On Large-Sample Estimation and Testing via Quadratic Inference Functions for Correlated Data

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Abstract

Hansen (1982) proposed a class of generalized method of moments (GMMs) for estimating a vector of regression parameters from a set of score functions. Hansen established that, under certain regularity conditions, the estimator based on the GMMs is consistent, asymptotically normal and asymptotically efficient. In the generalized estimating equation framework, extending the principle of the GMMs to implicitly estimate the underlying correlation structure leads to a quadratic inference function (QIF) for the analysis of correlated data. The main objectives of this research are to (1) formulate an appropriate estimated covariance matrix for the set of extended score functions defining the inference functions; (2) develop a unified large-sample theoretical framework for the QIF; (3) derive a generalization of the QIF test statistic for a general linear hypothesis problem involving correlated data while establishing the asymptotic distribution of the test statistic under the null and local alternative hypotheses; (4) propose an iteratively reweighted generalized least squares algorithm for inference in the QIF framework; and (5) investigate the effect of basis matrices, defining the set of extended score functions, on the size and power of the QIF test through Monte Carlo simulated experiments.

Key Words: Covariance structure; Extended score; Generalized estimating equations; Generalized least squares; Generalized method of moments; Longitudinal data; Quasi-likelihood.
1 Introduction

Correlated data arises when a response is measured at repeated instances on a set of subjects within a study design. A canonical problem is to determine a regression relationship between the measured responses and a set of covariates. Responses on different subjects are assumed to be independent, while the repeated measurements on individual subjects are correlated with an unknown correlation structure. Any inferential procedure must take account of this correlation (Crowder and Hand, 1990; Diggle et al., 1994).

Let $Y_{it}$ be a response, with a corresponding $q$-dimensional vector of covariates $X_{it}$, measured at the $t$th ($t = 1, \ldots, n_i$) time point on the $i$th ($i = 1, \ldots, N$) subject. Assuming a generalized linear model for $Y_{it}$ and $X_{it}$ yields

$$E(Y_{it}) = h(X_{it}^T \beta)$$  

and

$$\text{var}(Y_{it}) = \phi v(X_{it}^T \beta),$$  

where $\beta \in \mathcal{B}$ is a $q$-dimensional vector of unknown regression parameters, $\phi$ is a dispersion parameter, $h(\cdot)$ is a known inverse link function and $v(\cdot)$ is a known variance function. The principal objective is to derive inferential theory for the unknown parameter vector $\beta$.

For simplicity of exposition, we assume that each subject is observed at a common set of time points $t = 1, \ldots, n$. Let $Y_i = (Y_{i1}, \ldots, Y_{in})^T$ be the response vector and $h_i = E(Y_i) = \{h(X_{i1}^T \beta), \ldots, h(X_{in}^T \beta)\}^T$ be the vector of means. Furthermore, let the operator $\nabla$ denote a partial derivative with respect to the elements of $\beta$ so that $\nabla h_i$ represents the $(n \times q)$ matrix $(\partial h_i/\partial \beta_1, \ldots, \partial h_i/\partial \beta_q)$ for each $i = 1, \ldots, N$. 

1.1 Background

The quasi-likelihood estimating equation (Wedderburn, 1974) for $\beta$, under the generalized linear model framework is defined as

$$S(\beta) := \sum_{i=1}^{N} \{ \nabla h_i^T W_i^{-1} (Y_i - h_i) \} = 0,$$

where $W_i = \text{cov}(Y_i)$ is an $(n \times n)$ diagonal matrix with elements determined by the variance function (2). When the independence assumption within a subject for the responses is relaxed, the matrices $W_i$ are no longer diagonal, instead have an unknown correlation structure that needs to be incorporated into the model. In a seminal article, Liang and Zeger (1986) proposed generalized estimating equations (GEEs), based on the ingenious idea of using a working correlation matrix with a nuisance parameter vector to simplify $W_i$. In particular, they proposed the GEEs based on

$$W_i = A_i^{1/2} R(\alpha) A_i^{1/2} \quad \text{for} \quad i = 1, \ldots, N,$$

where $A_i$ is the diagonal matrix of marginal variance of $Y_i$ and $R(\alpha)$ is the working correlation matrix with an unknown nuisance parameter vector $\alpha$. Specific choices of $R(\alpha)$ correspond to common correlation structures, such as the exchangeable and AR-1.

The GEE approach yields a consistent estimator of $\beta$ even when the working correlation structure $R(\alpha)$ is misspecified. However, under such misspecification, the GEE estimator of $\beta$ is not efficient. Furthermore, Crowder (1995) established that there are difficulties with estimating the nuisance parameter vector $\alpha$ in the GEE framework and that in certain cases, the estimator of $\alpha$ does not exist.

Hansen (1982) proposed the class of generalized method of moments (GMMs) for estimating the vector of regression parameters from a set of score functions, where the dimension of the score function exceeds that of the regression parameter. Hansen established that, under certain regularity conditions, the GMM estimator is consistent,
asymptotically normal and asymptotically efficient. To overcome the difficulties associated with the GEEs, Qu et al. (2000) (henceforth abbreviated QLL) applied the principle of the GMMs in the GEE framework that implicitly estimates the underlying correlation structure: In particular, they proposed a clever approach based on the quadratic inference functions (QIFs) (1) to estimate the working correlation structure $\mathbf{R}(\alpha)$ such that the resulting estimator always exists and (2) to obtain better efficiency in estimating $\beta$ within the assumed family even under the misspecification of $\mathbf{R}(\alpha)$.

### 1.2 Main Results

In this article, we derive a unified large-sample theoretical framework for the QIF. The cornerstone of our theory is stated in Theorem 5 which establishes a uniform quadratic approximation to the QIF surface in a neighborhood of $\beta_0$, the true regression parameter vector. This result has two fundamental consequences. First, it provides the necessary machinery to establish that the QIF is asymptotically equivalent to the generalized least squares criterion. This leads to techniques for deriving large-sample results for the QIF estimators and test statistics, analogous to standard inferential theory for the generalized least squares methods. Second, it provides a flexible algorithm for finding the QIF estimators. Building on the quadratic approximation to the QIF, we create an iteratively reweighted generalized least squares (IRGLS) algorithm for estimation and testing in the QIF framework. This algorithm is stable and computationally more feasible than the Newton-Raphson algorithm recommended in the existing QIF literature (Figure 1 demonstrates the necessity for the IRGLS algorithm).

The QLL article has made important contributions to the analysis of correlated data. However, some of the asymptotic results in QLL are flawed, including the proof of their Theorem 1. QLL employ a Taylor series expansion in proving the Theorem 1;
however, there is a fundamental problem since the Taylor series expansion is in terms of the partitioned parameter vector $\beta = (\psi, \lambda)$ and not in terms of the sample size $N$. Even with the remainder terms, Taylor’s theorem does not provide any statements regarding the behavior of the error term as a function of the sample size $N$ and neither has this been established in QLL. It is not possible to patch up either the original proof or other asymptotic results in the QLL article (the reasons will be made clear in later sections). These difficulties have not been identified explicitly; hence, there is not yet any rigorous development of a unified asymptotic theory for the QIF. We develop a more broadly applicable inferential theoretical framework for the QIF that extends and corrects the results of QLL.

