On Semiparametric Efficiency of an Emerging Class of Regression Models for Between-subject Attributes

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Abstract

The semiparametric regression models have attracted increasing attention owing to their robustness compared to their parametric counterparts. This paper discusses the efficiency bound for functional response models (FRM), an emerging class of semiparametric regression that serves as a timely solution for research questions involving pairwise observations. This new paradigm is especially appealing to reduce astronomical data dimensions for those arising from wearable devices and high-throughput technology, such as microbiome Beta-diversity, viral genetic linkage, single-cell RNA sequencing, etc. Despite the growing applications, the efficiency of their estimators has not been investigated carefully due to the extreme difficulty to address the inherent correlations among pairs. Leveraging the Hilbert-space-based semiparametric efficiency theory for classical within-subject attributes, this manuscript extends
such asymptotic efficiency into the broader regression involving between-subject attributes and pinpoints the most efficient estimator, which leads to a sensitive signal-detection in practice. With pairwise outcomes burgeoning immensely as effective dimension-reduction summaries, the established theory will not only fill the critical gap in identifying the most efficient semiparametric estimator but also propel wide-ranging implementations of this new paradigm for between-subject attributes.

Keywords: Dimension-reduction Functional Response model (FRM); Dual orthogonality; Equivalence class; High-throughput Sequencing; Hilbert space.
1 Introduction

As a mainstream, the classical generalized linear model (GLM) encompasses nonnormal and noncontinuous responses (or dependent variables) to present a unified paradigm for different response types. The maximum likelihood estimators (MLE) for GLM enjoy consistency and asymptotic normality (CAN) if both the random and systematic components, as well as the link function, are correctly specified. Estimators with (asymptotic) variances achieving the Cramér-Rao bound are referred to as (asymptotically) efficient; MLEs are exact examples of efficient estimators for the parametric GLM.

By relaxing the nuisance parameter in the distributional assumption to be infinite-dimensional, the semiparametric GLM, also termed the restricted moment models (RMM), enables robust statistical inference for a broader class of data distributions. Under suitable regularity conditions, estimators from the generalized estimating equations (GEE) are optimal. They enjoy consistency and asymptotically normality and also achieve the semiparametric efficiency bound.

Despite its immense applicability, GLM predominantly focuses on the relationships within the same subject, termed “within-subject attributes”. But in the growing applications, of major interest are outcomes defined by a pair of subjects, or the “between-subject attributes.” The probability index \( Pr(Y_{i1} < Y_{i2}), (i_1, i_2) \in C_2^n \) in the Mann-Whitney-Wilcoxon (MWW) rank-sum test is a classical example. Fueled by innovative technologies such as high-throughput sequencing and wearable devices, the pairwise dissimilarity/distance metrics that summarize high-dimensional sequences also entail a between-subject nature. Modeling between-subject attributes are challenging due to the complex correlation structures among pairwise observations. To address this, a semiparametric framework of functional response models (FRM) has been proposed, which naturally enlarges GLM to involve between-subject attributes. This paradigm accommodates various types of between-subject distances and complements the prevailing regularization-based approach for high-dimensional data.

The FRM framework admits a wide range of applications. For instance, Liu et al. (2021) adopted the FRM to extend the predominant ANOVA-based approach to model microbiome Beta-diversity in a regression; Lin et al. (2021) implemented the MWW rank-sum test and FRM in survey data to address the restrictive test of equal distributions; Wu et al. (2014) incorporated the inverse probability weighting (IPW) into a rank-based statistic and applied FRM to deal with confounding effects in causal inference. Their estimators from the U-statistics-based generalized estimating equations (UGEE) all enjoy nice asymptotic properties just like their GEE counterparts for the semiparametric GLM.
Nevertheless, the efficiency of UGEE estimators for the semiparametric FRM has not been investigated thoroughly. Akin to the case for within-subject attributes, we aim to find estimator(s) with the smallest asymptotic variance, or the semiparametric efficient estimator(s) for between-subject attributes. To this end, one first needs to extend essential concepts (such as influence functions and asymptotic linearity) from the classical within-subject settings and then develop a coherent theory in the FRM regression for between-subject attributes. In this manuscript, we leverage the Hilbert-space-based semiparametric efficiency theory to demonstrate that the UGEE estimators also achieve the efficiency bound, just like GEE estimators for the semiparametric GLM. Hence, harmonizing the semiparametric efficiency and robustness, the modeling framework for between-subject attributes can facilitate knowledge discovery for scientific questions that call for such models and inform appropriate decision making.

The rest of the manuscript is organized as follows. We first introduce the FRM framework (with examples) in Section 2 and fundamentals for semiparametric efficiency in Section 3. We then generalize the Hilbert space tailored for between-subject attributes in Section 4. In Sections 5, 6, and 7, we show the semiparametric efficiency of UGEE estimators through a “conjugate” class of models, leveraging geometric perspectives built upon Hilbert spaces. Examples of efficient UGEE estimators are then demonstrated in Section 8. We also discuss adaptive estimators and present simulation studies in Section 9. In section 10, we give our concluding remarks.

2 Between-subject Functional Response Models

2.1 Between-subject Attributes

Fueled by technological advances such as next-generation sequencing and wearable devices, between-subject attributes are gaining popularity by reducing dimensions effectively. They have evolved into the center stage of biomedical and other burgeoning research areas, such as microbiome, single-cell RNA sequencing\textsuperscript{25}, etc. To illustrate, the human microbiome is now interrogated using high-throughput sequencing (e.g., 16s sequencing of gut microbiota) for insights in disease mechanisms. This procedure generates taxonomic sequence counts (for each subject) that are sparse and astronomically high-dimensional (e.g., in our data application, the dimension $m = 12,131$). Due to their additional sparsity and non-normality, the microbiome “diversity” has been introduced to summarize the raw sequence. This biologically-relevant concept constitutes a critical indicator of human health\textsuperscript{20}.

For example, the Beta-diversity defined by the pairwise distance of taxonomic sequence
counts naturally encompasses a between-subject nature. Consider a human microbiome dataset composed of $n$ subjects. Let $Y_i \in \mathbb{R}^m$ denote a column vector of relative abundance (proportions) of taxonomic units for the $i$-th subject, the Aitchison Beta-diversity\(^2\) between any pair $(i_1, i_2) \in C_2^n$ is

$$d_A(Y_{i_1}, Y_{i_2}) = \left[ \sum_{k=1}^{m} \left( \log \frac{Y_{i_1k}}{g(Y_{i_1})} - \log \frac{Y_{i_2k}}{g(Y_{i_2})} \right)^2 \right]^{1/2}, \quad g(Y_i) = \left( \prod_{k=1}^{m} Y_{ik} \right)^{1/m}, \quad (1)$$

where $C_q^n$ denotes the set of $q$-combinations $(i_1, \ldots, i_q)$ from the integer set $\{1, \ldots, n\}$, $g(Y_i)$ is the geometric mean of $Y_i$.

By integrating information from the raw high-dimensional sequences, Beta-diversity measures the dissimilarity/distance between two subjects across all (or a proportion of) the sequenced genomes thus merits its scientific interest.

The versatility of between-subject attributes motivates researchers to migrate such pairwise distances to the blooming real-time longitudinal sequences collected from wearables. For example, since the mean of squared Euclidean distance pertains to the variance, pairwise distances of those high-dimensional sequences can naturally capture the between-subject variability (beyond the population mean). By unraveling the intricate connections between physical activity and clinical traits, between-subject distances could facilitate personalized disease interventions.

Another example of between-subject attribute is the connection between two subjects in a social network. Since the connection is defined for more than one subject, the subject-level outcome is latent here.

For the examples above, main interests are shifted to the between-subject attributes (instead of the raw high-dimensional sequences). We refer to them as “endogenous” to distinguish them from another category called “exogenous” between-subject attributes, where the focus is still on the original within-subject attributes. For instance, for a scalar within-subject $Y_i$, the squared difference index $(Y_{i_1} - Y_{i_2})^2$ can extend the ANOVA to compare variances (rather than means) among groups\(^3\), and a probability index $Pr(Y_{i_1} < Y_{i_2})$ can compare groups in the MWW rank-sum test\(^4\) to address outliers. In these examples, we are interested in characteristics of the original within-subject attributes, such as variances or differences between two distributions.

The distinction between these two types of between-subject attributes is not as rigorous, but differentiating them will enable us to handle the raw data more systematically during statistical modeling.
2.2 Semiparametric GLM and Functional Response Model

Consider a study with \( n \) subjects, let \( Y_i \) denote a response, \( X_i \) an explanatory variable for the \( i \)-th subject. As a motivating example, the semiparametric GLM (SPGLM) characterizing the relationship between \( Y_i \) and \( X_i \) is:

\[
E(Y_i | X_i) = h(X_i; \beta), \quad 1 \leq i \leq n,
\]

where \( h(\cdot) \) is the inverse of some link functions\(^{38} \), additional explanatory variables can be added to the linear predictor. Compared with the classical parametric GLM, (2) is more flexible by removing the distributional assumption on \( Y_i \) thus yields valid inference even when the data deviate from such an assumption. However, limitations of this prevalent framework include: 1) it does not apply to the between-subject, or pairwise, attributes that are of interest in a mounting number of applications; 2) it fails to directly model a multivariate response \( Y_i \in \mathbb{R}^m (m \geq 1) \), especially when the dimension of \( Y_i \) is high.

Hence, we adopt an enlarged paradigm. Consider observing the raw data \((Y_i^\top, X_i^\top)\), where \( Y_i(X_i) \in \mathbb{R}^m (m \geq 1) \) is a column vector of multivariate response (explanatory variable) for the \( i \)-th subject. By concatenating \( Y_i \) into a (scalar) functional response of multiple \((s)\) subjects \( f(Y_{i_1}, \ldots, Y_{i_s}), (i_1, \ldots, i_s) \in C^m_s \), the semiparametric framework of functional response models (FRM) resolves the aforementioned challenges:

\[
E[f(Y_{i_1}, \ldots, Y_{i_s}) | X_{i_1}, \ldots, X_{i_s}] = h(X_{i_1}, \ldots, X_{i_s}; \beta), \quad (i_1, \ldots, i_s) \in C^m_s, \quad s \geq 1,
\]

where \( f(\cdot) \) is some scalar-valued function, \( h(\cdot) \) is some smooth function (e.g., with continuous derivatives up to the second order), \( \beta \) is a vector of parameters, \( s \) is a positive integer. Akin to (2), (3) is also semiparametric without any distributional assumption on the response \( f(Y_{i_1}, \ldots, Y_{i_s}) \). In practice, this introduces greater flexibility, which addresses the difficulty to specify such an assumption for the multi-subject based response function \( f(Y_{i_1}, \ldots, Y_{i_s}) \) that resembles the real study data. As a special case when \( m = s = 1 \) and \( f(Y_i) = Y_i \), (3) reduces to (2). The FRM is also readily extended to model a vector-valued response function (see Example 3 in Section 2.3).

We now implement (3) to model the between-subject attributes, which will be the focus of this paper. For notational consistency, we use \( i \) to index a subject and \( i = (i_1, i_2) \in C^n_2 \) to index a pair in what follows. Let \( s = 2 \), we construct a between-subject attribute \( f_i = f(Y_{i_1}, Y_{i_2}) \) with some mapping such as (1), then the semiparametric FRM below models \( f_i \) as a function of \( X_i = (X_{i_1}^\top, X_{i_2}^\top)^\top \):

\[
E(f_i | X_i) = h(X_i; \beta), \quad i = (i_1, i_2) \in C^n_2.
\]
extends the classical GLM from within- to between-subject attributes that are generally tricky to model. It not only achieves effective dimension-reduction but also establishes a complementing angle for data entailing an intrinsic between-subject nature. Hence, semiparametric FRM uniquely positions itself to facilitate data-driven knowledge discoveries, which could otherwise be hindered by the predominant paradigm of merely modeling within-subject attributes. We highlight the widespread applicability of semiparametric FRM with additional examples below. More applications can be found in the references of Section 1.

2.3 Examples of Functional Response Models

Example 1: The Beta-diversity for High-throughput Data in Microbiome

For many studies such as the microbiome, major interest is to compare characteristics of the between-subject attributes among subgroups, where FRM is desirable. We start with a categorical variable \( X_i \) with \( K \) levels (such as the disease status). To transform \( X_i \) to a between-subject attribute for the \( i \)-th pair, we define a set of pairwise indicators (or dummy variables) for \( X_i = \{ X_{i1}, X_{i2} \} \) through the one-hot encoding function \( \delta(\cdot) : \{ 1, \ldots, K \} \times \{ 1, \ldots, K \} \mapsto \{ 0, 1 \}^{K+\binom{K}{2}} \):

\[
\delta_{k_1,k_2}(X_i) = \begin{cases} 
1, & \text{if } X_i = \{ X_{i1}, X_{i2} \} = \{ k_1, k_2 \}, \\
0, & \text{otherwise.}
\end{cases}
\]

(5)

where the vector \( \delta(X_i) \in \mathbb{R}^{K+\binom{K}{2}} \) denotes all combinations. Thus, \( \delta_{k_1,k_2}(X_i) \) indicates the pair with the same \( k \)-th concordant \((k_1 = k_2 = k)\) or discordant \((k_1 < k_2)\) levels for \( X_i \).

