{1}{2} \text{tr} \left\{ \Sigma_b^{-1} \mu_{b,t} \mu_{b,t}^T + \sum_{i=1}^{n} \Sigma_{b_{i,t}} \right\}. \]

The update of \( \Sigma_b \) is \( \Sigma_{b,t+1} = \sum_{i=1}^{n} \Sigma_{b_{i,t}} / n + \mu_{b,t} \mu_{b,t}^T / n. \)

Now, we update \( \alpha, \beta \) and \( \Sigma_\varepsilon \) at the \( t + 1 \) step. Under the envelope assumptions, we have \( \Sigma_\varepsilon = \Sigma_1 + \Sigma_2 \), where \( \Sigma_1 = \Gamma \Theta \Gamma^T, \Sigma_2 = \Gamma \Theta_0 \Gamma^T \) with \( \Sigma_1 \Sigma_2 = 0 \), and \( \beta \) belongs to the subspace spanned by the column vectors in \( \Sigma_1 \). So we have \( \beta^T \Sigma_2 = 0 \). Moreover, we have \( \Sigma_{\varepsilon}^{-1} = \Sigma_1^t + \Sigma_2^t \), where the superscript \( ^t \) denotes generalized inverse.

When \( \beta \) and \( \Sigma_\varepsilon \) are fixed, the parameter \( \alpha \) maximizing \( Q_2(\alpha, \beta, \Sigma_\varepsilon | \theta_t) \) is \( \hat{\alpha} = \bar{Y} - \beta \bar{X} - \bar{\mu}_t \), where \( \bar{Y} = \sum_{ij} Y_{ij} / J, \bar{X} = \sum_{ij} X_{ij} / J, \) and \( \bar{\mu}_t = \sum_{ij} A_{ij} \mu_{b_{i,t}} / J \). According to this relationship, \( \alpha_{t+1} \) is a function of \( \beta_{t+1} \) and \( \Sigma_{\varepsilon,t+1} \). Substitute this into the formula of \( Q_2 \), we obtain
\[ Q_2(\alpha, \beta, \Sigma_\varepsilon | \theta_t) = -\frac{J}{2} \log |\Sigma_\varepsilon| - \frac{1}{2} \sum_{i=1}^{n} \sum_{j=1}^{J_i} \left\{ Y_{ij} - \beta X_{ij} - A_{ij} \mu_{b_{i,t}} - (\bar{Y} - \beta \bar{X} - \bar{\mu}_t) \right\}^T \]
\[ \cdot \Sigma_\varepsilon^{-1} \left\{ Y_{ij} - \beta X_{ij} - A_{ij} \mu_{b_{i,t}} - (\bar{Y} - \beta \bar{X} - \bar{\mu}_t) \right\} + \text{tr}(\Sigma_\varepsilon^{-1} A_{ij} \Sigma_{b_{i,t}} A_{ij}^T). \]

Let \( \Psi_{b,t} = \sum_{i=1}^{n} \sum_{j=1}^{J_i} A_{ij} \Sigma_{b_{i,t}} A_{ij}^T \). Also, let \( Y_c = Y - Y \otimes 1_{1 \times J}, X_c = X - X \otimes 1_{1 \times J}, \mu_{c,t} = (A_{11} \mu_{b_{1,t}}, \ldots, A_{nJ_n} \mu_{b_{n,t}}) - \bar{\mu}_t \otimes 1_{1 \times J}. \) Then we have
\[ Q_2(\alpha, \beta, \Sigma_\varepsilon | \theta_t) \]
\[ = -\frac{1}{2} J \log |\Sigma_1 + \Sigma_2| - \frac{1}{2} \text{tr} \left\{ (Y_c - \beta X_c - \mu_{c,t})^T (\Sigma_1^t + \Sigma_2^t) (Y_c - \beta X_c - \mu_{c,t}) + (\Sigma_1^t + \Sigma_2^t) \Psi_{b,t} \right\} \]
\[ = -\frac{1}{2} J \log \det \Sigma_1 - \frac{1}{2} \text{tr} \left\{ (Y_c - \beta X_c - \mu_{c,t})^T \Sigma_1^t (Y_c - \beta X_c - \mu_{c,t}) \right\} - \frac{1}{2} \text{tr}(\Sigma_1^t \Psi_{b,t}) \]
\[ - \frac{1}{2} J \log \det \Sigma_2 - \frac{1}{2} \text{tr} \left\{ (Y_c - \mu_{c,t})^T \Sigma_2^t (Y_c - \mu_{c,t}) \right\} - \frac{1}{2} \text{tr}(\Sigma_2^t \Psi_{b,t}). \]