As a first step in achieving the objectives, we re-formulate the estimated covariance matrix of the “extended score functions” defining the QIF. This formulation yields a consistent estimator of the covariance matrix, which in turn lays the foundation for deriving valid inferential theory for the QIF. The main results are summarized as follows:

1. We formulate an appropriate estimated covariance matrix for the set of extended score functions defining the QIF (Section 1.3). In Sections 2 and 3, we first formulate a unified large-sample theoretical framework for the QIF and next derive several important asymptotic properties for the QIF. These lay the necessary foundation for the development of the asymptotic results derived in later part of the article.

2. In Section 4, we first derive the principal result, the quadratic approximation to the QIF surface in a neighborhood of $\beta_0$, the true regression parameter vector. Next, we formulate a statistic based on the QIF for testing general linear hypotheses involving correlated data. Building on the quadratic approximation to the QIF, we establish the asymptotic distribution of the generalized QIF test statistic under both the null and local alternative hypotheses.

3. In Section 5, we propose a stable and computationally feasible IRGLS algorithm
for estimating $\beta$ in the QIF framework. This algorithm is a step in the direction of developing a unified framework for estimation, testing and model selection for correlated data within the QIF setting.

4. In Section 6, we illustrate the methods using a benchmark dataset consisting of the correlated binary data measuring the respiratory health effects of indoor and outdoor air pollution.

5. In Section 7, we investigate the effect of the basis matrices (defining the set of extended score functions) on the size and power of the QIF test through Monte Carlo simulation experiments from Bernoulli and Gaussian distributions.

This article derives asymptotic theory for testing general linear hypotheses based on the quadratic approximation of the QIF. However, a common thread underlying the recent literature in the context of nonlinear testing problems is in fact the Theorem 5:

1. Pilla et al. (2005) derived asymptotic distribution of the test statistic for order-restricted hypothesis testing problem; (2) Pilla (2005) developed inferential theory for testing under the general convex cone alternatives for correlated data; and (3) Loader and Pilla (2005a) derived several properties of the IRGLS algorithm which is more generally applicable while providing a flexible technique for estimation, testing and model selection with correlated data.

Having the correct asymptotic theory for the QIF is essential for further extensions as well as applications of the QIF, especially given that the QIF is elegant, simple and practical to implement with the proposed IRGLS algorithm for the analysis of correlated data.

1.3 The Quadratic Inference Function

QLL showed that the principle of GMMs can be applied in the GEE framework by implicitly estimating the underlying correlation structure. In particular, they assumed
that the inverse of the working correlation matrix $R(\alpha)$ can be expressed as a linear combination of pre-specified basis matrices $M_1, \ldots, M_s$ such that

$$R^{-1}(\alpha) = \sum_{j=1}^{s} \alpha_j M_j,$$

where $\alpha_1, \ldots, \alpha_s$ are unknown constants. For this article, we choose $M_1$ as the identity (of appropriate dimension) and $M_2, \ldots, M_s$ according to the form of the assumed underlying correlation structure. For example, (1) if $R(\alpha)$ is an exchangeable correlation matrix, then $s = 2$ and $M_2$ is a matrix of 1s; and (2) if $R(\alpha)$ is an AR-1 correlation matrix, then $s = 3$, $M_2$ takes 1 on the two main off diagonals and zero elsewhere and $M_3$ takes 1 at the elements $(1, 1)$ and $(n, n)$ and zero elsewhere. In general, $M_3$ is a minor boundary correction and can be omitted. If the covariate is time-independent, then the boundary correction does not have an effect on the inference since the corresponding components of the score vector (see equation (5) below) are linearly dependent on other terms.

The quasi-score estimating equations in (3) can be expressed, under the representation (4), as

$$\sum_{i=1}^{N} \nabla h_i^T A_i^{-1/2} (\alpha_1 M_1 + \cdots + \alpha_s M_s) A_i^{-1/2} (Y_i - h_i).$$

These estimating equations are linear combinations of elements of a set of extended score functions

$$\bar{g}_N(\beta) := \frac{1}{N} \sum_{i=1}^{N} g_i(\beta),$$

where a set of “subject-specific” basic score functions is defined as

$$g_i(\beta) = \begin{cases} \nabla h_i^T A_i^{-1/2} M_1 A_i^{-1/2} (Y_i - h_i) \\ \vdots \\ \nabla h_i^T A_i^{-1/2} M_s A_i^{-1/2} (Y_i - h_i) \end{cases} \quad \text{for} \quad i = 1, \ldots, N.$$  

Instead of directly estimating the parameters $\alpha_1, \ldots, \alpha_s$, the QIF introduces a sample covariance matrix in order to combine the score functions in an optimal manner. In
general, the equation $\overline{g}_N(\beta) = 0$ has no solution, since its dimension is greater than the number of unknown parameters. Instead, the parameter vector $\beta$ is estimated by minimizing the QIF defined as

$$Q_N(\beta) := N \overline{g}_N^T(\beta) \hat{C}^{-1}_N(\beta) \overline{g}_N(\beta),$$

(6)

where an estimator of the second moment matrix of $g_1(\beta)$ is

$$\hat{C}_N(\beta) := \frac{1}{N} \sum_{i=1}^{N} g_i(\beta) g_i^T(\beta).$$

(7)

If the extended score vector $\overline{g}_N(\beta)$ has mean zero, then $N^{-1} \hat{C}_N(\beta)$ is an estimator of the covariance matrix of $\overline{g}_N(\beta)$. The function $Q_N(\beta)$ measures the size of the score vector relative to its covariance matrix and large values of $Q_N(\beta)$ can be considered as an evidence against a particular value of $\beta$. In this sense, the QIF plays a role similar to the negative of the loglikelihood in parametric statistical inference. In particular, one can construct a goodness-of-fit test statistic $Q_N(\beta)$ for testing the model assumption in (1). It follows from the results of Hansen (1982) that the asymptotic distribution of $Q_N(\hat{\beta})$ is $\chi^2$ with $\{\dim(g) - \dim(\beta)\}$ degrees of freedom under the model assumption.

The second moment matrix estimator defined in (7) is an average and hence under certain regularity conditions it will converge to the true covariance of $g_1(\beta)$ as $N \rightarrow \infty$. This convergence result is fundamental to adapting the large-sample framework of the GMMs (Hansen, 1982) to the QIF setting. The role of the matrix $\hat{C}^{1/2}_N(\beta)$ is similar to that of the matrix $a^* N$ defined on p. 1040 of Hansen (1982), which is also required to converge to a non-degenerate limit.

Our covariance estimator $\hat{C}_N(\beta)$ differs from that of QLL, who define a covariance $C_N$ with a factor of $N^{-2}$ and correspondingly omit the factor of $N$ from the QIF in (6). This has led to a number of imprecise claims in QLL, centered around their statement on p. 829 that $C_N$ converges to $E(C_N)$. In fact, their $C_N$ converges to zero. Furthermore, the asymptotic result for $\hat{\beta}_N$ in Section 3.6 of QLL is incorrect.
since $\hat{C}_N$ in equation (8) of their article is approaching zero as $N \to \infty$ and is not a consistent estimator of $\Sigma_{\beta_0}(\beta)$, the true covariance matrix of $g_1(\beta)$ evaluated at $\beta_0$. However, our definition of the QIF matches that presented by Park and Lindsay (1999).