For example, if \( X_i \) is a binary indicator of disease, we form

\[
\delta(X_i) = (\delta_{DD}(X_i), \delta_{HH}(X_i), \delta_{HD}(X_i))^\top,
\]

where \( \delta_{DD}(X_i) \) and \( \delta_{HH}(X_i) \) index diseased-diseased and healthy-healthy pairs, and \( \delta_{HD}(X_i) \) represents the mixed healthy-diseased pairs.

Let \( f_i = f(Y_{i1}, Y_{i2}) \) denote the Beta-diversity for the \( i \)-th pair such as the Aitchison distance in (1), we can model its mean among subgroups adopting the FRM:

\[
E(f_i | X_i) = \exp[\beta^\top \delta(X_i)], \quad \beta = (\tau_{11}, \ldots, \tau_{KK})^\top, \quad \delta(X_i) = (\delta_{11}(X_i), \ldots, \delta_{KK}(X_i))^\top,
\]

(6)

where \( \exp(\cdot) \) ensures that the response is non-negative.
The coefficients of the dummy variables now reveal the heterogeneity in \( f_i \) among different subgroups defined by \( \delta(X_i) \). Such a pairwise one-hot encode also facilitates disentangling different types of heterogeneity (e.g., “location” or “scale” difference\(^{15} \)), which is laborious or not even feasible using existing approaches such as PERMANOVA. We can also include either between- or within-subject attributes as covariates in (6). For between-subject covariates, it is straightforward. For within-subject attributes, we can readily create their between-subject counterparts\(^{15} \) as shown above.

**Example 2: Mann-Whitney-Wilcoxon Rank-sum Test and Rank Regression**

Let \( Y_i \) \((1 \leq i \leq n)\) denote a univariate continuous within-subject response. In the presence of outliers, the Mann-Whitney-Wilcoxon rank-sum test offers a robust alternative to the two-sample t-test to compare the centers of two distributions\(^{17} \). Let \( X_i \) denote a vector of explanatory variables for the \( i \)-th subject, FRM readily extends the rank-sum test to a regression:

\[
E(f_i \mid X_i) = h(X_i, \beta) = \Phi[-\beta^T(X_{i1} - X_{i2})],
\]

where \( \Phi(\cdot) \) denotes the cumulative distribution function (CDF) of the standard normal distribution. The parameter \( \beta \) in (7) preserves its interpretation in the conventional linear model for within-subject attributes by regression \( Y_i \) on \( X_i \), but considerably addresses outliers in \( Y_i \). Unlike Example 1, in this exogenous example, research interest still centers on the relationship between \( Y_i \) and \( X_i \). It was further extended to longitudinal settings with missing values\(^7 \). More examples can be found in literatures for probability index models\(^{34} \).

**Example 3: Intraclass Correlations for Rater Agreement**

Consider a study of \( n \) subjects in which each subject is rated by \( K \) judges. Let \( Y_{ik} \) denote the rating for the \( i \)-th subject by the \( k \)-th judge \((1 \leq k \leq K)\), it is commonly characterized by a two-way mixed-effects model:

\[
Y_{ik} = \mu + \beta_i + \gamma_k + (\beta\gamma)_{ik} + \varepsilon_{ik}, \quad \varepsilon_{ik} \sim N(0, \sigma^2),
\]

\[
\beta_i \sim N(0, \sigma^2_\beta), \quad \sum_{k=1}^{K} \gamma_k = 0, \quad (\beta\gamma)_{ik} \sim N(0, \sigma^2_{\beta\gamma}), \quad \sum_{k=1}^{K} (\beta\gamma)_{ik} = 0,
\]

where \( N(0, \sigma^2) \) denotes a normal distribution with mean 0 and variance \( \sigma^2 \). If interest is in the agreement among \( K \) judges, a widely applied index is the intraclass correlation (ICC) \( \rho = [\sigma^2_\beta - \sigma^2_{\beta\gamma}/(K - 1)] / (\sigma^2_\beta + \sigma^2_{\beta\gamma} + \sigma^2) \), which can be computed after fitting the model in (8). But the major concern is the difficulty to validate the multiple imposed normal assumptions, especially for the random effects \( (\beta\gamma)_{ik} \) due to their latent nature. Hence, it
renders the likelihood-based approaches prone to invalid inference under the rating data that is usually non-normal.

This is readily fixed with a semiparametric alternative. Let

\[
\begin{align*}
Y_i \cdot &= \frac{1}{K} \sum_{k=1}^{K} Y_{ik}, \quad f_{i1} = \frac{1}{2} (Y_{i1} - Y_{i2})^2, \quad g_{ik} = \frac{1}{2} (Y_{ik} - Y_{i2})^2, \\
G_{i2} &= \frac{1}{K} \sum_{k=1}^{K} g_{ik}, \quad h_{i1} = \frac{1 + (K - 1) \rho}{K} \tau^2, \quad h_{i2} = \tau^2,
\end{align*}
\]

we construct the following (multivariate) FRM:

\[
E (f_i) = h_i (\theta), \quad f_i = (f_{i1}, f_{i2})^T, \quad h_i = (h_{i1}, h_{i2})^T, \quad \theta = (\tau^2, \rho)^T. \tag{9}
\]

The \( \rho \) in (9) is exactly the ICC\(^{22} \) that we aim to model. In addition to robustness, this model also allows for an immediate extension to longitudinal settings.

### 2.4 Inference for the U-statistics and UGEE

The FRM reinvigorates regression by extending within- to between-subject attributes. However, popular asymptotic methods such as central limit theorem (CLT) rely on the critical assumption of independence and as such are not directly applicable to FRM, since the functional responses are correlated. This is addressed via the theory of U-statistics\(^{12} \).

#### 2.4.1 Asymptotic Properties of U-statistics

Most statistics in modeling within-subject attributes are summations of \( i.i.d. \) elements, such as the score and estimating equations. However, statistics formed by between-subject attributes in the FRM are correlated. To resolve this issue, a class of U-statistics-based generalized estimating equations (UGEE) have been developed. We briefly review the U-statistics that are instrumental in studying multi-subject-based statistics.

**Definition.** Consider a sample of \( i.i.d. \) random vectors \( Y_i \in \mathbb{R}^m \) \( (1 \leq i \leq n) \). Let \( d^{ls} (Y_1, \ldots, Y_s) \) be a \( d \)-dimensional symmetric function with \( s \) input vectors (or arguments), i.e., \( d (Y_1, \ldots, Y_s) = d (Y_{i1}, \ldots, Y_{is}) \) for any permutation \( (i_1, \ldots, i_s) \) of \( (1, \ldots, s) \). A \( d \)-variate, one-sample, \( s \)-argument U-statistic is

\[
U_n = \begin{pmatrix} n \end{pmatrix}^{-1} \sum_{(i_1, \ldots, i_s) \in C^n_s} f (Y_{i1}, \ldots, Y_{is}), \quad s \geq 1, \tag{10}
\]
where \( C_s^n = \{(i_1, \ldots, i_s); 1 \leq i_1 < \ldots < i_s \leq n\} \) denotes the set of all distinct \( s \)-combinations from the integer set \( \{1, \ldots, n\} \). It is easily checked that \( E(U_n) = E[f(Y_{i_1}, \ldots, Y_{i_s})] = \theta \), i.e., \( U_n \) is an unbiased estimator of \( \theta \).

Since \( f(Y_{i_1}, \ldots, Y_{i_s}) \) (also termed the kernel function) involves multiple rather than a single subject, dependencies between any two kernel functions arise when they share at least one common subject (e.g., \( f(Y_{i_1}, Y_{i_2}) \) and \( f(Y_{i_1}, Y_{i_3}) \) are correlated as they share \( Y_{i_1} \)). This dependency is tackled through the Hájek projection:

\[
\tilde{U}_n = \frac{s}{n} \sum_{i=1}^{n} E[f(Y_1, \ldots, Y_s) | Y_i].
\] (11)

The conditional expectations of \( f(Y_1, \ldots, Y_s) \) given each \( Y_i \) (of the i.i.d. sample) are now i.i.d., permitting applications of conventional asymptotic techniques. As shown below, the U-statistic and its projection have the same asymptotic distribution.

**Theorem 1.** Let

\[ \tilde{v}_1(Y_1) = E[f(Y_1, \ldots, Y_s) | Y_1] - \theta, \quad e_n = \sqrt{n}(U_n - \tilde{U}_n), \quad \Sigma_e = Var[\tilde{v}_1(Y_1)]. \] (12)

Under mild regularity conditions, \( e_n \rightarrow_p 0 \) and thus,

(i) \( U_n \) is consistent, i.e., \( U_n \rightarrow_p \theta \).

(ii) \( U_n \) is asymptotically (multivariate) normal:

\[ \sqrt{n}(U_n - \theta) \rightarrow_d N(0, \Sigma_U = s^2 \Sigma_v), \] (13)

where \( \rightarrow_p(d) \) denotes convergence in probability (distribution).

### 2.4.2 U-statistics-based Generalized Estimating Equations

For notational brevity, here we focus on between-subject, or pairwise, attributes where the number of input vector \( s = 2 \). Extensions to \( s > 2 \) are straightforward.

To tackle the interlocking dependencies among pairwise outcomes for the inference of \( \beta \), we define a class of U-statistics-based Generalized Estimating Equations (UGEE)

\[
U_n(\beta) = \sum_{i \in C_2^n} U_{n,i}(\beta) = \sum_{i \in C_2^n} D_i^T V_i^{-1} S_i(\beta) = 0, \quad i = (i_1, i_2) \in C_2^n, \quad (14)
\]

\[
S_i(\beta) = f_i - h_i(X_i; \beta), \quad D_i = \frac{\partial}{\partial \beta} h_i(X_i; \beta), \quad V_i = Var(f_i | X_i).
\]
In practice, \( V_i \) is unknown and substituted by a working variance. Estimators \( \hat{\beta}_{\text{ugee}} \) are obtained by solving (14) numerically such as with the Newton-Raphson method. Although similar in appearance to GEE\(^{38}\), UGEE is not a sum of independent variables. But \( \hat{\beta}_{\text{ugee}} \) is consistent and asymptotically normal, which is a direct result from Theorem 1.

**Theorem 2.** Let

\[
\tilde{v}_{i_1} = 2E(U_{n,i} \mid Y_{i_1}, X_{i_1}), \quad B = E(D_i^T V_i^{-1} D_i), \quad \Sigma_U = Var(\tilde{v}_{i_1}), \quad \Sigma_{\beta}^{\text{ugee}} = B^{-1} \Sigma_U B^{-1}.
\]

Under mild regularity conditions, \( \hat{\beta}_{\text{ugee}} \) is a consistent and asymptotically normal (CAN) estimator of \( \beta \) in (4):

\[
\sqrt{n}(\hat{\beta}_{\text{ugee}} - \beta) \xrightarrow{d} N(0, \Sigma_{\beta}^{\text{ugee}}).
\]

A consistent estimator of \( \Sigma_{\beta}^{\text{ugee}} \) can be obtained by substituting consistent estimators of \( \beta \) and moment estimators of the respective quantities in (15). Conforming to the appealing features of its within-subject counterpart GEE, UGEE also yields valid inference without explicitly delineating the potentially more complex correlation structures.

Under suitable regularity conditions, the “sandwich” estimators from the GEE are not only consistent and asymptotically normal but also achieve the semiparametric efficiency bound\(^{36}\) for the semiparametric GLM. This semiparametric efficiency allows a sensitive signal-detection in practice while simultaneously harmonizing robustness to model misspecification.

Our goal is to study whether the UGEE estimator for between-subject attributes also attain the semiparametric efficiency bound for the semiparametric FRM (in addition to CAN). We start with essential concepts and models for pairs.