When \( \Sigma_1, \Sigma_2 \) are fixed, \( \hat{\beta} \) that maximizes \( Q_2 \) is
\[ \hat{\beta}_{t+1} = P_{\Sigma_1} U_c X_c^T (X_c X_c^T)^{-1}, \] (8)
where $\mathbf{P}_{\Sigma_1}$ denotes the projection matrix on the space spanned by the column vectors of $\Sigma_1$, i.e., $\mathbf{P}_{\Sigma_1} = \Sigma_1 (\Sigma_1^T \Sigma_1)^{-1} \Sigma_1^T$, and $\mathbf{U}_{c,t} = \mathbf{Y}_c - \mu_{c,t}$. Also, denote $\mathbf{Q}_{\Sigma_1} = \mathbf{I}_r - \mathbf{P}_{\Sigma_1}$.

Then, we split $Q_2$ into the following two parts:

\[
Q_{2,1}(\Sigma_1|\theta_t) = -\frac{J}{2} \log \det_0 \Sigma_1 - \frac{1}{2} \text{tr}(\mathbf{Q}_{X_c} \mathbf{U}_{c,t}^T \Sigma_1^T \mathbf{U}_{c,t} \mathbf{Q}_{X_c}) - \frac{1}{2} \text{tr}(\Sigma_1^T \Psi_{b,t}),
\]

\[
Q_{2,2}(\Sigma_2|\theta_t) = -\frac{J}{2} \log \det_0 \Sigma_2 - \frac{1}{2} \text{tr}(\mathbf{U}_{c,t}^T \Sigma_2^T \mathbf{U}_{c,t}) - \frac{1}{2} \text{tr}(\Sigma_2^T \Psi_{b,t}),
\]

where $\mathbf{Q}_{X_c} = \mathbf{I} - \mathbf{P}_{X_c}$, and $\det_0(A)$ is defined as the product of its non-zero eigenvalues. Suppose $\Gamma$ is given, then the maximizers of $Q_{2,1}$ and $Q_{2,2}$ respectively are $\hat{\Sigma}_{1,t+1} = \mathbf{P}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{Q}_{X_c}^T \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{P}_{\Gamma} / J$, $\hat{\Sigma}_{2,t+1} = \mathbf{Q}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{Q}_{\Gamma} / J$. The maximized functions are $Q_{2,1} = C_1 - J \log \det_0 \left\{ \mathbf{P}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{Q}_{X_c}^T \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{P}_{\Gamma} \right\} / 2$, $Q_{2,2} = C_2 - J \log \det_0 \left\{ \mathbf{Q}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{Q}_{\Gamma} \right\}$. Hence, $\hat{\Sigma}_{c,t+1} = \hat{\Sigma}_{1,t+1} + \hat{\Sigma}_{2,t+1}$.

The final step is to find the semi-orthogonal matrix $\Gamma$ to maximize the function $Q_2$, which is equivalent to minimizing the function

\[
F(\text{span}(\Gamma)) = \log \det \left\{ \mathbf{P}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{Q}_{X_c}^T \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{P}_{\Gamma} + \mathbf{Q}_{\Gamma}(\mathbf{U}_{c,t} \mathbf{U}_{c,t}^T + \Psi_{b,t}) \mathbf{Q}_{\Gamma} \right\}.
\]

We only need to identify the span of the column space of $\Gamma$ from minimizing the above objective function. We use the 1D algorithm [Cook and Zhang, 2016] to obtain $\hat{\Gamma}$, where $\text{span}(\hat{\Gamma})$ is a $\sqrt{n}$-consistent estimator of $\text{span}(\Gamma)$, rather than MLE (more details on 1D algorithm is given later in the Supplementary Material). In our simulation studies in Section 4 our 1D algorithm is feasible and fast converging.
Derivation of $\mu_{b_i,t}$ and $\Sigma_{b_i,t}$

We derive $\mu_{b_i,t}$ and $\Sigma_{b_i,t}$ in this section. They can be determined from $f(b_i, Y_i|X_i, Z_i, \theta_t)$.