While the correlation model (4) motivates our choice of the score vector, the fundamental property $E\{g_1(\beta_0)\} = 0$ holds whether or not the covariance assumption is correct. Similarly, $\hat{C}_N(\beta_0)$ consistently estimates $N \text{cov}\{\overline{g}_N(\beta_0)\}$. Therefore, inference based on the QIF is semiparametric, in the sense that procedures are asymptotically valid whether or not the covariance model is correct. Bickel et al. (1998) and Kosorok (2006) present a detailed exposition of the mathematical aspects of semiparametric inference.

2 Large-Sample Properties of the Extended Score Functions

In order to establish the asymptotic results in any regression problem, one must first state assumptions regarding the behavior of the design matrices as the sample size $N$ increases. Without formulating such assumptions, it is not possible to establish even the consistency of the QIF estimators. However, such assumptions are missing from the earlier QIF work.

The main requirement for our asymptotic theory is to be able to apply the strong law of large numbers to show that $\overline{g}_N(\beta)$, $\hat{C}_N(\beta)$ and other averages converge to appropriate non-degenerate limits. A sufficient condition is the following “random design” assumption.

Assumption A1. The pairs $(Y_i, X_i^T)$ are assumed to be an independent sample from a $\{n \times (q + 1)\}$-dimensional distribution $F$, where $X_i = (X_{i1}, \ldots, X_{in})$ is the
A $(q \times n)$-dimensional design matrix for the $i$th ($i = 1, \ldots, N$) subject.

Remark 1. The independence part of Assumption A1 is between different subjects, or with respect to the index $i$. The elements of $X_i$ need not be independent of each other; hence, this assumption incorporates both time-dependent and time-independent covariates. Note that there exists a dependence of $Y_i$ on $X_i$ through the link and variance functions in (1) and (2), respectively.

All throughout this article, $E_{\beta_0}(\cdot)$ denotes the expectation operator with respect to the true regression parameter vector $\beta_0$. Our results are based on the implicit assumption that all expectations are finite and the convergence statements are uniform for $\beta$ in bounded sets. Uniformity results for the strong law of large numbers are derived by Rubin (1956).

**Theorem 1.** [Asymptotic normality of $\bar{C}_N(\beta_0)$] Let $\beta_0$ be the true parameter vector. Under Assumption A1,

$$\bar{C}_N(\beta) \xrightarrow{a.s.} E_{\beta_0}\{g_1(\beta)\} = 0 \quad \text{if} \quad \beta = \beta_0$$

and

$$\sqrt{N}\bar{C}_N(\beta_0) \xrightarrow{d} N_r\{0, \Sigma_{\beta_0}(\beta_0)\}, \quad (8)$$

where $r = q s$ and $\Sigma_{\beta_0}(\beta_0)$ is the true covariance matrix of $g_1(\beta)$ evaluated at $\beta_0$.

It is easy to verify that $E_{\beta_0}\{g_1(\beta_0)\} = 0$. The following identifiability assumption is required to develop the large-sample theory for the QIF.

**Assumption A2.** The parameter $\beta$ is estimable, in the sense that $E_{\beta_0}\{g_1(\beta)\} = 0$ if and only if $\beta \neq \beta_0$.

Another application of the strong law of large numbers establishes that $\bar{C}_N(\beta)$ converges to its expected value, a non-degenerate limit, which is required to invoke the
results of Hansen (1982).

**Theorem 2.** [Consistency of $\hat{C}_N(\beta)$] Under Assumptions A1 and A2,
\[
\hat{C}_N(\beta) \xrightarrow{a.s.} E_{\beta_0} \left\{ g_1(\beta) g_1^T(\beta) \right\} := \Sigma_{\beta_0}(\beta) \quad \text{as} \quad N \to \infty. \tag{9}
\]

In this article we follow the prescription of Assumption 3.6 of Hansen (1982) which is restated for the current framework.

**Assumption A3.** The matrix $\Sigma_{\beta_0}(\beta)$ is strictly positive definite.

**Remark 2.** The estimator of second moment matrix $\hat{C}_N(\beta)$ may be singular. However, any vector in the null space of $\hat{C}_N(\beta)$ must be orthogonal to each of the subject-specific score functions $g_i(\beta) (i = 1, \ldots, N)$ and consequently to $\overline{g}_N(\beta)$. As a result, one can replace $\hat{C}_N^{-1}(\beta)$ by any generalized inverse such as the Moore-Penrose generalized inverse.

We first state several important assumptions required to establish the large-sample properties of $\overline{g}_N(\beta)$.

**Assumption A4.** The parameter space of $\beta$ denoted by $\mathcal{B}$ is compact.

**Assumption A5.** The expectation $E_{\beta_0} \left\{ \overline{g}_N(\beta) \right\}$ exists and is finite for all $\beta \in \mathcal{B}$ and is continuous in $\beta$.

The compactness assumption is necessary to invoke the uniformity results of Rubin (1956) and it is unavoidable since the QIF surface is often not convex. For non-compact parameter spaces, Lemma 1 is only applicable to a sequence of local minima.

From Theorem 2.1 of Hansen (1982), the following result holds.

**Lemma 1.** [Consistency of $\hat{\beta}_N$] Under Assumptions A4–A5, the QIF estimator
\[
\hat{\beta}_N := \arg \min_{\beta \in \mathcal{B}} Q_N(\beta)
\]
exists and $\hat{\beta}_N \xrightarrow{a.s.} \beta_0$ as $N \to \infty$. 

Our next goal is to derive the asymptotic distribution of $\hat{\beta}_N$. Let

$$D(\beta) := E_{\beta_0}\left\{ \frac{\partial}{\partial \beta} g_1(\beta) \right\} = E_{\beta_0}\{\nabla g_1(\beta)\}.$$ 

Once again, from the strong law of large numbers, it follows that

$$\nabla g_N(\beta) \xrightarrow{a.s.} E_{\beta_0}\{\nabla g_1(\beta)\} = D(\beta). \quad (10)$$

The extended score vector $g_N(\beta)$ is a random vector and hence $\nabla g_N(\beta)$ is a random matrix. Therefore, the claims on p. 829 of QLL that $\nabla g_N(\beta)$ is nonrandom and $E\{\nabla g_N(\beta)\} = g_N(\beta)$ cannot be true.

**Assumption A6.** The subject-specific score functions $g_i(\beta)$ ($i = 1, \ldots, N$) have uniformly continuous second-order partial derivatives with respect to the elements of the vector $\beta$.

Owing to Theorems 3.1 and 3.2 of Hansen (1982), the following result holds.