### 3 Asymptotic Linearity and Influence Function

To study the semiparametric efficiency for between-subject attributes, we first need to extend concepts of within to between-subject attributes, such as asymptotic linearity and influence functions\(^4\). Denote the within-subject attributes by \( Z_1, ..., Z_n \sim \text{i.i.d.} \{p(Z_i; \theta) ; \theta \in \Omega\} \), where \( p(Z_i; \theta) \) is a probability density or distribution function characterized by parameter \( \theta \). We assume \( \theta = (\beta^T, \eta)^T \) (i.e., \( \beta \) and \( \eta \) are variationally independent with no overlapping components), where \( \beta \) is a \( q \times 1 \) vector of parameters of interest and \( \eta \) is the nuisance parameter. The only component that differentiates parametric from semiparametric models is the dimension of \( \eta \); a finite-dimensional vector \( \eta \) yields the parametric while an infinite-dimensional nuisance parameter, denote by \( \eta(\cdot) \), leads to the semiparametric model\(^{36}\).}
In the literature of classical within-subject attributes, $\hat{\beta}$ is asymptotically linear (AL) if there exists an expansion $n^{1/2} (\hat{\beta} - \beta_0) = n^{-1/2} \sum_{i=1}^n \phi(Z_i; \theta_0) + o_p(1)$, where $\phi(Z_i; \theta_0)$ is termed the influence function (I.F.) for the $i$-th observation at $\theta_0$ (the truth). This I.F. has mean zero and finite and nonsingular $E(\phi\phi^T)$, its name reflects the influence of an observation unit on an estimator. The asymptotic normality is readily derived from this expansion with CLT, hence, $n^{1/2} (\hat{\beta} - \beta_0) \rightarrow_d N(0, E(\phi\phi^T))$, the asymptotic variance of $\hat{\beta}$ is determined by its I.F., or $\phi(Z_i)$ defines the efficiency of $\hat{\beta}$.

Those within-subject $Z_i$’s induce a sequence of i.d. (identically distributed but not necessarily independent) random vectors for pairs, $Z_i = (Z_{ij}^T, Z_{ik}^T)^T \sim \{p(Z_i; \theta); \theta \in \Omega\}$. We consider two classes of models for $Z_i$, each with associated estimators and I.F.s.

### 3.1 Non-overlap Model Class 1

To avoid dependencies, we first consider a subset of i.i.d. pairs $Z_{ij}, 1 \leq j \leq \lfloor n/2 \rfloor = m$, where $[\cdot]$ is the floor function. Namely, we reorganize the data into independent non-overlapping pairs. Although this reorganization is not unique, we choose one without loss of generality. For example, when $n = 4$, we can choose $\{Z_{i_1}, Z_{i_2}\}$ and $\{Z_{i_3}, Z_{i_4}\}$ to form two independent pairs $i_1 = (i_1, i_2)$ and $i_2 = (i_3, i_4)$. This removes the hurdle of dependencies originated from overlapping pairs, permitting definitions in parallel with the classical setting.

**Definition.** $\tilde{\beta}$ is an asymptotically linear (AL) estimator of between-subject attributes for the non-overlap model class 1 if it belongs to

$$\Omega_1^{\beta} = \left\{ \tilde{\beta}(Z_{ij}) : \sqrt{m} (\tilde{\beta} - \beta_0) = \sqrt{m} \frac{1}{m} \sum_{j=1}^m \psi(Z_{ij}; \theta_0) + o_p(1) \right\},$$

(16)

where $\psi^{q \times 1}(Z_i; \theta_0)$ is a measurable function with mean zero, finite and nonsingular $E(\psi\psi^T)$, termed the influence function 1 for the $i$-th pair at the truth. The set of all influence functions 1 is denoted by $\Gamma_1^{I.F.}$.

Under mild regularity conditions, CLT yields

$$\sqrt{m} (\tilde{\beta} - \beta_0) \rightarrow_d N(0, \Sigma_1), \Sigma_1 = E[\psi(Z_{ij}) \psi^T(Z_{ij})].$$

Thus, the asymptotic variance for $\tilde{\beta} \in \Omega_1^{\beta}$ is determined by its I.F. $\psi(Z_{ij})$, and the efficient estimator in $\Omega_1^{\beta}$ is the one with minimum variance.
In practice, we do not fit data with between-subject attributes using model class 1 as they only deploy part of the data. But this conceptual model will help us pinpoint the efficient estimator for the FRM as we now introduce.

### 3.2 Enumerated Model Class 2

If making the inference based on all possible pairs \( Z_i, i = (i_1, i_2) \in C^n 2 \), including those with overlapping subjects, we reimpose the dependencies and form a class of enumerated model 2. The FRM in (4) that engage all possible pairs is an example of this class.

**Definition.** \( \hat{\beta} \) is an AL estimator of between-subject attributes for the enumerated model 2 if it belongs to

\[
\Omega^2_{AL} = \left\{ \hat{\beta}(Z_i) : n^{1/2} \left( \hat{\beta} - \beta_0 \right) = \sqrt{n} \left( \frac{n}{2} \right)^{-1} \sum_{i \in C^n 2} \varphi(Z_i; \theta_0) + o_p(1) \right\},
\]

(17)

where the measurable function \( \varphi^{q \times 1}(Z_i; \theta_0) \) with mean zero and finite and nonsingular \( E(\varphi\varphi^\top) \) is defined as the enumerated influence function 2 for the \( i \)-th pair at the truth.

Denote the set of all such \( \varphi(Z_i; \theta_0) \) by \( \Gamma_{2.F}^I \). It is obvious that \( \hat{\beta}_{ngee} \in \Omega^2_{AL} \).

As (17) involves the summation of dependent \( \varphi(Z_i) \), we apply (12) to obtain:

\[
\sqrt{n} \left( \beta - \beta_0 \right) = \sqrt{n} \sum_{i=1}^n \frac{1}{n} \left( \frac{1}{n} \right)^{-1} \sum_{i \in C^n 2} \varphi(Z_i; \theta_0) + o_p(1) \rightarrow_d N(0, \Sigma_2),
\]

\[
\Sigma_2 = Var \left\{ 2E[\varphi(Z_i; \theta_0) \mid Z_{i_1}] \right\} = E \left\{ 2E[\varphi(Z_i; \theta_0) \mid Z_{i_1}] \cdot 2E[\varphi^\top(Z_i; \theta_0) \mid Z_{i_1}] \right\}.
\]

Hence, for \( \hat{\beta} \in \Omega^2_{AL} \) of model class 2, the asymptotic variance \( \Sigma_2 \) is also determined by its I.F.. \( \Sigma_2 \) apparently differs from \( \Sigma_1 \) in model class 1, since it involves an additional step of mapping from a function of between-subject attribute \( Z_i \) to a function of within-subject attribute \( Z_{i_1} \).

### 3.3 Relationships between I.F.s for the Two Model Classes

The influence function is the key to studying efficiency, we now elucidate the relationships between influence functions associated with each model class.

**Equivalence of Two Classes of AL estimators**

For AL estimators, the I.F.s for the two model classes are equivalent. Namely, for any \( \psi(Z_i; \theta_0) \in \Gamma_{1.F}^I \) and AL estimator \( \bar{\beta} \in \Omega_1^\beta \), we can construct another estimator \( \hat{\beta} = \)
\[ \beta_0 + \left( \frac{n}{2} \right)^{-1} \sum_{i \in C_n} \psi(Z_i; \theta_0). \] It is readily checked that this new \( \hat{\beta} \in \Omega_2^\beta \) by satisfying (17), indicating that \( \hat{\beta} \) is also AL for the model class 2 and \( \psi(Z_i; \theta_0) \in \Gamma_2^{I.F.} \).

Conversely, for any \( \varphi(Z_i; \theta_0) \in \Gamma_2^{I.F.} \) and corresponding AL estimator \( \hat{\beta} \in \Omega_2^\beta \) satisfying (17), we define an estimator \( \tilde{\beta} = \beta_0 + m^{-1} \sum_{j=1}^{m} \varphi(Z_i; \theta_0). \) It is again readily shown that this estimator satisfies (16), indicating that \( \tilde{\beta} \in \Omega_1^\beta \) and \( \varphi(Z_i; \theta_0) \in \Gamma_1^{I.F.} \), i.e., \( \varphi(Z_i; \theta_0) \) is also an I.F. for model class 1.

**Equivalence of Two Classes of Regular and AL estimators**

As in the literature, to avoid estimators with undesirable local properties such as super-efficiency\(^{15} \), we restrict considerations to regular estimators by considering a local data generating process (LDGP). Suppose the underlying within-subject attributes are generated from \( Z_{in} \sim i.i.d. \{ p(Z_{in}; \theta_n) \} \) for each \( \theta_n \), and \( n^{1/2} (\theta_n - \theta_*) \) converges to a constant where \( \theta_* \) denote some fixed parameter. Let \( \hat{\theta}(Z_{in}) \) denote an estimator of \( \theta_n \) based on the between-subject attributes, where \( Z_{in} = (Z_{in}^1, Z_{in}^2) \). Then \( \hat{\theta}(Z_{in}) \) is regular if, for some fixed \( \theta_* \), the limiting distribution of \( n^{1/2} \left( \hat{\theta}(Z_{in}) - \theta_n \right) \) does not depend on the LDGP (or \( \theta_n \)). In what follows, we focus on regular and asymptotically linear (RAL) estimators unless stated otherwise. The theorem below further declares the equivalence between the two classes of I.F.s for Regular AL estimators.

**Theorem 3.** For RAL estimators of between-subject attributes, the I.F.s in the set \( \Gamma_1^{I.F.} \) for model class 1 are equivalent to I.F.s in \( \Gamma_2^{I.F.} \) for model class 2, i.e., \( \Gamma_1^{I.F.} = \Gamma_2^{I.F.} \).

Although we aim to find the efficient I.F. for the FRM in model class 2, it is difficult to directly work with model class 2 due to the added complexity in computing asymptotic variance through Hájek projection. Accordingly, Theorem 3 can allow us to achieve the goal by virtue of the simplicity of model class 1.

### 4 The Hilbert Space and Projection

In this section, we start with a brief review of Hilbert space\(^{31} \) and its application to the within-subject attributes and then extend it to their between-subject counterparts. More details can be found in the Supplement S1.

#### 4.1 Within-subject Attributes

Let \( (L, A, P) \) be a probability space (where \( L \) is the sample space, \( A \) is the \( \sigma \)-algebra, and \( P \) is the probability measure). Consider a \( q \)-dimensional measurable function \( Z : L \to \mathbb{R}^q \).
Suppose we observe i.i.d. within-subject attributes $Z_1, ..., Z_n$, where $Z_i$ is the random vector for subject $i$. We denote by $\mathcal{H}_w$ the Hilbert space consisting of all $q$-dimensional functions of $Z_i$, $h : L \to \mathbb{R}^q$, that are measurable with mean zero and finite second-order moments. $\mathcal{H}_w$ is associated with an inner product, which also induces a norm (we emphasize quantities of $\langle h_1, h_2 \rangle$ and $\|h\|_\infty$).

For the induced pairwise observations $h(Z_i, Z_j)$, the closest point theorem [32] the projection of $h^q$ onto $\mathcal{U}_w$ is unique, denote by

$$\Pi_w \{h(Z_i) \mid \mathcal{U}_w\} = E \left[ h(Z_i) v(Z_i)^\top \right] E^{-1} \left[ v(Z_i) v(Z_i)^\top \right] v(Z_i).$$  \hfill (20)

### 4.2 Between-subject Attributes

For the induced pairwise observations $Z_i = (Z_{i1}, ..., Z_{i2})^\top$, we consider the Hilbert space $\mathcal{H}_b$ (with a subscript $b$ reflecting between-subject attributes) of all $q$-dimensional measurable and symmetric functions $h(Z_i) = h(Z_{i1}, Z_{i2})$ with $E[h(Z_i)] = 0$ and finite $E[h(Z_i) h^\top(Z_i)]$.

We consider two inner products and norms for $\mathcal{H}_b$.

**Definition.** The non-overlap inner product $b_1$ and associated norm $b_1$ are defined as

$$\langle h_1(Z_i), h_2(Z_i) \rangle_{b_1} = E \left[ h_1^\top(Z_i) h_2(Z_i) \right],$$

$$\|h(Z_i)\|_{b_1} = \langle h(Z_i), h(Z_i) \rangle_{b_1}^{1/2} = E^{1/2} \left[ h^\top(Z_i) h(Z_i) \right].$$

For the linear span of $v(Z_i) = (v_1(Z_i), ..., v_r(Z_i))^\top$ (as a function of $Z_i$ for the $i$-th pair):

$$\mathcal{U}_{b_1} = \{B v(Z_i) : \text{for an arbitrary matrix } B^{q \times r} \text{ of real numbers}\},$$

the projection of $h^q(Z_i) \in \mathcal{H}_b$ onto $\mathcal{U}_{b_1}$ is:

$$\Pi_{b_1} \{h(Z_i) \mid \mathcal{U}_{b_1}\} = E \left[ h(Z_i) v(Z_i)^\top \right] E^{-1} \left[ v(Z_i) v(Z_i)^\top \right] v(Z_i).$$ \hfill (22)

It follows from the Pythagorean triangle inequality that

$$\|h(Z_i)\|_{b_1}^2 = \|\Pi_{b_1} \{h \mid \mathcal{U}_{b_1}\}\|_{b_1}^2 + \|h - \Pi_{b_1} \{h \mid \mathcal{U}_{b_1}\}\|_{b_1}^2 \geq \|\Pi_{b_1} \{h(Z_i) \mid \mathcal{U}_{b_1}\}\|_{b_1}^2,$$ \hfill (23)
i.e., the norm $b_1$ of any element $h(Z_i)$ is larger than or equal to that of its projection onto the subspace $U_{b_1}$.