$$f(b_i, Y_i|X_i, Z_i, \theta_t) = (2\pi)^{-\frac{q_r}{2}} |\Sigma_{b,t}|^{-\frac{1}{2}} \exp \left\{ -\frac{1}{2} \vec{b}_i^T \Sigma_{b,t}^{-1} \vec{b}_i \right\}$$

$$= (2\pi)^{-\frac{q_r}{2}} |\Sigma_{b,t}|^{-\frac{1}{2}} \exp \left\{ -\frac{1}{2} (Y_{ij} - \alpha_t - \beta_t X_{ij} - b_i Z_{ij})^T \Sigma_{e,t}^{-1} (Y_{ij} - \alpha_t - \beta_t X_{ij} - b_i Z_{ij}) \right\}$$

$$\propto |\Sigma_{b,t}|^{-\frac{1}{2}} \exp \left\{ -\frac{1}{2} (\vec{b}_i - \mu_{b,i,t})^T \Sigma_{b,t}^{-1} (\vec{b}_i - \mu_{b,i,t}) \right\} .$$

Hence,

$$\mu_{b_i,t} = \left( \Sigma_{b,t}^{-1} + \sum_{j=1}^{J_i} A_{ij}^T \Sigma_{\epsilon,t} A_{ij} \right)^{-1} \sum_{j=1}^{J_i} \left\{ A_{ij}^T \Sigma_{\epsilon,t}^{-1} (Y_{ij} - \alpha_t - \beta_t X_{ij}) \right\} ,$$

$$\Sigma_{b_i,t} = \left( \Sigma_{b,t}^{-1} + \sum_{j=1}^{J_i} A_{ij}^T \Sigma_{\epsilon,t} A_{ij} \right)^{-1} .$$

The 1D algorithm

Here we discuss the 1D algorithm to estimate span($\Gamma$). The 1D algorithm was first proposed in (Cook and Zhang, 2016) for multivariate regression envelope model. It obtains an estimate of $\Gamma$ column-wisely. Specifically, assuming that the envelope dimension $u$ is given, we use
the following 1D algorithm to estimate $\Gamma$ under the mixed effects model.

**Algorithm 1: The 1-D algorithm**

1. Initialization: $g_0 = G_0 = 0$;
2. For $k = 0, 1, ..., u - 1$,
   (a) Let $G_k = (g_1, ..., g_k)$ if $k \geq 1$ and let $(G_k, G_{0k})$ be an orthogonal basis for $\mathbb{R}^r$.
   (b) Define the stepwise objective function
      $$D_k(w) = \log \left( w^T G_{0k}^T \Sigma_{\epsilon,t} G_{0k} w \right) + \log \left\{ w^T (G_{0k}^T \Sigma_{\epsilon,t} G_{0k} + G_{0k}^T \beta \beta^T G_{0k})^{-1} w \right\},$$
      where $w \in \mathbb{R}^{r-k}$.
   (c) Solve $w_{k+1} = \arg \min_w D_k(w)$ subject to a length constraint $w^T w = 1$.
   (d) Define $g_{k+1} = G_{0k} w_{k+1}$ to be the unit length $(k + 1)$th stepwise direction.

**The mixed effects envelope algorithm**

We combine the 1D algorithm with EM algorithm to obtain an estimator of the mixed effects model under conditions (i)$^*$ and (ii)$^*$ as follows, where $\delta$ can be chosen depending on the
Algorithm 2: The mixed effects envelope algorithm