**Theorem 3.** [Asymptotic normality of $\hat{\beta}_N$] Under Assumptions A1–A6, the asymptotic distribution of $\hat{\beta}_N$ is

$$\sqrt{N} \left( \hat{\beta}_N - \beta_0 \right) \xrightarrow{d} N_q \{0, J^{-1}(\beta_0)\} \quad (11)$$

as $N \to \infty$, where

$$J(\beta_0) = D^T(\beta_0) \Sigma^{-1}(\beta_0) D(\beta_0). \quad (12)$$

The claim by QLL on p. 835, below equation (A1), that $(\hat{\beta}_N - \beta_0)$ converges in law to a normal distribution is incorrect. In fact, $\sqrt{N}(\hat{\beta}_N - \beta_0)$ has an asymptotic normal distribution while $(\hat{\beta}_N - \beta_0)$ converges in probability to zero. The matrix $d_0$ is not defined and it is not possible to define this in a manner consistent with the remainder of their article. While the statement of Theorem 1 in QLL requires the non-centrality parameter (consequently the partitioned matrices $J_{\psi\psi}$ etc., $d_0$ and $\Sigma$) to be $O(1)$,
the equation (A1) on p. 835 requires $J_{\psi \psi}$ to be $O_p(N^{-1})$. We believe, based on comparison with other work on the QIF, that the authors probably intended to write $d_0 = E\{\nabla \bar{g}_N(\beta)\} = O_p(1)$ and $\Sigma = \text{cov}\{\bar{g}_N(\beta)\} = O(N^{-1})$. However, this means that the statement of their Theorem 1 is incorrect.

3 Fundamental Results for the Quadratic Inference Functions

In this section, we establish several fundamental results for the QIF which lay the foundation for deriving the asymptotic distribution of inference functions presented in the next section.

One main focus is on the vector $\nabla Q_N(\beta)$ of partial derivatives and matrix $\nabla^2 Q_N(\beta)$ of second-order partial derivatives. Along the way, we derive the correct versions of several claims made by QLL. For example, on p. 830, QLL incorrectly claim that $\nabla^2 Q_N(\beta)$ converges in probability. In fact, the second derivative matrix has size $O_p(N)$.

Assumption A7. The first and second-order partial derivatives of $\bar{g}_N(\beta)$ and $\tilde{C}_N(\beta)$ have finite means.

Theorem 4. Under Assumption A7,

$$\frac{1}{2\sqrt{N}} \nabla Q_N(\beta_0) \xrightarrow{d} N_q \{0, J(\beta_0)\}$$

(13)

as $N \to \infty$. There exists a non-random matrix $V(\beta)$, continuous in $\beta$, such that

$$\frac{1}{2N} \nabla^2 Q_N(\beta) = V(\beta) + o_p(1),$$

(14)

where $V(\beta_0) = J(\beta_0)$ and $o_p(1)$ error term is uniform on compact sets.

Proof: Differentiating $Q_N(\beta)$, with respect to the $k$th ($k = 1, \ldots, q$) element $\beta_k$ of $\beta$
yields

\[ \frac{\partial}{\partial \beta_k} Q_N(\beta) = 2 N \mathbf{g}_N^T(\beta) \mathbf{\bar{C}}^{-1}_N(\beta) \frac{\partial \mathbf{g}_N(\beta)}{\partial \beta_k} + N \mathbf{g}_N^T(\beta) \frac{\partial \mathbf{\bar{C}}^{-1}_N(\beta)}{\partial \beta_k} \mathbf{g}_N(\beta). \]

(15)

From Theorem 1, it follows that at \( \beta = \beta_0 \), \( \sqrt{N} \mathbf{g}_N(\beta_0) = O_p(1) \) and \( \partial \mathbf{\bar{C}}^{-1}_N(\beta)/\partial \beta_k \) has a finite limit by the strong law of large numbers. Consequently, the second term in (15) is \( O_p(1) \). Therefore, it follows that

\[ \frac{1}{2} \sqrt{N} \nabla Q_N(\beta_0) = \sqrt{N} \nabla \mathbf{g}_N^T(\beta_0) \mathbf{\bar{C}}^{-1}_N(\beta_0) \mathbf{g}_N(\beta_0) + o_p(1) \]

The last equation follows from the result (9) in Theorem 1 and the result (10). The asymptotic distribution of \( \sqrt{N} \mathbf{g}_N(\beta_0) \) given in (8) yields the result (13).

Similarly,

\[ \frac{1}{N} \frac{\partial^2}{\partial \beta_j \partial \beta_k} Q_N(\beta) = 2 \mathbf{g}_N^T(\beta) \mathbf{\bar{C}}^{-1}_N(\beta) \frac{\partial^2 \mathbf{g}_N(\beta)}{\partial \beta_j \partial \beta_k} + \mathbf{g}_N^T(\beta) \frac{\partial^2 \mathbf{\bar{C}}^{-1}_N(\beta)}{\partial \beta_j \partial \beta_k} \mathbf{g}_N(\beta) \]

As \( N \to \infty \), by the strong law of large numbers, each of these terms is converging to a non-degenerate limit, which in turn lead to result (14) for an appropriate \( \mathbf{V}(\beta) \). At \( \beta = \beta_0 \), all the terms involving \( \mathbf{g}_N(\beta) \) converge to zero, leaving only the third term:

\[ \frac{1}{N} \frac{\partial^2 Q_N(\beta_0)}{\partial \beta_j \partial \beta_k} = 2 \frac{\partial \mathbf{g}_N^T(\beta_0)}{\partial \beta_j} \mathbf{\bar{C}}^{-1}_N(\beta_0) \frac{\partial \mathbf{g}_N(\beta_0)}{\partial \beta_k} + o_p(1). \]

In matrix form, this can be restated as

\[ \frac{1}{2N} \nabla^2 Q_N(\beta_0) = \mathbf{J}(\beta_0) + o_p(1) \]

(16)

which establishes the result (14) at \( \beta = \beta_0 \), implying that \( \mathbf{V}(\beta_0) = \mathbf{J}(\beta_0) \).
From Theorem 4, we have the following corollary.

**Corollary 1.** The first and second derivatives of $Q_N(\beta)$ at $\beta = \beta_0$ satisfy

\[ \nabla Q_N(\beta_0) = O_p(\sqrt{N}) \quad \text{and} \quad \nabla^2 Q_N(\beta_0) = O_p(N), \]

respectively. The analysis of the first derivative vector as well as the second derivative matrix of $Q_N(\beta)$ are critical to the development of asymptotic theory for the QIF and numerical algorithms to find the QIF estimators. However, several inadequacies exist in the previous results provided by QLL. First, their derivation involves multiplication of three and four-way arrays which are not clearly defined, leading to an incorrect expression for the second derivative matrix, $\nabla^2 Q_N(\beta_0)$. The claims made by QLL about convergence of the first and second derivatives of $Q_N(\beta)$ contradict the results shown in Corollary 1. These problems in QLL lead to their claim on p. 835 that $(\hat{\psi} - \psi_0)$ and $(\hat{\lambda} - \lambda_0)$ have a limiting normal distribution, however, with a missing a factor of $\sqrt{N}$.

### 4 Testing for General Linear Hypotheses within the QIF Framework

In this section we first establish the quadratic approximation of the QIF in a local neighborhood of $\beta_0$. Next, we derive an asymptotic distribution of the test based on the QIF for testing a general linear hypothesis and demonstrate that the Theorem 1 of QLL becomes a special case of our result.