Under the $q$-replicating linear spaces\(^\text{(26)}\) that we consider, the multivariate Pythagoras holds: the orthogonality between $h(Z_i)$ and $U_{b_1}$ is equivalent to the uncorrelatedness between $h(Z_i)$ and $v(Z_i)$ (i.e., $E[h^\top(Z_i)v(Z_i)] = 0$ implies $E[h(Z_i)v^\top(Z_i)] = 0$). Thus \(^\text{(23)}\) shows that the variance (matrix) of the element $h(Z_i) \in H_b$ also satisfies

$$Var[h(Z_i)] = Var[\Pi_{b_1}\{h \mid U_{b_1}\}] + Var[h - \Pi_{b_1}\{h \mid U_{b_1}\}] \geq Var[\Pi_{b_1}\{h(Z_i) \mid U_{b_1}\}] \cdot (24)$$

Hence, the variance of any element $h(Z_i)$ is larger than or equal to its projection $\Pi_{b_1}\{h \mid U_{b_1}\}$ onto a subspace, i.e., their difference is non-negative definite. This will inspire the construction of the efficient estimator using the projection later.

As the norm $b_1$ for $H_b$ does not yield the asymptotic variance for the UGEE estimator, we now introduce another inner product motivated by the form of asymptotic variance for the enumerated model class 2.

**Definition.** The enumerated inner product 2 and norm $b_2$ are defined as

$$\langle h_1(Z_i), h_2(Z_i) \rangle_{b_2} = E\left\{ 2E[h_1^\top(Z_i) \mid Z_{i1}] \cdot 2E[h_2(Z_i) \mid Z_{i1}] \right\},$$

$$\|h(Z_i)\|_{b_2} = \langle h(Z_i), h(Z_i) \rangle_{b_2}^{1/2} = E^{1/2}\left\{ 2E[h^\top(Z_i) \mid Z_{i1}] \cdot 2E[h(Z_i) \mid Z_{i1}] \right\} \cdot (25)$$

**Definition.** Define a projection mapping\(^\text{(27)}\) $M: H_b \rightarrow H_w$, referred to as the U-statistics, or Hájek, projection, such that for $h(Z_i) \in H_b$,

$$M[h(Z_i)] = 2E[h(Z_i) \mid Z_{i1}] \in H_w \cdot (26)$$

Now consider a linear subspace of $H_w$ spanned by $M[B^{\times r}v(Z_i)] = BE[v(Z_i) \mid Z_{i1}]$, $U_{b_2} = M(U_{b_1}) = \{BE[v(Z_i) \mid Z_{i1}] \mid \text{for an arbitrary matrix } B^{\times r} \text{ of real numbers}\}$.

Projecting any $h(Z_i) \in H_b$ onto $U_{b_2}$ involves two steps: we first map $h(Z_i)$ to $M[h(Z_i)] \in H_w$ and then project it onto $U_{b_2}$ with the projection theorem for within-subject attributes in \(^\text{(20)}\), i.e.:

$$\Pi_{b_2}\{h(Z_i) \mid U_{b_2}\} = \Pi_w\{M[h(Z_i)] \mid U_{b_2}\} \cdot (27)$$

Similarly, the norm $b_2$ of any element $h(Z_i)$ is larger than or equal to that of its projection onto $U_{b_2}$, which by \(^\text{(27)}\), equals the squared norm of the mapped element $M[h(Z_i)]$, i.e.,

$$\|h(Z_i)\|^2_{b_2} \geq \|\Pi_{b_2}\{h(Z_i) \mid U_{b_2}\}\|^2_{b_2} = \|\Pi_w\{M[h(Z_i)] \mid U_{b_2}\}\|^2_w \cdot (28)$$
Accordingly, the variance of any $\mathcal{M} [h(Z_i)]$ is larger than or equal to its projection $\Pi_w \{\mathcal{M} [h(Z_i)] \mid U_{b_2}\}$:

$$\text{Var} \{\mathcal{M} [h(Z_i)]\} \geq \text{Var} [\Pi_w \{\mathcal{M} [h(Z_i)] \mid U_{b_2}\}] = \text{Var} [\Pi_{b_2} \{h(Z_i) \mid U_{b_2}\}] = \text{Var} [\Pi_{b_2} \{h(Z_i) \mid U_{b_2}\}]. \quad (29)$$

The above links norm $b_2$ with the asymptotic variance of the UGEE estimator. We now define equivalence classes within each norm and discuss the relationship between the two.

**Definition.** For a given norm, any two functions $h_1(Z_i)$ and $h_2(Z_i)$ are equivalent if the norm of their difference is zero. The equivalence class of $h(Z_i)$ under norm $b_1$ includes all $q$-dimensional measurable functions $g(Z_i) \in \mathcal{H}_b$ that equal $h(Z_i)$ almost surely (a.s.), denote by:

$$\Gamma^b_{b_1} = \{g(Z_i) \in \mathcal{H}_b : g(Z_i) = h(Z_i) \ \text{a.s.}\}.$$

The equivalence class under norm $b_2$ contains all functions $g(Z_i) \in \mathcal{H}_b$ whose U-statistics projection mapping are equal to that of $h(Z_i)$ a.s.:

$$\Gamma^b_{b_2} = \{g(Z_i) \in \mathcal{H}_b : \mathcal{M} [g(Z_i)] = \mathcal{M} [h(Z_i)] \ \text{a.s.}\}.$$

The projections onto subspaces, $\Pi_{b_1} \{h(Z_i) \mid U_{b_1}\}$ and $\Pi_{b_2} \{h(Z_i) \mid U_{b_2}\}$, are unique up to their respective equivalence classes $\Gamma^b_{b_1}$ and $\Gamma^b_{b_2}$. Since all estimators in the same equivalence class deliver the same asymptotic variance (or efficiency) under the respective norm, it suffices to find one of them. Since the projection mapping $\mathcal{M}$ is many-to-one, i.e., different elements in $\mathcal{H}_b$ can be mapped to the same element in $\mathcal{H}_w$, the origin of $\mathcal{H}_b$ under inner product 2 is not the equivalence class of $h(Z_i)$ with $h(Z_i) = 0$ a.s., but a larger one consisting of functions $h(Z_i)$ such that $\mathcal{M} [h(Z_i)] = 0$ a.s. (see Supplement for an example of $h(Z_i) \neq 0$, but $\mathcal{M} [h(Z_i)] = 0$ a.s.).

Akin to the classical theory for within-subject attributes, the I.F. $\psi(Z_i; \theta_0)$ for model class 1 is an element in $\mathcal{H}_b$, whose norm $b_1$ is always larger than or equal to its projection onto a subspace $U_{b_1}$, hence, this projection $\Pi_{b_1} \{\psi(Z_i; \theta_0) \mid U_{b_1}\}$ yields an RAL estimator with the minimum variance within class 1. Likewise, for model class 2, the projection of an I.F. onto $U_{b_2}$, $\Pi_{b_2} \{\varphi(Z_i; \theta_0) \mid U_{b_2}\}$, has the smallest norm $b_2$ thus also yields the efficient RAL estimator for class 2. Both $\Pi_{b_1} \{\psi(Z_i; \theta_0) \mid U_{b_1}\}$ and $\Pi_{b_2} \{\varphi(Z_i; \theta_0) \mid U_{b_2}\}$ are unique up to their respective equivalence classes.

## 5 Tangent Spaces and Dual Geometric Interpretations

The Hilbert space repositions searching for the efficient estimator to a geometric problem of searching for the (efficient) influence function, which has the smallest norm. Another
tool we implement is a “bridge” between parametric and semiparametric models, termed “parametric submodels”\textsuperscript{27}. We extend this idea to between-subject attributes next.

5.1 Parametric Submodels

The distribution of pairwise observations $Z_i = (Z_{i1}^T, Z_{i2}^T)^T$ can be characterized by $p_Z(Z_i)$ that belongs to

$$\mathcal{P} = \{p_Z(Z_i; \beta, \eta(\cdot)) ; \beta \in \mathbb{R}^q \text{ and } \eta(\cdot) \text{ is infinite-dimensional.} \}$$

Let $p_0(Z_i; \theta_0) = p_Z(Z_i; \beta_0, \eta_0(\cdot))$ denote the truth, where $\beta$ and $\eta(\cdot)$ are variationally independent as indicated previously. The infinite-dimensional nuisance parameter $\eta(\cdot)$ makes $\mathcal{P}$ a class of semiparametric models.

Consider as if the data were generated from a conceptual class of parametric models by substituting $\eta(\cdot)$ with a finite-dimensional vector $\gamma \in \mathbb{R}^r$:

$$\mathcal{P}_{\gamma}^{\text{sub}} = \{p_Z(Z_i; \beta, \gamma) ; \beta \in \mathbb{R}^q, \gamma \in \mathbb{R}^r \} \subset \mathcal{P},$$

termed the parametric submodels. We restrict that at the truth, $p_0(Z_i; \theta_0) = p_Z(Z_i; \beta_0, \gamma_0) = p_Z(Z_i; \beta_0, \eta_0(\cdot))$ for some $\gamma_0 \in \mathbb{R}^r$. Let $\theta_{\text{sub}} = (\beta^T, \gamma^T)^T \in \mathbb{R}^p$ denote the parameter vector for the submodel where $p = q + r$.

Distinct from usual parametric models that characterize real study data with model parameters, a parametric submodel is merely a “bridge” and not used to fit data since it requires $p_0(Z_i; \theta_0) \in \mathcal{P}_{\gamma}^{\text{sub}}$, where the truth is unknown.

In fact, an RAL estimator of $\beta$ (the parameter of interest) for a semiparametric model is also RAL for every parametric submodel\textsuperscript{36} in $\mathcal{P}_{\gamma}^{\text{sub}}$. But unlike semiparametric models involving the infinite-dimensional $\eta(\cdot)$, parametric submodels are granted the well-defined score vectors at the truth $\theta_0$:

$$S_{\theta_{\text{sub}}}^{p \times 1}(Z_i; \theta_0) = (S_{\beta}(Z_i; \theta_0), S_{\gamma}(Z_i; \theta_0))^T,$$

where $S_{\theta_{\text{sub}}}(Z_i; \theta_0) = \partial \log p_0(Z_i; \theta_0)/\partial \theta_{\text{sub}}^T$, for $\theta_{\text{sub}}$ (or $\beta, \gamma$).

5.2 Tangent Spaces

In $\mathcal{H}_b$ that consists of all measurable functions of $h^{q \times 1}(Z_i)$ with mean zero and finite variances, and equipped with both inner products $b_1$ and $b_2$, the score vectors for the submodels in (32) can span linear subspaces (with arbitrary matrix $B$ of real numbers), termed parametric submodel tangent spaces.
5.2.1 Parametric Submodel Tangent Spaces

Non-overlap Model Class 1  The parametric submodel tangent space for model class 1 spanned by $S_{\theta_{\text{sub}}}^{p \times 1} (Z_i; \theta_0)$ is a linear subspace of $H_b$, where

$$L_{\beta \gamma}^{\text{sub}} = \{ B S_{\theta_{\text{sub}}}^{p \times 1} (Z_i; \theta_0) ; \forall \text{ arbitrary matrix } B^{q \times p} \} = L_\beta \oplus \Lambda_\gamma,$$

$$L_\beta = \{ B S_{\theta}^{q \times 1} (Z_i; \theta_0) ; \forall B^{q \times q} \} , \quad \Lambda_\gamma = \{ B S_{\gamma}^{r \times 1} (Z_i; \theta_0) , \forall B^{r \times r} \} ,$$

(33)

with $\oplus$ denoting the direct sum. Since $\theta_{\text{sub}} = (\beta^T, \gamma^T)^T \in \mathbb{R}^p$, $L_{\beta \gamma}^{\text{sub}}$ is the direct sum of two linear subspaces: $L_\beta$, the tangent space for $\beta$; and $\Lambda_\gamma$, the tangent space for $\gamma$, also termed the parametric submodel nuisance tangent space (submodel n.t.s.), $\Lambda_\gamma$ is a key component to find efficiency.

Enumerated Model Class 2  For model class 2, the parametric submodel tangent space spanned by $M [ S_{\theta_{\text{sub}}} (Z_i; \theta_0) ]$ is

$$\tilde{L}_{\beta \gamma}^{\text{sub}} = \{ B M [ S_{\theta_{\text{sub}}} (Z_i; \theta_0) ] ; \forall \text{ arbitrary matrix } B^{q \times p} \} = \tilde{L}_\beta \oplus \tilde{\Lambda}_\gamma,$$

$$\tilde{L}_\beta = \{ B M [ S_\beta^{q \times 1} (Z_i; \theta_0) ] ; \forall B^{q \times q} \} , \quad \tilde{\Lambda}_\gamma = \{ B M [ S_\gamma^{r \times 1} (Z_i; \theta_0) ] , \forall B^{r \times r} \} ,$$

where $\tilde{L}_{\beta \gamma}^{\text{sub}}$, $\tilde{L}_\beta$ and $\tilde{\Lambda}_\gamma$ are the respectively subspaces after mapping from $H_b$ to $H_w$ using the U-statistics projection mapping $M$ in (26).