for $k = 1, 2, \ldots, u$ do
  Initialization: $t = 0$, $\Sigma_{b,0} = I_q$, $\Sigma_{\varepsilon,0} = I_r$, $\alpha_0 = 0$, $\beta_0 = 0$, $\theta_0 = (\Sigma_{b,0}, \Sigma_{\varepsilon,0}, \alpha_0, \beta_0)$, $\Delta_0 = \infty$.
  while $\Delta_t > \delta$ do
    1. Set $\Sigma_{b,t} = \left(\Sigma_{b,t}^{-1} + \sum_{j=1}^{J_t} A_{ij}^T \Sigma_{\varepsilon,t}^{-1} A_{ij}\right)^{-1}$, where $A_{ij} = I_r \otimes Z_{ij}^T$ and $\mu_{b,t} = \left(\Sigma_{b,t}^{-1} + \sum_{j=1}^{J_t} A_{ij}^T \Sigma_{\varepsilon,t}^{-1} A_{ij}\right)^{-1} \sum_{j=1}^{J_t} \{A_{ij}^T \Sigma_{\varepsilon,t}^{-1} (Y_{ij} - \mu_t - \beta_t X_{ij})\}$.
    2. The update of $\alpha$ is $\alpha_{t+1} = Y - \beta_{t+1} X - \mu_t$, where $Y = \sum_{i,j} Y_{ij}/J$, $X = \sum_{i,j} X_{ij}/J$, and $\mu_t = \sum_{i,j} A_{ij} \mu_{b,t}/J$.
    3. Using the 1D Algorithm to get $\Gamma_{t+1}$. Then, $\beta_{t+1} = P_{\Gamma_{t+1}} U_{c,t} X_{c}^T (X_c X_c^T)^{-1}$, where $Y_c = Y - Y \otimes 1_{1 \times NJ}$, $X_c = X - X \otimes 1_{1 \times NJ}$, $\mu_{c,t} = (A_{11} \mu_{b,1,t}, \ldots, A_{nJ} \mu_{b,nJ,t}) - \mu_t \otimes 1_{1 \times NJ}$ and $U_{c,t} = Y_c - \mu_{c,t}$.
    4. $\Sigma_{\varepsilon,t+1} = \Sigma_{1,t+1} + \Sigma_{2,t+1}$, where $\Sigma_{1,t+1} = P_{\Gamma_{t+1}} (U_{c,t} Q_{X_c} U_{c,t}^T + \Psi_{b,t}) P_{\Gamma_{t+1}}/J$,
      $\Sigma_{2,t+1} = Q_{\Gamma_{t+1}} (U_{c,t} U_{c,t}^T + \Psi_{b,t}) Q_{\Gamma_{t+1}}/J$, $\Psi_{b,t} = \sum_{i=1}^n \sum_{j=1}^{J_t} A_{ij} \Sigma_{b,t} A_{ij}^T$.
    5. Set $\Delta_{t+1} = \|\beta_{t+1} - \beta_t\|_1 / \|\beta_{t+1}\|_1$, $\theta_{t+1} = (\Sigma_{t+1}, \beta_{t+1}, \rho_{t+1})$, $t \leftarrow t + 1$.
  end end

Select $k$ which minimize $\text{BIC}_k$, and $\hat{\beta}_k$ is the mixed effects envelope estimator.
Table 1. The point estimates, bootstrap standard errors and $p$–values for the regression parameter with respect to those patients attended all the measurements

|                               | Our Method |                      |                  | Standard EM |                      |                  |
|-------------------------------|------------|----------------------|------------------|-------------|----------------------|------------------|
|                               | $\hat{\beta}$ | SE       | $p$–value  | $\hat{\beta}$ | SE       | $p$–value  |
| **Corresponding to Treatment** |            |          |            |              |          |            |
| Treatment Satisfaction        | 0.46       | 0.44     | 0.30       | 0.69        | 0.59     | 0.24       |
| Depression Scale              | -0.057     | 0.20     | 0.77       | 0.088       | 0.24     | 0.71       |
| Physical Score                | -2.13$\times 10^{-3}$ | 6.25$\times 10^{-3}$ | 0.73       | -1.81$\times 10^{-3}$ | 0.025 | 0.94       |
| Mental Score                  | 0.011      | 0.033    | 0.73       | 0.011       | 0.061    | 0.86       |
| Interference Score            | 4.57$\times 10^{-4}$ | 1.87$\times 10^{-3}$ | 0.81       | 2.83$\times 10^{-3}$ | 4.48$\times 10^{-3}$ | 0.52 |
| Symptom & Distress Score      | -0.99      | 1.89     | 0.60       | -0.77       | 2.30     | 0.74       |
| SBP                           | -0.32      | 0.39     | 0.41       | 0.074       | 0.69     | 0.91       |
| DBP                           | -0.27      | 0.39     | 0.49       | -0.22       | 0.46     | 0.64       |
| Heart Rate                    | 0.40       | 0.53     | 0.45       | 0.34        | 0.53     | 0.53       |
| **Corresponding to Age**      |            |          |            |              |          |            |
| Treatment Satisfaction        | 0.24       | 0.10     | 0.02       | 0.23        | 0.046    | < 0.01     |
| Depression Scale              | -0.039     | 0.019    | 0.04       | -0.071      | 0.013    | < 0.01     |
| Physical Score                | -2.66$\times 10^{-3}$ | 9.95$\times 10^{-4}$ | < 0.01     | -6.78$\times 10^{-3}$ | 1.87$\times 10^{-3}$ | < 0.01     |
| Mental Score                  | 5.40$\times 10^{-3}$ | 3.65$\times 10^{-3}$ | 0.14       | 0.012       | 4.14$\times 10^{-3}$ | < 0.01     |
| Interference Score            | 6.93$\times 10^{-5}$ | 2.12$\times 10^{-4}$ | 0.74       | 1.50$\times 10^{-4}$ | 2.71$\times 10^{-4}$ | 0.58       |
| Symptom & Distress Score      | -0.22      | 0.24     | 0.36       | -0.29       | 0.15     | 0.06       |
| SBP                           | 0.071      | 0.01     | 0.45       | 0.041       | 0.051    | 0.41       |
| DBP                           | -0.60      | 0.059    | < 0.01     | -0.61       | 0.035    | < 0.01     |
| Heart Rate                    | -0.34      | 0.037    | < 0.01     | -0.34       | 0.036    | < 0.01     |
Table 2. The point estimates, bootstrap standard errors and $p$-values for the regression parameter with respect to all the patients attended all four measurements