#### 4.1 Asymptotic Distribution of the Inference Functions

The fundamental principle underlying the large-sample results presented in this article is a quadratic approximation of the QIF in a local neighborhood of the true regression parameter vector $\beta_0$. Under this approximation, the problem of minimizing the QIF
is asymptotically equivalent to a generalized least squares criterion. Consequently, standard asymptotic results from linear models can be applied to the QIF framework.

**Definition:** A ball of radius $o(\sqrt{N})$ is defined as $\{\xi : \|\xi\| \leq r_N\}$, where $\{r_N : N > 1\}$ is a sequence of constants with $r_N = o(\sqrt{N})$.

For exposition, we define

$$Z_N := \frac{1}{2 \sqrt{N}} \nabla Q_N(\beta_0). \quad (17)$$

**Theorem 5.** [Quadratic approximation of the QIF] For a fixed $q$-dimensional vector $\xi$, the following representation holds:

$$Q_N \left( \beta_0 + N^{-\frac{1}{2}} \xi \right) = Q_N(\beta_0) + 2 \langle \xi, Z_N \rangle + \xi^T J(\beta_0) \xi + o_p(1) \quad (18)$$

as $N \to \infty$, where $\langle \cdot, \cdot \rangle$ is the vector inner product and the $o_p(1)$ term is uniform for $\xi$ in a ball of radius $r_N = o(\sqrt{N})$.

**Proof:** The Taylor series expansion yields

$$Q_N \left( \beta_0 + N^{-\frac{1}{2}} \xi \right) = Q_N(\beta_0) + 2 \langle \xi, Z_N \rangle + \frac{1}{2N} \xi^T \nabla^2 Q_N \left( \beta_N^\dagger \right) \xi,$$

where $\beta_N^\dagger$ lies between $\beta_0$ and $(\beta_0 + N^{-1/2} \xi)$ for each $N$. From the uniformity result (14), it follows that

$$\frac{1}{2N} \nabla^2 Q_N \left( \beta_N^\dagger \right) = V \left( \beta_N^\dagger \right) + o_p(1).$$

As $N \to \infty$, $\beta_N^\dagger \to \beta_0$. From the continuity result of Theorem 4, it follows that $V(\beta_N^\dagger) \to V(\beta_0) = J(\beta_0)$, yielding the desired result.

**Corollary 2.** The quadratic approximation in Theorem 5 can be expressed as

$$Q_N \left( \beta_0 + N^{-\frac{1}{2}} \xi \right) = \{Z_N + J(\beta_0) \xi\}^T J^{-1}(\beta_0) \{Z_N + J(\beta_0) \xi\}$$

$$+ Q_N(\beta_0) - Z_N^T J^{-1}(\beta_0) Z_N + o_p(1).$$
The representation in the above corollary establishes that the QIF is asymptotically equivalent to a generalized least squares criterion. This simplifies derivation of large-sample results, since known properties of the weighted least squares will hold asymptotically for the QIF. Second, it leads to an IRGLS algorithm for finding the QIF estimator $\hat{\beta}_N$.

The minimizer $\xi_N^*$ of the quadratic approximation in (18) is given by

$$
\xi_N^* = -J^{-1}(\beta_0) Z_N.
$$

Since $Z_N$ has a limiting distribution, it follows that $\xi_N^*$ lies in the ball of radius $r_N$ with probability converging to 1. This result, combined with the uniformity of the error term in (18), yields the following corollaries.

**Corollary 3.** Let $\hat{\xi}_N$ be the minimizer of $Q_N (\beta_0 + N^{-1/2} \xi)$, then $\hat{\beta}_N = (\beta_0 + N^{-1/2} \hat{\xi}_N)$. Equivalently,

$$
\hat{\xi}_N = -J^{-1}(\beta_0) Z_N + o_p(1)
$$

and

$$
\hat{\beta}_N = \beta_0 - N^{-\frac{1}{2}} J^{-1}(\beta_0) Z_N + o_p(N^{-1/2}).
$$

**Corollary 4.** The asymptotic distribution of $\hat{\beta}_N$ is given by

$$
\sqrt{N} \left( \hat{\beta}_N - \beta_0 \right) \xrightarrow{d} N_q \left\{ 0, J^{-1}(\beta_0) \right\} \text{ as } N \to \infty.
$$

**Corollary 5.** The following result holds:

$$
Q_N(\hat{\beta}_N) = Q_N(\beta_0) - Z_N^T J^{-1}(\beta_0) Z_N + o_p(1) \text{ as } N \to \infty.
$$

### 4.2 Asymptotic Distribution of a Generalized QIF Test Statistic

In this section, we derive the asymptotic theory for testing a general linear hypotheses. Consequently, the one presented in QLL becomes a special case.
Following the notation in Christensen (2002), we consider the problem of testing the general linear hypothesis

$$H_0: \Lambda^T \beta = b \quad \text{versus} \quad H_1: \Lambda^T \beta \neq b,$$

where, for some $p < q$, the $(q \times p)$ matrix $\Lambda$ imposes $p$ linearly independent constraints on the parameter vector $\beta$ and constant vector $b \in \mathbb{R}^p$.

The QIF-based test statistic for testing the general linear hypothesis problem (21) is

$$T_N := Q_N(\hat{\beta}_N) - Q_N(\tilde{\beta}_N),$$

where the unrestricted and constrained minimizers of $Q_N(\beta)$ respectively, are

$$\hat{\beta}_N = \arg \min_{\beta \in B} Q_N(\beta)$$

and

$$\tilde{\beta}_N = \arg \min_{\beta \in H_0} Q_N(\beta).$$

**Theorem 6.** [Null asymptotic distribution of $T_N$] For testing the hypothesis problem (21), the QIF-based test statistic has the asymptotic representation

$$T_N = \{\Lambda^T J^{-1}(\beta_0) Z_N\}^T \{\Lambda^T J^{-1}(\beta_0) \Lambda\}^{-1} \{\Lambda^T J^{-1}(\beta_0) Z_N\} + o_p(1),$$

where $J(\beta_0)$ is defined in (12). The asymptotic distribution of $T_N$ under the null hypothesis $H_0$ is

$$T_N \overset{d}{\to} \chi_p^2 \quad \text{as} \quad N \to \infty,$$

where $p$ is the number of linearly dependent constraints imposed by the matrix $\Lambda$.

**Proof:** Suppose that the null hypothesis $H_0$ is true, then $\Lambda^T \beta_0 = b$. Note that $\xi = \sqrt{N} (\beta - \beta_0)$ implies $\Lambda^T \xi = \sqrt{N} (\Lambda^T \beta - \Lambda^T \beta_0) = \sqrt{N}(\Lambda^T \beta - b)$. Therefore,
minimizing the QIF in (18) subject to $\Lambda^T \beta = b$ is equivalent to minimizing it subject to $\Lambda^T \xi = 0$. Following arguments similar to those in the previous section, we obtain

$$\tilde{\beta}_N = \beta_0 - N^{-\frac{1}{2}} J^{-1}(\beta_0) \left[ I - \Lambda \{ \Lambda^T J^{-1}(\beta_0) \Lambda \}^{-1} \Lambda^T J^{-1}(\beta_0) \right] Z_N + o_p(N^{-1/2})$$

and

$$Q_N(\tilde{\beta}_N) - Q_N(\beta_0) = + \left\{ \Lambda^T J^{-1}(\beta_0) Z_N \right\}^T \left\{ \Lambda^T J^{-1}(\beta_0) \Lambda \right\}^{-1} \left\{ \Lambda^T J^{-1}(\beta_0) Z_N \right\} - Z_N^T J^{-1}(\beta_0) Z_N + o_p(1).$$

(24)

Combining the results (20) and (24), we obtain (23). Equation (13) implies that $\Lambda^T Z_N$ has an asymptotic $N_p \left\{ 0, \Lambda^T J^{-1}(\beta_0) \Lambda \right\}$ distribution. The asymptotic $\chi^2_p$ distribution of $T_N$ as $N \to \infty$ follows immediately.