5.2.2 Semiparametric Tangent Spaces

We are now in a position to extend the parametric submodel tangent spaces to semiparametric tangent spaces, which is achieved with mean-square closure. As $\beta$ is unchanged for a semiparametric model, $L_\beta \left( \tilde{L}_\beta \right)$ remains the same, but the nuisance tangent spaces need to accommodate the infinite-dimensional nuisance parameter for semiparametric models.

Non-overlap Model Class 1  Let $\Upsilon$ be the collection of nuisance parameters $\gamma$ for all possible parametric submodels in $P_{\gamma_{\text{sub}}}$ defined in (31). Consider the unions of points $(h (Z_i))$ in all the parametric submodel nuisance tangent spaces $\Lambda_\gamma$. With a slight abuse of notation, we denote this union by $\Lambda^U = \cup_{\{ \gamma \in \Upsilon \}} \Lambda_\gamma$.

Definition. The semiparametric nuisance tangent space (semiparametric n.t.s.) $\Lambda_\eta$ for model class 1 is the mean-square closure (in terms of the norm b1) $\Lambda^U$. Namely, $\Lambda_\eta$ consists
of all \( h(Z_i) \) in \( H_b \) for which there exists a sequence of \( B_j S_{\gamma_j}(Z_i) \in \Lambda^U (j = 1, 2, ...) \) such that
\[
\lim_{j \to \infty} \| h^{q_1}(Z_i) - B_j^{q \times r_j} S_{\gamma_j}^{q_1}(Z_i) \|_{b_1}^2 = 0,
\]
(34)
where \( S_{\gamma_j}^{q_1}(Z_i) \) corresponds to a sequence of submodels characterized by \( \gamma_j \in \mathbb{R}^r \). Each submodel and its associated dimension \( (r_j) \) can vary with \( j \), but \( \Lambda_\eta \) covers all possibilities.

Denote the entire semiparametric tangent space for class 1 by \( \mathcal{E} = \mathcal{E}_\beta \oplus \Lambda_\eta \).

**Enumerated Model Class 2 Definition.** The semiparametric n.t.s. for model class 2, denoted by \( \tilde{\Lambda}_\eta \), is the mean-square closure of \( \tilde{\Lambda}^U = \cup_{\gamma \in \Gamma} \tilde{\Lambda}_\gamma \). It consists of all \( h(Z_i) \) in \( H_w \) which is either in \( \tilde{\Lambda}^U \) or the limit of a convergent sequence \( h_j(Z_i) \in \tilde{\Lambda}^U (j = 1, 2, ...) \), i.e., with the within-subject norm (19),
\[
\lim_{j \to \infty} \| h(Z_i) - h_j(Z_i) \|_w^2 = 0.
\]
(35)
The semiparametric tangent space for model class 2 is hence \( \tilde{\mathcal{E}} = \tilde{\mathcal{E}}_\beta \oplus \tilde{\Lambda}_\eta \).

Both \( \Lambda_\eta \) and \( \tilde{\Lambda}_\eta \) are closed spaces by definition. The theorem below shows that linearity and closedness are preserved under the projection mapping \( \mathcal{M} \).

**Theorem 4.** The semiparametric n.t.s. \( \Lambda_\eta \) and \( \tilde{\Lambda}_\eta \) are both linear subspaces and \( \tilde{\Lambda}_\eta = \mathcal{M}(\Lambda_\eta) \).

Therefore, all \( h(Z_i) \in H_b \) has a unique projection (up to its equivalence class) onto semiparametric n.t.s. \( \Lambda_\eta \) and \( \tilde{\Lambda}_\eta \).

### 5.3 Dual Geometric Interpretations for Semiparametric Models

We now introduce a fundamental connection for the two classes of models termed dual orthogonality, which is a direct generalization of properties for parametric models by leveraging the submodel bridge. It geometrically characterizes the semiparametric RAL estimators through influence functions and semiparametric nuisance tangent spaces.

**Theorem 5.** A semiparametric RAL estimator of \( \beta \) for either class of models must have an influence function (I.F.) \( \varphi(Z_i) \) satisfying
\[
(i) \ : \ \langle \varphi(Z_i), S_{\beta}(Z_i; \theta_0) \rangle_{b_1} = E \left[ \varphi(Z_i) S_{\beta}^\top(Z_i; \theta_0) \right] = I_q,
\]
\[
(ii) \ : \ \Pi_{b_1} \{ \varphi(Z_i) \mid \Lambda_\eta \} = 0,
\]
\[
(iii) \ : \ \Pi_{b_2} \left\{ \varphi(Z_i) \mid \tilde{\Lambda}_\eta \right\} = \Pi_w \left\{ 2E \left[ \varphi(Z_i) \mid Z_{i_1} \right] \mid \tilde{\Lambda}_\eta \right\} = 0.
\]
(36)
where $I_q$ is the $q \times q$ identity matrix, $\Pi_{b_1} \{ \phi (Z_i) \mid \Lambda_\eta \}$ denotes the unique projection (w.r.t. inner product 1) of $\phi (Z_i)$ onto $\Lambda_\eta$, $\Pi_{b_2} \{ \phi (Z_i) \mid \tilde{\Lambda}_\eta \}$ is the unique projection (w.r.t. inner product 2) of $\phi (Z_i)$ onto $\tilde{\Lambda}_\eta$. (ii) and (iii) imply that $\phi (Z_i)$ is deemed dual orthogonal to both the semiparametric n.t.s. $\Lambda_\eta$ (for model class 1) and its mapping $\tilde{\Lambda}_\eta$ (for model class 2).

While Theorem 3 asserts that the two classes of models share the same RAL estimators and I.F.s., Theorem 5 further identifies such estimators through the dual orthogonality between I.F.s and respective semiparametric n.t.s. $\Lambda_\eta$ and $\tilde{\Lambda}_\eta$. Recall that the variance of any element is always larger than or equal to its projection onto a linear subspace in (24) and (29). This intrinsic connection between the two model classes allows us to locate the efficient estimator for model class 2 through model class 1, which serves a “conjugate” model class.

6 Semiparametric Efficiency Bound

Again, we aim to identify the efficient semiparametric RAL estimator for the FRM in (4), or the model class 2. Directly tackling the efficiency for class 2 is difficult, but the dual orthogonality motivates a strategy to find efficient estimator via model class 1, which is more straightforward. Due to the many-to-one mapping $M$, the efficient I.F. for class 2 corresponds to multiple I.F.s in class 1, but our goal is fulfilled if we identify one of them in the equivalence class. We start by establishing the efficient I.F. for model class 1.

**Definition.** The efficient I.F. is the unique influence function (up to its equivalence class) belonging to the tangent space that has the smallest asymptotic variance.

Recall that a semiparametric RAL estimator of $\beta$ in $\mathcal{P}$ is an RAL estimator for every parametric submodel. In terms of influence functions, the class of I.F.s for a semiparametric model will be a subset of the class of I.F.s for all parametric submodels. Any semiparametric influence function must be orthogonal to all parametric submodel nuisance tangent spaces. Hence, the asymptotic variance of a semiparametric model must be greater than or equal to the parametric efficiency bound for any submodel, or the supremum of such bounds for all submodels.

We define the efficiency bound via this bridge for each model class.
6.1 Parametric Submodels

6.1.1 Non-overlap Model Class 1

The efficient I.F. for a parametric submodel in class 1, denoted by $\varphi_{\gamma, \text{eff1}}^{\text{sub}} (Z_i; \theta_0)$, is the unique I.F. in the tangent space $\mathcal{L}_{\beta, \gamma}^{\text{sub}} = \mathcal{L}_{\beta} \oplus \Lambda_{\gamma}$ with the smallest norm $b_1$, i.e., for any I.F. $\varphi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)$ of a submodel in $\mathcal{P}_{\gamma}^{\text{sub}}$, 

$$||\varphi_{\gamma, \text{eff1}}^{\text{sub}} (Z_i; \theta_0)||_{b_1}^2 \leq ||\varphi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)||_{b_1}^2, \quad \varphi_{\gamma, \text{eff1}}^{\text{sub}} (Z_i; \theta_0) = \Pi_{b_1} \{ \varphi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0) \mid \mathcal{L}_{\beta, \gamma}^{\text{sub}} \},$$

then the efficiency bound for parametric submodels of class 1 is its variance

$$v_{1, \gamma} = \text{Var} [\varphi_{\gamma, \text{eff1}}^{\text{sub}} (Z_i; \theta_0)].$$

The semiparametric efficiency bound for model class 1 is the supremum of $v_{1, \gamma}$ over all submodels:

$$v_1 = \sup_{\mathcal{P}_{\gamma}^{\text{sub}}} v_{1, \gamma} = \sup_{\mathcal{P}_{\gamma}^{\text{sub}}} \text{Var} [\varphi_{\gamma, \text{eff1}}^{\text{sub}} (Z_i; \theta_0)], \quad (37)$$

where sup is defined based on the non-negative definite criterion to compare matrices using their differences.

6.1.2 Enumerated Model Class 2

Likewise, the efficient I.F. for parametric submodels in class 2, $\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)$, is the I.F. lying in $\mathcal{L}_{\beta, \gamma}^{\text{sub}} = \mathcal{L}_{\beta} \oplus \Lambda_{\gamma}$ with the smallest norm $b_2$. Hence, any I.F. $\psi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)$ of a submodel satisfies 

$$||\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)||_{b_2}^2 = ||\mathcal{M} [\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)]||_w^2 \leq ||\mathcal{M} [\psi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)]||_w^2 = ||\psi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)||_{b_2}^2.$$

By the multivariate Pythagoras, any two I.F.s with zero difference in norm $b_2$ are equivalent as they determine the same efficiency (asymptotic variance). The equivalence class for $\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)$ is hence defined to be

$$\Gamma_{\text{eff2}}^{\text{sub}} = \{ \psi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0) \in \mathcal{L}_{\beta, \gamma}^{\text{sub}} : \mathcal{M} [\psi_{\text{sub}}^{\text{sub}} (Z_i; \theta_0)] = \mathcal{M} [\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)] \text{ a.s.} \}, \quad (38)$$

$\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)$ is unique up to this equivalence class $\Gamma_{\text{eff2}}^{\text{sub}}$. The efficiency bound for parametric submodels $v_{2, \gamma}^{\text{sub}}$ and the semiparametric efficiency bound for class 2 $v_2$ are respectively defined by 

$$v_{2, \gamma}^{\text{sub}} = \text{Var} \{ \mathcal{M} [\psi_{\gamma, \text{eff2}}^{\text{sub}} (Z_i; \theta_0)] \}, \quad v_2 = \sup_{\mathcal{P}_{\gamma}^{\text{sub}}} v_{2, \gamma}^{\text{sub}},$$

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The theorem below connects the two classes of submodels regarding the efficient I.F..

**Theorem 6.** The norm $b^2$ of the efficient I.F. for class 1, $\varphi_{\gamma,\text{eff1}}(Z_i; \theta_0)$, equals the norm $b^2$ of the efficient I.F. for class 2, $\psi_{\gamma,\text{eff2}}(Z_i; \theta_0)$, hence is in the equivalence class $\Gamma_{\text{eff2}}$ defined in (38), i.e.,

$$\| \varphi_{\gamma,\text{eff1}}(Z_i; \theta_0) \|_{b^2}^2 = \| \psi_{\gamma,\text{eff2}}(Z_i; \theta_0) \|_{b^2}^2,$$

or

$$\| \mathcal{M} \left[ \varphi_{\gamma,\text{eff1}}(Z_i; \theta_0) \right] \|_{w}^2 = \| \mathcal{M} \left[ \psi_{\gamma,\text{eff2}}(Z_i; \theta_0) \right] \|_{w}^2.$$  

By Theorem 3, $\varphi_{\gamma,\text{eff1}}(Z_i; \theta_0)$ is already a valid I.F. for model 2, now admitting the same norm $b^2$ as $\psi_{\gamma,\text{eff2}}(Z_i; \theta_0)$, it is indeed in the equivalence class $\Gamma_{\text{eff2}}$. It follows from Theorem 6 and the definition of norm $b^2$ that after mapping, $\mathcal{M} \left[ \varphi_{\gamma,\text{eff1}}(Z_i; \theta_0) \right] = \mathcal{M} \left[ \psi_{\gamma,\text{eff2}}(Z_i; \theta_0) \right]$ a.s., hence they determine the same asymptotic variance.