| Corresponding to Treatment | Our Method |          |          | Standard EM |          |          |
|----------------------------|------------|----------|----------|-------------|----------|----------|
|                            | $\hat{\beta}$ | SE       | $p$-value | $\hat{\beta}$ | SE       | $p$-value |
| Treatment Satisfaction     | -0.019     | 0.20     | 0.92     | 0.67        | 0.53     | 0.21     |
| Depression Scale           | 7.44×10^{-3} | 0.080 | 0.93     | 0.13        | 0.18     | 0.48     |
| Physical Score             | 6.16×10^{-4} | 1.41×10^{-3} | 0.66     | 3.59×10^{-5} | 0.019     | 0.99     |
| Mental Score               | -1.36×10^{-3} | 0.017 | 0.94     | -0.031      | 0.042     | 0.46     |
| Interference Score         | -3.77×10^{-5} | 9.39×10^{-4} | 0.97     | -6.49×10^{-4} | 2.72×10^{-3} | 0.81     |
| Symptom & Distress Score   | 0.14       | 1.50     | 0.93     | 1.23        | 1.69     | 0.47     |
| SBP                        | 8.19×10^{-3} | 0.088 | 0.93     | -0.45       | 0.63     | 0.47     |
| DBP                        | 4.56×10^{-3} | 0.050 | 0.93     | -0.60       | 0.36     | 0.10     |
| Heart Rate                 | 3.06×10^{-3} | 0.034 | 0.93     | 0.13        | 0.40     | 0.74     |
| Corresponding to Age       |          |          |          |            |          |          |
|                            | $\hat{\beta}$ | SE       | $p$-value | $\hat{\beta}$ | SE       | $p$-value |
| Treatment Satisfaction     | -1.67      | 0.34     | < 0.01   | 0.23        | 0.51     | < 0.01   |
| Depression Scale           | -0.65      | 0.12     | < 0.01   | -0.071      | 0.16     | < 0.01   |
| Physical Score             | -0.061     | 0.011    | 0.40     | -6.78×10^{-3} | 0.018     | < 0.01   |
| Mental Score               | -0.17      | 0.023    | < 0.01   | 0.012       | 0.050     | < 0.01   |
| Interference Score         | -0.015     | 1.21×10^{-3} | < 0.01   | 1.50×10^{-4} | 3.27×10^{-3} | < 0.01   |
| Symptom & Distress Score   | 1.22       | 2.16     | < 0.01   | -0.29       | 1.88     | < 0.01   |
| SBP                        | 0.72       | 0.18     | < 0.01   | 0.041       | 0.50     | 0.59     |
| DBP                        | 0.40       | 0.097    | < 0.01   | -0.61       | 0.39     | 0.85     |
| Heart Rate                 | 0.27       | 0.082    | < 0.01   | -0.34       | 0.45     | < 0.01   |