4.3 Testing Under Local Alternatives

We consider the hypothesis testing problem (21), but assume that the alternative hypothesis is true. Specifically, consider a sequence of local alternative parameter vectors $\beta_N = (\beta_0 + N^{-1/2} \vartheta)$, where $\Lambda^T \beta_0 = b$ and $\vartheta$ is a fixed $q$-dimensional vector.

In order to establish the large-sample properties of the test statistic $T_N$ under this model, we can proceed essentially as before with the exception that $\sqrt{N} \mathbf{g}_N(\beta_0)$ has non-zero mean. The multivariate central limit theorems become, respectively

$$\sqrt{N} \mathbf{g}_N(\beta_0) \xrightarrow{d} N_r\{-D(\beta_0) \vartheta, \Sigma_{\beta_0}(\beta_0)\}$$

and

$$Z_N = \frac{1}{2\sqrt{N}} \nabla Q_N(\beta_0) \xrightarrow{d} N_q\{-J(\beta_0) \vartheta, J(\beta_0)\}$$

as $N \to \infty$. The asymptotic representation (23) continues to hold under the local alternatives; therefore, we have the following asymptotic distribution for $T_N$.

**Theorem 7.** [Asymptotic distribution of $T_N$ under local alternatives] Under $\beta_N = (\beta_0 + N^{-1/2} \vartheta)$, the asymptotic distribution of the test statistic $T_N$ is non-central
chi-squared with a non-centrality parameter defined as

$$\delta^2 := \vartheta^T \Lambda \left\{ \Lambda^T J^{-1}(\beta_0) \Lambda \right\}^{-1} \Lambda^T \vartheta. \quad (25)$$

**Example:** QLL partitioned the regression parameter vector as $\beta^T = (\psi^T, \lambda^T)$ and considered testing the hypothesis $H_0: \psi = \psi_0$. This corresponds to $\Lambda^T = (I \ 0)$ and $b = \psi_0$ in the hypothesis problem (21).

The result of Theorem 7 is applicable if we partition the asymptotic covariance matrix of $\hat{\beta}_N$ as

$$J(\beta_0) = \begin{pmatrix} J_{\psi_0, \psi_0} & J_{\psi_0, \lambda_0} \\ J_{\lambda_0, \psi_0} & J_{\lambda_0, \lambda_0} \end{pmatrix},$$

where $\beta_0 = (\psi_0, \lambda_0)$ is the null value of $\beta = (\psi, \lambda)$. From standard results for the inversion of a partitioned matrix, the non-centrality parameter can be expressed as

$$\delta^2 = \vartheta^T \Lambda \left( J_{\psi_0, \psi_0} - J_{\psi_0, \lambda_0} J_{\lambda_0, \lambda_0}^{-1} J_{\lambda_0, \psi_0} \right)^{-1} \Lambda^T \vartheta.$$

This agrees with the result in QLL, subject to the concerns over the scaling of $J_{\psi, \psi}$ discussed earlier.

## 5 The IRGLS Algorithm

In this section, we derive the iteratively reweighted generalized least squares (IRGLS) algorithm for finding the QIF estimator of $\beta$. The necessity for such an algorithm is illustrated first using a simulated experimental data.

We assumed ten subjects ($i = 1,\ldots,10$) and four observations per subject ($t = 1,\ldots,4$) under an AR-1 correlation structure with autocorrelation $\rho = 0.5$. We
constructed the extended score vector $\tilde{g}_N(\beta)$ using $M_1 = I$ and

$$M_2 = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{pmatrix}$$

as the basis matrices. The fitted models are $\mu_{it} = \beta_0 + \beta_1 (t - 2.5)$ and

$$\log \left\{ \frac{\mu_{it}}{1 - \mu_{it}} \right\} = \beta_0 + \beta_1 (t - 2.5) \quad \text{for} \quad i = 1, \ldots, 10; t = 1, \ldots, 4,$$

respectively, for the Gaussian and Bernoulli responses. Let $\beta = (\beta_0, \beta_1)^T$. Figure 1 displays the QIF surface $Q_N(\beta)$ for simulated correlated data generated from the Gaussian and Bernoulli distributions, respectively. Notice the strikingly different behavior under these two models. For the correlated responses from the Gaussian distribution, the QIF surface is bounded above by $N = 10$ and converges to 10 as $\|\beta\| \to \infty$ in any direction. Even in such a scenario, the Newton-Raphson algorithm can diverge. In the Bernoulli case, the surface has multiple ridges, valleys as well as local minima as $\|\beta\| \to \infty$ in some directions. It is clear that, carefully designed algorithms are necessary to reliably find the global minimum of $Q_N(\beta)$.

The QIF surface plots amplify the necessity for the development of a stable algorithm for finding the QIF estimator of $\beta$. The Newton-Raphson algorithm, recommended by QLL, requires accurate starting values to converge, especially in situations resembling that of Figure 1(b). Furthermore, in order to implement the Newton-Raphson algorithm, we need to find the matrix $\nabla^2 Q_N(\beta)$ which can be a computationally daunting task even for small $N$.

**IRGLS Algorithm:** The equation (19) forms the basis of our algorithm.

**Step 1.** Start with an initial value of the parameter vector $\beta^{(1)}$.

**Step 2.** Find the updated value for $\beta$ via

$$\beta^{(j+1)} = \beta^{(j)} - \frac{1}{2N} \tilde{J}_N^{-1} \left( \beta^{(j)} \right) \nabla Q_N \left( \beta^{(j)} \right) \quad \text{for} \quad j = 1, 2, \ldots$$
Figure 1: The surface plot of $Q_N(\beta)$, where $\beta = (\beta_0, \beta_1)^T$, under the AR-1 correlation structure for the correlated (a) Gaussian responses and (b) Bernoulli responses.
where
\[ \hat{J}_N(\beta) := \nabla g_N^T(\beta) \hat{C}_N^{-1}(\beta) \nabla g_N(\beta). \]

(27)

If the above iterative scheme converges to a limit \( \beta^\infty \), then the limit must be a stationary point satisfying \( \nabla Q_N(\beta^\infty) = 0 \). An S-Plus library implementing this IRGLS algorithm is developed by Loader and Pilla (2005b).