Not surprisingly, $\varphi_{\gamma,\text{eff1}}(Z_i; \theta_0)$ delivers exactly what we aim to find: one element lying in the submodel tangent space $\mathcal{L}_{\beta,\gamma}^{\text{sub}}$ that yields the smallest variance for model class 2.

### 6.2 Semiparametric Models

Now we switch from parametric submodels to semiparametric models by considering the semiparametric n.t.s. $\Lambda_{\eta}$ defined in (34). To differentiate from those of submodels in notation, we drop the superscripts (of “sub”) and subscripts $\gamma$ for quantities of semiparametric models. By definition, the efficient I.F. for the semiparametric model 1 is the I.F. in $\mathcal{L}$ whose variance achieves the semiparametric efficiency bound $\nu_1$. With variationally independent parameters $\theta = \{\beta, \eta(\cdot)\}$, an important result is that the efficient score is the residual of the score vector for $\beta$ after projecting it onto the nuisance tangent space $\Xi$. For model class 1, the semiparametric efficient score is easily found to be

$$S_{\text{eff1}}(Z_i; \theta_0) = S_{\beta}(Z_i; \theta_0) - \Pi_{\beta \parallel} \{ S_{\beta}(Z_i; \theta_0) \mid \Lambda_{\eta} \}. \quad (39)$$

Below shows how to find the efficient I.F. from this score.

**Theorem 7.** Let

$$\varphi_{\text{eff1}}(Z_i; \theta_0) = E^{-1} (S_{\text{eff1}} S_{\text{eff1}}^\top) S_{\text{eff1}}(Z_i; \theta_0). \quad (40)$$

Then $\varphi_{\text{eff1}}(Z_i; \theta_0)$ is the unique element in $\mathcal{L} = \mathcal{L}_{\beta} \oplus \Lambda_{\eta}$ whose variance achieves $\nu_1$.

Akin to submodels, this semiparametric efficient I.F. $\varphi_{\text{eff1}}(Z_i; \theta_0)$ for model class 1 is also mapped to an element in $\tilde{\mathcal{L}}$ that achieves the efficiency for the model class 2, summarized in the following theorem that generalizes Theorem 6 for submodels.
Theorem 8. Let $\psi_{\text{eff2}}(Z_i; \theta_0)$ denote the efficient I.F. for the semiparametric model class 2. $\varphi_{\text{effl}}(Z_i; \theta_0)$ has the same norm $\|\psi_{\text{eff2}}(Z_i; \theta_0)\|_w^2$ as $\psi_{\text{eff2}}(Z_i; \theta_0)$ and hence is in its equivalence class denoted by $\Gamma_{\text{eff2}}$, i.e.,

$$\|\varphi_{\text{effl}}(Z_i; \theta_0)\|_w^2 = \|\psi_{\text{eff2}}(Z_i; \theta_0)\|_w^2,$$

where $\Gamma_{\text{eff2}} = \{\psi(Z_i; \theta_0) \in L : \mathcal{M}[\psi(Z_i; \theta_0)] = \mathcal{M}[\psi_{\text{eff2}}(Z_i; \theta_0)] \text{ a.s.}\}$. Again, the multivariate Pythagoras implies that the variance of $\mathcal{M}[\psi_{\text{eff2}}(Z_i; \theta_0)]$ equals the semiparametric efficiency bound $\nu_2$ for model class 2, as a direct result of Theorem 8, we have

$$\text{Var} \{\mathcal{M}[\varphi_{\text{effl}}(Z_i; \theta_0)]\} = \text{Var} \{\mathcal{M}[\psi_{\text{eff2}}(Z_i; \theta_0)]\} = \nu_2.$$

Based on Theorem 8, we can identify the efficient estimator for model class 2 via model class 1, where constructing the efficient I.F. $\varphi_{\text{effl}}(Z_i; \theta_0)$ is apparently more straightforward. We now apply those results to the regression setting of FRM.

### 7 The Efficiency for the FRM

By the conditions in Theorem 5 that any I.F. satisfies, to derive the semiparametric efficient I.F. $\varphi_{\text{effl}}(Z_i; \theta_0)$ for model class 1, we first identify the form of the semiparametric n.t.s. $\Lambda_\eta$ and then find elements that are orthogonal to it. These elements in the orthogonal complement $\Lambda_\eta^\perp$ form a pool of candidates for the optimal one.

Consider $Z_i = (Y_i^T, X_i^T)^T$, $Y_i = (Y_{i1}, Y_{i2})^T$, $X_i = (X_{i1}, X_{i2})^T$, $i = (i_1, i_2) \in C_2^n$, where $X_i$ ($Y_i$) is a $q \times 1$ ($m \times 1$) vector of explanatory variables (outcomes) for the $i$-th subject. Let $f_i(Y_{i1}, Y_{i2})$ be a univariate continuous response for the $i$-th pair such as the microbiome Beta-diversity in $\Pi$ (same considerations apply to more general response types). The semiparametric FRM for a continuous $f_i$ is

$$f_i = h(X_i; \beta) + \varepsilon_i, \ E(\varepsilon_i \mid X_i) = 0, \quad (41)$$

where $\varepsilon_i = f_i - h(X_i, \beta)$ is the residual of between-subject attributes.

The goal is to identify the semiparametric RAL estimator of $\beta$ with the smallest variance for the FRM, but we can tackle it by finding $\varphi_{\text{effl}}(\varepsilon_i, X_i; \theta_0)$ for model class 1 first.

#### 7.1 Identifying $\Lambda_\eta$ with the Joint Likelihood and Score

The joint density of observed between-subject attributes $(\varepsilon_i, X_i)$, belongs to a class of semiparametric models

$$\mathcal{P} = \{p_{\varepsilon, X}(\varepsilon_i, X_i; \beta, \eta(\cdot)) : \beta \in \mathbb{R}^q \text{ and } \eta(\cdot) \text{ is infinite-dimensional}\}. \quad (42)$$
We assume that the underlying true data are generated from \( p(Y_i, X_i; \theta_0) \), which induces \( p(Y_1, X_1; \theta_0) = p(Y_{i_1}, X_{i_1}) \cdot p(Y_{i_2}, X_{i_2}) \). By independence and the change of variables, \( \theta_0 \) remains the same for describing the individual-level \( p(Y_i, X_i) \) and pairwise-level \( p(Y_1, X_1) \) or \( p(\varepsilon_1, X_1) \). We denote the truth by \( p_{\varepsilon, X}(\varepsilon_1, X_1; \theta_0) \). The parametric submodels for \( P \) are given by

\[
\mathcal{P}_{\gamma}^{\text{sub}} = \{ p_{\varepsilon, X}(\varepsilon_1, X_1; \beta, \gamma) : \beta \in \mathbb{R}^q, \gamma \in \mathbb{R}^r \} \subset \mathcal{P},
\]

which contain the truth \( \theta_0 = \{ \beta_0, \eta_0(\cdot) \} \). Let \( \Lambda_\eta \) denote the semiparametric n.t.s. for model class 1 resulting from the mean-square closure of \( \Lambda^\cup = \bigcup_{\gamma \in \gamma} \Lambda_\gamma \), the union of all parametric submodels n.t.s. We can readily determine the form of \( \Lambda_\eta \) by applying arguments similar to those for the classical within-subject semiparametric models\(^{[36]}\), summarized below.

**Theorem 9.** The space \( \Lambda_\eta \) contains all mean-zero functions \( \lambda(\varepsilon_1, X_1) \) satisfying the constraint on the conditional mean in \((41)\), namely,

\[
\Lambda_\eta = \{ \lambda^{q_1} \varepsilon_1 : E[\lambda(\varepsilon_1, X_1) \varepsilon_1 | X_1] = 0^{q_1} \}.
\]

Its orthogonal complement (w.r.t. inner product \( b_1 \)) is defined by

\[
\Lambda_\eta^\perp = \{ \lambda^{q_1} \varepsilon_1 \in H_b : \langle \lambda(\varepsilon_1, X_1), \lambda(\varepsilon_1, X_1) \rangle_{b_1} = 0 \}.
\]

The form of \( \Lambda_\eta \) for model class 1 above is conformable with that for the semiparametric GLM\(^{[36]}\), as both models have restrictions only on the conditional mean.

### 7.2 The Efficient Influence Function of the FRM

Recall that the efficient score is the residual after projecting \( S_\beta \) onto \( \Lambda_\eta \) by \((39)\). In \( H_b \), the projection (w.r.t. inner product \( 1 \)) of an arbitrary element \( g(\varepsilon_1, X_1) \in H_b \) onto \( \Lambda_\eta \) is readily shown to satisfy:

\[
\Pi_{b_1} \{ g(\varepsilon_1, X_1) | \Lambda_\eta^\perp \} = g - \Pi_{b_1} \{ g(\varepsilon_1, X_1) | \Lambda_\eta \} = E[g(\varepsilon_1, X_1) \varepsilon_1 | X_1] E^{-1}(\varepsilon_1^2 | X_1) \varepsilon_1,
\]

which is verified by the fact that \( \langle \Pi_{b_1} \{ g | \Lambda_\eta^\perp \} , \lambda^* (\varepsilon_1, X_1) \rangle_{b_1} = 0 \) for any \( \lambda^* (\varepsilon, X) \in \Lambda_\eta \).

Substituting \( S_\beta (\varepsilon_1, X_1) \) in place of \( g(\varepsilon_1, X_1) \) in \((44)\) yields the efficient score for model 1:

\[
S_{\text{eff}1}(\varepsilon_1, X_1; \theta_0) = S_\beta - \Pi_{b_1} \{ S_\beta (\varepsilon_1, X_1) | \Lambda_\eta \} = E[S_\beta (\varepsilon_1, X_1) \varepsilon_1 | X_1] V^{-1}(X_1) \varepsilon_1,
\]

where \( V(X_i) = E(\varepsilon_i^2 | X_i) \). By fixing \( \eta(\cdot) \) at the truth \( \eta_0(\cdot) \) and taking partial derivatives w.r.t. \( \beta \) of the conditional mean restriction \( E[f_i - h(X_i; \beta) | X_i] = 0 \), we obtain

\[
E[\varepsilon_i S_\beta^\top (\varepsilon_i, X_i) | X_i] = \frac{\partial}{\partial \beta} h(X_i; \beta_0) \overset{\text{def}}{=} D(X_i),
\]

which completes the proof.
which is the partial derivatives of $\beta$ for the mean function $h(X_i; \beta_0)$ in (41). Then the efficient score in (45) simplifies to

$$S_{\text{eff1}}(\varepsilon_i, X_i; \theta_0) = E[S_{\beta} (\varepsilon_i, X_i) \varepsilon_i | X_i] V^{-1}(X_i) \varepsilon_i = D^T(X_i) V^{-1}(X_i) \varepsilon_i. \quad (47)$$

By (40) in Theorem 7, the unique efficient I.F. for model class 1 is obtained by scaling $S_{\text{eff1}}(\varepsilon_i, X_i; \theta_0)$:

$$\varphi_{\text{eff1}}(\varepsilon_i, X_i; \theta_0) = E^{-1}(S_{\text{eff1}} S_{\text{eff1}}^T) S_{\text{eff1}} = E^{-1}(D_i^T V_{i}^{-1} D_i) D_i^T V_{i}^{-1} [f_i - h(X_i; \beta_0)], \quad (48)$$

which is easily verified to satisfy (i) - (iii) in (36).

By Theorem 8, this semiparametric efficient I.F. $\varphi_{\text{eff1}}(\varepsilon_i, X_i; \theta_0)$ is in the equivalence class of the efficient I.F. for model class 2, thus achieving the semiparametric efficiency bound $\nu_2$:

$$\nu_2 = Var \{M [\varphi_{\text{eff1}}(\varepsilon_i, X_i; \theta_0)] \} = Var [2E(\varphi_{\text{eff1}}(\varepsilon_i, X_i; \theta_0) | Z_{i1})] = B^{-1} \Sigma_U B^{-1}, \quad (49)$$

where

$$B = E[D^T(X_i) V^{-1}(X_i) D(X_i)], \quad \tilde{v}_{i_1} = 2E \{D^T(X_i) V(X_i)^{-1} [f_i - \mu(X_i; \beta_0)] | Z_{i1} \},$$

$$\Sigma_U = Var(\tilde{v}_{i_1}) = v_{i_1} v_{i_1}^T, \quad i = (i_1, i_2) \in C_2^n, \quad Z_{i1} = (Y_{i_1}^T, X_{i_1}^T)^T. \quad (50)$$

Consequently, the efficient score equations

$$\sum_{i \in C_2^n} S_{\text{eff1}}(\varepsilon_i, X_i) = \sum_{i \in C_2^n} D^T(X_i) V^{-1}(X_i) [f_i - h(X_i, \beta)] = 0, \quad (51)$$

yield an estimator $\hat{\beta}_{\text{eff}}$ whose variance (after mapping) is the smallest among all semiparametric RAL estimators of the FRM.