The IRGLS algorithm proposed here inherits the standard advantages of the IRLS methods (Green, 1984) over the Newton-Raphson algorithm: (1) it avoids the complexity of computing \( \nabla^2 Q_N(\beta) \); and (2) the algorithm is guaranteed to move in a descent direction of the QIF surface. This second property ensures that the algorithm cannot converge to a local maximum. With simple bounds on the step size, the IRGLS algorithm converges to the QIF estimator from almost any starting point (Loader and Pilla, 2005a).

6 Analysis of Respiratory Health Effects Data

We analyze part of the longitudinal binary data on respiratory health effects of indoor and outdoor air pollution in six U.S. cities measured on 537 children at ages 7 to 10. One of the interests of the study is to determine the effect of maternal smoking on the children’s respiratory illness. Laird et al. (1984) considered the data collected on children from Ohio and treated the maternal smoking habit as fixed at the first visit. The response is binary indicating the presence or absence of respiratory illness. The maternal smoking habit, in the preceding year, is recorded as a binary covariate. The mean response is modeled as a function of Age, Smoking habit and the interaction. One of the goals of this study was to assess the effect of maternal smoking on children’s respiratory illness. Note that measurements observed on each child are serially correlated.
We fit the following logistic model to the binary data
\[
\log \left( \frac{\mu_{it}}{1 - \mu_{it}} \right) = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \beta_3 X_{i1} X_{i2}
\]
for \( i = 1, \ldots, 537 \) and \( t = 0, \ldots, 4 \), where \( X_{i1} \) and \( X_{i2} \) are the time-independent covariates for the age of the child and maternal smoking habit, respectively. The matrix \( A_i \) is diagonal with elements \( v(\mu_{it}) = \mu_{it}(1 - \mu_{it}) \). The extended score vector \( \overline{g}_N(\beta) \) is constructed by choosing \( s = 2 \), \( M_1 = I \) and \( M_2 \) as in (26).

The standard errors of \( \hat{\beta} \), denoted by \( s(\hat{\beta}) \), are computed as the square root of diagonal elements of \( J_N^{-1}(\hat{\beta}) \), where \( \hat{J}_N(\cdot) \) is defined in (27). Table 1 presents the estimators \( \hat{\beta} \) and their corresponding standard errors \( s(\hat{\beta}) \), obtained via the QIF library (Loader and Pilla, 2005a). The t-ratios suggest that Age is the significant covariate to include in the model. The t-ratio for age has a negative sign indicating that older children are less likely to have a respiratory illness, whereas mother’s smoking habit has a positive effect on children’s respiratory disease, although not statistically significant. The interaction between the age of the child and maternal smoking is also not statistically significant.

Table 1: The parameter estimators and corresponding estimated standard errors for the Respiratory Health Study under the AR-1 Correlation Structure.

| Covariates        | \( \hat{\beta} \)     | \( s(\hat{\beta}) \) | t-ratio   |
|-------------------|------------------------|-----------------------|-----------|
| Intercept         | -1.89404               | 0.11903               | -15.91226 |
| Age               | -0.12933               | 0.05671               | -2.28062  |
| Smoke             | 0.26384                | 0.18962               | 1.39144   |
| Age \( \times \) Smoke | 0.06070               | 0.08791               | 0.69048   |

In order to assess whether the sub-models are adequate, we compute the QIF under various sub-models with certain parameter restrictions to perform chi-square tests for comparing different models.
Each row of the Table 2 represents results for a given model and the last row provides the full model. For each model, we compute the parameter estimate \( \tilde{\beta} \) and report the corresponding \( Q_N(\tilde{\beta}) \). The test statistic \( T_N \) is obtained via (22) which compares with the full model. The “df” column is the degrees-of-freedom for the test statistic and \( P \) is the P-value. From the table, the models “Intercept” and “Intercept, Smoke” are rejected \( (P < 0.05) \). The remaining models that include the Age variable cannot be rejected.

Table 2: Testing of hypotheses for the longitudinal data on children’s respiratory disease. The column \( Q_N(\tilde{\beta}) \) is minimum of the QIF obtained under the submodel, \( T_N \) is the value of the test statistic, df is the degrees of freedom and \( P \) is the p-value for the test statistic.

| Covariates                      | \( Q_N(\tilde{\beta}) \) | \( T_N \) | df | \( P \) |
|---------------------------------|---------------------------|-----------|----|--------|
| Intercept                       | 11.898                    | 7.926     | 3  | 0.048  |
| Intercept, Smoke                | 10.337                    | 6.365     | 2  | 0.041  |
| Intercept, Age                  | 5.823                     | 1.851     | 2  | 0.396  |
| Intercept, Smoke, Age           | 4.449                     | 0.477     | 1  | 0.490  |
| Intercept, Smoke, Age \( \times \) Smoke | 3.972                     | 0         | -  | -      |

Remark 3. The discrepancy between our results and those of QLL is apparently due to their use of undocumented modifications of the covariance estimators of \( \text{cov}(\mathbf{g}_N(\beta)) \). The results in Table 2 are based on minimization of \( Q_N(\beta) \) as defined in (6).
7 Assessing the Effect of Basis Matrices on the QIF Test

In this section we investigate the effect of the choice of basis matrices, defining the extended score vector \( \mathbf{g}_N(\beta) \), on the performance of the QIF test. The basis matrices are often unknown in advance; hence, it is necessary to assess the effect of their misspecification. We calculate the size and power of the QIF test based on \( T_N \) through the simulated correlated data from Bernoulli and Gaussian distributions.

The QIF test statistic is robust to the choice of basis matrices, in the sense that the null asymptotic chi-squared distribution of \( T_N \) is valid whether or not the basis matrices \( M_j \) \((j = 1, \ldots, s)\) are correctly specified. However, misspecification may adversely affect the power of the test, since the asymptotic covariance matrix \( \mathbf{J}^{-1}(\beta_0) \) defined in (12) [consequently, the non-centrality parameter \( \delta^2 \) in (25)] depends on the true covariance matrix of \( \beta_0 \).

The following is the trade-off for misspecification of the basis matrices: (1) If too few basis matrices are included in the model, then the estimator of \( \beta \) may not be efficient; consequently leads to a loss of power of the test based on \( T_N \). (2) If too many basis matrices are specified in the model, then the dimensionality of the extended score vector \( \mathbf{g}_N(\beta) \) increases. This can lead to numerical instability while affecting the power of the QIF test based on \( T_N \) as more components of \( \widehat{\mathbf{C}}_N(\beta) \) are being estimated.

We conducted two simulation experiments each with \( N = 50 \) subjects and \( n = 5 \) observations per subject to investigate the effect of the basis matrices on the QIF-based inference.

Let AR-1 refer to representing \( \mathbf{R}^{-1}(\alpha) = (\alpha_1 \mathbf{M}_1 + \alpha_2 \mathbf{M}_2) \) and AR-2 refer to expressing \( \mathbf{R}^{-1}(\alpha) = (\alpha_1 \mathbf{M}_1 + \alpha_2 \mathbf{M}_2 + \alpha_3 \mathbf{M}_3) \), where \( \mathbf{M}_1 = \mathbf{I} \) (the identity matrix of
dimension 5),

\[
M_2 = \begin{pmatrix}
0 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
0 & 1 & 0 & 1 & 0 \\
0 & 0 & 1 & 0 & 1 \\
0 & 0 & 0 & 1 & 0
\end{pmatrix}
\quad \text{and} \quad
M_3 = \begin{pmatrix}
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0
\end{pmatrix}.
\]

**Binary Correlated Responses:** For each subject, binary responses \(Y_{it}\) for \(i = 1, \ldots, 50\) and \(t = 1, \ldots, 5\) were generated according to the following two-state Markov chain with the transition matrix

\[
\begin{pmatrix}
1 - \rho \\
\rho
\end{pmatrix}
\begin{pmatrix}
1 & \mu_i \\
1 - \mu_i & \mu_i
\end{pmatrix}
+ (1 - \rho)
\begin{pmatrix}
1 - \mu_i \\
1 - \mu_i & \mu_i
\end{pmatrix},
\]

where \(\mu_i\) is defined in (28) below. The response vector \(Y_{it}\) has the stationary distribution \(\begin{pmatrix}1 - \mu_i & \mu_i\end{pmatrix}\) and the AR-1 correlation structure with autocorrelation \(\rho\). We fit the following logistic model to the binary data

\[
\log \left\{ \frac{\mu_i}{1 - \mu_i} \right\} = \beta_0 + \beta_1 X_i \quad \text{for} \quad i = 1, \ldots, 50, \tag{28}
\]

where the covariate \(X_i\) is chosen to be equally spaced on the interval \([-1, 1]\).

For each simulation experiment, the QIF test statistic \(T_N\), defined in (22), for \(H_0: \beta_1 = 0\) versus \(H_1: \beta_1 \neq 0\) was compared with the critical value 3.8415, based on the 95th percentile of the \(\chi^2_1\) distribution. We chose the following true parameters for the simulation experiment: \(\beta_0 = \beta_1 = 0\) under \(H_0\) and \(\beta_0 = 0, \beta_1 = 0.5\) under \(H_1\).

**Gaussian Correlated Responses:** The same design and parameter values were used for this simulation experiment; however, we fit the following model to the continuous data

\[
Y_{it} = \beta_0 + \beta_1 X_i + \epsilon_{it} \quad \text{for} \quad i = 1, \ldots, 50; \ t = 1, \ldots, 5,
\]

where for each \(i\), \(\epsilon_{it}\) is assumed to be a Gaussian AR-1 process with variance 1 and correlation \(\rho\).
Table 3: Achieved significance level and power under three different assumed correlation structures for the QIF test based on $T_N$. Results are based on 10,000 replications under the true AR-1 correlation structure with autocorrelation $\rho$.

| Model     | $\rho$ | Level of Significance | Power        |
|-----------|--------|-----------------------|--------------|
|           |        | Identity AR-1 AR-2    | Identity AR-1 AR-2 |
| Identity  | 0.2    | 0.048 0.048 0.048     | 0.473 0.463 0.447 |
| Logistic  | 0.5    | 0.050 0.049 0.049     | 0.325 0.327 0.322 |
| Logistic  | 0.8    | 0.047 0.050 0.048     | 0.226 0.228 0.227 |
| Gaussian  | 0.2    | 0.050 0.047 0.048     | 0.968 0.954 0.933 |
| Gaussian  | 0.5    | 0.044 0.046 0.044     | 0.843 0.822 0.795 |
| Gaussian  | 0.8    | 0.052 0.050 0.051     | 0.644 0.633 0.601 |

Table 3 presents the simulation results under the logistic and Gaussian models, respectively. Under each scenario, we achieve significance levels close to the nominal level of 5%, while the power decreases as the correlation $\rho$ increases. However, for a fixed $\rho$, there is a minimal difference between the powers attained under the three different correlation structures. In particular, there is essentially no power loss when we assumed (albeit incorrectly) the identity correlation structure.

To investigate further, we estimated the non-centrality parameter based on (25) under different scenarios by finding

$$\hat{\delta}^2 = N \beta_1 \left\{ \Lambda^T \hat{J}^{-1}_N(\hat{\beta}) \Lambda \right\}^{-1} \beta_1,$$

averaged over all 10,000 replications, where $\beta_1 = 0.5$ is the slope parameter under $H_1$, $\Lambda^T = (0 \ 1)$ and $\hat{J}^{-1}_N(\cdot)$ is defined in (27).

Table 4 presents the $\hat{\delta}^2$ values along with the power of the QIF test calculated under the theoretical asymptotic non-central chi-squared distribution of $T_N$. These results
demonstrate that the model with a misspecified identity correlation structure yields a slightly smaller $\hat{\delta}^2$ and correspondingly slightly lower power. However, this difference is not reflected by the finite-sample simulation results presented in Table 3.

Table 4: Estimated non-centrality parameter $\hat{\delta}^2$ values and powers for the QIF test based on $T_N$ under three different assumed correlation structures. Results are based on 10,000 replications under the true AR-1 correlation structure with autocorrelation $\rho$.

| Model     | $\rho$ | $\hat{\delta}^2$ | Power |
|-----------|--------|-------------------|-------|
|           |        | Identity | AR-1 | AR-2 | Identity | AR-1 | AR-2 |
| Identity  | 0.2    | 4.122     | 4.286 | 4.437 | 0.528     | 0.544 | 0.558 |
| Logistic  | 0.5    | 2.452     | 2.609 | 2.678 | 0.347     | 0.365 | 0.373 |
|          | 0.8    | 1.431     | 1.515 | 1.517 | 0.223     | 0.234 | 0.234 |
| Gaussian  | 0.2    | 17.982    | 19.263 | 20.478 | 0.989    | 0.992 | 0.995 |
|          | 0.5    | 11.067    | 12.189 | 12.961 | 0.914    | 0.937 | 0.950 |
|          | 0.8    | 6.837     | 7.582 | 8.071 | 0.744     | 0.786 | 0.811 |

The conclusion from the simulation experiments is that not much is lost when only the identity correlation structure is assumed. This does not mean that correlation structure is not important, but rather that correlation is being adequately modeled through the empirical covariance matrix $\hat{\mathbf{C}}_N(\hat{\beta})$ even under the misspecification of the basis matrices.
8 Conclusions

The QIF is a powerful tool for building regression models for correlated data. The large-sample properties of the inference functions are similar to those of the loglikelihood in parametric statistical inference with test statistics based on the QIF having asymptotic chi-squared distributions. As shown in Section 1.3, the covariance matrix for the extended score functions defining the QIF employed by QLL can lead to breakdown of the asymptotic theory.

In this research, we established a unified large-sample theoretical framework for the QIF. First, we formulated an accurate estimator for the covariance of the extended score functions \( g_N(\beta) \) and second, we derived relevant asymptotic results necessary for the estimation and testing within the QIF setting. The key principle underlying our asymptotic treatment is the quadratic approximation in Theorem 5. The consequences of this approximation are wide-ranging, providing the necessary machinery for deriving large-sample theory for the QIF estimators and test statistics, analogous to standard inferential theory for the generalized least squares criteria, while leading to a stable and flexible algorithm for finding the QIF estimators. Our simulation experiments demonstrate that the QIF test statistic \( T_N \) is robust to the choice of basis matrices, in the sense that the null asymptotic chi-squared distribution of \( T_N \) holds true even under the misspecification of the basis matrices.

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