This $\nu_2$ coincides with $\Sigma_{\text{ugee}}^\beta$ in (15), which is the asymptotic variance of the UGEE estimator. Hence, the UGEE in (14) for between-subject FRM is exactly the efficient estimating equation (51), and the resulting UGEE estimator does achieve the semiparametric efficiency bound $\nu_2$, provided $V(X_i)$ is specified correctly.

### 8 Examples of UGEE and Efficient I.F.

In this section, we demonstrate examples of UGEE estimators that achieve the semiparametric efficiency bound. For space consideration, more examples of binary or count responses are included in the Supplements.
8.1 Exogenous Between-subject Responses

Consider a classical linear regression

\[ Y_i = X_i \beta + \varepsilon_i, \quad Y_i \sim \text{i.i.d} \ N \left(0, \sigma_Y^2\right), \quad 1 \leq i \leq n, \]

assume \( X_i \sim \text{i.i.d} \ N \left(0, \sigma_X^2\right) \) without loss of generality. The maximum likelihood estimator (MLE) of \( \beta \) reaches the Cramér-Rao (CR) bound \( \sigma_Y^2 \sigma_X^{-2} \).

Now construct (exogenous) between-subject attributes for the \( i \)-th pair with \( f_i = Y_{i1} - Y_{i2} \) and \( X_i = X_{i1} - X_{i2} \). Consider an FRM that restricts the mean \( E(f_i \mid X_i) = X_i \beta \). Let

\[ S_i = f_i - X_i \beta, \quad D_i = \frac{\partial}{\partial \beta} (X_i \beta) = X_i, \quad V_i = \text{Var}(f_i) = 2\sigma_Y^2. \]

The UGEE and associated I.F. are given by

\[ U_n(\beta) = \sum_{i \in C_n} D_i V_i^{-1} S_i = \sum_{i \in C_n} X_i \left(2\sigma_Y^2\right)^{-1} (f_i - X_i \beta) = 0, \quad (52) \]

\[ \varphi_{\text{ugee}}(\varepsilon_i, X_i; \beta_0) = E(X_i V_i^{-1} X_i) X_i V_i^{-1} (f_i - X_i \beta_0) = \left(2\sigma_X^2\right)^{-1} (\varepsilon_i X_i). \]

The asymptotic variance calculated based on norm \( b^2 \) is

\[ \nu_2 = \|\varphi_{\text{ugee}}(\varepsilon_i, X_i; \beta_0)\|_{b^2}^2 = \text{Var} \left[2E(\varphi_{\text{ugee}}(\varepsilon_i, X_i; \beta_0) \mid \varepsilon_i, X_i)\right] = \sigma_Y^2 \sigma_X^{-2}, \]

which exactly achieves the CR bound for the MLE of \( \beta \) in the classic linear regression. Hence, the semiparametric UGEE estimator by solving for (52) is efficient.

8.2 Endogenous Between-subject Responses

Now consider i.i.d. (identically but not independently distributed) endogenous between-subject responses \( f_i = f_{i1,i2} \) with mean \( \mu \) and variance \( \sigma^2 \), where, unlike the exogenous example above, their subject-level outcomes may be latent. Denote \( \beta = (\mu, \sigma^2)^\top \) the parameters of interest and \( \beta_0 = (\mu_0, \sigma_0^2)^\top \) the truth. To first obtain an efficient (parametric) estimator for \( \beta \) as our benchmark, we assume \( f_i \sim \text{i.i.d} \ N(\mu, \sigma^2) \). Then the efficient (parametric) I.F. for model class 1 is

\[ \varphi_{\text{eff1}}(f_i) = (f_i - \mu_0, -\sigma_0^2 + (f_i - \mu_0)^2)^\top, \quad (53) \]

which is also in the equivalent class of the efficient I.F. \( \psi_{\text{eff2}}(f_i) \) for the model class 2 whose variance (based on norm \( b^2 \)) is

\[ \Sigma_{\beta_0}^{\text{eff2}} = 4E \left[ E(\varphi_{\text{eff1}}(f_i) \mid f_{i1}) E(\varphi_{\text{eff1}}^\top(f_i) \mid f_{i1}) \right]. \]
For endogenous responses where the benchmark based on individuals is intractable, we use this $\Sigma_{\beta_0}^{\text{eff2}}$ as the efficiency bound.

Now consider a semiparametric FRM by modeling $E(f_i) = \mu$, $E[(f_i - \mu)^2] = \sigma^2$, let

$$S_i = (f_i - \mu, (f_i - \mu)^2 - \sigma^2)^\top, \quad D_i = \frac{\partial}{\partial \beta}\beta, \quad V_i = \text{diag}(\text{Var}(f_i), \text{Var}[(f_i - \mu)^2]),$$

The UGEE, the resulting estimator, and the associated I.F. for the FRM are

$$U_n(\beta) = \sum_{i \in C_2} D_i^\top V_i^{-1} S_i = 0, \quad \hat{\beta}_{\text{ugee}} = \left(\frac{n}{2}\right)^{-1} \sum_{i \in C_2} \left(f_i, (f_i - \bar{f}_i)^2\right)^\top,$$

$$\varphi_{\text{ugee}}(f_i) = (f_i - \mu_0, -\sigma_0^2 + (f_i - \mu_0)^2)^\top.$$

Since here $\varphi_{\text{ugee}}(f_i) = \varphi_{\text{eff}}(f_i)$ in (53), this $\hat{\beta}_{\text{ugee}}$ does achieve the benchmark $\Sigma_{\beta_0}^{\text{eff2}}$ and hence is optimal. Therefore, in the endogenous case, UGEE also yields the most efficient semiparametric RAL estimator.

## 9 Adaptive Semiparametric Estimator for FRM

Recall that we have proved that UGEE estimator achieves the semiparametric efficiency bound $\nu_2$, provided $V(X_i)$ is specified correctly. Here we need to differentiate local and global efficiency. Local efficiency refers to the efficiency for particular assumptions of the nonparametric component of the model. Such estimators are optimal for a particular distribution, subject to the constraint implied by the semiparametric model, while the more ambitious global efficiency refers to the efficiency for all values of the nonparametric component.

We define local and global efficiency for FRM in the same vein as for within-subject models. Namely, any semiparametric RAL estimator $\hat{\beta}$ with the asymptotic variance achieving the bound $\nu_2$ in (49) for the true model $p_0(f_i, X_i) = p(f_i, X_i; \theta_0)$ is locally efficient at $p_0(f_i, X_i)$. If the same $\hat{\beta}$ is semiparametric efficient regardless of $p_0(f_i, X_i) \in \mathcal{P}$, then it is globally efficient. For FRM, the nonparametric component refers to the unknown true conditional distribution $p_0(f_i | X_i)$ left unspecified, which yields an unknown conditional variance $V(X_i) = \text{Var}(f_i | X_i)$.

To resolve this chicken and egg situation, a feasible approach is adaptive estimators, where we find approximations to $V(X_i)$ by imposing additional assumptions to improve
efficiency, as shown in our simulations (see Section 9.3 and Supplements). In the following, we discuss global and local efficiency for FRM.

9.1 Globally Efficient Estimators

Example 1. (Binary responses) Consider an FRM for binary responses $f_i$ with a vector of explanatory variables $X_i$, where $E(f_i \mid X_i) = \expit(\beta^\top X_i) = \exp\left(\beta^\top X_i \right) \left[1 + \exp(\beta^\top X_i)\right]^{-1}$.

The variance of the binary $f_i$ conditional on $X_i$ takes the form

$$V(X_i; \beta) = \exp(\beta^\top X_i) \left[1 + \exp(\beta^\top X_i)\right]^{-2}, \quad (55)$$

which does not involve any additional unknown parameter (aside from $\beta$). By (48), the optimal UGEE is:

$$\sum_{i \in C^2} D_i^\top V_i^{-1} S_i = \sum_{i \in C^2} X_i [f_i - \expit(\beta^\top X_i)] = 0.$$ 

Since the above only contains $\beta$ with no other parameter, the resulting UGEE estimator $\hat{\beta}$ has the efficient I.F. depending only on $\beta_0$:

$$\varphi_{\text{eff}}(f_i, X_i; \beta_0) = E^{-1} \left[X_i V(X_i; \beta_0) X_i^\top \right] X_i [f_i - \expit(\beta_0^\top X_i)] .$$

This $\hat{\beta}$ is semiparametric efficient regardless of $p(f_i, X_i; \theta_0) \in P$ and thus is globally efficient.

9.2 Locally Efficient Estimators

Example 2. (Count responses) Consider modeling count responses $f_i$ with $E(f_i \mid X_i) = \exp(\beta^\top X_i)$, where $f_i$ is over-dispersed. For the unknown $V(X_i)$, we can specify a working variance that is proportional to the conditional mean, $V(X_i; \tau^2, \beta) = \tau^2 \exp(\beta^\top X_i)$, with $\tau^2 = 1$ for non-overdispersed and $\tau^2 > 1$ for overdispersed $f_i$. We then estimate $\tau^2$ and $\beta$ by iterating between (1) minimizing the squared sum of residuals $\left\{ [f_i - \exp(\beta_0^\top X_i)]^2 - V(X_i; \tau^2, \beta) \right\}^2$ for $\tau^2$ with a given $\hat{\beta}$ and (2) solving the UGEE for $\beta$ with a given $\hat{\tau}^2$, until convergence.

Under mild regularity conditions, $\hat{\tau}^2 \rightarrow_p \tau^2_*$ (a constant may or may not be the truth), leading to a UGEE estimator $\hat{\beta}^P$ with the efficient I.F.

$$\varphi_{\text{eff}}(f_i, X_i; \tau^2_*, \beta_0) = E^{-1} \left[X_i \exp(\beta_0^\top X_i) X_i^\top \right] X_i [f_i - \exp(\beta_0^\top X_i)] . \quad (56)$$
This estimator is locally efficient; if the conditional variance is indeed proportional to the conditional mean, i.e., \( \tau^2 \sim \tau^2_0 \), then it is semiparametric efficient.

Alternatively, we can specify a working variance motivated by the form of Negative Binomial (NB) distribution. With a dispersion parameter \( \zeta \), we substitute \( \exp (\beta^\top X_i) \left[ 1 + \zeta \exp (\beta^\top X_i) \right]^{-1} \) in place of \( V(X_i; \zeta, \beta) \), yielding an UGEE estimator \( \hat{\beta}^{NB} \) with a different I.F.

\[
E^{-1} \left\{ X_i \left[ 1 + \zeta \exp (\beta_0^\top X_i) \right]^{-1} \exp (\beta_0^\top X_i) X_i^\top \right\} X_i \left[ 1 + \zeta \exp (\beta_0^\top X_i) \right]^{-1} \left[ f_i - \exp (\beta_0^\top X_i) \right].
\]

Again, it has the form of the efficient I.F., but with respect to the limiting point \( \zeta^* \) that may or may not be true. If the working variance is the same as the true variance, then the resulting \( \hat{\beta}^{NB} \) is semiparametric efficient.

The distinct forms of efficient I.F.s between (56) and (57) result from different working variance assumptions we made. For count responses, other forms of non-negative working variance can be assumed, each leads to a different variance (or local efficiency bound) of \( \hat{\beta} \).

Adaptive estimators have been shown empirically to improve efficiency for classical semi-parametric GLMs for within-subject attributes\(^{36}\). Our simulation studies also demonstrate this feature, some of which are discussed below.

### 9.3 Simulation Studies

To illustrate the local efficiency of adaptive estimators, we consider again overdispersed count responses. We generated data from the Negative Binomial distribution and estimated parameters using both parametric and semiparametric models (but with different working variances). For Monte Carlo (MC) simulations, we set total MC iterations \( M = 1,000 \) and sample sizes \( n = 100, 300, 500 \). All analyses are performed with the R software platform\(^{35}\), with code optimized using Rcpp\(^{8}\) for run-time improvement. We demonstrate between-subject attributes here, similar performances of within-subject attributes are observed but omitted here.

Without loss of generality, we include one continuous predictor. By first generating \( X_i \sim^\text{i.i.d} U(a, b) \) with \( U(a, b) \) denoting a uniform distribution over \( (a, b) \), we create between-subject \( X_i \) with \( X_i = X_{i1} + X_{i2} \). Given \( X_i \), we then generate \( f_i \sim NB(\zeta, h(X_i; \beta)) \), where \( h(X_i; \beta) = \exp (\beta_0 + \beta_1 X_i) \) and \( NB(\zeta, \mu) \) denotes a Negative Binomial with mean \( \mu \) and dispersion parameter \( \zeta \).

We estimate \( \beta = (\beta_0, \beta_1)^\top \) using (i) MLE from Negative Binomial (NB); and (ii) semiparametric UGEE with working variances from (1) NB, (2) Poisson and (3) as a constant
(See the Supplement S2 for details). We set $\zeta = 10$, $\beta_0 = 3$, $\beta_1 = 3$, $a = 0$, $b = 1$ and report the parameter estimators (Est.), asymptotic (Asy.) and empirical (Emp.) variances under different sample sizes in Table 1.

Table 1 goes here

The MLE from NB is the benchmark for efficiency in this setting. As expected, Table 1 shows that UGEE estimators with the working variance of NB reach the local efficiency bound, while the other two yield larger variances. As expected, the constant working variance yields the largest variance, since the Poisson working variance has a better approximation to the true variance than a constant. Thus, akin to within-subject attributes, adaptive estimators demonstrate efficiency gains for semiparametric models of between-subject attributes as well, but the improvement depends on how well the working variance resembles the true variance.

10 Discussion

By leveraging the Hilbert-space-based semiparametric efficiency theory, we demonstrated that UGEE estimators are semiparametric efficient for functional response models (FRM) based on between-subject attributes. Such estimators deliver the smallest asymptotic variances among a class of regular and asymptotic linear (RAL) estimators for this emerging class of semiparametric models. Specifying mathematical distributions such as normality for between-subject attributes is far more challenging than for their within-subject counterparts, because between-subject attributes are not only correlated, but generally follow more complex distributions. Extending the semiparametric efficiency theories to between-subject attributes will not only enrich the body of research on this topic, but will also greatly facilitate the implementations of FRM for valid and efficient inference in practice.

To show the efficiency of UGEE estimators for FRM, or model class 2, we first generalized relevant results to between-subject attributes, such as asymptotic linearity, regular estimators, and efficiency bounds. Since directly establishing the efficiency theory is difficult for UGEE estimators, we also introduced a class of models involving only a subset of independent pairs of between-subject responses, or model class 1. Although this “conjugate” class of models has no practical utility given its lower efficiency, this powerful tool helps determine the efficiency of UGEE estimator for the FRM. By connecting estimators from the two classes of models with a dual orthogonality property between their respective nuisance tangent spaces, we pinpointed the efficient estimator for FRM through first finding the efficient estimator for the “conjugate” model class. This is more straightforward by leveraging the existing Hilbert-space-based semiparametric efficiency theory.

Therefore, not only does UGEE enjoy the semiparametric robustness, but also the effi-
ciency in inference, just like its counterpart GEE for the classical within-subject attributes. With blooming implementations of between-subject attributes as effective summary metrics of high-dimensional data, our developed efficiency will greatly propel applying FRM for scientific discovery.

One limitation is that we only focus on the efficiency bound for semiparametric FRM when applied to the cross-sectional data. Extending the results to clustered data such as repeated assessments in longitudinal studies is the next goal to undertake, where major challenges are to address the missing data arising from study dropouts and elucidate its impact on estimators through different missing data mechanisms.
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| Method       | Assumption | $\beta_0$ | Est. Variance | $\beta_1$ | Est. Variance |
|--------------|------------|-----------|---------------|-----------|---------------|
|              |            | Asy.      | Asy.          | Emp.      | Asy.          |
| Working-MLE  | NB         | 2.9911    | 0.0002        | 2.9990    | 0.0001        |
| UGEE         | NB         | 3.0000    | 0.0002        | 3.0000    | 0.0001        |
|              | Pois       | 3.0003    | 0.0007        | 2.9997    | 0.0005        |
|              | Const.     | 2.9989    | 0.0060        | 3.0005    | 0.0028        |
|              |            |           |               |           |               |
|              |            | Asy.      | Asy.          | Emp.      | Asy.          |
| Working-MLE  | NB         | 2.9970    | 1.79e-05      | 2.9997    | 1.49e-05      |
| UGEE         | NB         | 2.9998    | 1.77e-05      | 3.0002    | 1.47e-05      |
|              | Pois       | 3.0000    | 7.53e-05      | 3.0000    | 5.12e-05      |
|              | Const.     | 3.0003    | 0.0007        | 2.9998    | 0.0003        |
|              |            |           |               |           |               |
|              |            | Asy.      | Asy.          | Emp.      | Asy.          |
| Working-MLE  | NB         | 2.9983    | 6.33e-06      | 2.9997    | 5.28e-06      |
| UGEE         | NB         | 3.0000    | 6.27e-06      | 3.0000    | 5.23e-06      |
|              | Pois       | 2.9998    | 2.73e-05      | 3.0001    | 1.85e-05      |
|              | Const.     | 2.9998    | 0.0002        | 3.0001    | 0.0001        |
S1. Details about the Hilbert Space for Between-subject Attributes

For the norm \( b \) of the between-subject attributes that encompass an FRM form for the correlated \( h(Z_i) \)'s, we equipped the Hilbert space \( H_b^{(q)} \) with

\[
\langle h_1 (Z_i), h_2 (Z_i) \rangle_{b^2} = E \left\{ 2E \left[ h_1^\top (Z_i) \mid Z_{i_1} \right] \cdot 2E \left[ h_2 (Z_i) \mid Z_{i_1} \right] \right\},
\]

\[
\| h (Z_1) \|_{b^2} = \langle h (Z_i), h (Z_i) \rangle_{b^2}^{1/2} = \left( 2E \left[ h^\top (Z_i) \mid Z_{i_1} \right] \cdot 2E \left[ h (Z_1) \mid Z_{i_1} \right] \right)^{1/2}.
\]

It is readily checked that this definition of inner product 2 satisfies conditions 1) - 3) below,

1). \( \langle h_1 (Z_i), h_2 (Z_i) \rangle_{b^2} = \langle h_2 (Z_i), h_1 (Z_i) \rangle_{b^2} \),
2). \( a \langle h_1 (Z_i), h_2 (Z_i) \rangle_{b^2} = a \langle h_1 (Z_i), h_2 (Z_i) \rangle_{b^2} \),
3). \( \langle h_1 (Z_i) + h_2 (Z_i), h_3 (Z_i) \rangle_{b^2} = \langle h_1 (Z_i), h_2 (Z_i) \rangle_{b^2} + \langle h_1 (Z_i), h_3 (Z_i) \rangle_{b^2} \),
4). \( \langle h (Z_i), h (Z_i) \rangle_{b^2} \geq 0 \), \( \langle h (Z_i), h (Z_i) \rangle_{b^2} = 0 \) iff \( E \left[ h (Z_1) \mid Z_{i_1} \right] = 0 \) a.s..

For 4), we have that if \( E \left[ h (Z_1) \mid Z_{i_1} \right] = 0 \) a.s., then \( \| h (Z_1) \|_{b^2}^2 = \langle h (Z_1), h (Z_1) \rangle_{b^2} = 0 \).

Conversely, \( \langle h (Z_i), h (Z_i) \rangle_{b^2} = 0 \) implies that for all \( 1 \leq s \leq q \),

\[
E \left\{ E \left[ h_s (Z_i) \mid Z_{i_1} \right] E \left[ h_s (Z_i) \mid Z_{i_1} \right] \right\} = E \left\{ E^2 \left[ h_s (Z_i) \mid Z_{i_1} \right] \right\} = 0,
\]

we then have:

\[
E \left[ h_s (Z_i) \mid Z_{i_1} \right] = 0 \) a.s. for all \( 1 \leq s \leq q \), i.e., \( E \left[ h (Z_i) \mid Z_{i_1} \right] = 0 \) a.s..

Thus,

\[
\langle h (Z_i), h (Z_i) \rangle_{b^2} = 0 \) iff \( E \left[ h (Z_1) \mid Z_{i_1} \right] = 0 \) a.s..
\]

In general, \( \langle h (Z_i), h (Z_i) \rangle_{b^2} = 0 \) does not imply \( h (Z_i) = 0 \) a.s.. To see this, consider a counterexample

\[
Z_{i_1}, Z_{i_2} \sim N (1, 1), \quad h (Z_i) = h (Z_{i_1}, Z_{i_2}) = (1 - Z_{i_1}) (1 - Z_{i_2}).
\]

Then, \( h (Z_1) = h (Z_{i_1}, Z_{i_2}) \) is symmetric and although \( \langle h (Z_1), h (Z_1) \rangle_{b^2} = \| h (Z_1) \|_{b^2}^2 = 0 \), since

\[
E \left[ h (Z_1) \mid Z_{i_1} \right] = (1 - Z_{i_1}) E (1 - Z_{i_2}) = 0 \) a.s.,
in general, 
\[ h(Z_i) \neq 0 \text{ a.s.}, \]
i.e., here \( \|h(Z_i)\|_{l_2}^2 = 0 \) iff \( E[h(Z_i) | Z_{i_1}] = 0 \) a.s., but \( \|h(Z_i)\|_{l_2}^2 = 0 \) does not imply \( h(Z_i) = 0 \) a.s..

Thus, unlike the origin of \( \mathcal{H}_b \) under the inner product 1, the origin of \( \mathcal{H}_b \) under inner product 2 is not the equivalence class of \( h(Z_i) \) with \( h(Z_i) = 0 \) a.s., but a larger equivalence class consisting of functions \( h(Z_i) \) such that \( E[h(Z_i) | Z_{i_1}] = 0 \) a.s..

S2. Detailed Simulation Settings

We conduct a similar simulation for between-subject attributes, to demonstrate the local efficiency of UGEE for count responses. We first simulate \( X_i \sim \text{i.i.d } \text{Unif}(a, b) \), then construct 
\[ X_i = X_{i_1} + X_{i_2}. \]
Let 
\[ E(f_i | x_i) = \exp(\beta_0 + \beta_1 x_i) = h_i(\beta), \quad \beta = (\beta_0, \beta_1), \]
we can simulate overdispersed \( f_i \sim \text{NB}(\tau, h_i(\beta)) \) following a Negative Binomial distribution with mean \( h_i(\beta) \) and dispersion parameter \( \tau \) (or the shape parameter of the gamma mixing distribution).

We then estimate \( \beta \) using
1) The working-MLE of Negative Binomial through \( f_i \);
2) Semiparametric UGEE with
\[ U_n(\beta) = \sum_{i \in C_2^n} D_i^T V_i^{-1} S_i, \quad S_i = f_i - h_i, \quad D_i = \frac{\partial}{\partial \beta} h_i(\beta). \]

For the unknown \( V_i \), we respectively chose
a) the true variance of Negative Binomial for \( f_i \). Let 
\[ V_i = \text{Var}(f_i | x_i) = \frac{h_i(\beta)}{p_i(\beta)} \]
\[ p_i(\beta) = \frac{\tau}{\tau + h_i(\beta)}. \]

The optimal UGEE for estimating \( \beta \) then becomes
\[ U_n(\beta) = \sum_{i \in C_2^n} D_i^T V_i^{-1} S_i = \sum_{i \in C_2^n} X_i^T p_i(\beta) [f_i - h_i(\beta)] = 0, \]
yielding the asymptotic variance of
\[ \text{Var}(\beta) = B^{-1} 4 \text{Var} \left[ X_i^T p_i(\beta) \{f_i - h_i(\beta)\} | f_{i_1}, X_{i_1} \right] B^{-1}, \]
\[ B = E \left[ X_i^T p_i(\beta) h_i(\beta) E \{h_i(\beta)\} \right]. \]
In the simulation, we estimate $\tau$ from the sample.

b) a (wrong) variance assumption of Poisson for $\theta$ through $f_i$. Let

$$V_i = Var(f_i \mid x_i) = h_i(\beta).$$

The optimal UGEE for estimating $\beta$ is

$$U_n(\beta) = \sum_{i \in C_2} D_i^T V_i^{-1} S_i = \sum_{i \in C_2} X_i^T \{f_i - h_i(\beta)\} = 0,$$

yielding the asymptotic variance of

$$Var(\beta) = E [X_i^T h_i(\beta) X_i]^{-1} 4 Var [X_i^T \{f_i - h_i(\beta)\} \mid f_i, X_i] E [X_i^T h_i(\beta) X_i]^{-1}.\)


c) a bad (wrong) variance assumption (Constant) through $f_i$. Let

$$V_i = Var\{f_i \mid x_i\} = C.$$

The optimal UGEE for estimating $\beta$ is now

$$U_n(\beta) = \sum_{i \in C_2} D_i^T V_i^{-1} S_i = \sum_{i \in C_2} C^{-1} X_i^T h_i(\beta) \{f_i - h_i(\beta)\} = 0,$$

yielding the asymptotic variance of

$$Var(\beta) = E [X_i^T h_i(\beta)^2 X_i]^{-1} 4 Var [X_i^T h_i(\beta) \{f_i - h_i(\beta)\} \mid f_i, X_i] E [X_i^T h_i(\beta)^2 X_i]^{-1}.\)

In the simulation, we used $C = \overline{Var}(f_i)$.

We set $\tau = 10, \beta_0 = 3, \beta_1 = 3, a = 0, b = 1$ in all our simulations.